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Der Pharmacia Sinica, 2010, 1 (3): 172-182



Der Pharmacia Sinica

ISSN: 0976-8688
CODEN (USA): PSHIBD

Recent advancement in imidazole as anti cancer agents: A review

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ABSTRACT

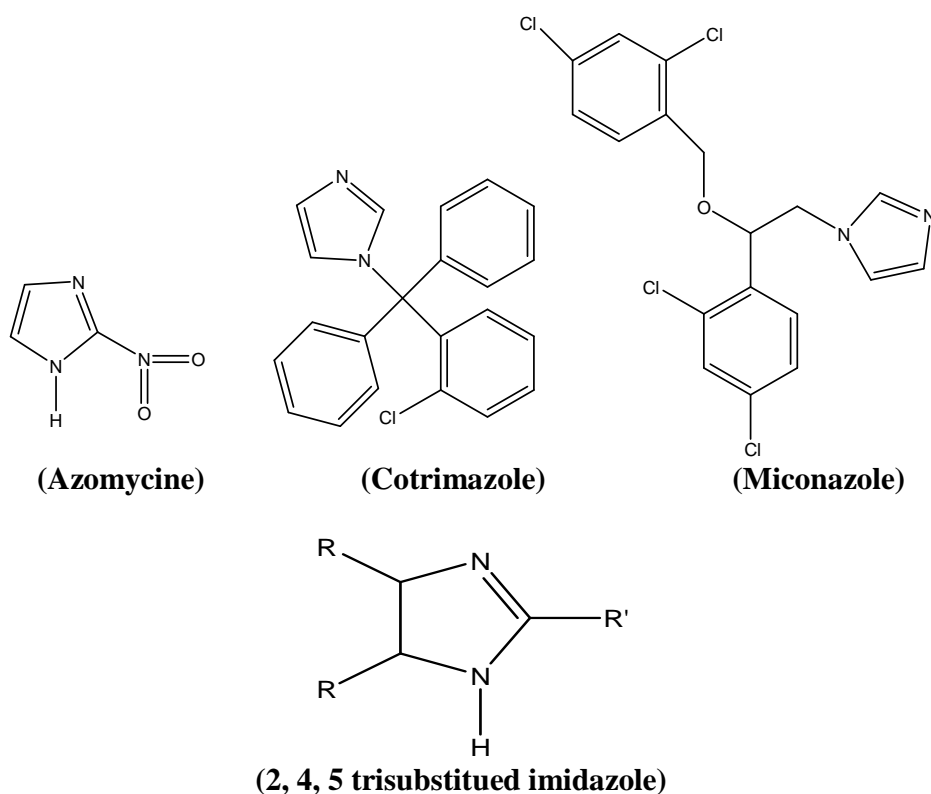
Cancer is the second leading cause of death world wide after heart disease. A number of noble drugs are discovered for the treatment of cancer. In the present time imidazole plays an important part in the development of new drug for treatment of cancer. Imidazole is a nitrogen containing heterocyclic ring which possesses biological and pharmaceutical importance. Imidazole ring consists of variety of important natural product like histidine and purine. Imidazole derivatives have an important application in cancer treatment and an important agent used in medicinal chemistry. Despite these progresses the majority of patient diagnosed with their major malignancies will die of their disease and therefore, there is a need for few new agents with novel mechanism of action. Though much effect has been focused on the development of novel tyrosine-kinase inhibitors and antibiotics directed at signal transduction, exploration of new compound directly against traditional target of DNA and tubulin continues to be important.

Keywords: Imidazole, Benzimidazole, Anticancer, Thiopurines, Pyrimidines.

