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Synthesis and Anticancer Activity of Benzoxazole Derivatives: A Review

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***Abstract*: Benzoxazole and its derivatives of heterocylic compounds possessing nitrogen, oxygen and oxazole moieties which are the important structures of several pharmacologically active compounds. Benzoxazole analogues shows vigorous effects. According to the previous research, benzoxazole is produced by reflexing CS2 and O-aminophenol. These derivatives of benzoxazole produce Good anti- breast cancer activity. This review includes the synthesis and the anticancer activity of benzoxazole and its analogues. This study can help the future chemists focusing on the synthesis of drugs related to anticancer activity.**

***Keywords*: Benzoxazole, heterocylic compounds, vigorous effects, anti-breast cancer activity.**

1. Introduction

Synthetic organic chemistry is very key part of highly integrated and multidisciplinary process of anticancer development. The five membered heterocylic ring is present among the biologically active compounds. The number of deaths are constantly increasing in the world because of infectious diseases. It has been seen that there is rapid increase in multidrug resistant infections these days causing increase in various health problems. There are many kinds of diseases which are hard to treat with conventional antibiotics.

Another most dangerous disease is Cancer despite of advanced treatments; cancer has become reason for the second most leading cause of death. The exact biology of the cancer is mysterious and has lot to experiment to produce new products. Understanding the drug action and pathogenesis of different types of neoplasm becomes clearer, it becomes easy to produce new drugs which helps in selective targeting if the tumor with less amounts of side effects.

Benzoxazole are having key role in the medicinal chemistry due to their wide spectrum of pharmacological activity. The biological activities shown by benzoxazole and its analogues are mainly antifungal, antihistaminic, anti-cancer, anti-inflammatory, anti-viral, anti-bacterial. Benzoxazoles gained importance because of use in intermediates for the preparation of new drugs.

Benzoxazole can be considered as the structural isosteres of naturally produced nucleic acid bases like adenine and Guanine, which helps in the interaction with polymers of living system. Different research groups have done much development in designing compounds with benzoxazole, synthesising and collecting anti-cancer activity data of those against various human cancer cells. In the present study, we report the synthesis and anticancer activity of benzoxazole and its derivatives.

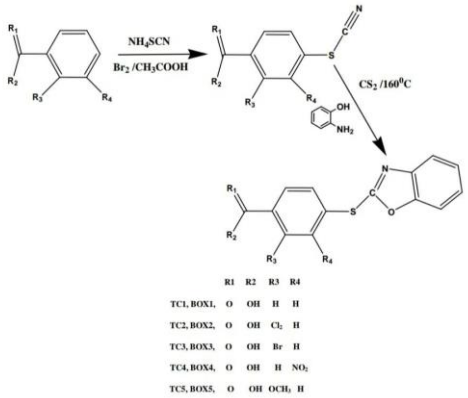
2. Literature Survey

A. Chemistry of Benzoxazole Nucleus

Benzoxazole is an aromatic organic compound having benzene fused oxazole ring structure with molecular formula C7H5NO.Molar mass 119.12g/mole and odour same as pyridine with IUPAC name 1-oxa-3-aza-1H- indene, Insoluble in water and melting point of 27-30°C.

1) Synthesis of benzoxazole

Method-1: A mixture of thiocynate (0.01mol), O-aminophenol (0.01 mol, 1.08g) and carbon disulphide (0.1 mil, 8ml) was heated in oil bath at 160°c for 6hrs.the benzoxazole produced is cooled and recrystallized from ethanol.



	R1	R2	R3	R4
TC1, BOX1,	O	OH	H	H
TC2, BOX2,	O	OH	Cl_2	H
TC3, BOX3,	O	OH	Br	H
TC4, BOX4,	O	OH	H	NO_2
TC5, BOX5,	O	OH	OCH_3	H

Method-2: Batley carried out a copper catalysed one pot synthesis of benzoxazoles utilizing bromoanilines and acyl halides in the presence of base and solvent giving intermediates which finally gave pure benzoxazole (21-97%) isolated yields exhibiting a broad range of biological activities. They can also be used as precursor in the synthesis of drugs.

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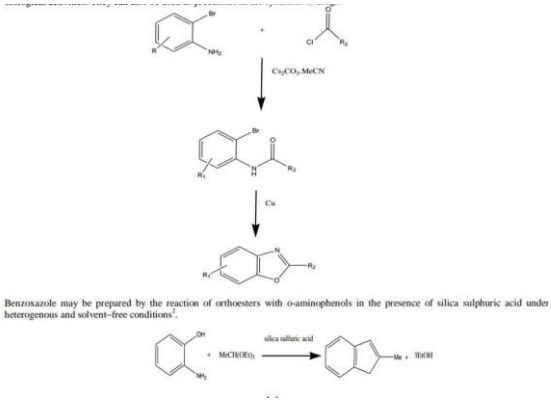
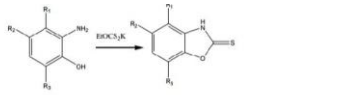


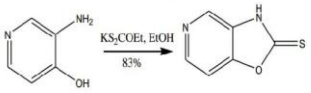
Benzoxazole may be prepared by the reaction of orthoesters with o-aminophenols in the presence of silica sulphuric acid under heterogenous and solvent-free conditions[2].

