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Overview on Anticancer Potential of Benzimidazole

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ABSTRACT

Benzimidazole is a unique heterocyclic nucleus consisting of conjugation of six-membered benzene with five-membered imidazole. The benzimidazole nucleus is one of the most researched or utilized nuclei in organic chemistry. Benzimidazole nucleus is quite abundant in the various pharmaceutical active compounds. Benzimidazole is extensively explored for various biological potentials like antimicrobial, anticancer, antihistaminic, antiulcer, analgesic, etc. The physicochemical properties which are associated with benzimidazole have been the key to the increased interest of various scientists. Some benzimidazole derivatives with anticancer properties have been reported in the recent decade. This review is mainly focused on the anticancer potential of the benzimidazole nucleus.

INTRODUCTION

Benzimidazole is one of the most common heterocycles observed frequently in various synthetic protocols. Benzimidazole is a conjugated heterocyclic system in which six-member rings are conjugated with the five-member system as shown in figure no. 1.

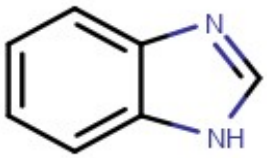
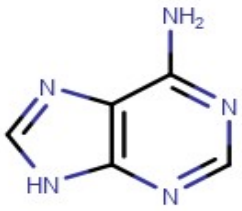
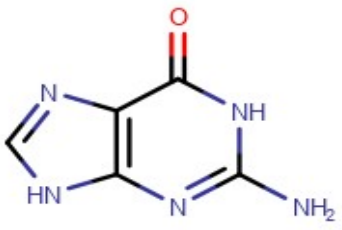


Figure no1: Benzimidazole Nucleus

Biological applications of benzimidazole are well established. The first application of the benzimidazole nucleus was reported in 1944 when the structural similarity between the purine and benzimidazole was established to show some biological application. The physicochemical properties of benzimidazole were one of the reasons for its profound biological potential. Benzimidazole nuclei have been observed in various biological molecules as shown in the following figure no. 2.



Adenine

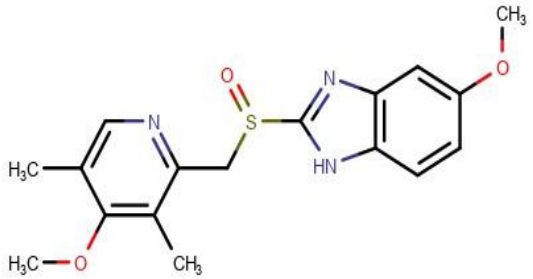


Guanine

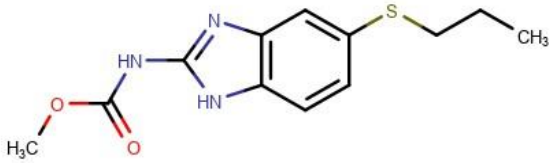
Caffeine

Figure no 2: Benzimidazole nucleus containing natural compounds

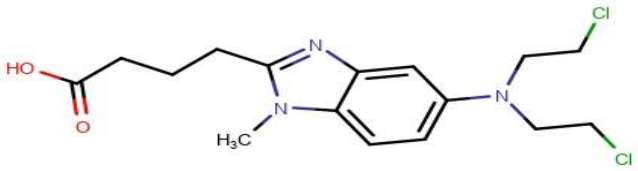
Benzimidazole has been an interregnal component of many important medicinal compounds that are in clinical use which are shown in figure no. 3.



Omeprazole



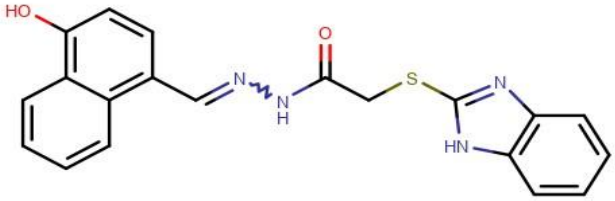
Albendazole



Bendamustine

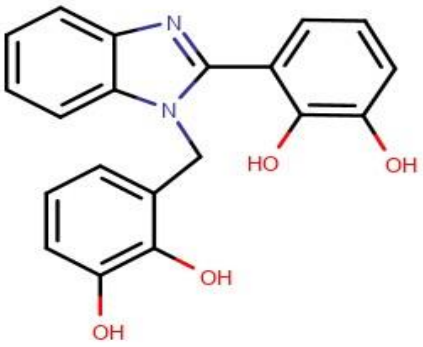
Figure no 3: Benzimidazole nucleus containing drugs

Benzimidazole has been reported in various anticancer compounds. Several compounds with profound anticancer activity were found to possing benzimidazole as the main pharmacophore. Here we have summarized some anticancer applications of the benzimidazole as anticancer agents. Narasimhan et. al. (2017) reported the anticancer and antimicrobial activity of benzimidazole derivatives (1) synthesized via reaction of 2-mercaptobenzimidazole and Ethyl chloroacetate in alkaline conditions. Results indicated OH substitution at the 2nd position yields compound with improved anticancer activity while di- and tri-substitution on phenyl ring may result in a compound with less activity.



