International Journal for Pharmaceutical Research Scholars (IJPRS)

V-10, I-4, 2021 ISSN: 2277 - 7873

REVIEW ARTICLE

NOVEL NEW RESEARCH STRATEGIES OF BENZIMIDAZOLE DERIVATIVES: A REVIEW

*Sonali Pawar[1]; Rohit Jaysing Bhor[*1]; Sagar Magar[2]*

[1]Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy Pravaranagar, Tal-Rahata, District-Ahmednagar, Maharashtra, India

[*2]Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy Pravaranagar, Tal-Rahata, District-Ahmednagar, Maharashtra, India Lakshmi Narain Collage of Pharmacy (RCP), Indore, India

Manuscript No: IJPRS/V10/I4/00001, Received: 01/12/2021, Accepted: 03/12/2021, Published: 30/12/2021

ABSTRACT

Benzimidazole is an example of aromatic heterocyclic organic compound. It is a bicyclic compound. It contains the fusion of benzene with imidazole which ultimately gives a privileged structure. Benzimidazole and its derivatives play an important role in the medicinal chemistry and drug discovery with many pharmacological activities. Substitution of various chemicals on benzimidazole nucleus gives important synthetic product and strategy in the drug discovery process. Benzimidazole derivatives contain versatile nitrogen containing heterocyclic compounds. The methods for the synthesis of benzimidazole and its derivatives have become a focus of synthetic organic scientist, Benzimidazole and its derivatives were used as building blocks for the important therapeutic compounds in medicine. Benzimidazole nucleus plays a very important role as a therapeutic agent. Benzimidazole and its derivatives exhibit pharmacological activities such as antimicrobial, antiviral, anticancer, anti-inflammatory, analgesic activity, anti-ulcer, anti-diabetic activity etc. Benzimidazole nucleus gives active sites for the reaction like 2 and 5 position which gives potent therapeutic agents. The present review covers the chemistry and pharmacological activities of substituted benzimidazole. In the present review, benzimidazole derivatives with different synthetic derivatives and their pharmacological activities are given. The main aim of review is to help medicinal chemists for the development of SAR on benzimidazole for each activity and to review the work reported, chemistry and pharmacological activities of benzimidazole derivatives during past years.

KEYWORDS

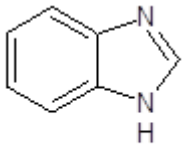
OPD, Antimicrobial, Antiviral, Anti-inflammatory, Analgesic Activity, Anti-ulcer, Anti-diabetic Activity

INTRODUCTION

*Address for Correspondence:
ROHIT JAYSING BHOR,
Department of Pharmaceutical Chemistry,
Pravara Rural College of Pharmacy,
Pravaranagar, Maharashtra,
India.

Benzimidazole is an example of aromatic heterocyclic organic compound. The new method of benzimidazole based on poly heterocycles draw the attention of pharmacists from last few decades[1]. It has important pharmocophore in medicinal chemistry and pharmacology. Benzimidazole and its derivatives are an example of bicyclic compound consisting of the fusion of benzene with imidazole[2]. The structure of

benzimidazole and its derivatives are given below; The worsening of asthma at night, is commonly referred to as nocturnal asthma (NA).



