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REVIEW

Biological Activities of Schiff Bases Incorporating Benzothiazole Moiety

Archana Ratnakar Baraskar[1], Ratnamala P. Sonawane[1,✉], Nilesh Kshirsagar[1] and Sultan Pathan[2,✉]

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ABSTRACT

The functionalization of organic molecules with the Schiff bases having benzothiazole moiety has grown rapidly due to its multiple therapeutic and pharmacological properties. They have driven enormous studies on their stereochemistry, bioactivity and synthetic attempts. The benzothiazole moiety is infinitesimal but broadly used for industrial purposes and also exhibits a broad range of biological activities. Study carried out on Schiff bases having benzothiazole had well-known promising activities like antimicrobial, antimalarial, antifungal, antitubercular, antiviral, antitumor, analgesic, anti-inflammatory and many more. This review brings forward a systematic and comprehensive survey of the reactivity and biological properties associated with the Schiff bases-benzothiazole derivatives and their analogs.

KEYWORDS

Benzothiazoles, Biological activities, Heterocycles, Schiff base, Thiazole, Synthesis.

INTRODUCTION

The benzothiazole is a privileged heterocyclic scaffold having a benzene ring fused with a five-membered thiazole ring. This benzothiazole-moiety is very small but widely used for industrial purposes and also exhibits a broad range of biological activities. The related research and developments in benzothiazole-based medicinal chemistry have become a rapidly developing and increasingly active topic. The potential of benzothiazole in the management of various types of cancers such as ovarian, prostate, central nervous system, renal, gastric, pancreatic, liver, breast and colon cancers. Also, the SAR studies revealed that the anticancer activity of benzothiazole scaffolds depends upon the nature of substituent present in these molecules, being multifactorial and not always easy to rationalize. The plethora of research on the anticancer profile of benzothiazole derivatives and their rationalization based on the drug targets of these derivatives may be useful for the development of novel agents [1]. In 1887, 2-substituted benzothiazole was first synthesized by A.W. Hofmann then because of diversified activity as well as simple cyclization mechanism; number of synthetic routes has been reported. 2-Substitued benzothiazole has emerged in its usage as a core structure in the diversified therapeutically applications. The studies of SAR interestingly

Author affiliations:

[1]The Institute of Science, Dr. Homi Bhabha State University, Mumbai-400032, India
[2]Department of Chemistry, Bhupal Nobles' University, Udaipur-313001, India

✉To whom correspondence to be addressed:

E-mail: archanabaraskar94@gmail.com; pathansultan83@gmail.com

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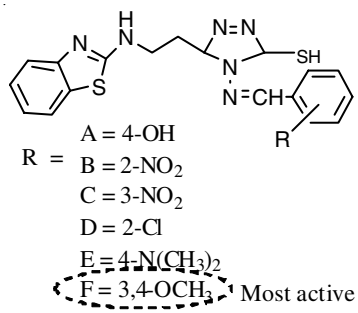

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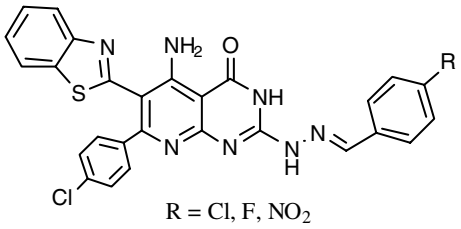

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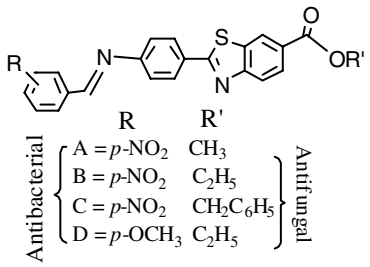

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reveal that change of the structure of substituent group at C-2 position commonly results the change of its bioactivity [2].

