IJPSR (2020), Volume 11, Issue 6 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 10 August 2019; received in revised form, 03 May 2019; accepted, 11 May 2020; published 01 June 2020

MEDICINAL SIGNIFICANCE OF BENZIMIDAZOLE ANALOGUES: A REVIEW

Sharanabasappa B. Patil

Department of Chemistry, Ramaiah Institute of Technology, Bangalore - 560054, Karnataka, India.

Keywords:

Benzimidazole derivatives and Medicinal Significance

Correspondence to Author:
Dr. Sharanabasappa B. Patil

Assistant Professor,
Department of Chemistry,
Ramaiah Institute of Technology,
Bangalore - 560054, Karnataka, India.

E-mail: sbp7910@gmail.com

ABSTRACT: Benzimidazoles are well known biologically active N-containing heterocycles, widely used as drugs such as antifungal, antibacterial, antiparasitic, and antihelmintic. In addition, N_1 and C_2-substituted benzimidazoles and their derivatives have been found to be potent biologically active compounds as well. Further, N_1-substituted benzimidazoles have exhibited anti-microbial, antihelmintic activities and also antiviral activity against human cytomegalovirus and herpes simplex virus type-1. Specifically, N_1-substituted benzimidazole like 5,6-dichloro-1-β-D-ribofuranosylbenzimidazole is known for inhibition of transcription elongation by RNA polymerase II. Another N_1-substituted benzimidazole derivative called enviroxime [2-amino-1- (isopropyl-sulphonyl)-6-benzimidazole phenyl ketone oxime] was reported to be a potent inhibitor of rhinovirus replication in human embryonic nasal organ cultures. The biological activities of these compounds depend upon the substitution on the benzimidazole at the N-1 or C-2 position. Since the benzimidazole heterocyclic ring system mimics the purine bases like adenine and guanine of nucleic acids, the N_1-substituted benzimidazole may incorporate into viral nucleic acid by enzymatic process and subsequently can alter the structure and/ or function of viral growth.

INTRODUCTION ON BENZIMIDAZOLES:

Benzimidazole **Fig. 1** is a heterocyclic aromatic organic compound. This bicyclic compound consists of the fusion of benzene with imidazole. Historically the first benzimidazole was prepared by hoebecker in 1872, who obtained 2,5 or (2,6) dimethyl benzimidazole. The benzimidazoles are also known as benzoglyoxalines. This tautomer is analog to that found in imidazole and amidines. The benzimidazole is, in fact, may be considered as a cyclic analog of amidine **Fig. 2**.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(6).2649-54

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(6).2649-54

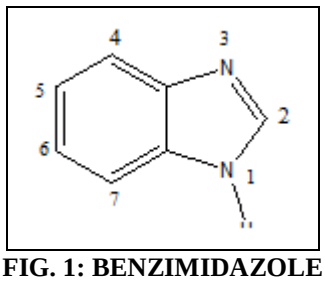

FIG. 1: BENZIMIDAZOLE

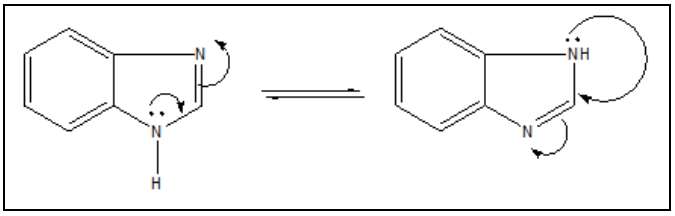

FIG. 2: CYCLIC ANALOG OF AMIDINE

Benzimidazoles are weakly, somewhat less basic than imidazoles. Benzimidazoles are also sufficiently acidic to be generally soluble in

aqueous alkali and form N-metallic compounds. The acidic properties like those of imidazole seem to be stabilization due to resonance. The dipole moment of benzimidazole determined to be 3.93 D. Benzimidazole rings possess a high degree of stability. Benzimidazole, for example, not effected by concentrated sulphuric acid when heated under pressure at 270 °C, nor by vigorous treatment with concentrated hydrochloric acid. Oxidation cleaves the benzene ring of benzimidazole only under vigorous conditions. Further, benzimidazole undergoes a variety of reactions such as alkylation, acylation, halogenation, nitration, *etc*. The compounds of benzimidazole analogs are mainly classified into the following two types, namely, N_1-substituted benzimidazole analogs and C_2-substituted benzimidazole analogs.