INTRODUCTON

Cancer is a class of diseases in which a cell, or a group of cells display uncontrolled growth, invasion and sometimes metastasis.. These three malignant properties of cancers differentiate them from benign tumors, which are self-limited, and do not invade or metastasize. Most cancers form a tumor [1]. The branch of medicine concerned with the study, diagnosis, treatment, and prevention of cancer is oncology. In 2004, worldwide cancer caused 13% of all deaths. The leading causes were lung cancer, stomach cancer, colo-rectal cancer, liver cancer and breast cancer [2,3]. Cancers are primarily an environmental disease with 90-95% of cases due to lifestyle and environmental factors and 5-10% due to genetics. Common environmental factors

leading to cancer death include: tobacco, diet, obesity, infections, radon exposure, radiation, stress, lack of physical activity and environmental pollutants [4]. These environmental factors cause abnormalities in the genetic material of cells [5]. Cancer affects people at all ages with the risk for most types increasing with age. The traditional anticancer drugs are the basis for the new drug development for cancer in which imidazole is an important moiety. Imidazole is a heterocyclic ring containing basically 3C and 2N atom present in 1st and 3rd positions [6]. The substitution on different positions gives a number of compounds of interest. Thus, imidazole compounds have been an interesting source for researchers for more than a century. Structure-activity relationship were reduced from biological results and will be used in further design of new active compound. Presently a number of drugs are used in the treatment of the cancer, but majority of them were produced controlled effect on the cancer cell. By application of these drugs the disease can be controlled. Imidazole and its derivatives are reported to be physiologically and pharmacologically active and find applications in the treatment of several diseases. In the drug discovery the imidazole is the most important synthetic strategy. Many imidazoles are reported as pharmacological agents like Azomycine, Clotrimazole, Miconazole, Ergothionine, Clonidine and Moxonidine. One of the most important applications of imidazole derivatives is their used as material for treatment of denture stomatitis and in cancer [7,8]. Mostly synthetic compounds which are biologically active have five-membered nitrogen containing [6].

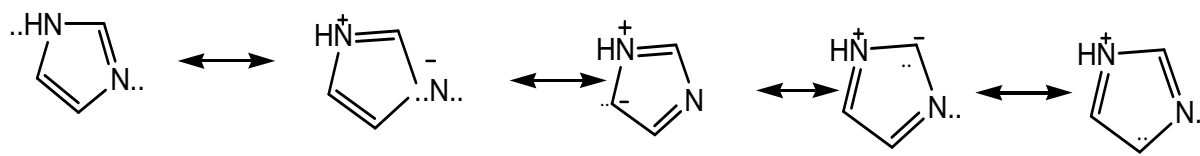


Chemistry

Imidazoles are generally well known as anticancer agents. These are heterocyclic compounds containing 5-membered planar ring, soluble in water and other polar solvents. Imidazoles are of two equivalent tautomeric forms because of hydrogen atom which is located on either of the two

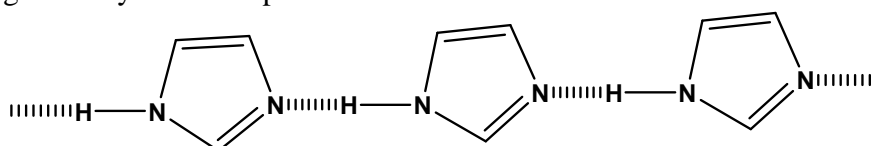
nitrogen atoms. They are amphoteric and therefore can function as both an acid and base. Imidazoles are aromatic compounds because of the presence of a sextet of π -electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring [1].

Some resonance structures of imidazole are shown below[1]:



Properties of Imidazole

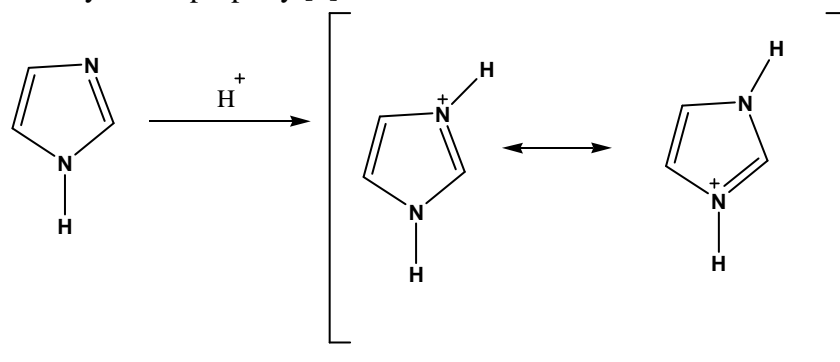
Physical properties: Imidazole is a colourless organic compound having melting point 89-91 °C and boiling point is 256 °C. It has high boiling point as compared all other five membered heterocyclic compounds. In marked contrast to imidazole, the boiling point of 1- methylimidazole is comparatively low. It demonstrates that hydrogen bonding exists in imidazole ring and may consists upto 20 molecules.