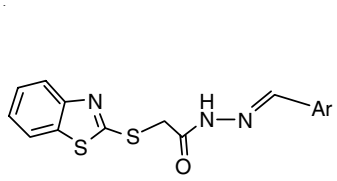
Schiff bases are the compounds containing an azomethine group (-CH=N-), which were reported in the 19th century by German scientist Hugo Schiff [3] and are formed by the condensation of a primary amine with a carbonyl compound. Schiff bases of aliphatic aldehydes are less stable as compared to those of aromatic aldehydes with an effective conjugation system [4]. Schiff bases having benzothiazole are the most important heterocyclic compounds, which have attracted strong interest due to their biological and pharmacological properties. The substituted benzothiazole compound fascinated by its hidden potential. Since then, a range of methods for the synthesis of Schiff bases has been described. A pleasant comprehensive review was reported by Keri *et al.* [5] on current developments of benzothiazole-based molecules in medicinal chemistry. Different studies describe the *N*-heterocyclic ring system is a core structure in many synthetic compounds exhibiting a broad range of biological activities. The studies of these compounds suggested that they showed their antitumor activities through multiple mechanisms including inhibiting protein kinase (CDK, MK-2, PLK1, kinesin-like protein Eg5 and IKK), topoisomerase I and II, microtubule inhibition and many others [6].

Pharmacological activities

Antimicrobial activities: Antimicrobial activity is the most important characteristic of medical textiles, to provide an adequate protection against microorganisms, biological fluids and aerosols, as well as disease transmission. Microbial infections are becoming the salient issue for worldwide health. These infections can range from common cold, cough, typhoid, malaria, cholera to even some severe disease conditions like tuberculosis and AIDS. The researches carried out on benzothiazole moiety had established promising antimicrobial activities like antimalarial, antifungal, antitubercular, antiviral as well as antitumor, analgesic and anti-inflammatory activities.

Schiff bases of benzothiazole-triazole derivatives, compound were reported by Soni *et al.* [7] and evaluated for their antimicrobial activities against a group of bacterial and fungal stains. From the activity studies, it was concluded that among all the derivatives (**1**) shows antibacterial activity increases with *p*-substitution *i.e.*, 4-OH, 4-N(CH_3)$_2$, 3,4-OCH_3) and decreases when there is *o*-substitution *i.e.*, 2-NO_2, 2-Cl and vice versa for antifungal activity. Benzothiazole-pyrimidine conjugated derivatives reported as microbial agents (**2**), have an excellent antibacterial and antifungal activities. The compounds having electron-withdrawing substituents on the aromatic ring displayed greater antibacterial activity [8]. 4-(Benzylideneamino)phenyl substituents at position-2 and different carboxylate substituents at position-6 (**3**) were synthesized by Pande *et al.* [9] with a view of enhancing the antimicrobial and antifungal activity.

The possible effective molecules were designed and studied by incorporating the oxadiazole into the benzothiazole derivatives (**4**) for their antimicrobial activity. The activity was found to be better in ligands with electron donating substituent on the aromatic ring *i.e.* hydroxyl group present at 2nd and 4th position, amino group present at 4th position and methoxy group at 3rd position. Ligand with furan ring on the side chain also had shown comparably good antimicrobial activity with the standard [10]. Patil *et al.* [11] explains the antibacterial activity of azomethine compounds, synthesized from 2-amino benzothiazoles and 4-chlorobenzaldehyde. These compounds were screened for their antibacterial activities against strain of bacteria *E. coli* and *S. typhi* using disk diffusion method. Waghamode and Shinde [12] synthesized some benzothiazole-dihydropyrimidin-2-thiones derivatives (**5**) which were studied for their antibacterial activity against Gram-positive and Gram-negative bacterial culture following agar gel diffusion procedure and they found that, the entire synthesized compound possessed good antibacterial activity.