This part deals mainly with the study of biological and medicinal applications of N_1-substituted benzimidazole analogs and C_2-substituted benzimidazole analogs.

1.1. Medicinal Applications of Benzimidazole Analogues: Most of the benzimidazole analogs are also known for their clinical use. Some of them are as follows.

1.1.1. Benzimidazole Analogues as Antibacterial and Antifungal Agents: Most of the benzimidazole derivatives also exhibit antibacterial activity. For example, derivatives of pyrimido[1,6-a] benzimidazole represent a new class of DNA-gyrase inhibitors, which are effective antibacterial agents [1]. Antimicrobial and antifungal properties were reported for 3-alkylthiomethyl-l-ethyl-, 3-alkoxy-methyl-l-butyl-, and 3-alkylthiomethyl-l-butylben-zimidazolium chlorides, as well as for 2-chloromethyl-5H-methylbenzimidazoles [2, 3].

Some 5-nitrobenzimidazole derivatives also exhibit fungicidal activity [4]. The certain antimicrobial and antifungal potential were observed in heterocyclic benzimidazole derivatives [5].

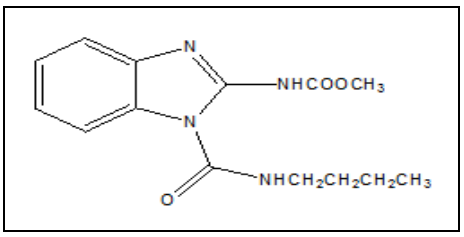

FIG. 3: BENOMYL

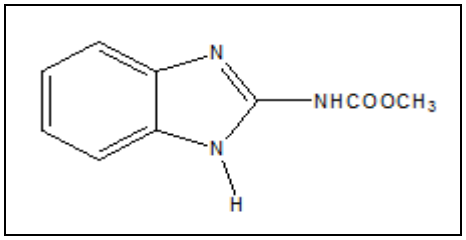

FIG. 4: CARBENDAZIM

Benzimidazole derivatives such as benomyl **Fig. 3**, carbendazim **Fig. 4**, fuberidazole **Fig. 5** and thia-bendazole are developed as fungicides which have high activity against many opportunistic fungi.

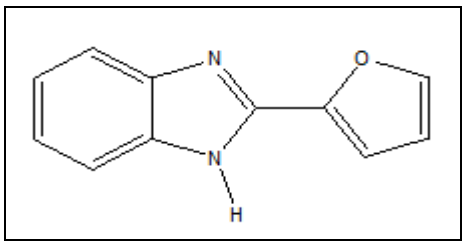

FIG. 5: FUBERIDAZOLE

Z. Kazimierczuk *et al.*, [6] reported antimicrobial and antiprotozoal activities of 5,6-dinitro and 2-dialkylamino substituted benzimidazoles.

T. C. Kuhler *et al.*, [7] reported novel structure derived from 2-{[(2-pyridyl) methyl]thio}-*1H*-benzimidazole and also many fluorine-containing benzimidazole analogs are known for their antibacterial activity [8].

G. A. Kilcigil *et al.*, [9] have reported the synthesis and antifungal properties of some benzimidazole derivatives.

Recently Mashelkar *et al.*, [10] reported syntheses, antibacterial, anti-asthmatic and anti-diabetic activities of novel N_1-substituted benzimidazoles.

1.1.2. Benzimidazole Analogues as Analgesic, Anti-inflammatory, and Antipyretic Agents: In recent years, much effort was devoted to studying the analgesic drug etonitazene, a benzimidazole analog selectively interacting with opiate receptors of the μ-subtype [11-15]. Etonitazene **Fig. 6** is a highly potent analgesic drug, has approximately 1000-1500 times more potency than morphine. However, it has a strong dependency potential similar to that of morphine, and a strong tendency to produce respiratory depression and is therefore not used in humans. It is, however, useful in addiction studies on animals.

