WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 13, 204-217. Review Article ISSN 2277– 7105

SUBSTITUTED BENZIMIDAZOLE A POTENTIAL DRUG CANDIDATE: AN OVERVIEW

Avinash P. Tupe *[1], Ganesh V. Devkate[2], Sandeep S. Tate[3], Sonali B. Deokate[4], Atul S. Bhujbal[5] and Dr. Rajendra N. Patil[6]

[1,6]Department of Pharmaceutical Chemistry, Shivnagar Vidya Prasarak Mandal's College of Pharmacy, Malegaon (BK), Baramati-413115, India.

[2,3,4]Department of Pharmaceutics, Shivnagar Vidya Prasarak Mandal's College of Pharmacy, Malegaon (BK), Baramati-413115, India.

[5]Department of Pharmacology, Shivnagar Vidya Prasarak Mandal's College of Pharmacy, Malegaon (BK), Baramati-413115, India.

Article Received on
24 August 2017,

Revised on 14 Sept. 2017,
Accepted on 05 October 2017

DOI: 10.20959/wjpr201713-9653

***Corresponding Author**
Avinash P. Tupe
Department of Pharmaceutical Chemistry, ShivnagarVidyaPrasarakMandal's College of Pharmacy, Malegaon (BK), Baramati-413115, India.

ABSTRACT

Benzimidazole has diverse biological potential and the easy synthetic routes for synthesis have taken attention of the chemists, pharmacologists and researchers. The review of synthetic methods of substituted benzimidazoles and this new class of substituted benzimidazole has shown a wide spectrum of biological activities. The biological profile of these new generations of benzimidazoles presents much progress with regards to the old compounds. The anti-inflammatory, analgesic, antibacterial, antifungal activities are the most reported activities on benzimidazole compounds. The currently used analgesic and anti-inflammatory drugs have limitations for therapeutic use since they cause gastrointestinal and renal side effects that are inseparable from their pharmacological activities. For this purpose, the synthesis of new compounds devoid of such side effects has become an important goal for medicinal chemists.

KEYWORDS: Benzimidazole, wide spectrum, anti-inflammatory, analgesic.

INTRODUCTION

Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical

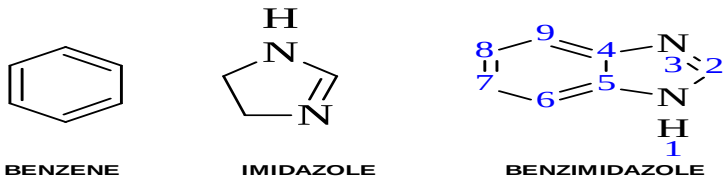
and veterinary products. Among a wide variety of nitrogen heterocycles that have been explored for developing pharmaceutically important role in medicinal chemistry and subsequently have emerged as a Pharmacophore.

Benzimidazoles are classes of heterocycles that are of considerable interest because of the diverse range of their biological properties. Among a wide variety of nitrogen heterocycles that have been explored for developing pharmaceutically important molecules. Many derivatives of benzimidazoles are used in the pharmaceutical industry, in medicine and in agriculture due to their useful properties.

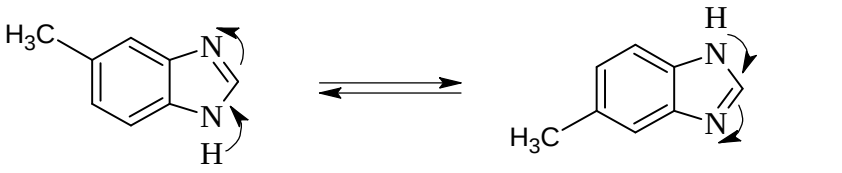
The benzimidazole scaffold is a useful structural motif for the development of molecules of pharmaceutical or biological interest. Appropriately substituted benzimidazole derivatives have found diverse therapeutic applications such as in antiulcers, antihypertensive, antivirals, antifungals, anticancers, antihistaminics., antimicrobial, anti-inflammatory, anticonvulsant, antidepressant, antioxidant, radioprotective and anti-leishmanial. The benzimidazoles are broad–spectrum group of drug discovered in the 1960 with activity against helminthes[1].

Chemistry of Benzimidazole

Benzimidazole is fused aromatic imidazole ring system where a benzene ring is fused to the 4 and 5 postion of an imidazole ring.[2]

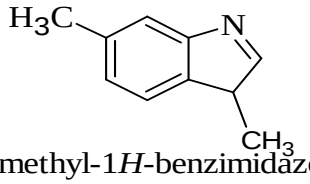


Benzimidazoles which contain a hydrogen atom attached to nitrogen in the first position readily tautomerize. This may be depicted as follows.