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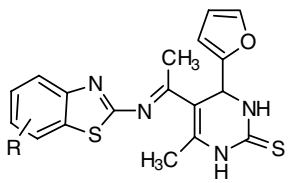

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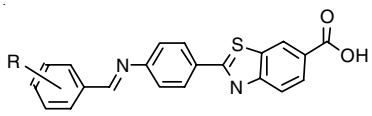
A number of derivatives (**6**) were synthesized from *p*-nitrobenzothiazole carboxylic acid by Jacobson synthesis has shown significant antibacterial activity with the reference standard ampicillin and ketoconazole. Compounds *m*-F, *p*-OCH_3, (4-F, 3-OCH_3), *p*-CH_3, *p*-OH have shown significant antibacterial activity against *S. aureus*, *B. subtilis*. Compound *p*-CH_3 was most significant against *E. coli*, *S. aureus* and *B. subtilis*. Also, significant activity of compound *p*-OCH_3, *p*-CH_3 against *Candida albicans* and *Aspergillus niger* was observed. While other compound shown less substantial activity against bacteria and fungi [13]. The compounds exhibited significant activity against microorganisms which were prepared from Schiff bases of 2-aminobenzothiazole, 4-aminosalicylic acid and 4-aminophenol. The results of antimicrobial screening indicate that

Schiff bases show significant activity against *S. aureus*, *E. coli*, *B. subtilis* than *A. niger* and *C. corda* while compound found to be more active against all tested bacterial strains because of the presence of chloro-group in the aldehydic group which itself is active against microbes [14]. The condensation of 6-nitrobenzothiazol-2-amine with aromatic aldehydes afforded N-(substituted benzylidene)-6-nitrobenzothiazol-2-amine (**7**). These derivatives have shown good antibacterial activity when compared with standard antibiotic ampicillin and no activity when compared with standard fluconazole [15].



R= H, *p*-Cl, *m*-F, *p*-NO_2, *p*-OCH_3 *p*-CH_3, *p*-OH, (4-F, 3-OCH_3)

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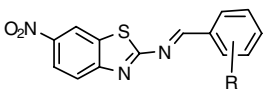
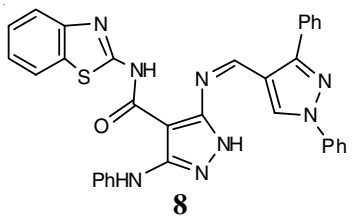


R= H, 2',5'-OCH_3, 3'-NO_2, 4'-OCH_3

7

Schiff bases and their derivatives with formazans have been synthesized using microwave method, which shown antimicrobial activity against *B. substilis, E. coli* and *S. aureus.* These compounds also exhibited the antifungal activity against *C. albicans* and *A. niger* by filter paper disc technique [16]. It is worth mentioning that incorporation of benzothiazole to pyrazole nucleus at position-3 *via* a carboxamide linker produced a high antimicrobial activity. The conversion of aminopyrazole to Schiff base (**8**) enhances the antimicrobial activity. High biological activity can be correlated with low electron density of ring systems. They were also evaluated for their *in vitro* antifungal potential against *F. oxysporum* and *A. fumigatus* fungal strains. Chloroamphenicol, cephalothin and cycloheximide were used as standard antibacterial and antifungal agents, respectively. Compounds that showed significant growth inhibition zones (> 12 mm) using the twofold serial dilution technique, were further evaluated for their minimal inhibitory concentrations (MICs) [17].



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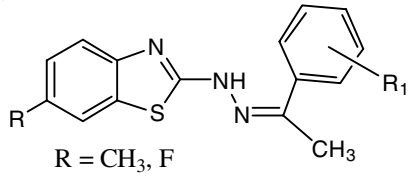
Schiff bases of 2-hydrazinobenzothiazole derivatives (**9**) were synthesized and screened for their antibacterial activity against *E. coli*, *S. aureus* and *B. cereus*. They were also examined for their antiquorum-sensing activity against *Chromobacterium violaceum* ATCC-12472, which showed moderate activity. The cytotoxicity of the synthesized compounds was performed against cervical cancer (Hela) and kidney fibroblast cancer (COS-7) cell lines *in vitro* having IC_{50} values > 50 mM [18]. Alang *et al.* [19] synthesized derivatives of 2{(substituted)-1′-ethylhydrazinyl)}-6-methyl benzothiazole (**10**) and evaluated for their antibacterial activity. Novel *N*-2-benzothiazolyl-thiourea derivatives have been synthesized in order to examine their *in vitro* antimicrobial activities against various Gram-positive and Gram-negative microorganisms in comparison with drug ampicillin (**11**), exhibited an excellent activity against *P. aeruginosa* and *E. coli*, respectively [20].