2) Synthesis of benzoxazole analogues

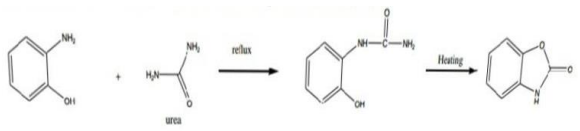
Synthesis of benzoxazole-2(3H)-thione: A mixture of 2-amino-4-methylphenol (12.3g, 0.01mol) was mixed and refluxed for 2hrs.It was cooled to room temperature and poured into mixture of ice water (400ml) and conc. HCl (40ml). The solid was collected, washed with H2O and dried in Hood overnight and then in vaccum oven at 45°c for several hours to give a coffee colured powder. Yield: 16.0g (97%).



R1	R2	R3	Conditions	Yield(%)
H	Me	H	KS_2COEt, Pyridine, reflux	97
H	Ms	H	KS KS_2COEt, Pyridine, reflux	57
H	Cl	H	KS_2COEt, Pyridine, reflux	94
H	CO_2 Me	H	K_2COEt, Pyridine, reflux	96
H	NO_2	H	KOH, CS_2 EtOH	66
H	H	H	KOH, CS_2 EtOH	61
Me	Cl	iPr	KOH, CS_2 MeOH	87
H	OMe	H	KOH, CS_2 EtOH	90



3) Synthesis of 2-benzoxazole-2-one via reflux of amino phenol and urea



4) Anti-cancer activity

Benzoxazole and its analogues have potent activity against cancer they give moderate to good anti – breast cancer activity and also effective against human colorectal carcinoma Human colorectal carcinoma cancer cells line was used for evaluating the anticancer activity of the prepared benzoxazole compounds using sulforhodamine B assay. C27H25N5O5S exhibited the best anti-cancer activity.

5) Anticancer activity of benzoxazole attached with different moieties

Benzoxazole-piperazine moiety: Benzoxazole attached to piperazine is tested over A-549 lung carcinoma cell. At first the results were not satisfactory because of low solubility of aryl piperazine and these piperazine compounds are precipitated in cell culture. The solubility can be increased by using n-methylpiperazine at position 6 of benzoxazole and methyl group at position-2. Long chain piperazines attached to benzoxazole couple with oxadiazoles have shown anti-cancer effect.

Benzoxazole-1, 3,4-oxadiazole moiety: 1,3,4- oxadiazole is very effective and shows variety of biological activity. Benzoxazole-1, 3,4-oxadiazole was prepared and anti-cancer activity was screened against human cancer cells i.e. lung cancer, breast cancer, melonoma cancer, colon cancer and it's anticancer activity against HT 29 cancer cell line and the results were better than the standard drug.

Benzoxazole-pyrazolinone derivative: New derivatives of benzoxazole, benzothiazolebenzothiazole and benzimidazole are prepared. By the observation, we got to know that absence of substitution at N-2 shows very poor anti proliferative activity as compared to substitution at N-2 of pyrazolinone. N-2 Substituted pyrazolinone derivatives are active towards the cancer cell lines.

Benzoxazole-1,2,4-oxidiazole moiety: 1,2,4 -oxidiazole show potent anti-proliferative activity. Benzoxazole fused with benzofuran and 1,2,4-oxidiazole was Synthesised in minimum steps and it is active against human breast cancer, lung cancer, melonoma cancer and colon cell lines.

Benzoxazole-combrestatin derivative: Series of ten benzoxazole derivatives of combrestatin A-4 were synthesized and evaluated against various cancer cell lines like Coco-205 (colon), A-549(lung), MCF-7(breast) cell line and it was observed that compound 8d was more potent than the standard compound against MCF-7 and A-549 cell lines. Combrestatin A-4 is a natural product isolated from South African willow tree *Combretum caffrum* in 1989 and it shows anti- cancer activity against various cell lines.

3. Conclusion

The synthesis, structures and biological activities of benzoxazole derivatives have been focused of research interest in the field of medicine from long time due to potent activity shown by them. Therefore, the recent approach is to study the QSAR of benzoxazole derivatives, synthesize certain newer derivatives of benzoxazole according to the reaction schemes producing higher yield and screen them for their biological activity.

As the concentration of compound being tested increased, the in- vitro anticancer activity also increased. Further molecular modification is required in order to arrive at more accurate structure activity relationship with their anticancer activity on breast cancer cell lines or different crystals structure of tyrosine kinase domain.

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