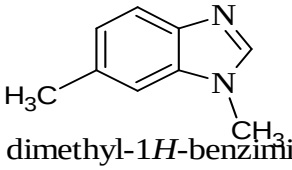


This tautomerism is analogous to that found in the imidazoles and amidines. The benzimidazoles, in fact, may be considered as cyclic analogs of the amidines. Because of this

tautomerism in benzimidazoles certain derivatives which appear at first to be isomers are in reality tautomers, although two nonequivalent structures can be written, only one compound is known. This may be illustrated with 5 (or 6)-methylbenzimidazole.[3]



1,5dimethyl-1*H*-benzimidazole



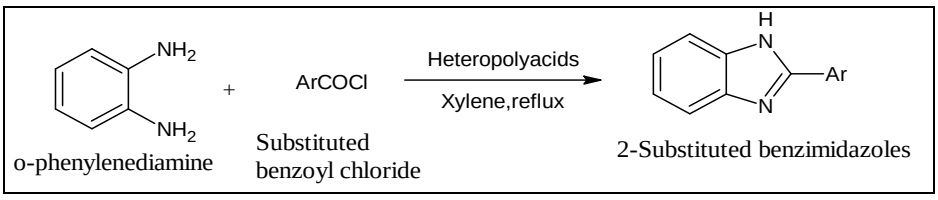
1,6 dimethyl-1*H*-benzimidazole

Thus, 5-methylbenzimidazole is a tautomer of 6-methylbenzimidazole**,** and both structures represent the same compound. When the group attached to the nitrogen in the first position is larger than hydrogen, such tautomerism is not indicated and isomeric forms exist. Thus, 1, 5 dimethylbenzimidazole and 1, 6-dimethylbenzimidazole are separate and distinct compounds.

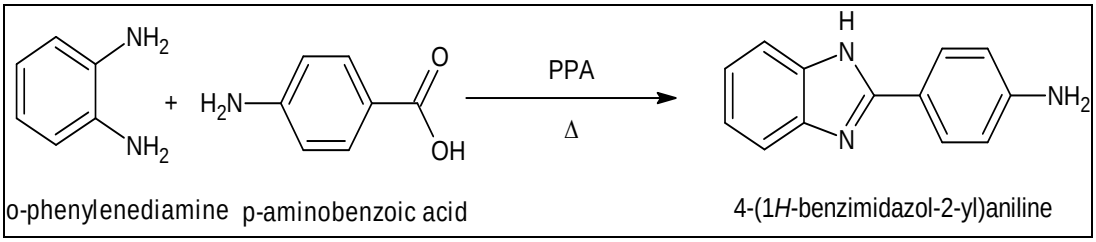
The benzimidazole ring possesses a high degree of stability. Benzimidazole, for example, is not affected by concentrated sulfuric acid when heated under pressure to 270°C or by vigorous treatment with hot hydrochloric acid or with alkalis. Oxidation cleaves the benzene ring of benzimidazole only under vigorous conditions. The benzimidazole ring is also quite resistant to reduction, however, tetrahydro and hexahydrobenzimidazoles in which the benzene ring is reduced may be prepared by catalytic reduction under certain conditions. Benzimidazole gives a negative test with sodium nitroprusside and alkali.[3]

Synthesis of Benzimidazole

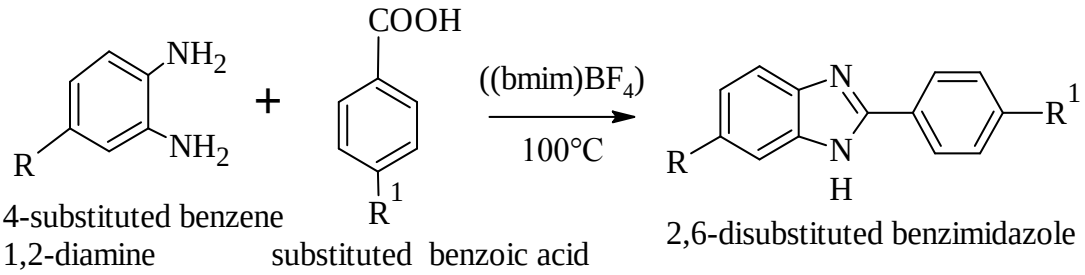
F. F. Bamoharram *et al*[4] were synthesized benzimidazole using o-phenylenediamine reacts with benzoyl chloride derivatives in the presence of heteropolyacids as catalyst .The reaction proceeds very cleanly under reflux condition and free of side product. In absence of the catalysist the reaction does not completes.