R = CH_3, F

R_1 = 2-F, 3-F, 2-Cl, 4-OH, 2,5-$(OH)_2$, 3,4-$(OCH_3)_2$

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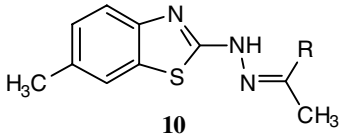

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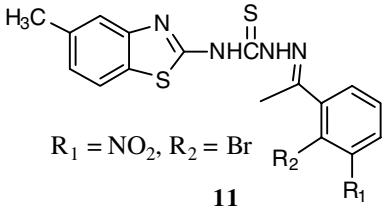
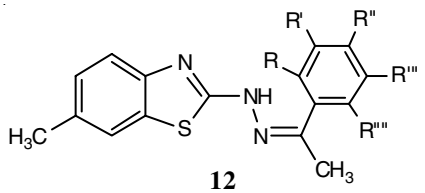


R_1 = NO_2, R_2 = Br

11

(*E*)-1-(1-(Substituted phenyl)ethylidene)-2-(6-methyl benzo[*d*]thiazol2-yl)hydrazine (**12**) were synthesized and evaluated against antifungal activity [21]. 6-Methyl-2(3*H*)-benzo-1,3-thiazolyl-1′-ethylidene-2-(*o*,*p*-substituted acetophenones) hydrazine analogs (**13**) were synthesized and evaluated against *Staphylococcus aureus* (MTCC 737), *Pseudomonas aeruginosa* (MTCC 424), *Escherichia coli* (MTCC 1687) and yeast-like fungi *Candida tropicalis*. The presence of –NO_2, –Br, –OCH_3 and –Cl groups to the substituted benzothiazole enhanced the antibacterial and antifungal activities [22].



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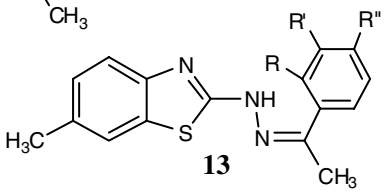

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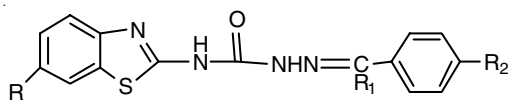
Anticonvulsant and neurotoxicity: Anticonvulsants are a diverse group of pharmacological agents used in the treatment of epileptic seizures. Anticonvulsants are also increasingly being used in the treatment of bipolar disorder and borderline personality disorder, since many seem to act as mood stabilizers and for the treatment of neuropathic pain. A series of 1,3-benzothiazol-2-yl-semicarbazones (**14**) synthesized and evaluated for their anticonvulsant, neurotoxicity and other toxicity studies by maximal electroshock method. Also, SAR study reveals that, substituents like –CH_3, –OCH_3 at the aryl ring with –NO_2 and unsubstituted distant phenyl ring lead to highly potent compounds having longer duration of activity. Majority of the compounds were active in MES screen. They were also checked for their lipophilic character [23].



a.) R=Cl, R_1=CH_3, R_2=H;
b.) R=CH_3, R_1=CH_3, R_2=NO_2;
c.) R=OCH_3, R_1= CH_3, R_2=NO_2;
d.) R=OCH_3, R_1=C_6H_5, R_2=H

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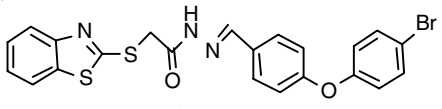
N^4-(Naphtha[1,2-*d*]thiazol-2-yl)semicarbazides which are active against tonic convulsions induced by electrical and chemical stimuli in mice and rats. Biochemical study showed that preventing oxidative injury by semicarbazides produces important neuroprotective and anticonvulsive effects against PTZ-induced NT [24]. Benzothiazol-2-yl-hydrazones (**15**) showed the good anticonvulsant activity, especially compound **15**, which showed 75% protection (3/4, 1.0 h) and 50% protection (2/4, 0.5 h) at a dose of 100 mg/kg in mice. The presence of 4-bromo phenyl in 1,3-benzothiazol-2-yl-acetohydrazones showed good anticonvulsant activity [25]. Schiff bases of benzothiazol-2-ylamine and thiazolo[5,4-*b*]pyridin-2-ylamine were synthesized, characterized and screened for their anticonvulsant activity using maximal electroshock (MES) test and isoniazid (INH) induced convulsions test. *In silico* toxicity profiling of all the synthesized compounds was done through "Lazar" and "Osiris" properties explorer. Compound benzothiazol-2-yl-(1*H*-indol-2-ylmethylene)amine (**16**) was the most potent member of the series against both types of convulsions [26].