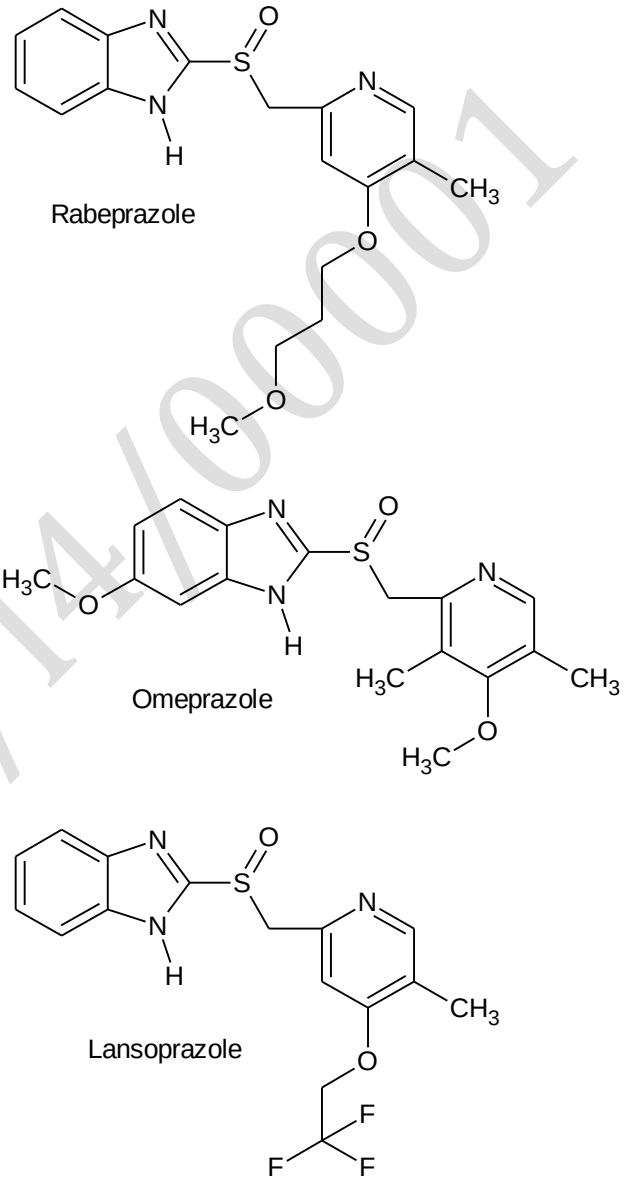
1*H*-benzimidazole

Fig. 1 – 1H- Benzimidazole

It has magical properties with many pharmacological properties. Benzimidazole possess many biological activities such as anti-microbial, anti-fungal, anti-histaminic, anti-inflammatory, anti- viral, anti-oxidant, anti-cancer, anti-ulcerative[4-6] etc so that it having important moiety for the development of molecules of pharmaceutical interest. Many benzimidazole derivatives having heterocyclic building blocks is due to the structural similarity to purine nucleobase. It selectively inhibits the endothelial cell growth and then suppresses the process of angiogenesis in vitro as well as in vivo biological activity [7]. Benzimidazole is also known as 1*H*-benzimidazole or 1,3-benzodiazole. Five-membered nitrogen-containing heterocyclic ring was present in the structures of various biologically active synthetic compounds. The magical properties of the benzimidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel derivatives with chemotherapeutic agents. Benzimidazole and its derivatives are commonly used for the prevention and treatment of parasitic infections [8]. Some examples of benzimidazole containing drug are given below;

- Omeprazole
- Rabeprazole
- Lansoprazole
- Pantoprazole
- Esomeprazole

They are well known discovered benzimidazole drugs. There are some other drugs with different hetero atoms like Thiabendazole (TBZ); Parbendazole (PAR) Cambendazole (CAM) Mebendazole (MBZ) Oxibendazole. Thiabendazole (TBZ)was the first benzimidazole to be marked over 40 years ago[9].



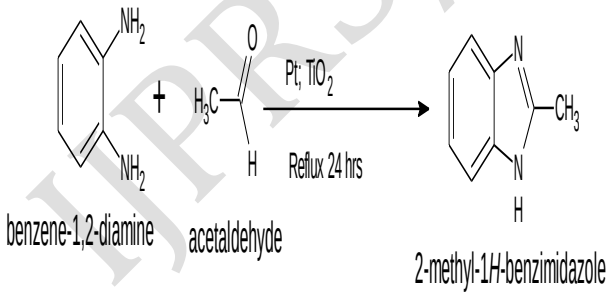
Benzimidazoles having the well known heterocyclic compounds which have common and characteristic features of a variety of medicinal agents. Benzimidazole is soluble in water and other polar solvents. Benzimidazoles exist in two equivalent tautomeric forms because the hydrogen atom can be located on either of the two nitrogen atoms. It having calculated dipole of 3.61D, and it was soluble in water [10]. Benzimidazole and its derivatives are classified as aromatic due to the presence of

a sextet of π-electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring. When it having acidic pka is 14.5, then it gives less acidic than carboxylic acids, phenols, and imides, but slightly more acidic than alcohols. When it having basic pka is approximately 7 then it gives benzimidazole approximately sixty times more basic than pyridine [11].