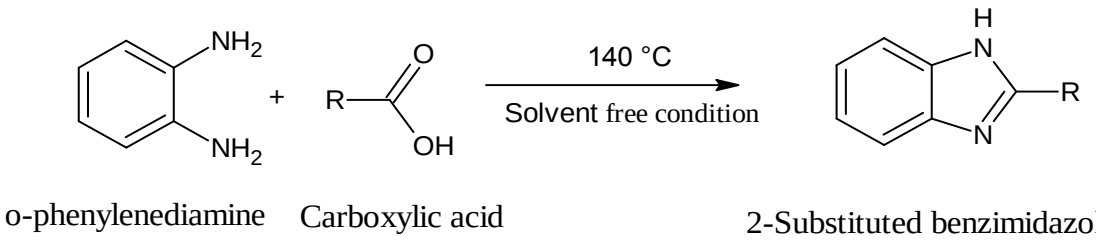
P. Kumar *et al*[5] were reported synthesis of 2- phenyl benzimidazole derivatives using o-phenylenediamine reacts with p-aminobenzoic acid in the presence of poly phosphoric acid at 190-195^{0}C for 4 hours.



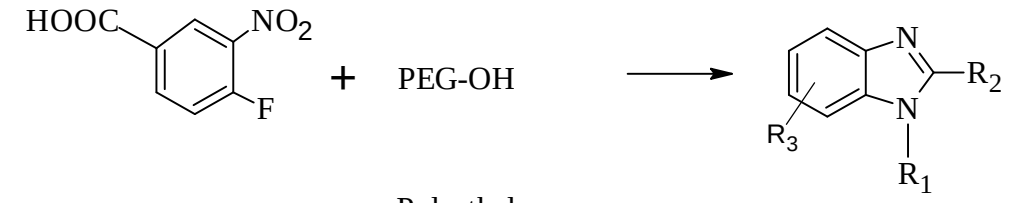
M. B. Maradolla *et al*[6] were reported the rapid and efficient synthesis of benzimidazoles in excellent yields by condensing a variety of carboxylic acids with 1, 2-phenylenediamines under ambient conditions using the ionic liquid 1-butyl 3-methyl imidazolium tetraflouroborate [(bmim) BF_4] at higher temperatures. The ambient reaction conditions, absence of a catalyst and recyclability of the non-volatile liquids makes this an environment friendly methodology amenable for scale up.



Harjyoti Thakuria and Gopal[7] Das reported synthesis of benzimidazole derivatives from *o*-phenylenediamine and carboxylic acids.

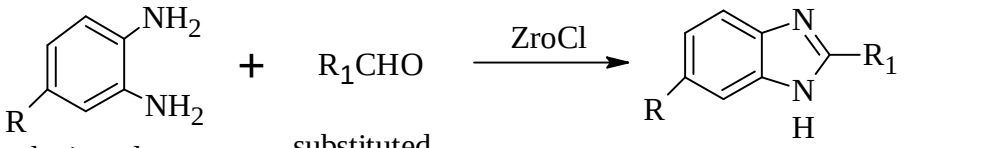


L. J. Chang *et al*[8] were reported liquid phase combinatorial synthesis using a soluble polyethylene glycol (PEG) polymer support and commercially available 4-fluoro3-nitro benzoic acid is carried out in order to create a molecular library of trisubstituted benzimidazoles. The polymer support was cleaved releasing the desired products in high yields and purity. All reactions were performed at room temperature.



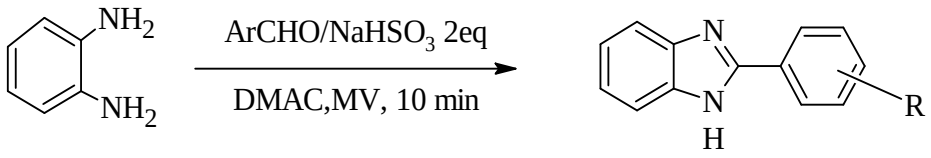
4-fluoro-3-nitrobenzoic acid | Polyethylene glycol | Trisubstituted benzimidazole

R. R. Nagawade *et al*[9] were reported synthesis of benzimidazole derivatives in the presence of a catalytical amount of zirconyl chloride (ZroCl) under very mild solvent free condition. The method is advantageous due to high conversion short reaction time, clean reaction profile, solvent free condition and simple experimental and workup procedure.



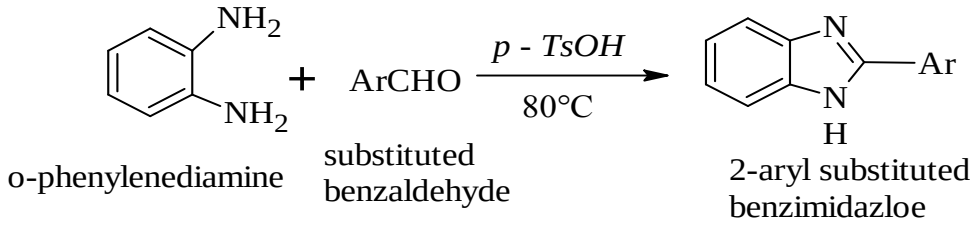
4-substituted benzene 1,2-diamine | substituted benzaldehyde | 2,6-disubstituted benzimidazole

S. E. Lopez *et al*[10] have developed a rapid and efficient method for the preparation of 2-aryl-substituted-1*H*-benzimidazole derivatives under microwave irradiation. The improving of reaction times and easy product isolation-purification employing a simple household microwave oven, as well as the use of inexpensive reagents makes this an alternative and attractive method for the organic synthesis of such compounds.