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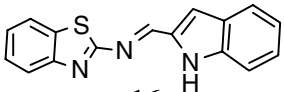

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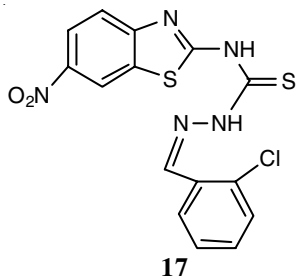
6-Substituted benzothiazolyl-2-thiosemicarbazones were synthesized and screened for anticonvulsant activity in maximal electroshock induced seizure (MES) and subcutaneous pentylenetetrazole (scPTZ) induced seizure models in mice. The neurotoxicity was assessed using the Rotorod method. 6-Methylbenzothiazolyl-2-thiosemicarbazones showed anticonvulsant activity in both mice i.p. and rat oral MES screen. 6-Nitrobenzothiazolyl thiosemicarbazone derivative (compound **17**) emerged as the most promising one with anti-MES activity in mice i.p., rat i.p. and rat p.o. evaluations. The isatinimino derivatives had shown better activity when compared to the benzylidene or acetophenone derivatives [27].



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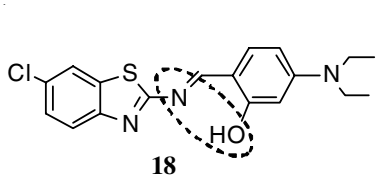
Anti-Alzheimer's agents: Alzheimer's disease is believed to occur when abnormal amounts of amyloid beta (Aβ), accumulating extracellularly as amyloid plaques and tau proteins or intracellularly as neurofibrillary tangles, form in the brain, affecting neuronal functioning and connectivity, resulting in a progressive loss of brain function. This altered protein clearance ability is age-related, regulated by brain cholesterol and associated with other neurodegenerative diseases [28]. Alzheimer's disease (AD) is a complex multifactorial syndrome. Metal chelator and Aβ inhibitor are showing promise against AD. Amyloid-β peptides and their metal-associated aggregated states have been implicated in the pathogenesis of Alzheimer's disease.

The synthesis of a small, neutral, lipophilic benzothiazole Schiff base, *E*-2-((6-chlorobenzo[*d*]thiazol-2-ylimino)methyl)-5-diethylamino)phenol (CBMDP) (**18**), explores its multifunctionalty as a potential metal chelator/fluorophore, by using UV-visible absorption, steady-state fluorescence, single molecule fluorescence correlation spectroscopic (FCS) techniques which is further verified by *in silico* studies [29]. Three small hybrid compounds (**19**) have been designed and synthesized utilizing salicylaldehyde based Schiff bases as the chelators and benzothiazole as the recognition moiety for Alzheimer treatment. These conjugates can capture Cu^{2+} from Aβ and become dimers upon Cu^{2+} coordination and show high efficiency for both Cu^{2+} elimination and Aβ assembly inhibition. Besides, the complexes have superoxide dismutase (SOD) activity and significant antioxidant capacity and are capable of decreasing intracellular reactive oxygen species (ROS) and increasing cell viability. All these results indicate that the multifunctional metal complexes, which have Aβ specific recognition moiety and metal ion chelating elements show the potential for Alzheimer treatment [30].



