



A REVIEW ON THERAPEUTIC AND SYNTHETIC STUDIES OF BENZOTHIAZOLE AS MOLECULAR TEMPLET FOR MEDICINES.

Mukta Ojha^{1*}, Rachna Yadav², Jatolia S.N.³

Abstract:

Benzothiazole (1, 3-benzothiazole) is one of the heterocyclic compounds, which is a weak base having varied biological activities. The unique methine center present in the thiazole ring makes benzothiazole as the most important heterocyclic compound. Various compounds such as hormones, alkaloids antibiotic, essential amino acids, hemoglobin, vitamins, dyestuffs and pigments have heterocyclic structure. In this review an extensive literature survey over the last decenary describes the role of benzothiazole (heterocyclic compounds) derivatives in the sector of medicine and pharmaceutical. The Delta and Omicron variants have also made the situation more challenging. To overcome this critical situation thiazole/thiadiazol /benzothiazole based thiazolidin-4-one is the most active compound with the higher inhibitory capacity to SARS-CoV-2 protease have been reported Such compounds are effective against various types of cancer cell lines through a legion of mechanisms.

Keywords: Benzothiazole, Heterocyclic compounds, Medicinal Properties.

^{1*,2}Dept. of chemistry S K D University Hanumangarh Rajasthan.

³Govt. Dungar College Bikaner Rajasthan, India. Email id: satyanarayanjatolia@gmail.com

***Corresponding Author:** Mukta Ojha

*Dept.of chemistry S K D University Hanumangarh Rajasthan.

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INTRODUCTION

Heterocyclic¹ can be easily classified based on their electronic structure. Heterocyclic compounds are primarily classified as saturated and unsaturated. The saturated heterocyclic compounds behave like the acyclic derivatives with modified steric properties². Piperidine and tetrahydrofuran are the conventional amines and ethers of this category., unsaturated heterocyclic compounds of 5- and 6- member rings have been studied extensively because of their unstrained nature. The unstrained unsaturated heterocyclic compounds include Pyridine, Thiophene, Pyrrole, Furan and their benzo fused derivatives. Quinoline, Isoquinoline, Indole, Benzothiophene, and Benzofuran are some important examples of benzo fused heterocycles. Heterocyclic compounds have a wide application in pharmaceuticals, agrochemicals and veterinary products. Among them, sulphur and nitrogen containing heterocycles¹ have attracted the attention of chemical and pharmaceutical research because their unique structural systems are the core structure of many pharmaceuticals and bioactive natural products, which makes them therapeutically interesting. Therefore, nitrogen and Sulphur containing five-membered thiazole ring is an important heterosystem and its derivatives² have emerged as active pharmaceutical ingredients in several drugs due to their potential antiinflammatory,³ antitumor,⁴ antihyperlipidemic,⁵ and antihypertensive⁶ properties, among several other biological properties.⁷

STRUCTURAL ANALYSIS OF BENZOTHAZOLE DERIVATIVES IN MEDICINAL ASPECTS

As a privileged heterosystem, benzothiazole is present as a core structure in many pharmaceuticals and agrochemicals that exhibit remarkable biological activities.⁸ Benzothiazoles find their applications in drug discovery and development for the treatment of diabetes,⁹ epilepsy,¹⁰ inflammation,¹¹ amyotrophic lateral sclerosis,¹² analgesia,¹³ tuberculosis,¹⁴ and viral infections.¹⁵

2-Aminobenzothiazole derivatives : 2-Aminobenzothiazole derivatives are also well-known motifs in medicinal chemistry due to their broad applications in drug development for treatment of allergies, hypertension, inflammation, and bacterial infections¹⁶ as well as displaying high affinity for the neuropeptide Y5 (NPY5) receptor for the treatment of nutrition disorders such as obesity and hyperphagia.¹⁷

Riluzole: Riluzole, 2-amino-6-trifluoromethoxy benzothiazole, is a highly specific blocker of inactivated Na channels,¹⁸ and used to cure amyotrophic lateral sclerosis). (Figure-2.1)

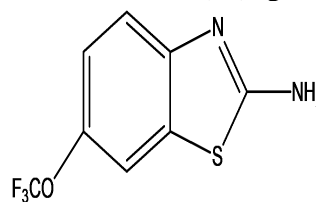


Figure.2.1

• **R116010 :** R116010, a potent and selective inhibitor of the all-*trans*retinoic acid metabolism, reduces tumour growth in breast and prostate cancer¹⁹ (Figure-2.2).