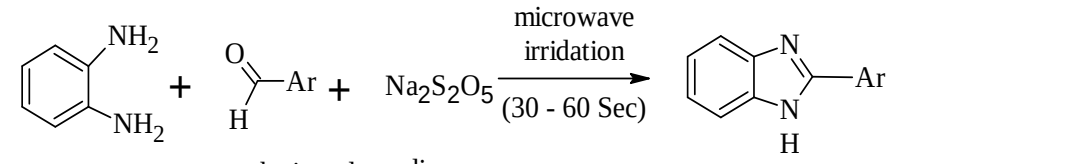
o-phenylenediamine | 2-aryl-substituted-1H-benzimidazole

H. Xiangming *et.al* [11] have developed a simple, one-pot synthesis of 2-arylsubstituted benzimidazoles by the condensation of *o*-phenylenediamine with arylaldehyde catalyzed by *p*-toluenesulfonic acid (*p*-TsOH). Simple and convenient procedure, easy purification and shorter reaction time are the advantageous features of this method.



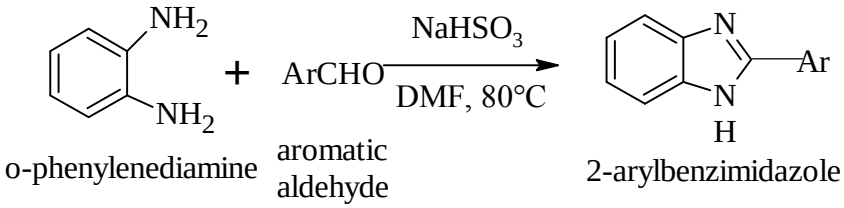
o-phenylenediamine substituted benzaldehyde 2-aryl substituted benzimidazloe

G. N. Vazquez *et al*[12] have reported a simple, fast, and efficient method for the preparation of several 2-(alkyloxyaryl)-1*H*-benzimidazole derivatives. Compounds were synthesized through a rapid one-pot three component reaction *via* microwave irradiation, starting from commercially available aldehydes and *o*-phenylenediamine, in the presence of sodium metabisulfite ($Na_2S_2O_5$) and solvent-free conditions.



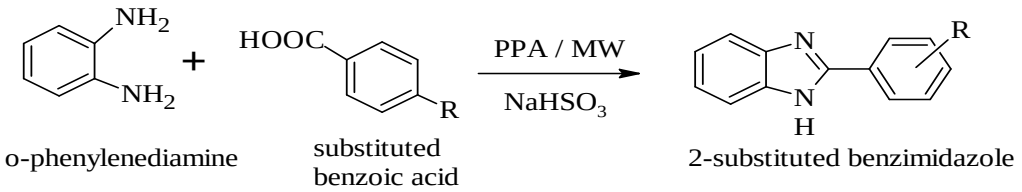
o-phenylenediamine substituted aldehyde sodium metabisulfite 2-aryl substituted benzimidazole

H. Xiangming *et al*[13] have developed the procedure to obtain the corresponding 2-arylbenzimidazoles which is simple and convenient, and it implies inexpensive promoter and is characterized by short reaction time and easy purification of the final products. Sodium hydrogen sulfite ($NaHSO_3$) was used to promote condensation of *o*-phenylenediamine with aromatic aldehydes in dimethylformamide.

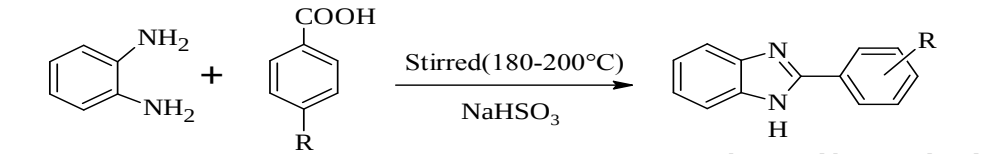


o-phenylenediamine aromatic aldehyde 2-arylbenzimidazole

O. Algul *et al*[14] have done comparative studies on conventional and microwave synthesis of some benzimidazole. The microwave method was observed to be more beneficial as it provides an increase of yield from 3 % to 113 % and 95 to 98 % reduction in time.