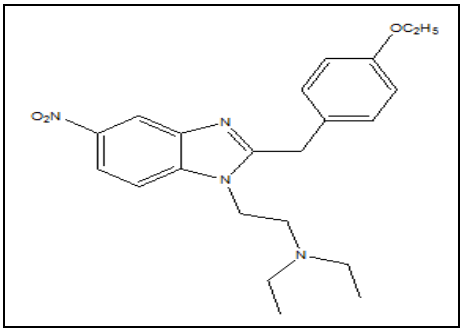

FIG. 6: ETONITAZENE

Further analgesic and anti-inflammatory activity were observed in some derivatives of 3-(benzimidazol-2-yl) propanoic acid [16] **Fig. 7** and 2-aminobenzimidazole [17] **Fig. 8**. Some of the benzimidazole derivatives also possess selective anti-inflammatory and antipyretic activity[18].

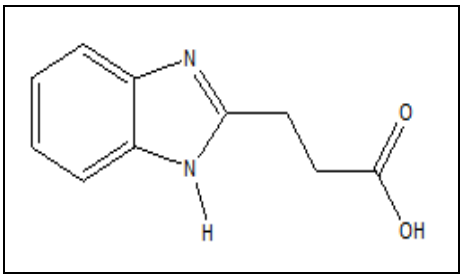

FIG. 7: BENZIMIDZOL-3-PROPIONIC ACID

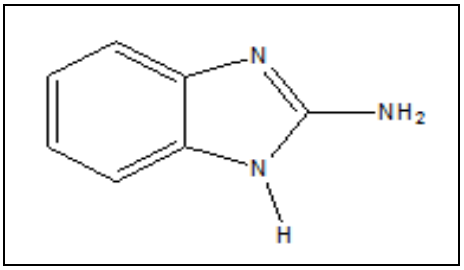

FIG. 8: 2-AMINOBENZIMIDAZOLE

1.1.3. Benzimidazole Analogues as CNS Depressants: Some benzimidazole derivatives produce various, in type and strength, effects upon the central nervous system, including psycho-stimulant, neuroleptic, antidepressant, tranquilizer (anxiolytic), anticonvulsant, and hypnotic action. It was shown that dibazole and 5,6-dimethyl-benzimidazole (dimedazole, dimezole) **Fig. 9** are capable of eliminating some neurological disorders accompanying experimental brain traumas and can be used for the prophylaxis of pain shock [19]. A single administration of bemithyl, ethomerzole (5-ethoxy-2-ethylthiobenzimidazole hydrochloride), and 2-phenylthio-6-ethylbenzimidazole hydro-bromide **Fig. 10** also produced an anxiolytic action not accompanied by sedative effects [20].