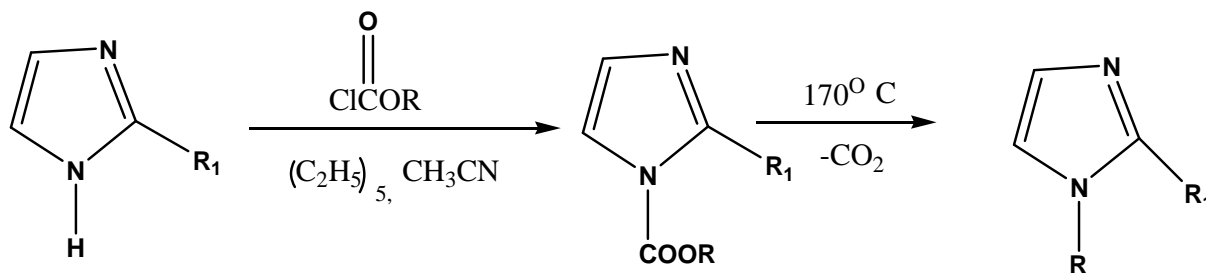
Imidazole is more basic having pK_a value is about 7.2. It contains pyrrole type amino nitrogen in the the ring and forms metallic salts with NaNH₂ and RMgX which are extensively hydrolyzed by water. The introduction of alkyl groups into the ring increases the basicity. Imidazole is an aromatic compound and possesses a resonance energy of 14.2Kcal/mole. The dipole moment of imidazole has been measured in several solvents [9].

Chemical Properties:

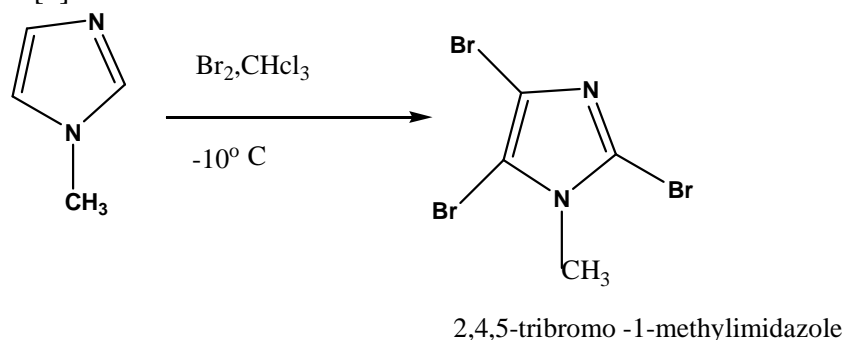
1) **Reaction with acids:** Imidazole is a mono acidic base. It forms a crystalline salts with acids. It also possesses weakly acidic property [9].



2) **Quaternization:** Quaternization of the nitrogen atom of the imidazole is normally achieved by the reaction of alkyl halides or dialkyl sulfates in an organic solvent under strongly basic conditions. Alkylation of imidazoles is achieved by heating 1-carboethoxyimidazoles [9,10].

