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Review Article

Recent Overview on Synthesis of *2-Mercaptobenzimidazole* Derivatives and its Activities

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Abstract

A novel series 2-(1H-benzimidazol-2-ylsulfanyl) -N-(4-oxo-2-phenyl-thiazolidin-3yl) Various aldehydes and 2-acetamides have been used to synthesise -acetamide 5a–j (5-phenyl-[1,3,4]-oxadiazol-2-ylmethylsulfanyl) - 1H-benzimidazole 6a–j derived from a variety of benzoic acids. These compounds were tested in vitro for antibacterial activity against Gram positive bacteria Staphylococcus aureus and Enterococcus faecalis, Gram negative bacteria Klebsiella pneumoniae and Escherichia coli, and antifungal activity against Aspergillus fumigatus and Candida albicans. The in vitro cytotoxic properties of brine shrimp were investigated using a bioassay. Compounds 5b, 5d, 5g, 5i, 6b, 6e, 6f, and 6i demonstrated excellent activity against a panel of microorganisms, according to the results. 5b, 5g, 5i, 6b, 6f, 6h, and 6i were found to have good cytotoxic activities. Elements, IR, 1H-NMR, 13C-NMR, and MS were used to characterise all of the newly synthesised compounds.

Keywords: Antibacterial, Antifungal, 4-Thiazolidinone,1,3,4-Oxadiazole, Cytotoxicity.

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INTRODUCTION

The design and synthesis of heterocyclic compounds is a major concern for organic chemists all over the world. Heterocycles play a crucial role in medicine, biology, environmental protection, and coordination chemistry. For the creation of new physiologically active molecules with a variety of characteristics, a simple heterocyclic scaffold is used. Heterocycles like benzimidazole and 2-mercaptobenzimidazoles are included (2-MBI). They have a wide range of pharmacological properties, including antibacterial[1], and antihistamine properties· Antiparasitic, antimicrobial, antifungal, antidepressant[2] antidiabetic, antihypertensive, anticoagulants, analgesic, anti-inflammatory, antihistaminic, anticonvulsant[3] and proton pump inhibitors[4] all contain the benzimidazole nucleus. Several investigations into the corrosion inhibitory effects of 2-mercaptobenzimidazole (MBI) have already been carried out [5]. 2-mercaptobenzimidazole with possible surfactant properties to assess acute oral toxicity as well as analgesic and psychotropic effects on the nervous system. 5-Methoxy-2-mercaptobenzimidazole (5-M-2-MBI) is an Esomeprazole/Omeprazole intermediate. According to previous research, 5-M-2-MBI can operate as a reaction initiator for a variety of active chemicals[6,7]. In the pharmaceutical industry, and is a component of numerous medications[8].

The condensation of carboxylic acids and their products is extensively used for the manufacture of benzimidazoles from carboxylic acids. In the presence of concentrated o-diaminobenzene derivatives under reflux circumstances, hydrochloric acid[9]. Antiviral (Enviradine), antihistaminic (Astemizole), antihypertensive (Telmisartan), and anthelmintic (Thiabendazole) are 2- MBI[10].

The photographic industry has found application for 2-mercaptobenzimidazole and various other benzimidazole derivatives. These chemicals have found usage in photographic developing and fixing solutions because they eliminate "fog" and boost speed. Rubber antioxidant 2-mercaptobenzimidazole has been discovered to be useful. Sunburn preventatives contain several benzimidazole derivatives. By absorbing UV rays, these chemicals shield the skin. In this study, kinetics, UV visible absorption spectroscopy, fluorescence spectroscopy, and molecular docking techniques were used to investigate the inhibitory effect and mechanism of 5-Methoxy-2-Mercaptobenzimidazole on tyrosinase.

Many research organisations from all over the world have lately reported on the production and glucosidase inhibitory actions of various heterocycles[11,12]. This study was designed to synthesise novel acyl hydrazone Schiff's base derivatives of the 2-mercaptobenzimidazole nucleus with potential applications as glucosidase inhibitors because this nucleus has found tremendous applications in biological systems. Additionally, the antioxidant activity of the produced compounds was assessed.