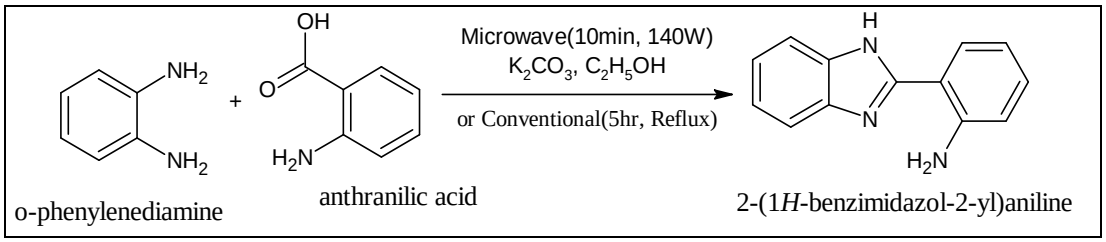


o-phenylenediamine substituted benzoic acid 2-substituted benzimidazole



o-phenylenediamine substituted benzoic acid 2-substituted benzimidazole

S. B. Mohan *et al*[15] reported synthesis of Benzimidazole is by reaction between anthranillic acid and orthophenylenediamine.



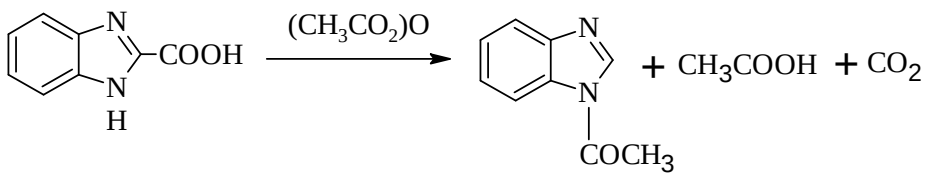
o-phenylenediamine anthranilic acid 2-(1*H*-benzimidazol-2-yl)aniline

Reactions of Benzimidazole[15,16]

Benzimidazoles form salts with acids readily. Thus, benzimidazole readily forms a monohydrochloride, monopicrate, mononitrate, monoacetate. Benzimidazole also forms a salt with 2-nitro-l, 3-indanedione and with copper azide.

Acylation

1-Acetylbenzimidazole has been prepared by heating 2-benzimidazolecarboxylic acid with acetic anhydride, decarboxylation occurring at the same time.

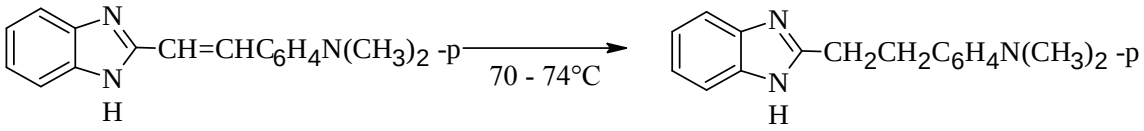


2-benzimidazolecarboxylic acid 1-acetylbenzimidazole

Reduction

Catalytic reduction of benzimidazole even under high pressure with nickel as the catalyst is reported to give negative results. 2-Phenylbenzimidazole gives only 2-

cyclohexylbenzimidazole**.** Hydrogenation of 2-(*p*-dimethylaminostyryl) benzimidazole with nickel at atmospheric pressure saturates only the olefinic linkage in the 2-position.

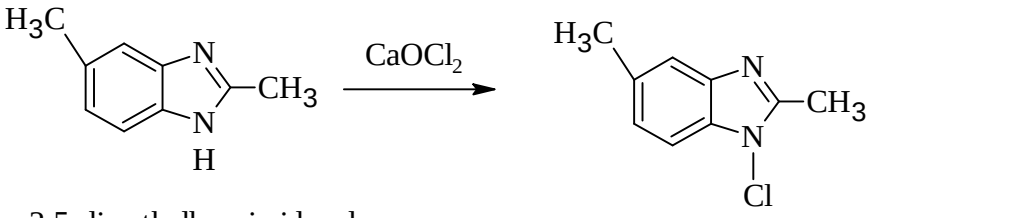


4-[(*E*)-2-(1*H*-benzimidazol-2-yl)ethenyl]-*N*,*N*-dimethylaniline

4-[2-(1*H*-benzimidazol-2-yl)ethyl]-*N*,*N*-dimethylaniline

Halogenation

When 2, 5 (or 2, 6)-dimethylbenzimidazole in an aqueous acid solution is treated with a saturated solution of bleaching powder at 0-5°C and thus l-chloro-2, 5 (or 2, 6) dimethyl-benzimidazole is obtained.