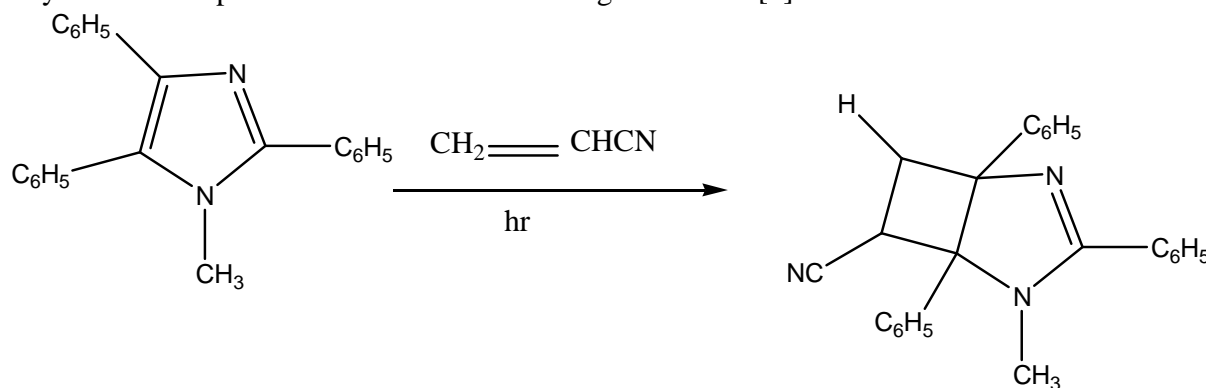


3) **Halogenation:** Halogenation of imidazole is very complex. Its depends on the substrste, reagents and reaction conditions. Direct chlorination gives undefined products. Bromination yields 2,4,5-tribromo derivative. Iodination takes place in alkaline conditions to give 2,4,5-triiodoimidazole [9].



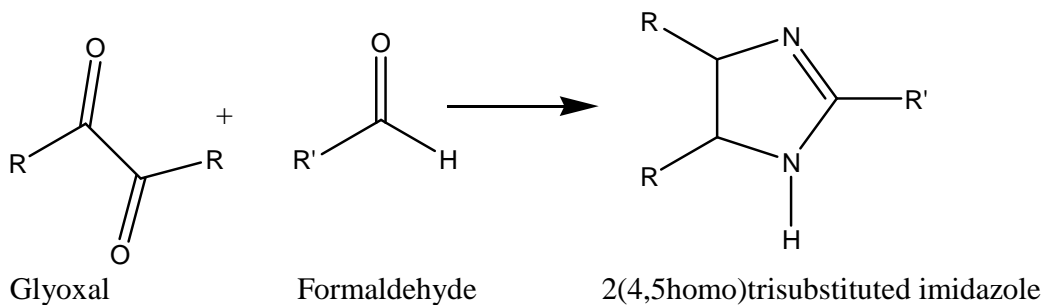
4) **Reaction with Oxidizing and Reducing Agents:** Imidazole shows stability for autoxidation. Oxygen in the presence of sensitizer reacts to give an imidazole derivative. Imidazolium Dichromate, a mild oxidizing agent which is employed for the oxidation of allylic and benzylic alcohols [9].

5) **Cycloaddition Reactions:** Imidazoles gives addition across the carbon-carbon double bond. This kind of reaction performed under photochemical conditions. The reaction of imidazole with acrylonitrile is representative from the reaction given below [9].

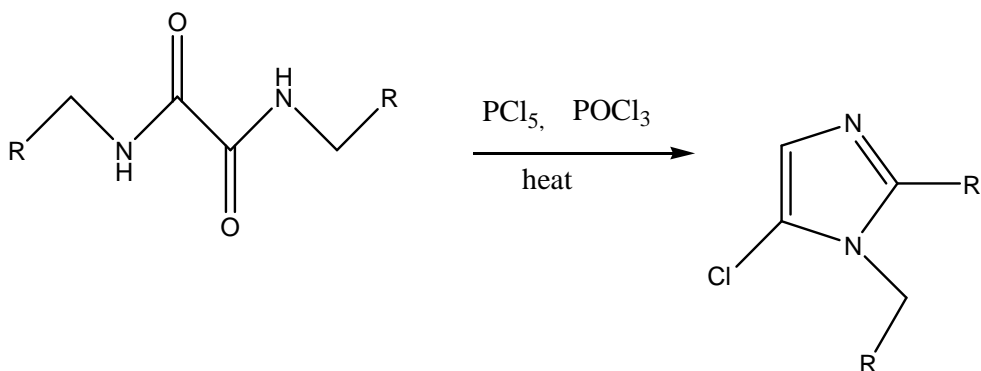


General Synthesis of Imidazole

1) **Debus synthesis:** This reaction provide 2-mono substituted and 2, 4, 5- homo trisubstituted imidazole.