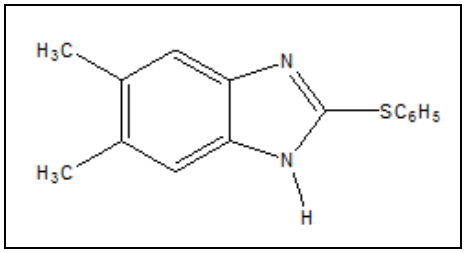

FIG. 9: 2-PHENYLTHIO- 5,6-DIMETHYLBENZIMIDAZOLE

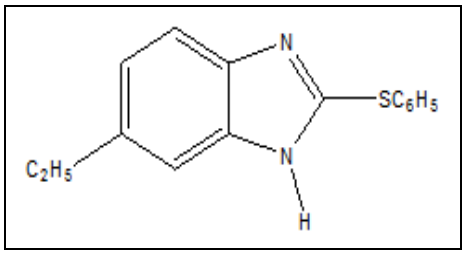

FIG. 10: 2-PHENYLTHIO-6- ETHYLBENZIMIDAZOL

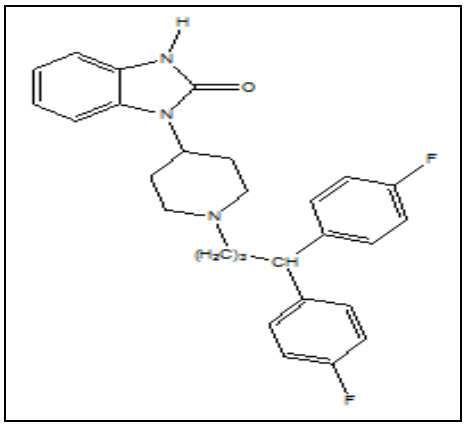

FIG. 11: PIMOZIDE

Pimozide **Fig. 11** is capable of inhibiting the release of dopamine-induced *in-vitro* by electric depolarization of membranes in the brain tissue [21] and enhances dopamine synthesis and circulation in the brain [22, 23]. The effect of pimozide on other catecholamines is less pronounced. In the human organism, pimozide reduces amphetamine-induced euphoria and arrests anxiety manifestations in schizophrenes and patients with psychic disorders of a neurotic type [24, 25].

1.1.4. Benzimidazole Analogues as Antihypoxic and Antioxidant Agents: Some benzimidazole derivatives are capable of exhibiting antihypoxic and antioxidant activities. For example, ethomerzole exhibited a protective effect in tests on animals having different degrees of resistance with respect to hypoxic states and accelerated the restoration of behavioral, dynamometric, and locomotor characteristics in animals upon hypoxic trauma [26].

1.1.5. Benzimidazole Analogues as Antiaggregant Agents: Diabenol is capable of inhibiting platelet aggregation induced by ADP, adrenalin, collagen, PAF, and arachidonic acid, which is explained by suppression of the synthesis of thromboxane A_2. It was reported that diabenol not only influences the aggregation process but produces a certain disaggregating effect as well [27].

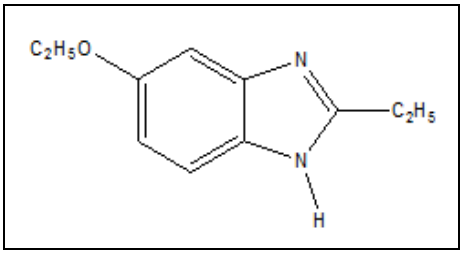

FIG. 12: ETHOMERZOLE

The antiaggregant properties were also observed for dibazole [28] and ethomerzole [29] (5-ethoxy-2-ethylthiobenzimidazole) **Fig. 12**.

1.1.6. Benzimidazole Analogues as Hypoglycemic Agents: The condensed benzimidazole derivative 9-(2-diethylaminoethyl)-2,3-dihydroimidazo[1,2-a]benzimidazole dihydrochloride (diabenol) **Fig. 13** was reported to possess hypoglycemic and antiaggregant properties [27].

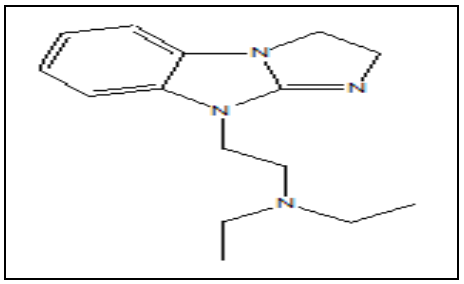

FIG. 13: DIABENOL

1.1.7. Benzimidazoles Analogues as Antiallergic Agents: The group of effective long-action blockers of the histamine receptors includes astemizole [30] **Fig. 14** and mizolastine [31] **Fig. 15**.