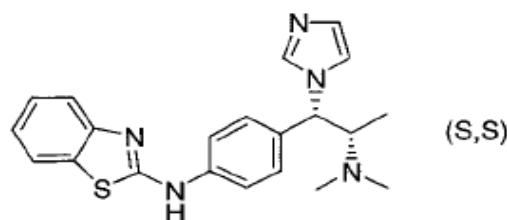


Figure-2.2

• **2-(4'-Amino-3'-methylphenyl)/AMPB:** 52-(4'-Amino-3'-methylphenyl) benzothiazole (AMPB)²⁰ has been reported to exhibit anticancer activity against a variety of cancers including breast cancer, ovary and kidney cancers in animal studies (Figure-2.3).

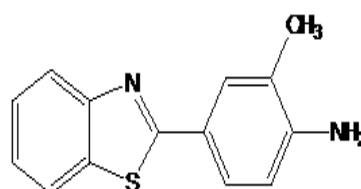
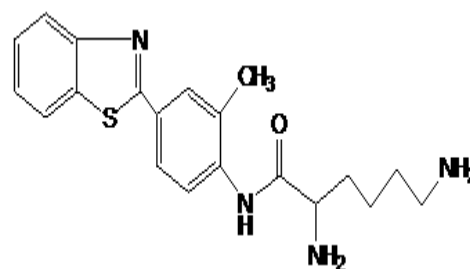


Figure-2.3 AMPB

• **Phortress:** Phortress with benzothiazole structural system has shown effective anticancer activity against xenografts in two different rodents models²¹ (Figure-2.4)



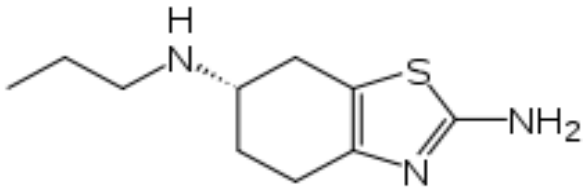
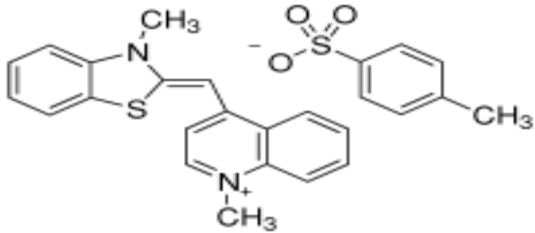
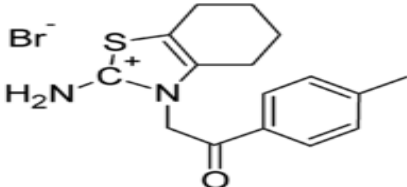
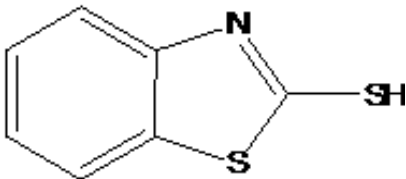
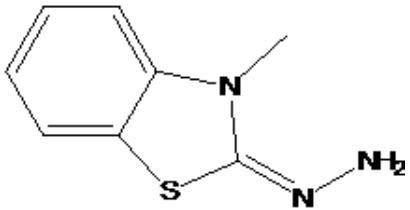
Phortress (Figure-2.4)