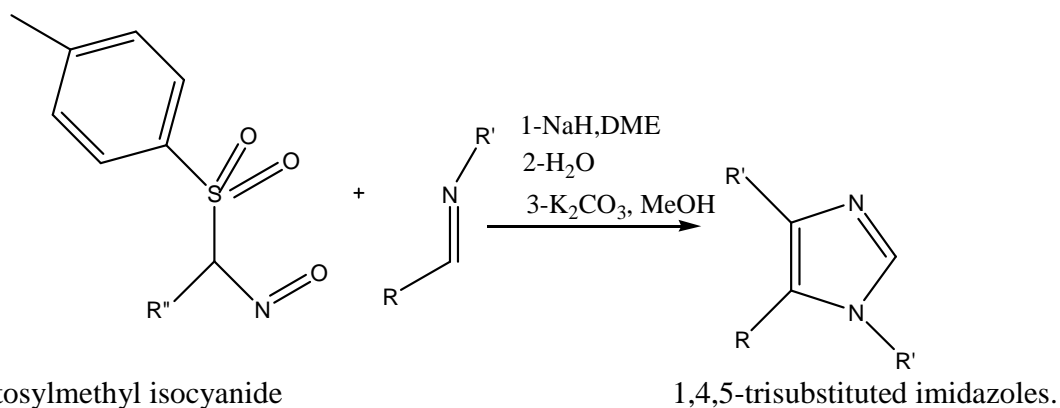


2) **Wallach Chloroimidazole Synthesis:** This reaction provides 1,2 disubstituted chloroimidazole

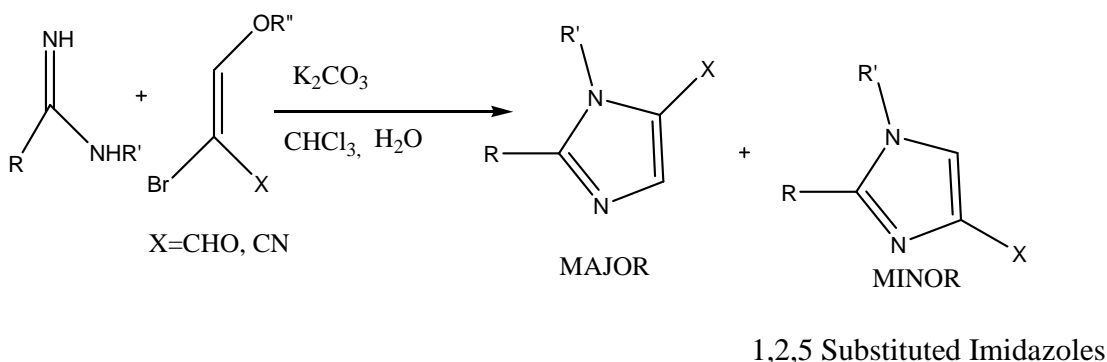


1,2 Disubstituted chloroimidazole.

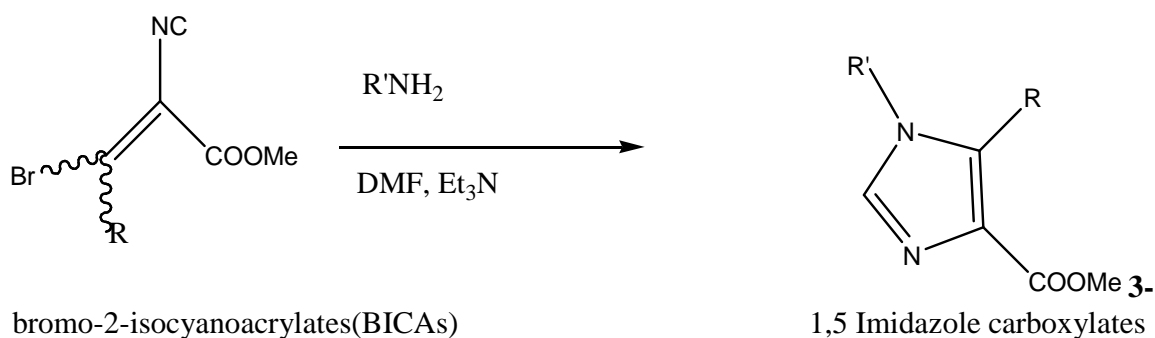
3) **Tos MIC Based Imidazole Synthesis:** This reaction provides 1,4,5-trisubstituted imidazoles.