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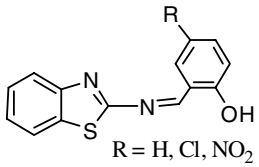

R = H, Cl, NO_2

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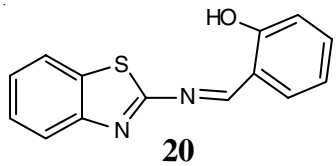
Anticancer activities: Cancers comprise a large family of diseases that involve abnormal cell growth with the potential to invade or spread to other parts of the body. They form a subset of neoplasms. A neoplasm or tumour is a group of cells that have undergone unregulated growth and will often form a mass or lump, but may be distributed diffusely. Kachwal *et al.* [31] tried to redefine the unexplored potentiality of benzothiazole type of Schiff-base which is well known as an active molecule (**20**) and exhibits excited-state intramolecular proton transfer (ESIPT). Interestingly, this compound shows ultrasensitivity and selectivity to the detection of Al(III) and is also capable of showing pH sensing. Further, it is tested for internalization in the cancerous cell with intracellular imaging.

Ma *et al.* [32] reported the synthesis of semicarbazone containing benzothiazole-Schiff base derivatives and evaluated their anticancer activity against four different cancer cell line such as human colon cancer cells (HT29), human lung cancer cell (H460), non-small cell lung cancer (A549) and human



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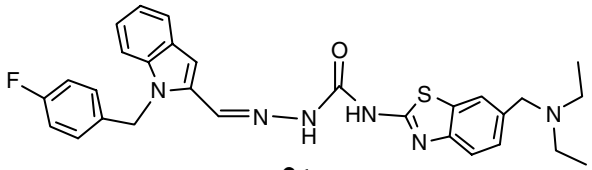
breast cancer (MDA-MB-231). Among these derivatives, the indole-based hydrazine carboxamide (**21**) showed potent antitumor activity with IC_{50} values of 0.015 mM for HT29, 0.28 mM for H460, 1.53 mM for A549 and 0.68 mM for MDA-MB-231. The structure-activity relationship (SAR) explained that compound exhibited the highest antitumor activity due to the presence of electron withdrawing groups *i.e.*, fluorine in the 4th position of benzyl ring. Osmaniye *et al.* [33] synthesized benzothiaole-Schiff base acylhydrazone derivatives and studied for their anticancer activities against rat brain glioma (carcinogenic C6) cell line, human lung adenocarcinoma epithelial (A549) cell line, human breast adenocarcinoma (MCF-7) cell line, human colorectal adenocarcinoma (HT-29) cell line and mouse embryo fibroblast (NIH3T3) cell line. The piperidine based acetohydrazide derivative (**22**) showed modest activity having IC_{50} value 1 < mM, 0.03 mM, 0.10 mM, 0.30 mM and 1 < mM for A549, HT-29, MCF-7, C6 and NIH3T3 cell lines respectively against reference drug cisplatin.



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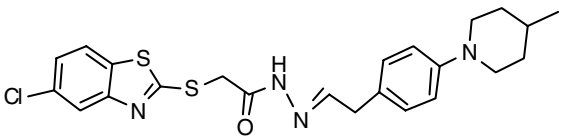

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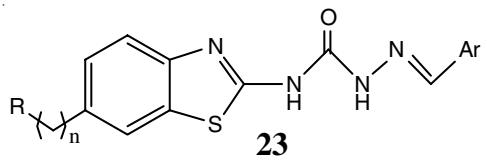
Benzothiazole derivatives bearing the *ortho*-hydroxy *N*-carbamoylhydrazone moiety (**23**) were synthesized and their cytotoxic activities against five cancer cell lines (NCI-H226, SK-N-SH, HT29, MKN45 and MDA-MB-231) were screened *in vitro*. Most of them showed moderate to excellent activity against all the tested cell lines. The structure-activity relationship (SAR) analyses indicated that the introduction of a lipophilic group (benzyloxy or heteroaryloxy group) at the 4-position of the 2-hydroxy phenyl ring was beneficial to antitumor activity and the presence of substituents containing nitrogen that are positively charged at physiological pH could also improve antitumor activity. It was also confirmed that the steric effect of the 4-position substituent of the benzyloxy group had a significant influence on cytotoxic activity [34].