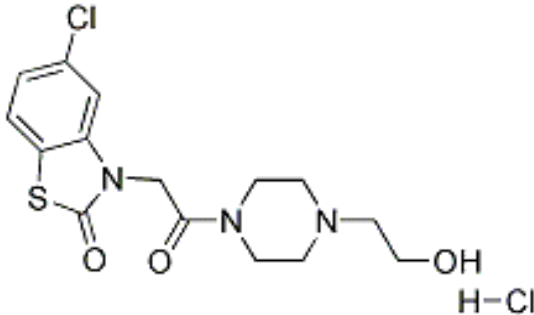
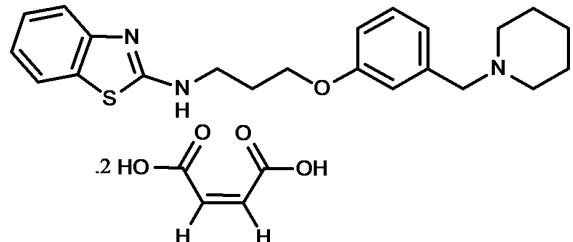
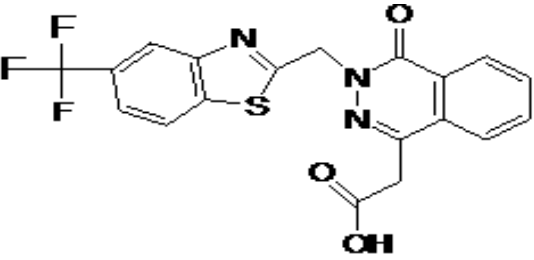
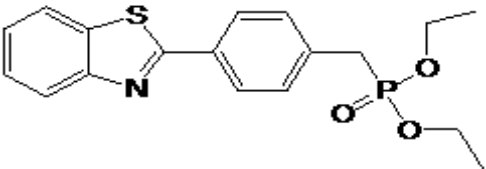
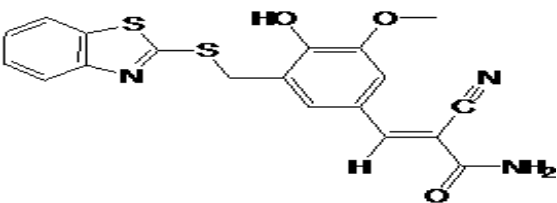
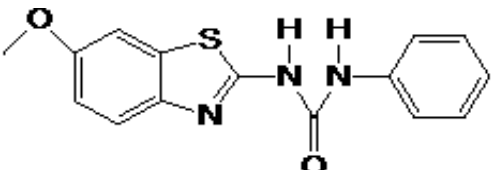
RADIOLABELLING OF BENZOTHAIAZOLE DERIVATIVES

