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REVIEW SYNTHESIS OF VARIOUS BENZIMIDAZOLE DERIVATIVES AND ITS POTENTIAL BIOLOGICAL ACTIVITY

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ABSTRACT

Benzimidazole is an important pharmacophore which was included in several biologically active compounds resulted in the development of several classes of drugs.[1] Compounds having benzimidazole as a structural motif have been widely used in medicinal chemistry and drug development, and researchers are actively seeking new uses and applications of this heterocycle.[2] In 1990 various benzimidazole derivatives were synthesized with substitution of fluorine, propylene, tetrahydroquinoline and cyclized compound which resulted in compounds with increased stability, bioavailability and significant biological activity.[3] This review summarizes some potential biological activities shown by benzimidazole derivatives in recent years.

KEYWORDS: Benzimidazole, Heterocycle, Biological Activity.

INTRODUCTION

Benzimidazole is a heterocyclic aromatic organic compound. It is an important pharmacophore and a privileged structure in medicinal chemistry. This compound is bicyclic in nature which consists of the fusion of benzene and imidazole. Nowadays is a moiety of choice which possesses many pharmacological properties. Different heterocyclic motifs can be incorporated to produce molecules with enhanced biological properties.[4] Benzimidazole containing compounds have numerous medical and biological activities such as antitumor, antibacterial, antifungal, antiviral, anticonvulsant, antidepressant, analgesic, anti-inflammatory and anti-diabetic properties.[5]

LITERATURE REVIEW

1. Na Zhao *et al; 2005*[6]

Reported an efficient and a quick microwave-assisted synthesis of Benzimidazole and trisubstituted imidazole's. Three Benzimidazole were obtained as a result of the condensation of 1,2phenylenediamine with carboxylic acids and acetoacetic ester without catalyst.

2. Hassan Y Aboul-Enein *et al; 2015*[7]

Reported an efficient synthesis of several novel benzimidazole derivatives that possess anti-diabetic activity. Several agents demonstrated potential activities that they were marketed as useful agents for the treatment of type 2 diabetes operating on various mechanism(s) of actions. Efforts are still going on in the search of new benzimidazole derivatives that are pharmacologically effective and safe as anti-diabetic agents.

3. Fatmah A. S. Alasmary *et al; 2015*[5]

Reported synthesized of library of 53 benzimidazole derivatives, with substituent's at positions 1, 2 and 5, and screened against a series of reference strains of bacteria and fungi of medical relevance. The compounds have some common features; three possess 5-halo substituent's; two are derivatives of (S)-2-ethanaminebenzimidazole; and the others are derivatives of one 2-(chloromethyl)-1Hbenzo[d]imidazole and (1H-benzo[d]imidazol-2-yl)methanethiol.

4. Bijo Mathew *et al; 2016*[8]

Reported the synthesis of some novel (1-*H*) benzimidazole bearing pyrimidine-trione based MAO-A inhibitors were achieved by the reaction between 2*E*)-1-(1*H*-benzimidazol-2-yl)-3-phenylprop-2-en-1-ones and barbituric acid in the presence of a catalytic amount of acetic acid medium. All the synthesized derivatives showed good antidepressant activity when compared to the standard clomipiramine at a dose level of 20 mg/kg. The compound 5-{(2*E*)-1-(1*H*-benzimidazol-2-yl)-3-[4-(dimethylamino)phenyl] prop-2-en-1-ylidene} pyrimidine-2, 4, 6(1*H*,3*H*,5*H*)-trione significantly reduced the duration of immobility.[10]

5. Sandeep Waghulde *et al;2012*[9]

Reported synthesis and anti-inflammatory activity of novel 2-(Substituted alkyl or aryl pyridynyl) benzimidazole derivatives. It has been reported that 2-(Substituted pyridynyl) benzimidazole possess anti-inflammatory activity. Cut-off LD50 was determined for all the test compounds. Cut-off LD50 of test compounds were found to be 2000mg/kg. The anti-

inflammatory activity was determined using carrageenan induced rat paw edema method Most of the obtained compounds exhibit anti-inflammatory activity, especially some compounds showed significant activity and some showed moderate activity when compared with that of ibuprofen used as standard drug with reduced toxicity.

6. Shobith Srivastava *et al ;2013*[10]

Reported synthesis of a series of novel 2- phenylhydrazinomethyl and 2-(2-hydroxyphenyl)-benzimidazole derivatives substituted at the N1-position of benzimidazole nucleus were synthesized as well as screened for analgesic activity. Some of these compounds showed promising analgesic activity when compared with the standard drug diclofenac sodium. The incorporation of a phenylhydrazinomethyl nucleus at 2-position of benzimidazole compound gave a biologically active pharmacophore.

7. Mushtaq A. Tantray *et al ;2016*[11]

A series of novel benzimidazole-based 1,3,4-oxadiazole-1,2,3-triazole conjugates has been synthesized and evaluated for GSK-3β inhibitory activity *in vitro*. Compounds exhibited significant inhibition with sub-micromolar IC_{50} values (0.15, 0.27, 0.32 and 0.39 μM respectively) and were examined further for antidepressant activity by forced swim test (FST) and tail suspension test (TST) models in Wistar rats. In both TST and FST models, all the test compounds were found to significantly reduce the immobility time period (displaying antidepressant-like activity) in comparison to a normal saline treated control group. Compound 7q was found to be the most active. Molecular docking studies of the active compounds 7q**,** 7b**,** 7e and 7n were also performed against GSK-3β to gain an understanding of their binding interactions.