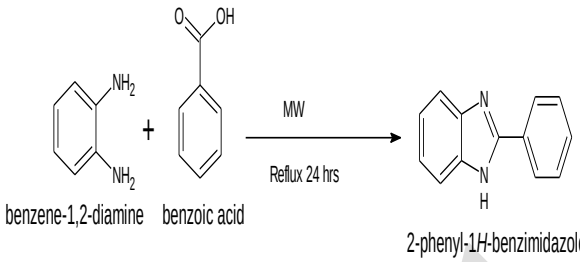
SYNTHETIC APPROACHES FOR BENZIMIDAZOLE DERIVATIVES:

Synthesis of benzimidazole and its derivatives through the direct condensation reaction by OPD i.e. o-Phenylene diamine and formic acid was reported but sometimes in many synthetic reaction; a few shortcomings like less yield, extreme reaction conditions, longer reaction time and difficult workup process were noticed. Some synthetic reaction of benzimidazole and its derivatives are given below;

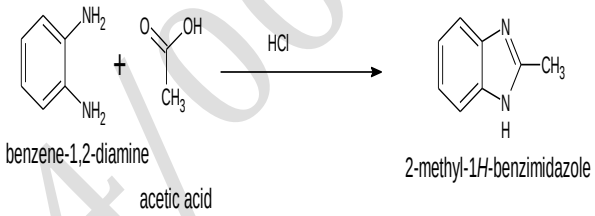
Scheme 1: Synthesizing Benzimidazoles through the coupling of benzne-1,2-diamine or OPD with different Aldehydes in ethanol at room temperature. These chemical easily available cheap catalysts are more efficient than various reported expensive heterogeneous catalysts. Yields of Pt, TiO2 catalyst are higher (72-88%) in shorter reaction time (3-7h) (Scheme 1).



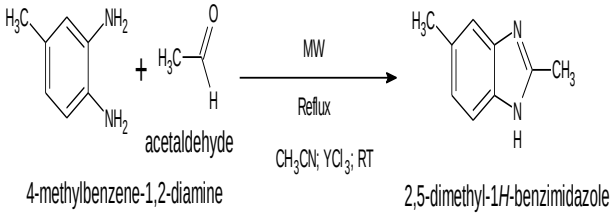
Scheme 2: Literature survey has revealed that o-phenylenediamine or benzne-1,2-diamine react readily with most carboxylic acids to give 2-substituted benzimidazole, usually in very good yields. (Scheme 2).



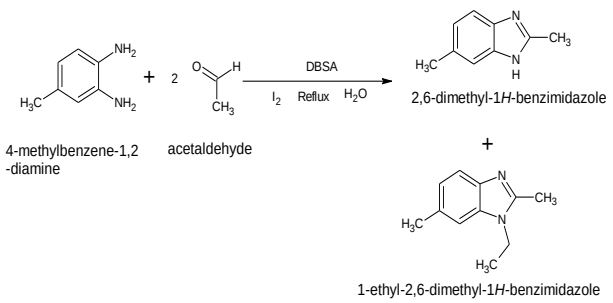
Scheme 3: The most commonly used (Phillip's method[12], involves the condensation of o-diaminobenzenes or Benzne-1,2-diamine with carboxylic acids or its derivatives, including heating the reagents together in the presence of concentrated hydrochloric acid (Scheme 3),



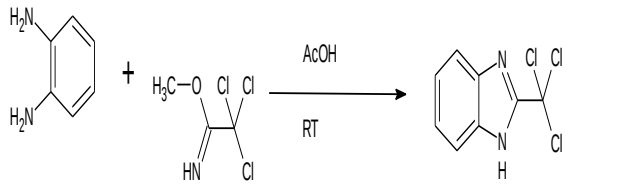
Scheme 4: In the same context, Ghosh[13] and coworkers employed a new, potent, less toxic catalyst: CH3CN for the synthesis of substituted benzimidazole from 1, 2-phenylenediamine with aryl, heteroaryl aldehydes (Scheme 4). High yield, clean reaction profile, cheaper and green in nature are the significant features of this methodology.