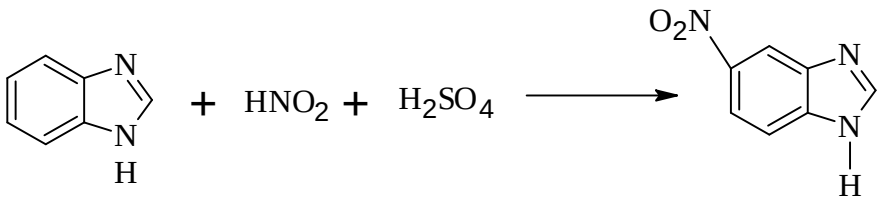


2,5-dimethylbenzimidazole

1-chloro-2,5-dimethyl-benzimidazole

Nitration

The nitration of benzimidazoles proceeds readily. In most cases nitration appears to take place preferentially at the 5- or 6-position. However, the nitro group may also enter the 4- or 7-position especially if the 5- or 6-position is blocked.

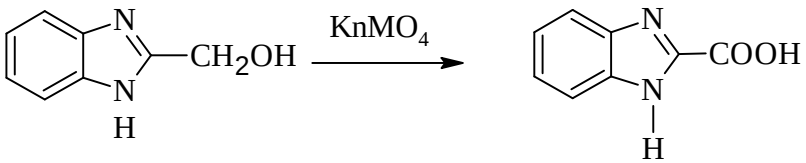


1*H*-benzimidazole

5-nitro-1*H*-benzimidazole

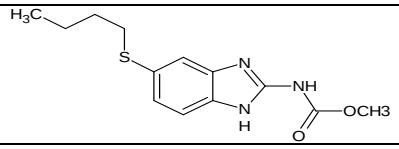
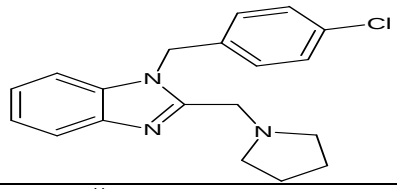
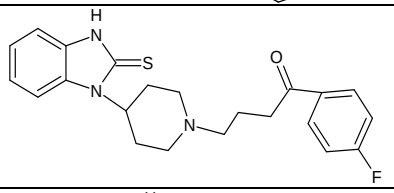
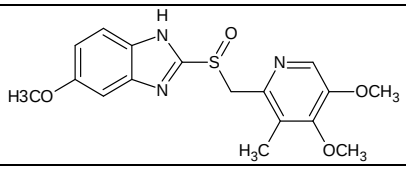
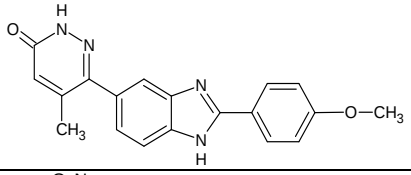
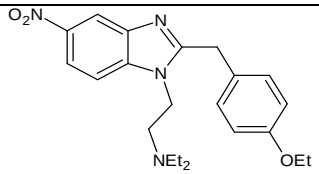
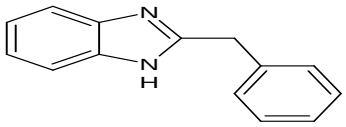
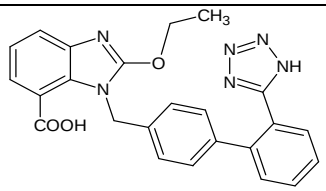
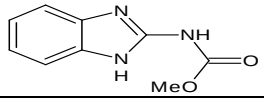
Oxidation

2-Benzimidazolecarboxylic acid may be conveniently prepared in good yield by the oxidation of 2-hydroxymethylbenzimidazole, which may be prepared by the action of glycolic acid on *o*-phenylenediamine.



2-hydroxymethylbenzimidazole 2-benzimidazolecarboxylic acid

Table 1: Biological Profile of Benzimidazole Derivatives.[3]

Sr. No.	Drugs	Structure	Therapeutic category
1.	Albendazole		Anthelmintic
2.	Clemizole		Antihistaminic
3.	Timiperole		Antipsychotic
4.	Omeprazole		Proton pump inhibitor/Antiulcer
5.	Pimobendan		Cardiotonic
6.	Etonitazene		Analgesic
7.	Bendazol		Coronary vasodilator
8.	Candensarten		Antihypertensive
9.	Carbendazim		Antifungal

Physiology of Pain

Analgesic activity

Analgesics are a medicine that relives pain.

Pain[17]

Pain has been classified as productive pain and non-productive pain, while this distinction has no physiological meaning it may serve as guide to treatment. "Productive" pain has been described as a warning of injury and so may be both an indication of need for treatment and a guide to diagnosis, "Non reproductive" pain by definition serve no purpose either as a warning or diagnostic tool.

Although pain syndromes may be dissimilar, the common factor is a sensory pathway from the affected organ to brain. Analgesics work at the level of the nerve, either by blocking the signal from the peripheral nervous system, or by distorting the interpretation by the central nervous system. Selection of appropriate analgesics is based on the type of pain and risk of adverse effects.