8. Rashmi Arora *et al; 2012*[12]

A novel series of pyrazole derivatives of benzimidazole was synthesized by the reaction between o-phenylenediamine and equimolar quantities of lactic acid**.** The products obtained were treated with phenylhydrazine in the presence of ethanolic sodium acetate to synthesize various pyrazole derivatives of benzimidazole i.e., 2-[5-(4-chloro-phenyl-2H-pyrazol-3-yl]-1H-benzimidazole (1a), 2-[5-(3-bromo-phenyl)-2-phenyl-2H-pyrazol-3-yl]-1H-benzimidazole (1b), {4-[5-(1H-benzimidazol-2-yl)-1-phenyl-1H-pyrazol-3yl]-phenyl}-dimethyl-amine (1c), 2-[5-(3-Chloro-phenyl)-2-phenyl-2H-pyrazol-3-yl]-1H-benzimidazole (1d) and 3-[5-(1H-benzimidazol-2-yl)-1-phenyl-1h-pyrazol-3-yl]-phenol (1e) having %age yield 55, 62, 80, 58, 66, respectively. The synthesized Compounds was evaluated for

analgesic as well as anti-inflammatory activity. The compound 1a-1e showed significant analgesic activity at 7.36±0.05, 7.50±0.08, 8.43±0.12, 7.88±0.02 and 7.64±0.08 at 90 min when compared with standard i.e., 9.45±0.28 at 90 min, respectively. Further the compounds 1a-1e were evaluated for anti-inflammatory activity and showed significant % inhibition of edema i.e., 59.09, 63.63, 62, 60.60 and 57.57% at a dose of 200 mg mL^{-1} as compared to standard drug i.e., 69.6% at 3 h, respectively. The compound 1b showed significant anti-inflammatory where as compound 1c showed potent analgesic activity and the other compounds showed moderate activity. This comprehensive study summarizes the different pyrazole derivatives of benzimidazole were showed excellent significant analgesic and anti-inflammatory activities.

9. R.V. Shingalapur *et al; 2010*[13]

In seeking broad spectrum pharmacological activities of benzimidazole derivatives, a group of 4-thiazolidinones 5(a–j) and 1,3,4-oxadiazoles 6(a–j) containing 2-mercapto benzimidazole moiety were synthesized and screened for in vivo anticonvulsant activity by Maximal Electroshock (MES) model and antidiabetic activity using Oral Glucose Tolerance Test (OGTT). Compounds (5c), (5d), (5g) and (5i) exhibited potent anticonvulsant results and (6c), (6d), (6h) and (6i) showed excellent antidiabetic activities and also pharmacophore derived from active molecules suggested that presence of –OH group was a common feature in all active compounds. In DNA cleavage studies, compound (5d) cleaved DNA completely as no trace of DNA was found. On the other hand, a sharp streak was found for compounds (5c), (6a) and (6d).

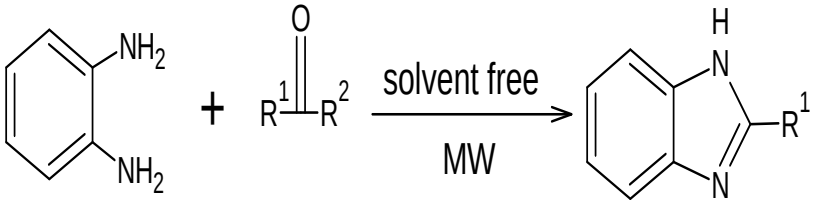
10. Parmender Singh Rathee *et al; 2011*[14]

Two series of novel benzimidazole derivatives were synthesized. The first one comprise of 2-methyl, the second one comprise of 2-phenyl substitution on benzimidazole moiety. Seven novel benzimidazole derivatives were synthesized successfully in appreciable yields and characterized physico-chemically. The structures of all the synthesized derivatives were confirmed by IR and 1HNMR. Furthermore, the synthesized compounds were screened for antimicrobial activity (antibacterial activity and antifungal activity) by tube dilution method. Some of the synthesized compounds showed appreciable antifungal activity.

METHODOLOGY FOR SYNTHESIS

Equimolar mixture of 1, 2 Phenylenediamine (1mmol) and carboxylic acids/esters (1mmol) and their derivatives were mixed thoroughly in an agate mortar and then placed in a little

glass bottle. The mixture was irradiated in the microwave oven with 495W for 15 minutes. Cooled the solution and added 10% NaOH solution with constant stirring until the mixture is alkaline to litmus paper. Crude benzimidazole is then filtered and washed with little ice cold water dissolved in 40 ml of hot water. 250 mg decolorized charcoal was added and digested for 15 minutes. Filtered rapidly and cooled the filtrate and resulting precipitate was filtered and dried. After the reaction was completed (monitored by TLC), the crude products were re-crystallized with alcohol.



Several studies indicate that product achieved using microwave synthesis method gave better yields, have cleaner reactions which is a better and more practical eco-friendly alternative to existing methods.

CONCLUSION

This review discusses several novel benzimidazole derivatives that possess antidiabetic, anti-bacterial activity, anti-inflammatory, anti-depressant and analgesic activity. Several agents demonstrated good response for these potential activities. Also it discusses an effecient procedure to synthesize benzimidazole derivatives using microwave synthesis method in a solvent free medium which produces better yields of benzimidazoles.

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