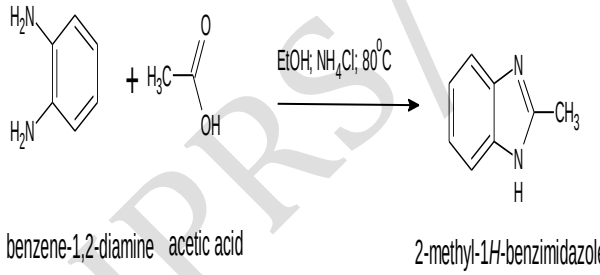
Scheme 5: In the same context, phylum[14] and coworkers employed a new, potent, less toxic catalyst such as DBSA; for the synthesis of substituted benzimidazole from 4 methylbenzne-1,2-diamine and aliphatic aldehyde; it gives different benzimidazole derivatives (Scheme 5).



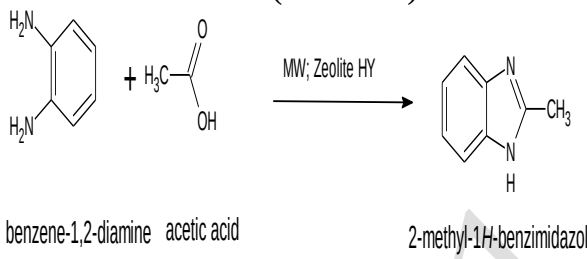
Scheme 6: Hollan[15] et al. who have reported the reaction of the appropriate Trichloro acetimidate with o- phenylenediamine or benzene-1,2-diamine; it gives the 2-trichloromethyl benzimidazole (Scheme 6) only at room temperature.



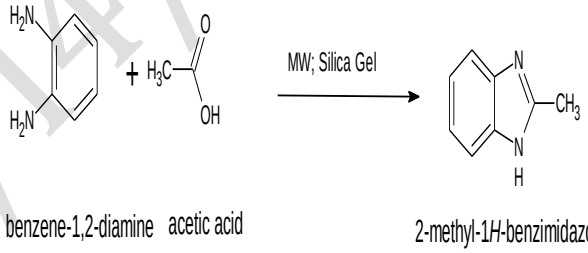
Scheme 7: o-phenylenediamine (0.01 mol) and different aromatic acid (0.01 mol) in the presence of ammonium chloride as catalyst at 80–90 °C (Scheme 7). The reaction is green and economic.



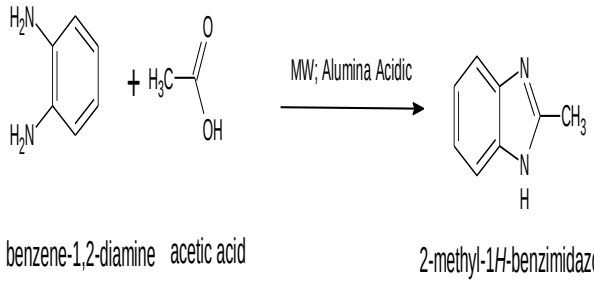
Scheme 8: Recently Saberi[16] has reported synthesis of 2-benzimidazoles under microwave irradiation and solvent-free conditions which is catalyzed by zeolite HY. As shown in scheme 8, o-phenylenediamine (2 mmol) with aromatic, aliphatic and heterocyclic carboxylic (2 mmol) and 50 mg of Zeolite was mixed thoroughly in a mortar. The reaction mixture was then irradiated in a domestic microwave oven for 5–9 min at 160–560 W (Scheme 8).



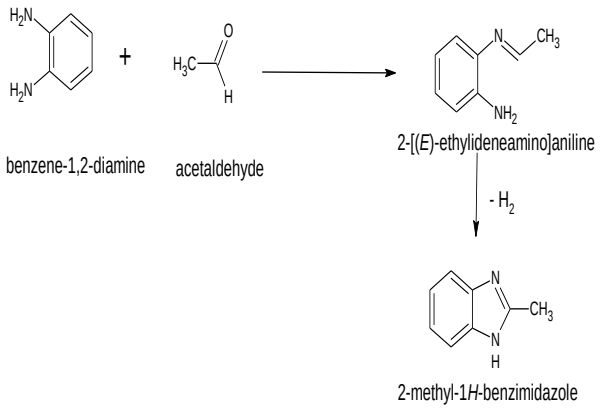
Scheme 9: Recently Saberi has reported synthesis of 2-benzimidazoles under microwave irradiation and solvent-free conditions which is catalyzed by Silica Gel. As shown in scheme 9, o-phenylenediamine (2 mmol) with aromatic, aliphatic and heterocyclic carboxylic (2 mmol) and 50 mg of Silica gel was mixed thoroughly in a mortar. The reaction mixture was then irradiated in a domestic microwave oven for 5–9 min at 160–560 W(Scheme 9).