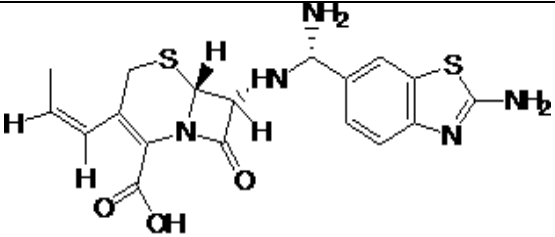
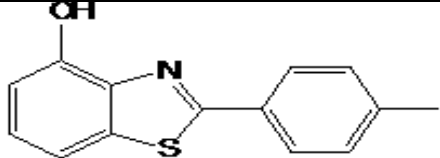
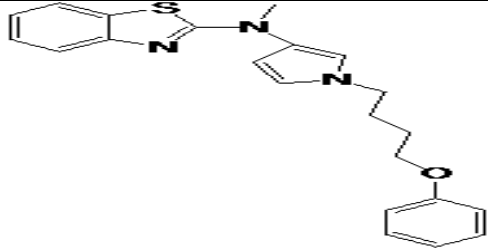
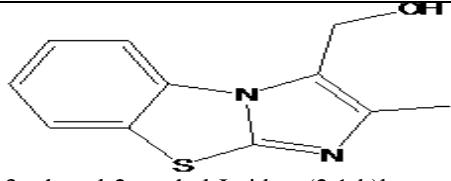
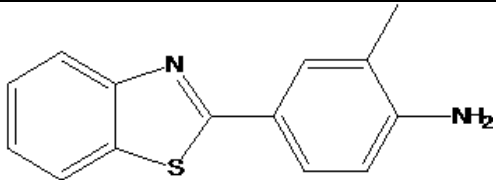
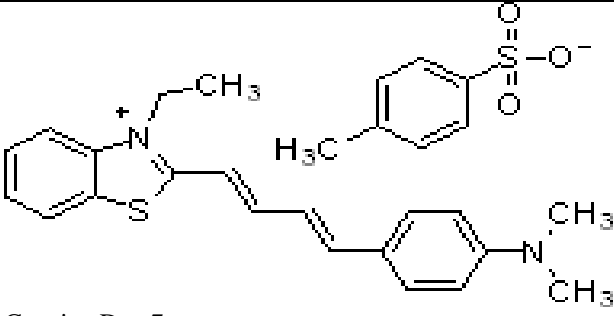
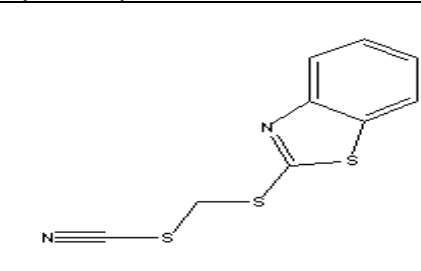
Recently radiolabelling of benzothiazole derivatives has been developed for PET imaging in the detection of alzheimer diseases²². 2-Aminobenzothiazoles and its derivatives, on the other hand, have been used as precursors for the

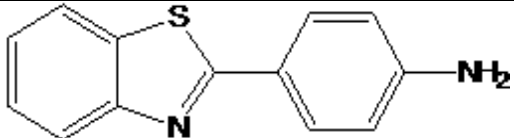
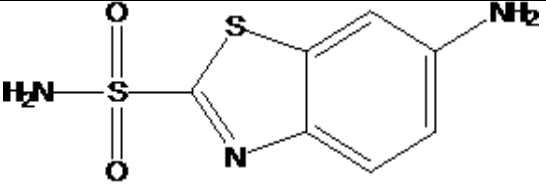
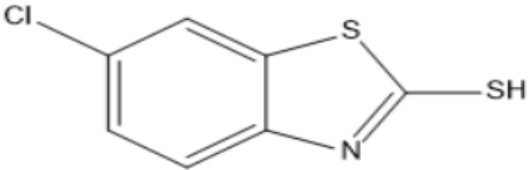
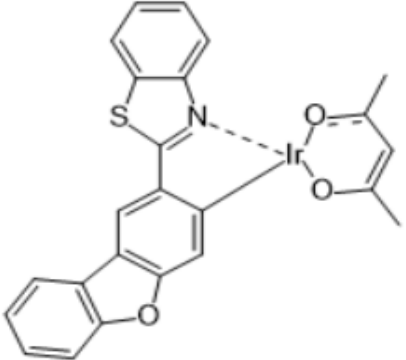
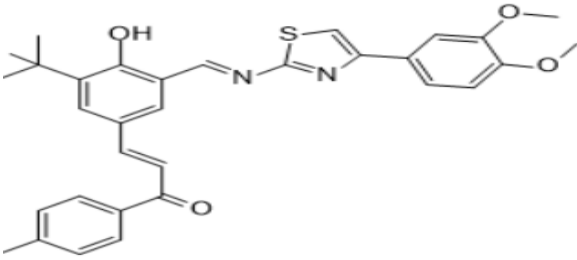
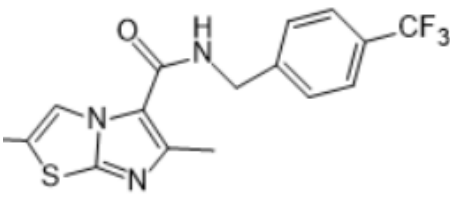
synthesis of many bioactive molecules for a long time.²³ They have also been considered as one of the key building blocks in drug discovery and more than 500 structures of diverse pharmaceuticals containing 2-Aminobenzothiazole moiety are reported in the Derwent World Drug Index.²⁴