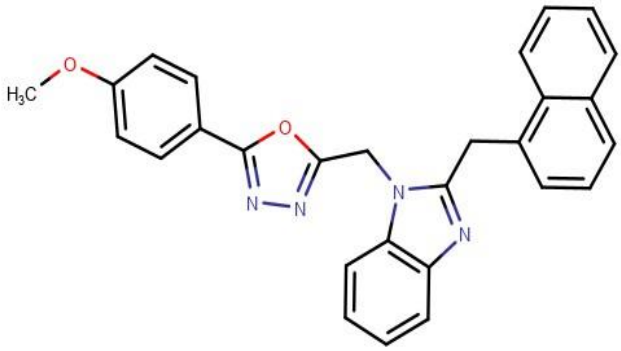
1

Kaur et. al. (2019) reported the development of the organic nanoparticles of benzimidazole (2) and reported their cytotoxicity in breast cancer. The developed nanoparticles showed enhanced cell uptake in the cancer cell than in normal cells which resulted in higher anticancer activity.



2

Anticancer activity of 2-(naphthalene-1-ylmethyl/naphthalene-2-yloxymethyl)-1-[5-(substituted phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-1H-benzimidazole (3) against 60 different cancer cell lines was reported by the Salahuddin et al (2015). They have developed the benzimidazole derivatives via the reaction of o- phenelenediamine and carboxylic acid.

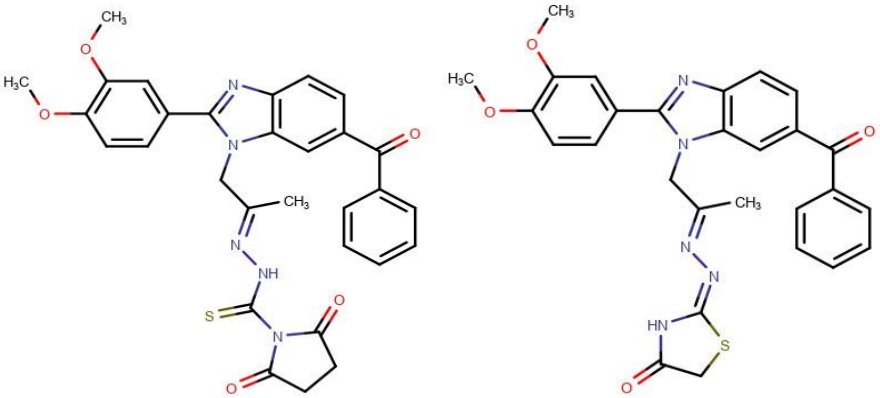


3

Benzimidazole conjugated with heterocycles like oxadiazole, thiadiazole and triazolothiadiazines have been developed by Husain et. al. (2019). Results indicated compound 3-((5-(3-(1H-benzo[d]imidazol-2-yl)-3-oxopropyl)-1,3,4-oxadiazol-2-yl)methyl)-5-methyl pyrimidine-2,4 (1H, 3H)-dione (4) was found to be the lead compound which also showed excellent binding potential with the topoisomerase enzyme.

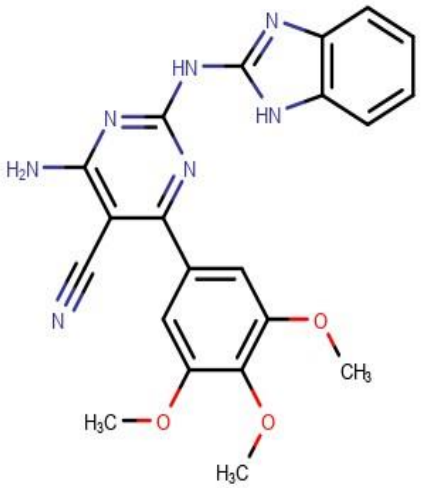
4

Abd El-Meguid et. al.(2020) reported development of the benzimidazole derivatives as anti-cervical cancer agents which are developed targeting kineases. (E)-N'-(1-(6-benzoyl-2-(3,4-dimethoxyphenyl)-1Hbenzo[d]imidazol-1-yl) propan-2-ylidene)-2,5-dioxopyrrolidine-1-carbothiohydrazide (5a) and (E)-2-(((E)-1-(6-benzoyl-2-(3,4-dimethoxyphenyl)- 1H-benzo[d]imidazol-1-yl) propan-2-idene)hydrazineylidene) thiazolidin-4-one (5b) are two promising anticancer agents which can be utilised for the cervical cancer.