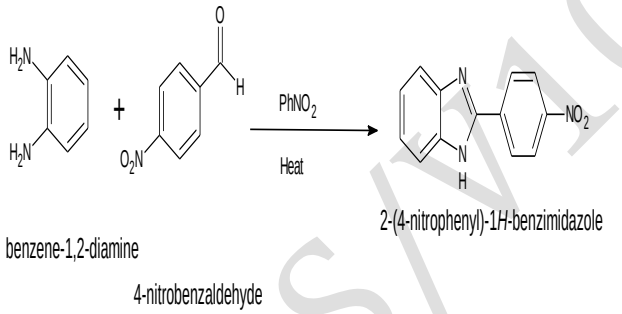
Scheme 10: Recently Saberi has reported synthesis of 2-benzimidazoles under microwave irradiation and solvent-free conditions which is catalyzed by Alumina. As shown in scheme 10, o-phenylenediamine (2 mmol) with aromatic, aliphatic and heterocyclic carboxylic (2 mmol) and 50 mg of Alumina was mixed thoroughly in a mortar. The reaction mixture was then irradiated in a domestic microwave oven for 5–9 min at 160–560 W. (Scheme 10).



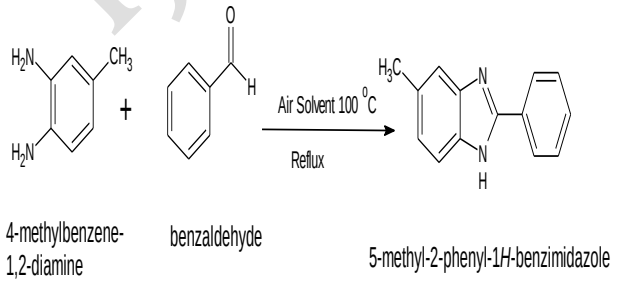
Scheme 11: Under the correct conditions aldehydes may react with o-phenylenediamines to yield 2-substituted benzimidazoles(Scheme 11).



Scheme 12: heating in the presence of nitro benzene Mann[17] et al used a mixture of unsubstituted or substituted phenylenediamine and appropriate aldehyde in nitrobenzene heated at 140 °C., the mixture was cooled and filtered after adding water which gives benzimidazole (Scheme 12).



Scheme 13: The other way was synthesized by Lin[17] et al. involving a direct one step synthesis of various benzimidazoles from phenylenediamines and aldehydes that includes air as oxidant(Scheme 13).



Conclusion

The review has concluded with the key synthetic approaches and pharmacological activities of the Benzimidazole. It gives one of the most useful biological activities. Benzimidazoles and its derivatives are utilized in much therapeutic or biological activity such as anti-inflammatory, anti anxiety and antimicrobial activity. The efficient and economical methods of synthesizing benzimidazole and its derivatives by condensation reaction between OPD i.e. orthophenylenediamine and various compounds in the presence of various conditions presented in this review. This review helps to other chemist chemists to get the first hand information for the synthesis of benzimidazole and become very useful for chemists and workers in this field. This can be developed from year to year to produce new economical and environmental clean protocols for the large scale production of important heterocyclic compounds.