4) **Synthesis of Imidazole from Amidines:** This reaction provides 1,2,5-substituted imidazoles.



5) Synthesis of Imidazole Carboxylate from BICAs: This reaction provides 1,5 imidazole carboxylates from amines and 3-bromo-2-isocyanoacrylates (BICAs) [11].



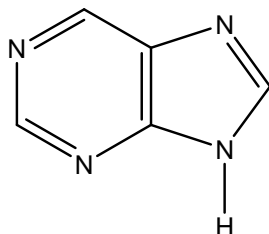
General Mechanism of Action of Imidazole

Generally imidazoles come under the category of antimetabolite which have specific mechanism of action in cancer. Antimetabolite is a type of chemical that inhibits the use of a metabolite. They have toxic effects on cells, such as halting cell growth and cell division. That's why these compounds are used as chemotherapy for cancer. Antimetabolites can be used in cancer treatment, as they interfere with DNA production and therefore cell division and the growth of tumors. These are the chemicals which become the building blocks of DNA. They prevent these substances becoming incorporated into DNA during the S phase of the cell cycle, stopping normal development and division. They also affect RNA synthesis because thymidine is used in DNA but not in RNA where uracil is used instead of cytosine, inhibition of thymidine synthesis via thymidylate synthase selectively inhibits DNA synthesis over RNA synthesis [1,12].

Main representatives of these drugs are:

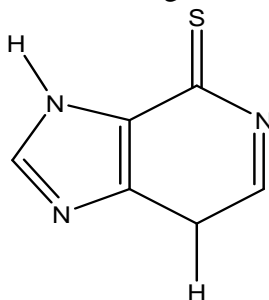
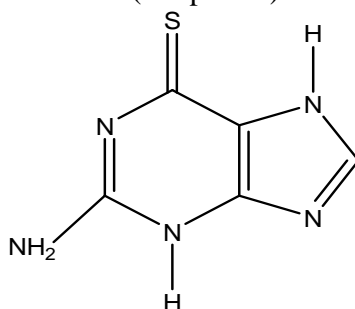
- Purine Analogues
- Pyrimidine Analogues

Purine Analogue: These inhibit DNA / RNA synthesis [1,12].

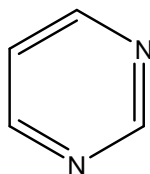


(7H-Purine)

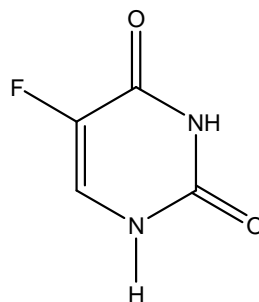
Example: Thiopurines (Mercaptopurine [6-MP]; Thioguanine [6-TG])

3,7-dihydro-6-thione
(thiopurine)2-amino-7H-Purine-6-thiol
(thioguanine)

Pyrimidine Analogues: Its one derivative, 5-fluoro-2'-deoxyuridine 5'-phosphate (FdUMP), inhibits thymidylate synthase and its cofactor, a tetrahydrofolate derivative, resulting in inhibition of thymidine nucleotide synthesis. Another derivative, 5-fluorouridine triphosphate is incorporated into RNA, interfering with RNA function. Cytotoxicity effects on both RNA and DNA. An example is flurouracil [1,12].