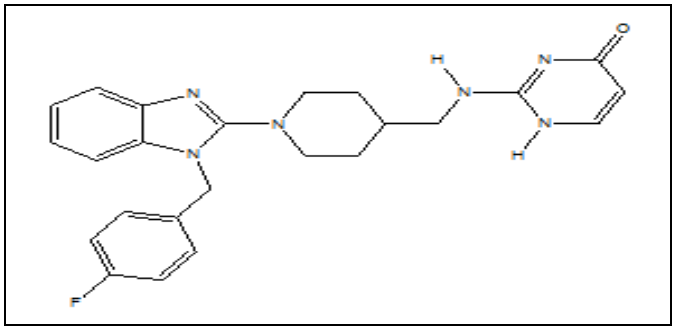

FIG. 14: ASTEMIZOLE

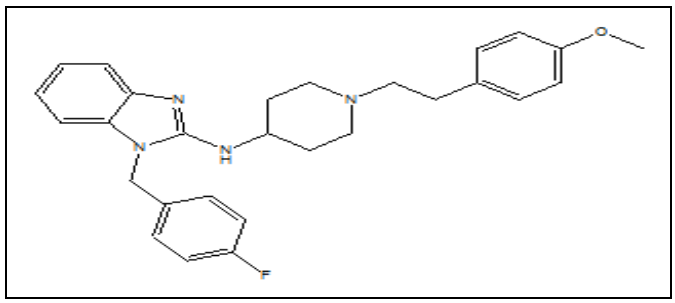

FIG. 15: MIZOLASTINE

T. Satoh *et al.*, [32] mentioned the synthesis of benzimidazole derivatives as antiallergic agents with 5-lipoxygenase inhibiting action.

G. A. Kilcgil *et al.*, [33] studied synthesis and antioxidant properties of some novel benzimidazole derivatives on lipid peroxidation in the rat liver.

T. Sakai *et al.*, [34] reported pharmacokinetics properties of an antiallergic agent, 1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-*1H*-1,4-diazepin-1-yl)-*1H*-benzimidazole.

G. F. Caselli *et al.*, [35] studied antihistaminic/ antiallergic activity of 2- dialkylaminoalkyl-thio(oxy)-1-substituted benzimidazoles.

M. L. Richards *et al.*, [36] reported substituted 2-phenyl benzimidazole derivatives novel compounds that suppress key markers of allergy.

1.1.8. Benzimidazole Analogues as Cardiovascular Agents: In the 1940s, a group of researchers including Porai-Koshits, Ginzburg, and Efros synthesized 2-benzylbenzimidazole [37] (dibazole) **Fig. 16**, which was capable of decreasing the tone of smooth muscles of the blood vessels and internal organs. This compound is widely used as a spasmolytic and hypotensive remedy [38]. Further pronounced antihypertensive activity is characteristic of most of benzimidazole derivatives which are capable of blocking calcium channels [39-43].

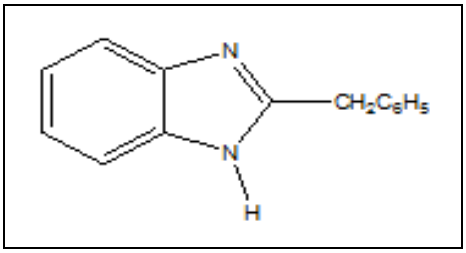

FIG. 16: DIBAZOLE

Another benzimidazole analog, pimobendan [44] **Fig. 17** is a phosphodiesterase inhibitor with calcium sensitizing properties.

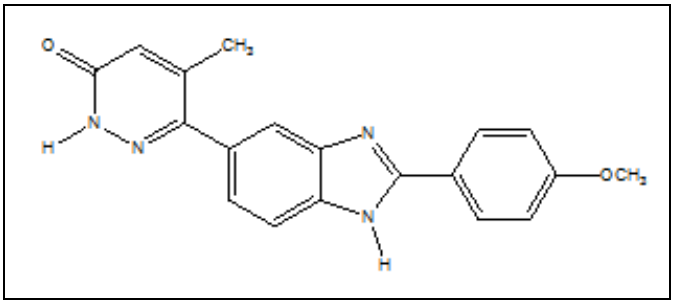

FIG. 17: PIMOBENDEN

1.1.9. Benzimidazole Analogues As Antitumor Agents: Bendamustine **Fig. 18**, benzimidazole analog, which is available in the market and used for the treatment of leukemia. It belongs to the family of drugs called alkylating agents. It is also being studied for the treatment of sarcoma. Another promising group of antitumor compounds is represented by benzimidazo[t, 2-c]quinazolines and thiazolo[3,4-a]benzimidazoles [45, 46].