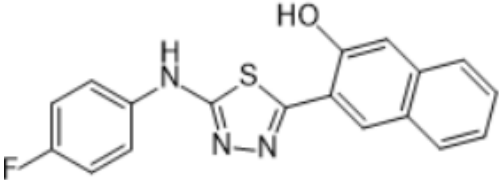
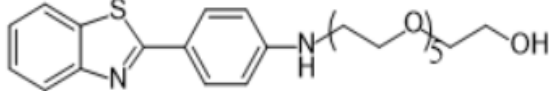
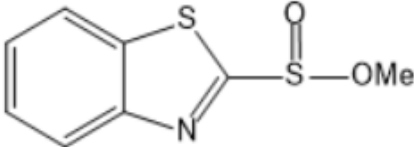
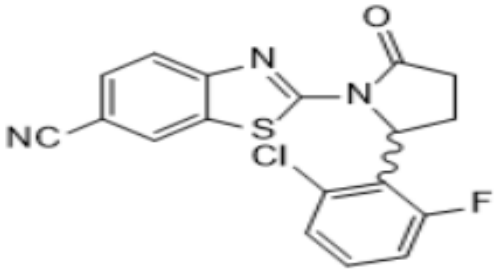
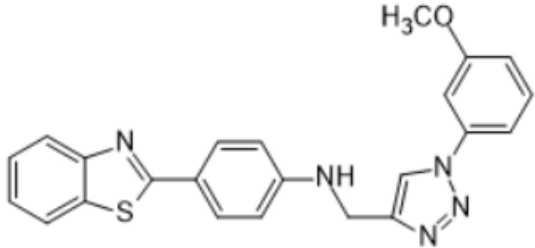
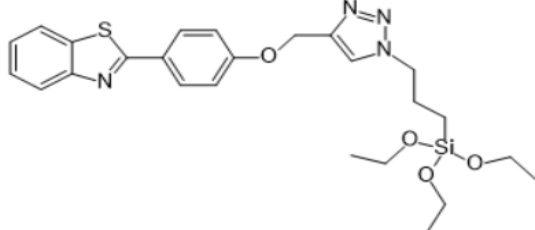
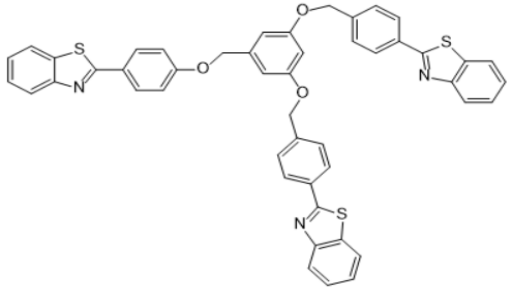
Table 2.1: Various activities of Benzothiazoles.

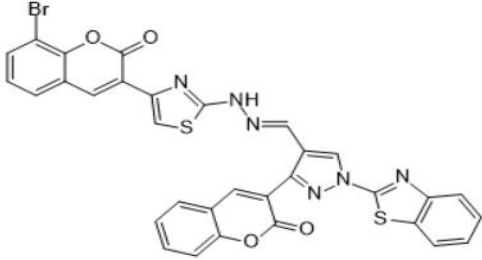
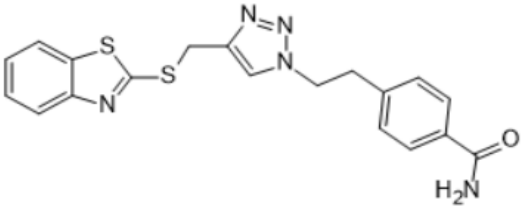
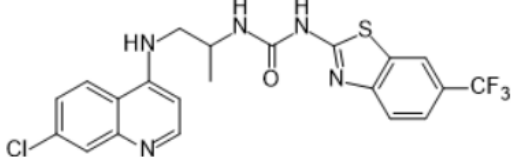
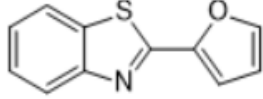
Benzothiazoles	Biological Activity	Reference
 <p>Pramipexol</p>	antioxidants, antiparkinson agents, dopamine agonists	25
 <p>Thiazole orange</p>	reticulocyte analysis fluorescent dyes	26
 <p>Pifithrin</p>	inhibitor of p53 transcriptional activity	27
 <p>2-Mercaptobenzothiazole</p>	antifungal agents	28
 <p>3-methyl-2-benzothiazolone hydrazone</p>	estrogens determination	29