Guanine, adenine, purine, caffeine, and uric acid are examples of biomolecules that contain benzimidazole as a basic component[13]. A range of benzimidazole compounds with anticancer properties against various types of solid tumours have also been produced. The synthesised compounds were then examined in vitro for antiproliferative activity and shown to have a non-specific antiproliferative effect on the cell lines that were tested. The purpose of this study is to synthesise 2-mercaptobenzimidazole (2-MBI), radiolabel it with [99mTc (CO)3(H2O)3] + to produce 99mTc-2-MBI, and evaluate its ability to target tumour hypoxia. The production of a 99mTc-labeled complex was investigated and confirmed using analytical characterization methods[14].

USES:

2-Mercaptobenzimidazole can be utilised in the following ways:

By reacting aromatic ketones with 2-benzimidazolylthioacetophenones, a crucial step in the production of thiazolo[3,2a] benzimidazole.

CuI and 1,10-phenanthroline were used to make S-arylated 2-mercapto-benzimidazoles by S-arylation with substituted aryl iodides.

In the photographic business, 2-Mercaptobenzimidazole and various other benzimidazole derivatives have been used.

These are mainly use as anticonvulsant, anticoagulant, antiinflammatory etc.

METABOLISM:

Because of their low water solubility, benzimidazoles are poorly absorbed from the GI tract (a fatty meal will increase absorption). Because the medications are primarily used to treat intestinal Helminthes, poor absorption may be advantageous. The medications are rapidly metabolised in the liver and eliminated in the bile to the extent that they are absorbed. In most situations, the parent molecule is digested quickly and virtually entirely, with oxidative and hydrolytic reactions taking precedence. The phase I oxidative reaction is usually conducted by cytochrome P-450, and it is followed by a phase II conjugation.

MECHANISM OF ACTION:

The capacity of 2-mercaptobenzimidazoles to bind to the protein tubulin and hence impede tubulin polymerization to microtubules is the principal effect of these medicines. Tubulin is a dimeric protein that coexists with polymeric microtubules in a dynamic equilibrium. Binding to tubulin prevents subunits from self-associating and results in a "capping" of the microtubule at the associating end. With a net reduction in microtubule length, the microtubulin continues to detach from the opposite end. Although benzimidazole has been demonstrated to bind to mammalian tubulin, when administered as anthelmintics, these medications are very lethal to the helminths while causing negligible damage to the host.

PROPERTIES OF 2-MERCAPTOBENZIMIDAZOLE:

Benzimidazole with the imide nitrogen (i.e., hydrogen in the 1-position) is typically more soluble in polar solvents and less soluble in hot water, but it is difficult to dissolve in ether and insoluble in benzene. The addition of other non-polar substituents in various positions of the benzimidazole ring increases its solubility in non-polar solvents, resulting in 2-methylbenzimidazole being easily soluble in ether. The incorporation of a polar group into the molecule increases its solubility in polar solvents; for example, 2-aminobenzimidazole is soluble in water.

*2-mercaptobenzimidazole are weakly basic, slightly less basic than imidazoles.

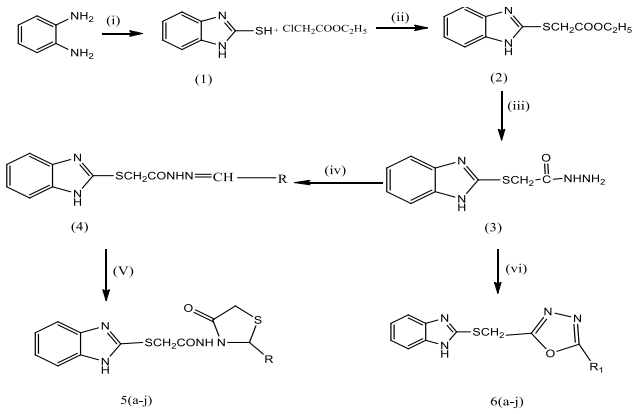
*In general, they are soluble in dilute acids.

*More acidic benzimidazoles may be soluble in less basic solutions like potassium carbonate solution.