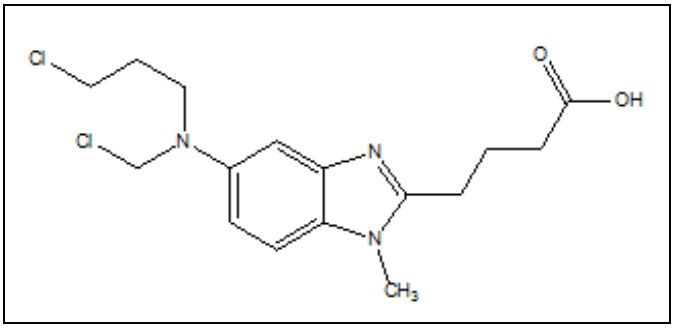

FIG. 18: BENDAMUSTINE

E. B. Skibo *et al.*, [47] have reported structure-activity studies of antitumor agents based on pyrrolo[1,2-a]benzimidazoles.

A. Da Settimo *et al.*, [48] have reported synthesis and antitumor activity of pyridopyrimidobenzimidazole.

CONCLUSION: Nil

ACKNOWLEDGEMENT: Nil

CONFLICTS OF INTEREST: Nil

REFERENCES:

1. Hubschwerlen C, Pflieger P, Specklin JL, Gubernator K, Gmuender H, Angehrn P and Kompis I: J Med Chem 1992; 35(8): 1385.
2. Pernak J, Skrzypezak A and Michalak L: Arch Pharm 1993; 326(4): 237-40.
3. Mishra L, Singh VK, Dubey NK and Mishra AK: Biosci Biotechnol Biochem 1993; 57(6): 989.
4. Hrelia P, Morotti M, Vigagni F, Burnelli S, Guruti L, Sabatino P and Cantelli-Forte G: Mutagenesis 1993; 8(3): 183.
5. Pedini M, De Meo G, Ricci A, Tassi C and Bastianin L: Farmaco 1994; 49(4): 303.
6. Kazimierczuk Z, Upcroft JA, Upcroft P, Gorska A, Starooeciak B and Laudy A: Acta Biochemica Polina 2002; 49: 185.
7. Kuhler TC, Swanson M, Christenson B, Klintenberg AC, Lamm B, Fagerhag J, Gatti RM, Halvarsson O, Shcherbuchin V and Elebring T: J Med Chem 2002; 45: 4282.
8. Bishop BC, Chelton ETJ and Jones AS: Biochem Pharmacol 1964; 13: 751.
9. Kilcigil GA and Altanlar N: Turk J Chem 2006; 30: 223.
10. Vinodkumar R, Vaidya S. D, Siva Kumar B. V, Nanasaheb U, Bhirud S. B and Mashelkar U. C. Eu. J. Med. Chem., 2008, 43, 986.
11. Elmer GI, Pieper JO, Goldberg SR and George FR: Psychopharmacology (Berlin) 1995; 117(1): 23.
12. Hyyatia P and Sinclair JD: Psychopharmacology (Berlin) 1993; 111(4): 409.
13. Burke TF, Woods JH, Lewis JW and Medzihradsky FJ: Pharmacol Exp Ther 1994; 271(2): 715.
14. Sala M, Braida D, Calcaterra P, Leone MP and Gori E: Eur J Pharmacol 1992; 217(1): 37.
15. Suzuki T, George FR and Meisch RA: Pharmacol Biochem Behav 1992; 42(4): 579.
16. Kuzmierkiewiez W, Fox H and Hac E: Pharmazie 1985; 40(4): 462.
17. Taniguchi K, Shigenaga S, Ogohara T, Fujitsu T and Mutsuo M: Chem Pharm Bull Tokyo 1993; 41(2): 301.
18. Geratz JD, Pryzwansky KB, Schwab JH, Andarale SK and Tidwell RR: Am J Pathol 1993; 142(4): 1227.
19. Lazarev NV and Rozin MA: Sov Med 1951; 4: 24.
20. Sigh JM: J Med Chem 1969; 12: 962.
21. Seeman P and Lee T: Science 1975; 188: 1217.
22. Nyback H, Schubert J and Sedvall G: J Pharm Pharmaco1 1970; 22: 622.
23. Jonsson LE: Eur J Clin Pharmacol 1972; 4: 206.
24. Kline F, Burgoyne RW and Yamamoto J: Curt Ther Res 1977; 21: 768.
25. Rotrosen MB, Wallach B, Angrist C and Gershon S: Psychopharmacologia 1972; 26: 185.
26. Kosolapov VA, Ostrovskii VA and Spasov AA: Exp Klin Farmakol 1996; 59(6): 51.
27. Spasov AA, Dudchenko GP and Turchaeva AF: Vestn Volgograd, Med Akad 1995; 1: 33.
28. Plotnikova TM, Kulakova ZV and Plotnikov MB: Byull Exp Biol Med 1991; 111(4): 386.
29. Stangier J, Eriksson BI, Dahl OE, Ahnfelt L, Nehmiz G, Stahle H, Rathgen K and Svard R: J Clin Pharmacol 2005; 45(5): 555.
30. Astemizole - Another Non-Sedating Antihistamine. Med. Lett. Drugs Ther 1989; 31: 43.
31. Danjou P, Molinier P, Berlin I, Patat A, Rosenzweig P and Morshelli PL: Br. J. Clin. Pharmacol 1992; 34(4): 328.
32. Nakano H, Inoue T, Kawasaki N, Miyataka H, Matsumoto H, Taguchi T, Inagaki N, Nagai H and Satoh T: Chem Pharm Bull 1999; 47(11): 1573.
33. Canan K, Kilcgil GA, Can Ekel B and Mümtaz I: Arch Pharm Res 2004; 27(2): 156.
34. Sakai T, Hamada T, Awata N and Watanabe J: J Pharmacobiodyn 1989; 12(9): 530.