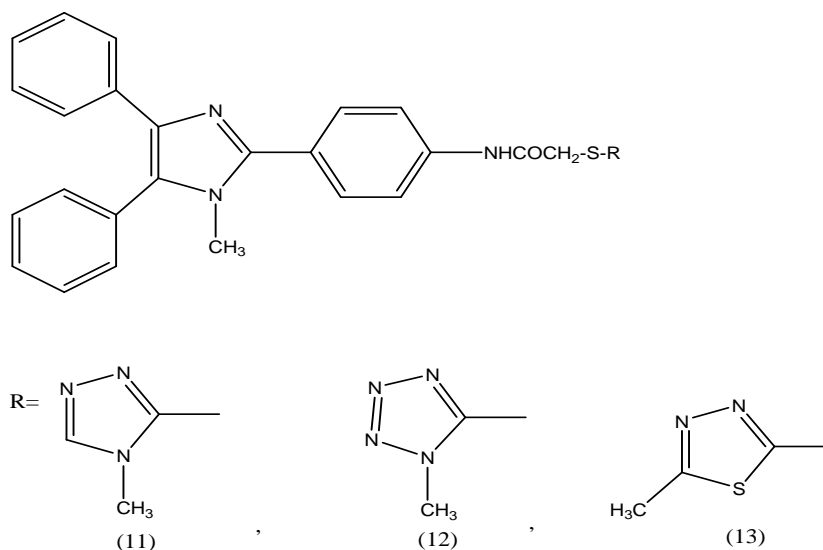
1,3-Diazine



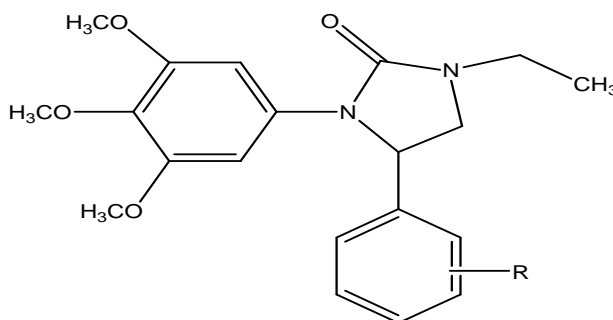
(Flurouracil)

Anticancer activity of different imidazole derivatives

Ozkay *et al.* studied 18 novel imidazole-(benz)azole and imidazole piperazine derivatives. The structures of the compounds were confirmed by IR, ¹HNMR and EI-MS spectral data. Most of the compounds, showed greater activity against carcinogenic cell lines. Anticancer activity screening results revealed that **(11)**, **(12)** and **(13)** were the most active compounds in the series [13].



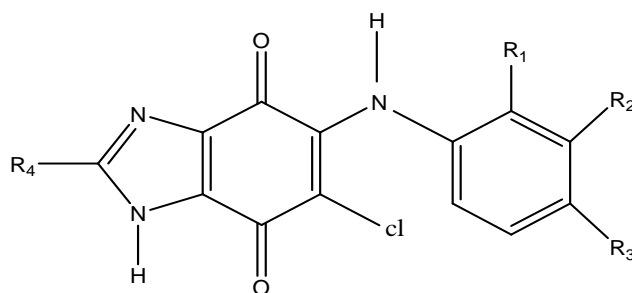
Xue *et al.* synthesized a new series of aryl substituted imidazol-2-one derivatives structurally related to combretastatin A-4 (CA-40) and evaluated for their cytotoxic activities *in vitro* against various human cancer cell lines. The cytotoxic effects of compounds **(7b)** and **(7i)** proved to be similar to or greater than that of docetaxel. The highly active compound **(7b)** exhibited excellent inhibitory activity on tumor growth *in vivo* [14].



(7b) R=4-Cl

(7i) R=3NH₂-4-OCH₃

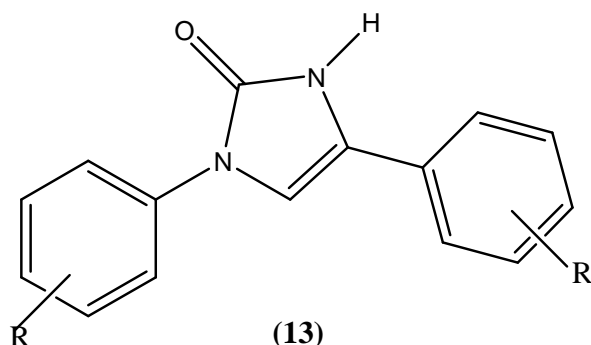
Chung *et al.* synthesized 5-Arylamino-1H-benzo[d]imidazole-4,7-dione and tested for their inhibitory activities on the proliferation of human umbilical vein endothelial cell and the smooth muscle cells. Among them compound **(2b)** exhibited the selective antiproliferative activity on the of human umbilical vein endothelial cell [15].