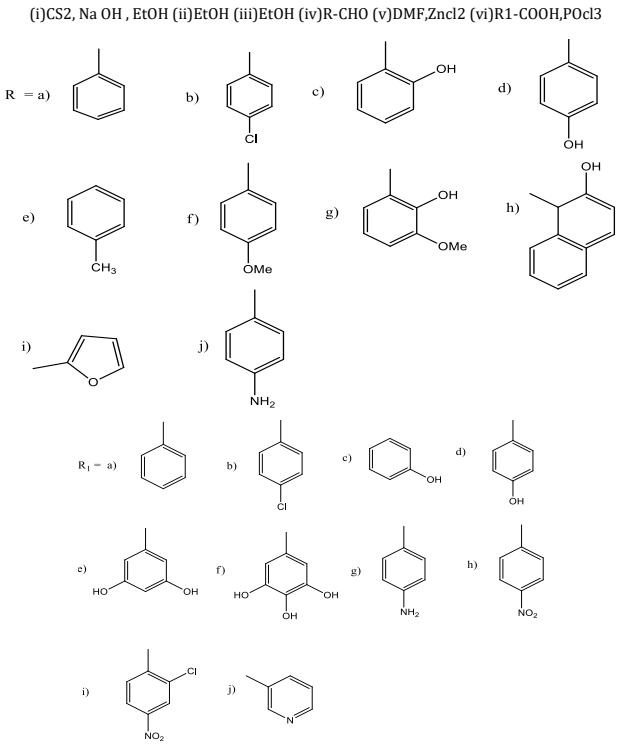
*In dilute sodium hydroxide solution, 2(3H)-benzimidazolone is difficult to dissolve. It is insoluble in dilute hydrochloric acid, but soluble in slightly warmed concentrated hydrochloric acid. In dilute acids, 2-benzimidazolecarboxylic acids dissolve easily.

*The molecular weight of a number of benzimidazoles was calculated using freezing point data in naphthalene solution at various concentrations. In compounds with an unsubstituted NH grouping, evidence of molecular association was obtained via N-H-N bonds. The resonance of the benzimidazole nucleus clearly strengthens this bond. Substances that have an alkyl, aryl, acyl, or amino group substituted in the 1-position are not highly associated.

SYNTHESIS OF 2-MERCAPTOBENZIMIDAZOLE



Scheme1.Synthesis of 1,3,4-Oxadiazole and 4-thiazolidinone derivatives[15]



All of the compounds prepared herein were tested for potential biological activities such as antibacterial, antifungal, and cytotoxic activity. The study uses gram-positive bacterial strains like Staphylococcus aureus [ATCC-25923] and Enterococcus faecalis [ATCC-29212], gram-negative strains like Klebsiella pneumoniae [ATCC-13883] and Escherichia coli [ATCC-25922], and fungal strains like Candida albicans [ATCC-10145] and Aspergillus fumigatus [36607]. The minimum inhibitory concentrations (MICs) were defined as the lowest concentrations of compounds that prevented visible growth. The solvent was found to have no antimicrobial activity against any of the test microorganisms.

ANTI-BACTERIAL ACTIVITY:

Table 1 shows the MIC values for the compounds 5a–j, 6a–j, and the standard in vitro anti-bacterial studies. All of the compounds demonstrated good anti-bacterial activity against Gram positive bacteria like S. aureus and E. faecalis, as well as Gram negative bacteria like K. pneumoniae and E. coli, when compared to the control drug ciprofloxacin. Among the synthesised compounds, 5b, 5d, 5i, 6b, 6e, 6f, and 6i demonstrated very good to moderate activity against all bacterial strains, with MIC values ranging from 16–2 mg/mL. The activity was greatly influenced by the electron withdrawing nature of the aromatic ring substituents –NO2, –Cl, and –OH. It was discovered that as the number of –OH groups increased, so did the activity, which could be seen for compound [15].

Table 1: In vitro anti-bacterial activity of compounds 5a-j and 6a-j in MIC (ug/ml)[15].