35. Dini S, Caselli GF, Basilico C, Lavezzo A and Giani R: Inflammation Research 1990; 30: 1.
36. Richards ML, Cruz Lio S, Sinha A, Banie H, Thomas RJ, Major M, Tanji M and Sircar JC: Eu J Med Chem 2006; 41: 950.
37. Porai-Koshits BA, Ginzburg SF and Efros LS: Zh Ohshch Khim 1947; 17(10): 1768.
38. Paskov DS: Farmakol Toksikol 1948; 11(3): 18.
39. Ogihara T, Nagano M, Mikami H, Higaki J, Kohara K, Azuna J and Aoki T: Clin Ther 1994; 16(1): 74.
40. Li XC and Widdop RE: Hypertension 1995; 26(6): 989.
41. Delacretaz E, Nussberger J, Biollaz J and Waeber B: Hypertension 1995; 25(l): 14.
42. Kim S, Kawamura M, Wanibuchi H and Ohta K: Circulation 1995; 92(1): 88.
43. Mehrke V, Zong XG, Flockcrzi V and Hofinann FJ: Pharmacol Exp Ther 1994; 271(3): 1483.
44. Takahashi R and Endoh M: J Cardiovascular Pharmacology 2001; 37(2): 209.
45. Chimirri A, Grasso S, Montforte AM, Montforte P, Zappalla M and Carotti A: Farmaco 1994; 49(5): 337.
46. Brana MF, Castellano JM and Keilhauer G: Anticancer Drug Des 1994; 9(6): 527.
47. Islam I, Skibo EB, Dorr RT and Albert DS: J Med Chem 1991; 34: 2954.
48. Da Settimo A, Da Settimo F, Maria Marini A, Primofiore G, Salerno S, Viola G, Dalla Via L and Marciani S: M Eur J Med Chem 1998; 33: 685.

How to cite this article:
Patil SB: Medicinal significance of benzimidazole analogues: a review. Int J Pharm Sci & Res 2020; 11(6): 2649-54. doi: 10.13040/IJPSR.0975-8232.11(6).2649-54.