 <p>4-[(5-chloro-2-oxo-2H-benzothiazol-3-yl)acetyl]piperazine-1-ethanol monohydrochloride</p>	<p>anti-inflammatory agents, non-steroidal ; bronchodilator agents</p>	<p>30</p>
 <p>Zolantidine</p>	<p>histamine H2 antagonists</p>	<p>31</p>
 <p>Zopolrestat</p>	<p>enzyme inhibitors, hypoglycemic agents</p>	<p>32</p>
 <p>Fosfedil</p>	<p>calcium channel blockers</p>	<p>33</p>
 <p>Tytrphostin AG825</p>	<p>tyrosine kinase inhibitor</p>	<p>34</p>
 <p>Frentizole</p>	<p>immunosuppressive, azathioprine</p>	<p>35</p>
	<p>cephalosporin, antibacterial</p>	<p>36</p>

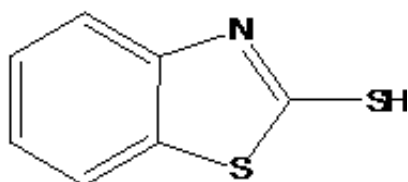
 <p>Bay v</p>		
 <p>4-hydroxy-2-(4-methylphenyl)benzothiazole</p>	anti-rheumatic agent	37
 <p>2-Benzothiazolamine,N-methyl-N-(1-(4-phenoxybutyl)-1H-pyrrol-3-yl)</p>	anti-ischemic compounds	38
 <p>3-ethanol-2-methyl-Imidazo(2,1-b)benzothiazole</p>	antisecretory, antiulcer activities	39
 <p>NSC 674495 2-(4-amino-3-ethylphenyl)benzothiazole</p>	antitumor	40
 <p>Cyanine Dye 7</p>	photo-voltage induction	41
 <p>2-(Thiocyanomethylthio)benzothiazole</p>	biocide	42

 <p>2-(4-Aminophenyl)benzothiazoles,</p>	anti-tumour activity	43
 <p>6-amino-2-benzothiazole sulfonamide</p>	topical carbonic anhydrase inhibitor	44
 <p>6-chloro-1,3-benzothiazole-2-thiols</p>	antifungal and antibacterial activity	45
 <p>2-dibenzofuran-2-yl benzothiazole bis-cyclometalated iridium(III) [Ir(O- bt)2(acac)].</p>	Yellow OLED	46
 <p>chalcone-Thiazole</p>	antibacterial activity	47
 <p>imidazole[2,1-b]thiazole-5-carboxamides</p>	anti-tuberculosis	48

 <p>1,3,4-thiadiazole</p>	<p>antimicrobial activity</p>	<p>49</p>
 <p>Benzothiazole amphiphiles</p>	<p>Treat Alzheimer's disease other Aβ-related neurologic diseases</p>	<p>50</p>
 <p>methyl benzothiazole sulfinate</p>	<p>slow and sustained SO₂ release at physiological pH</p>	<p>51</p>
 <p>Benzothiazole derivative</p>	<p>inhibitory activity against main protease of SARS-CoV-2</p>	<p>52</p>
 <p>2-(4-aminophenyl) benzothiazole triazole derivatives</p>	<p>Anticancer activity</p>	<p>53</p>
 <p>Synthesis of benzothiazole derived silane</p>	<p>anti-parasitic, anti bacterial and anti oxidant activity</p>	<p>54</p>
 <p>tris(benzothiazole)</p>	<p>Anticancer activity</p>	<p>55</p>