Comp	S. aureus (25923)[a]	E. faecalis (29212)	K. pneumonia (13883)	E. coli
5a	16.125	31.25	62	31.25
5b	4	8	8	8
5c	16.125	62.5	4	16.125
5d	8	8	16.125	16.125
5e	62.5	62.5	31.25	31.25
5f	31.25	31.25	62.5	31.25
5g	62.5	16	2	16.125
5h	31.25	31.25	31.25	31.25
5i	16.125	16.125	16.125	16.125
5j	62.5	62.5	16.25	31.25
6a	125	125	62.5	62.5
6b	4	4	2	8
6c	8	8	16.125	8
6d	8	8	16.125	8
6e	4	4	2	4
6f	1	1	1	2
6g	62.5	62.5	31.25	62.5
6h	16.125	16.125	16.125	8
6i	8	2	4	4
6j	31.25	62.5	125	62.5
ciprofloxacin	0.78	0.7	0.19	0.19

ANTI-FUNGAL ACTIVITY:

Table 2 shows the MIC values for the compounds 5a–j, 6a–j, and the standard in in vitro antifungal studies. Among the test compounds, 5b, 5c, 5d, 5g, 5i, 6b, and 6i induced significantly higher antifungal activity against Candida albicans and Candida fumigatus than standard fluconazole, with MIC values ranging from 8–2 mg/mL. Compounds 5e, 5f, 5h, 6a, 6g, and 6j had at least 62–125 mg/mL of activity against both fungi. The presence of an OH group, as per fluconazole's structural demand, was responsible for the increase in activity of these compounds. The presence of halogen–Cl and the electron withdrawing group–NO2 also had an equal impact on the activities [15].

Table 2: In vitro anti- fungal activity of compounds 5a-j and 6a-j in MIC (ug/ml) [15].

Comp	C. albicans (10145)[a]	A. fumigatus (36607)
5a	62.5	62.5
5b	16.125	8
5c	16.125	4
5d	8	8
5e	62.5	125
5f	125	62.5
5g	16.125	16.125
5h	31.25	31.25
5i	16.125	16.125
5j	16.125	31.25
6a	31.25	62.5
6b	4	8
6c	8	8
6d	4	8
6e	4	2
6f	2	2
6g	62.5	62.5
6h	4	8
6i	4	4
6j	31.25	62.5
fluconazole	2	2

ANTI-CYTOTOXICITY ACTIVITY:

Using the protocol [16], all of the synthesised compounds 5a–j and 6a–j was tested for cytotoxicity (brine shrimp bioassay). Table 3 shows that compounds 5b, 5g, 5i, 6b, 6f, 6h, and 6i had potent cytotoxic activity against Artemia salina, while the other compounds had moderate activity. In the current series of compounds, compound 6f had the highest activity (LD50 of 14.6.330 104 M). Thus, structure-activity relationship studies of these compounds revealed that R and R1 with functional groups-Cl, -OH at 2,3, or 4 positions and -NO2 at position showed good cytotoxicity.

Table 3: Brine shrimp data compounds 5a-j and 6a-j[16].

Comp	LD_{50}(Mm)
5a	3.425
5b	0.5825
5c	4.28
5d	3.725
5e	3.21
5f	2.458
5g	0.5616
5h	2.023
5i	0.5616
5j	3.72
6a	4.789
6b	0.6221
6c	4.39
6d	4.781
6e	3.693
6f	0.633
6g	5.23
6h	0.5628
6i	0.5956
6j	5.616

CONCLUSION:

The goal of this study is to synthesise thiazolidinone and oxadiazole-containing benzimidazole derivatives and test them in various bioassays in the hopes of discovering new structural leads that could be used as broad-spectrum pharmacological agents. Among the synthesised compounds, 5b, 6b, 6e, and 6f were found to be highly antimicrobial active, with excellent MIC values when compared to reference drugs such as ciprofloxacin and fluconazole. SAR studies revealed the importance of the OH function in the target compounds, which demonstrated very promising in-vitro activities. Compounds with Cl, NO2, and OH functional groups exhibited appealing cytotoxicity.

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