Traditionally, pain has been divided into two classes.

a) Acute pain

b) Chronic pain

a) Acute pain

Acute pain is self-limiting in duration and includes post-operative pain, pain of injury and childbirth. Because pain of these types is expected to be short term, the term side effects of analgesic therapy may be routinely be ignored. Thus, these patients may safely be treated with narcotic analgesics without concern about possible addiction or NSAIDs with concern for the risk of ulcers. Drugs and doses should be adjusted based upon observation of healing rate switching patients from high to low doses and from narcotic to non-narcotic analgesics when circumstances permit.

An important consideration of pain management in severe pain is that patient should not be subject to the return of pain. Analgesics should be dose adequately to ensure that the pain is at least tolerable and frequently enough to avoid anxiety that accompanies the anticipated return of pain. Analgesics should never be dosed on an as needed basis but should be

administered often enough to assure constant blood levels of analgesics. This applies to be both narcotic and non-narcotic analgesics.

b) Chronic pain

Chronic pain, pain lasting over three months and severe enough to impair function, is more difficult to treat, since the side effects of analgesic are more difficult to manage. In the case of narcotic analgesics this means the addiction potential, as well as respiratory depression and constipation.

In chronic pain, the abnormal activity of the pain –mediating afferent system continues irrespective of the original cause. Simply blocking of the normal pathways therefore, may not be helpful. Several mediators of chronic pain have now been demonstrated that is cytokines, bradykinin substances etc and countering their effects may be useful.

For e.g chronic cancer pain, pain is common problem in cancer patients and 70% of patient with advanced cancer have it as a major symptom. It can be caused by the cancer itself or by other associated condition such as osteoarthritis, bedsores or surgery. It may be related to bones, nerve compression and metastasis in soft tissues, further physiological reactions to the illness including depression and a sense of helplessness may worsen pain. Unremitting pain itself can cause secondary symptoms such as reduced appetite, disturbed sleep, irritability and impaired concentration. It is therefore necessary to acess the cause of pain, as well as its effects, at the very outset in a patient with cancer, further periodic reassessment of both is neccessory so as to be able to offer to the patient treatment appropriate to a given stage. The therapy consist of drug treatment and alternative method, like radiation.

Inflammation[18]

Inflammation is a part of complex biological responses of vascular tissues to harmful stimuli, such as pathogen damaged cells or irritants. Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process. Inflammation is not a synonym for infection. Although infection is caused by a microorganism, inflammation is one of the responses of the organism to the pathogen inflammation can be classified as either acute or chronic. Acute inflammation is the initial response of the body to the harmful stimuli and is achieved by the increased movement of the plasma and leukocytes especially granulocytes from the blood into the injured tissues. A cascade of biochemical events propogates and mature the inflammatory response, involving the local vascular system, the

immune system and various cells within the injured tissues. Prolonged inflammation, known as chronic inflammation, leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process.

Signs of inflammation

a) Rubor (redness)
b) Tumor (Swelling)
c) Calor (Heat)
d) Dolor (Pain)

Mechanism of action[19,20]

Almost all classes of NSAIDs strongly inhibit the conversion of arachidonic acid into prostaglandins. This occurs at the stage of coversion of arachidonic acid released by the action of phospholipase A by damaged tissue by prostaglandin H_2 synthetase now called cyclooxygenase, to the cyclic endoperoxidase. These are known to cause vasoconstriction and pain. They in turn are converted in part to PGE_2 and $PGF_{2\alpha,}$ which can cause pain and vasodilation. This effect of the NSAIDs parallels their relative potency in various tests and stereospecific.

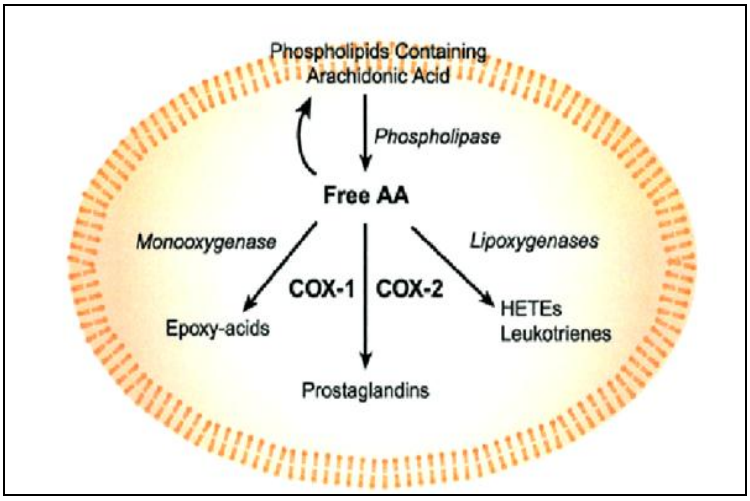


Fig. 1: Mechanism of inflammation.