REFERENCE

1. Walia, R., Hedaitullah, M. D., Naaz, S. F., Iqbal, K., & Lamba, H. S. (2011). Benzimidazole derivatives-an overview. *Int. J. Res. Pharm. Chem*, *1*(3), 565-574.
2. Luo, Y., Yao, J. P., Yang, L., Feng, C. L., Tang, W., Wang, G. F., ... & Lu, W. (2011). Synthesis and Anti-Hepatitis B Virus Activity of a Novel Class of Thiazolylbenzimidazole Derivatives. *Archiv der Pharmazie*, *344*(2), 78-83.
3. Arjmand, F., & Aziz, M. (2009). Synthesis and characterization of dinuclear macrocyclic cobalt (II), copper (II) and zinc (II) complexes derived from 2, 2, 2′, 2′-S, S [bis (bis-N, N-2-thiobenzimidazolyloxalato-1, 2-ethane)]: DNA binding and cleavage studies. *European journal of medicinal chemistry*, *44*(2), 834-844.
4. DUBCY, P., Mahesh Kumar, N. D., Chaitanya, M. V. S. R. K., Naidu, A., & George Vineel, B. (2010). Synthesis of

novel benzimidazole β-keto sulfones and β-hydroxy sulfones and their regiospecific alkylation studies. *Indian journal of chemistry. Sect. B: Organic chemistry, including medical chemistry*, *49*(7), 937-943.

5. Palit, R., Kumar, R., Saraswat, N., Wal, A., & Upadhyaya, P. K. www. ijrap. net.
6. Lopez-Vallejo, F., Medina-Franco, J. L., Hernández-Campos, A., Rodríguez-Morales, S., Yépez, L., Cedillo, R., & Castillo, R. (2007). Molecular modeling of some 1H-benzimidazole derivatives with biological activity against Entamoeba histolytica: a comparative molecular field analysis study. *Bioorganic & medicinal chemistry*, *15*(2), 1117-1126.
7. Palit, R., Kumar, R., Saraswat, N., Wal, A., & Upadhyaya, P. K. www. ijrap. net.
8. Thakurdesai, P. A., Wadodkar, S. G., & Chopade, C. T. (2007). Synthesis and anti-inflammatory activity of some benzimidazole-2-carboxylic acids. *Pharmacologyonline*, *1*, 314-329.
9. Palit, R., Kumar, R., Saraswat, N., Wal, A., & Upadhyaya, P. K. www. ijrap. net.
10. Achar, K. C., Hosamani, K. M., & Seetharamareddy, H. R. (2010). In-vivo analgesic and anti-inflammatory activities of newly synthesized benzimidazole derivatives. *European journal of medicinal chemistry*, *45*(5), 2048-2054.
11. 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. *European journal of medicinal chemistry*, *45*(6), 2245-2249.
12. Mohamed, B. G., Abdel-Alim, A. A. M., & Hussein, M. A. (2006). Synthesis of 1-acyl-2-alkylthio-1, 2, 4-triazolobenzimidazoles with antifungal, anti-inflammatory and analgesic effects. *Acta Pharmaceutica*, *56*(1), 31-48.
13. K. Synthesis and biological evaluation of Mannich bases of benzimidazole derivatives.Indian J. Chem 2011; 50Suppl B:1216-1219
14. Jesudason EP, Sridhar SK, Mala EJP, Shanmugapandiyan P, Inayathullah M, Arul V, Selvaraj D and Jayakumar R. Synthesis, pharmacological screening, quantum chemical and in-vitro permeability studies of N-Mannich bases of benzimidazoles through bovine cornea. Eur. J. Med. Chem 2009; 44: 2307-2312
15. Shanmugapandiyan P,Denshing KS, Ilavarasan R, Anbalagan N and Nirmal R. 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. Int. J. Pharm. Sci. Drug Res. 2010; 2, Suppl 2: 115-119
16. Reddy, B. A. (2010). Synthesis, characterization and biological evaluation of 1, 2-disubstituted benzimidazole derivatives using Mannich bases. *E-journal of Chemistry*, *7*(1), 222-226.
17. Leonard, J. T., Jeyaseeli, L., Rajesh, O. S., Murugesh, K., Sivakumar, R., & Gunasekaran, V. (2006). Synthesis, antiinflammatory and antibacterial activities of 4-substituted phenyl benzimidazoles. *Asian Journal of Chemistry*, *18*(2), 1104-1108.

HOW TO CITE THIS ARTICLE

Pawar, S., Bhor, R. J., Magar, S. (2021). Novel New Research Strategies of Benzimidazole Derivatives: A Review. *International Journal for Pharmaceutical Research Scholars, 10(4);01 - 08.*

THIS PAGE IS INTENTIONALLY LEFT BLANK.