(2b)

R₁, R₂, R₃ =H, F...
R₄ =CH₃

Congiu *et al.* synthesized a series of new 1,4-diarylimidazol-2(3H)-one derivatives and their 2-thione analogues has been prepared and evaluated *in vitro* for antitumor activity. Compounds bearing a 3,4,5-trimethoxyphenyl ring linked to either N-1 or C-4 position of the imidazole core demonstrated an interesting profile of cytotoxicity with preferential activity against leukemic celllines. Compound (13) exhibited a potent antitumor activity [16].



(13)

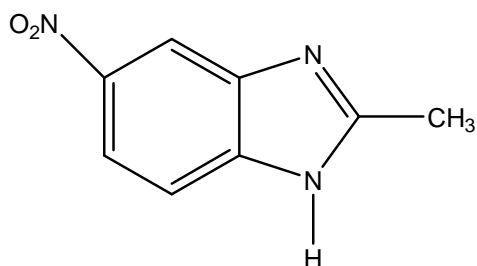
R=4Cl, R'=3,4,5-(MeO)₃

Ramla *et al.* introduced different substituent in position 1 of 2-methyl-5(6)-nitro-1H-benzimidazole (2) in order to obtain different side chains having different heterocyclic compounds. The antitumor effect of different compounds were studied against breast cancer and among them compounds (2) and (7) were found to be active [17].

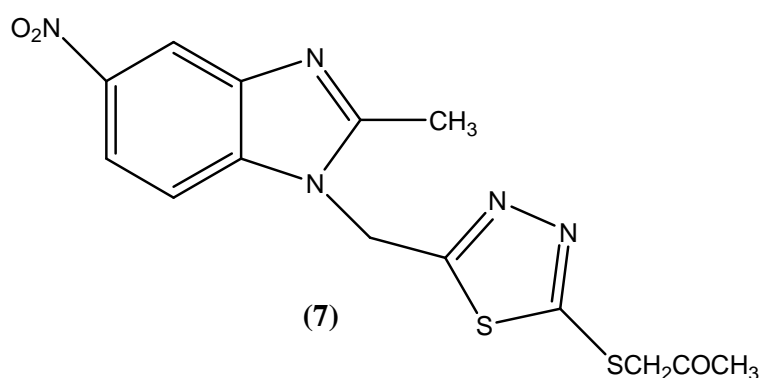
Biological significance of imidazole in cancer

The number of researchers concentrated toward the development of novel anticancer agents. The anticancer agents containing imidazole nucleus screened are described-

Tiazofurin (2-B-D-ribofuranisylImidazole-4-carboxamide) is an oncolytic c-nucleoside with potent inhibitory activity against ionosine 5'-monophosphate dehydrogenase. Generally it is known as Imidazofurin. This compound screened anticancer activity. Result of the screening suggested that this compound possess good anticancer activity [18].



(2)



(7)

CONCLUSION

On the basis of various literature survey imidazole derivatives shows activity against cancer. The possible improvements in the activity can be further achieved by slight modifications in the substituents on the basic imidazole nucleus. Having structural similarity with histidine imidazole compound can bind with protein molecules with ease compared to the some other heterocyclic moieties. Thus imidazole offers better pharmacodynamic characteristics. Furthermore, some imidazole drugs, at high concentrations, could exert direct inhibitory effects on membranes, without interference with sterols and sterol esters. Various recent new drugs developments in imidazole derivatives show better effect and less toxicity. A lot of work has been done and a lot to do in this field. But in the near future we will get the desirable treatment of the cancer.

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