REFERENCES

1. C. Mahiuddin Alamgir, David St. C. Black, Naresh Kumar, Synthesis, Reactivity and Biological Activity of Benzimidazoles, Top heterocyl chem, 2007; 9: 87-118. DOI: 10.1007/7081_2007_088.

2. M. J. Oniel, M. Smith, P. E. Heckelman, The merck index, 13th ed. Merck and Co. Inc., New Jersey, 2001; 2368-2415-5378-5791-6913-861-3915.
3. L. B. Townsend, G. R. Revankar, Benzimidazole nucleosides, nucleotides, and related derivatives, *Chemical Reviews*. 1970; 70(3): 389-440. DOI: 10.1021/cr60265a005.
4. F. F. Bamoharram, M. M. Heravi, M. Hosseini, K. Bakhtiarib, Heteropolyacid–Catalyzed Efficient and Convenient Synthesis of 2-Substituted Benzimidazoles, *Iranian Journal of Organic Chemistry*, 2009; 1: 25-27.
5. P. Kumar Y S. Chhonker, B. Veenu, S R. Hasim, N. Kaushik, D. Kumar Synthesis and Pharmacological Evaluation of Some New 2-Phenyl benzimidazoles Derivatives and their Schiff's Bases *E-Journal of Chemistry*, 2009; 342-346.
6. M. B. Maradolla, S. K. Allam, A. Mandha, G. V. P. Chandramouli, One pot synthesis of benzoxazoles, benzthiazoles and benzimidazoles from carboxylic acids using ionic liquids, *ARKIVOC*, 2008; 15: 42-46.
7. H. Thakuria, G. Das, An expeditious one-pot solvent-free synthesis of benzimidazole derivatives *ARKIVOC*, 2008; 321-328.
8. L. J. Chang, M. V. Kulkarni, C. M. Sun, Parallel synthesis of novel benzimidazoles on a soluble polymer support, *Central European Science Journals*, 2005: 3(2): 288–294.
9. R. R. Nagawade, D. B. Shinde, Zirconyl chloride-promoted synthesis of benzimidazole derivatives, *Russ. J. Org. Chem*., 2006; 42(3): 453–454. DOI: 10.1134/S1070428006030201
10. S. E. Lopez, J. Restrepo, B. Perez, S. Ortiz, J. Salazar, One pot microwave promoted synthesis of 2-aryl-*1H*-benzimidazoles using sodium hydrogen sulfite, *Bull. Korean Chem. Soc.*, 2009; 30(7): 1628-1631. DOI: 10.5012/bkcs.2009.30.7.1628.
11. H. Xiangming, Ma Huiqiang, W. Yulu, *p*-TsOH Catalyzed synthesis of 2-arylsubstituted benzimidazoles, *ARKIVOC*, 2007; 13: 150-154.
12. G. N. Vazquez, H. M. Diaz, F. A. Crespo, I. L. Rivera, R. V. Molina, O. M. Munizd, S. E. Soto, Design, microwave-assisted synthesis, and spasmolytic activity of 2-(alkyloxyaryl)-1*H* benzimidazole derivatives as constrained stilbene bioisosteres, *Bioorg. Med. Chem. Lett*., 2006; 16: 4169–4173. DOI: 10.1016/j.bmcl.2006.05.082.
13. H. Xiangming, M. Huiqiang, Y. Wang, A simple and efficient synthesis of 2-aryl-substituted benzimidazoles, *Russ. J. Org. Chem*., 2008; 44(6): 863–865. DOI: 10.1134/S1070428008060146

14. O. Algul, A. Kaessler, Y. Apcin, A. Yilmaz, J. Jose, Comparative studies on conventional and microwave synthesis of some benzimidazole, benzothiazole and indole derivatives and testing on inhibition of hyaluronidase, *Molecules*, 2008; 13: 736-748. DOI: 10.3390/molecules13040736
15. S. B. Mohan, T. P. Behera, B.V.V. Ravi Kumar, Microwave Irradiation Versus Conventional Method: Synthesis of Benzimidazolyl Chalcone Derivatives, *International Journal of ChemTech Research*, 2010; 2(3): 1634-1637.
16. J. B. Wright, The chemistry of the benzimidazoles, 391-525.
17 http://www.articleshub.org/article/6290/What-is--Helminthiasis-disease-html.
18 http://www.antibioticslist.com/antihelmintic-drugs.html.
19 L. L. Thomas, D. A. Williams, V. F. Roche, S. W. Zito, Foye' s Principles of medicimal Chemistry, Lippincott Williams and Wilkins, Sixth edition, 1101-1105.
20 Harsh Mohan, Text book of Pathology, fifth edition, Jaypee Brothers, Medical Publisers (P) Ltd, New Delhi, 193.