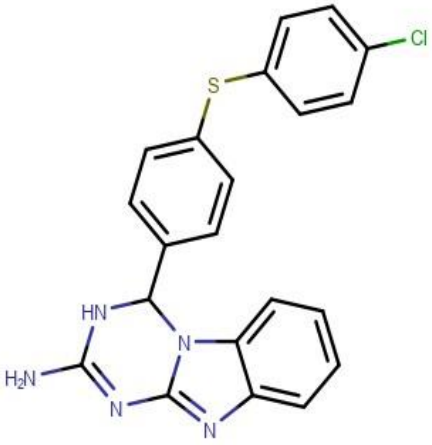


5a 5b

Ismail et. al. (2020) reported the development of the Hybrids of Pyrimidine/Benzimidazole Scaffolds for anticancer potential. 4-Amino-2-(1-H-benzimidazol-2-ylamino)-6-(3,4,5-trimethoxyphenyl)pyrimidine)-5-carbonitrile(6a) and 4-f4-[(4-Chlorophenyl)sulfanyl]phenylg-3,4-dihydro[1,3,5]triazino[1,2-a]benzimidazol-2-amine (6b) are the two promising compounds which are developed the compound 6a was found to be a more promising anticancer agent.

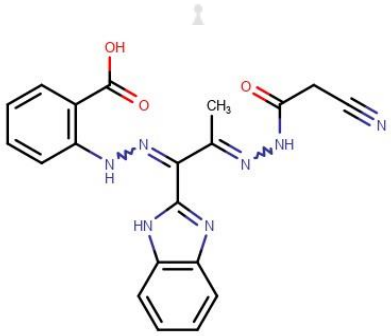


6a



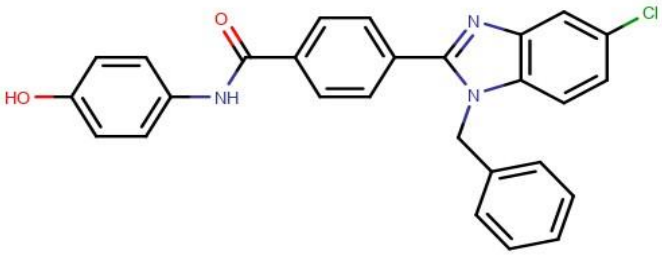
6b

Abed-Elrahman Shaaban et. al. (2016) reported the development of 2-substituted benzimidazole (7) compounds as anticancer agents. They have found that the anticancer activity of seven compounds was greater than the doxorubicin.



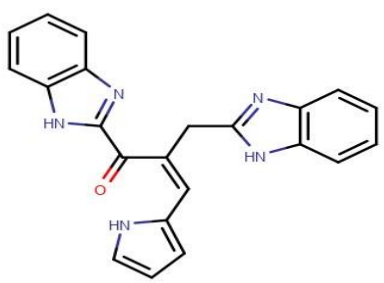
7

Sridhar Goud et. al. (2019) developed 1-benzyl-1H-benzimidazoles derivatives as galectin-1 mediated anticancer compounds. 4-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)-N-(4-hydroxyphenyl) benzamide(8) is the most promising derivative from the developed series.

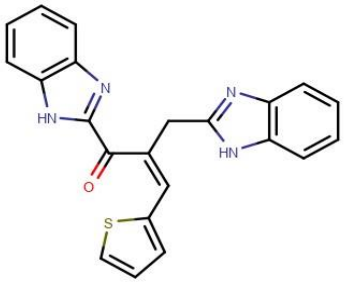


8

Rashid et. al. (2020) developed Bis-benzimidazole as anticancer agent and reported their ADMET studies. (Z)-2-((1H-benzo[d]imidazol-2-yl) methyl)-1-(1H-benzo[d]imidazol-2-yl)-3-(1H-pyrrol-2-yl)prop-2-en-1-one(9a) and (Z)-2-((1H-benzo[d]imidazol-2-yl) methyl)-1-(1H-benzo[d]imidazol-2-yl)- 3-(thiophen-2-yl)prop-2-en-1-one (9b) are the two most promising anticancer compounds which are developed from this series.



9a



9b

SUMMARY:

Benzimidazole is one of the most promising heterocyclic agents utilized as a synthetic intermediate or scaffold. Various benzimidazole derivatives have shown profound anticancer activity, so the development of anticancer agents keeping benzimidazole nucleus will be an attractive methodology for anticancer drug design.

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