 <p>8-bromocoumarinyl</p>	<p>Antibacterial activity</p>	<p>56</p>
 <p>4-((4-((benzo[d]thiazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzamide</p>	<p>Anti-inflammatory activity</p>	<p>57</p>
 <p>quinoline-urea-benzothiazole hybrid</p>	<p>antitubercular inhibitory activity</p>	<p>58</p>
 <p>2-(Furan-2-yl) benzothiazole</p>	<p>Anti-oxidant and anti-tumor activity</p>	<p>59</p>

2-mercapto-1,3-benzothiazole isosteres: 2-mercapto-1,3-benzothiazole isosteres were screened for their in vitro antibacterial and antifungal activities. Results revealed that the presence of the mercapto moiety at the 2-position of the heterocyclic nucleus is important for activity against bacteria and 6-substituted-1,3-benzothiazole-2-thiols as the most auspicious compound as antifungal against *Candida albicans* and *tropicalis*⁶⁰.



2-mercapto-1,3-benzothiazole

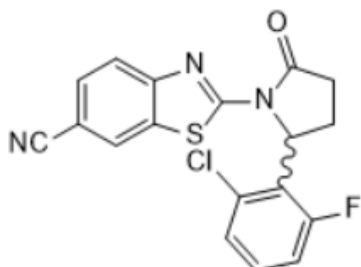
• BENZOTHAZOLE DERIVATIVES APPLICATIONS IN SYNTHETIC CHEMISTRY

- 2-dibenzofuran-2-yl benzothiazole bis-cyclometalated iridium-(III), [Ir(O-bt)₂(acac)],

yellow OLED with CIE coordinates of (0.45, 0.52) have been reported so far. The good performance indicates the potential application of these iridium complexes in large-scale OLED⁶¹. A library of new hybrids possessing chalcone and thiazole compounds were synthesized and reported for their antibacterial activities against *Staphylococcus aureus*.⁶² Anti-tuberculosis activity against *Mycobacterium tuberculosis* have been showed by imidazo[2,1-b]thiazole-5-carboxamides.⁶³ Anti-microbial activity of 1,3,4-thiadiazole have been determined by using the Lipinski's Rule⁶⁴. Benzothiazole amphiphiles have been reported for treating amyloid- β induced cell damage associated with Alzheimer's disease⁶⁵.

- Sulfur dioxide (SO₂) has been contemplated a noxious environmental pollutant and byproduct of industrial processing. At recent time, it may also have wide role in mammalian pulmonary systems. However, there will be a problem in managing SO₂ in an authentic manner. To overcome this difficulty slow and sustained SO₂ release by benzothiazole sulphinate at physiological pH have been reported. At present time, COVID-19 has spread worldwide

and the Delta and Omicron variants have also made the situation more challenging. To overcome this critical situation thiazole/thiadiazole/benzothiazole based thiazolidin-4-one is the most active compound with the higher inhibitory capacity to SARS-CoV-2 protease have been reported⁶⁶.



Inhibitory activity against main protease of SARS-CoV-2

CONCLUSION: -

Benzothiazole is a molecular templet for this decennary in the area of medicine as well as synthetic purpose in chemical sciences. Benzothiazole is used for various kind of disease i.e., anticancer drugs, tuberculosis, antidiabetic drugs, etc. even in corona times the higher inhibitory capacity to SARS-CoV-2 protease have been reported. This inclusive review will be highly useful to the researchers working in area of medicinal and chemical sciences. They can do research for methods of synthesis of benzothiazole more derivatives as it has a scaffold heterocyclic ring so that society will get rid of the scary diseases. They can further explore this class to increase the domain of existing biological activity contour.

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