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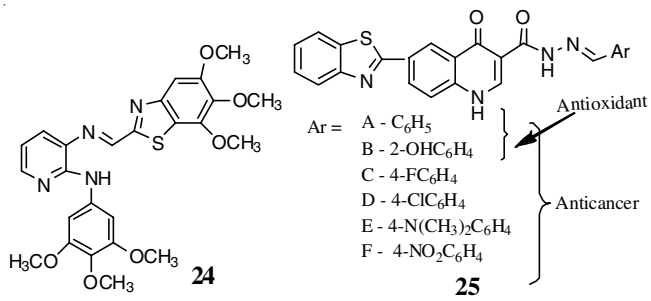
Furthermore, modifications of the benzothiazole scaffold could yield an improved cytotoxicity profile which has been demonstrated in a series of 2-anilinopyridinyl-benzothiazole Schiff base conjugates reported by Kamal *et al.* [35]. The binding energies of the docked molecules were better than the E7010 and the Schiff base with trimethoxy group on benzothiazole moiety was the best. Compound **24** exhibited good antiproliferative activity with a GI_{50} value of 3.8 µM specifically against the cell line DU145. In agreement with the docking results, compound **24** exerted cytotoxicity by the disruption of the microtubule dynamics by inhibiting tubulin polymerization *via* effective binding into colchicine domain, comparable to E7010. Furthermore, it induced apoptosis as evidenced by biological studies like mitochondrial membrane potential, caspase-3 and Annexin V-FITC assays. Derivatives of quinolone linked to the benzothiazole was synthesized by Abdelgawad *et al.* [36] and screened for their high to moderate anticancer activity (**25**, A-F). The 4-nitrobenzylidene (F) and 2-hydroxybenzylidine (B) showed antitumor activities against the MCF-7 cell line, having IC_{50} values of 0.058 mM and 0.052 mM, respectively. In addition, substituents like 2-hydroxybenzylidene (B) and benzylidene (A) derivatives shows good antioxidant activity.

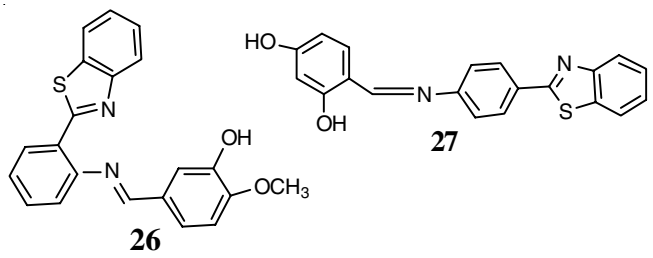


24 **25**

Ma *et al.* [37] reported an indole based benzothiazole-Schiff base derivatives and studied for their anticancer activities. Among all these derivatives, the chlorobenzyl indole-semicarbazide benzothiazole exhibited anticancer activity against four cancer cell lines such as HT-29, H460, A549 and MDA-MB-231. These derivatives showed IC_{50} values of 0.024 mM for HT-29, 0.29 mM for H460, 0.84 mM for A549 and 0.88 mM for MDA-MB-231, respectively. Cabrera-Perz*et al.* [38] designed and synthesized two benzothiazole compounds named *E*-5-(((benzothiazole-2-yl-imino)methylthio)methylamino)-2-hydroxybenzoic acid and S/E-2-((benzothiazole-2-ylimino)methylthio)methylamino)-3-(4-hydroxyphenyl)-propionic acid exhibited potent scavenging activity, resulting to increase in the reduced glutathione content and decrease in the malondialdehyde level. They were also effective in inhibiting cytochrome P_{450}, giving a protective effect against the reactive intermediary N-acetyl-*p*-benzoquinoneimine [38].

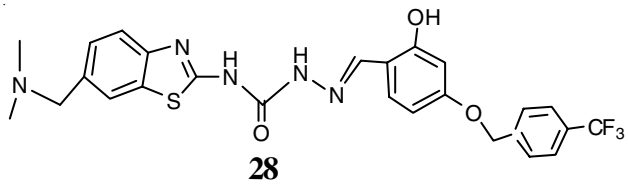
Arafath *et al.* [39] synthesized a potent drug (**26**) that shows the cytotoxic effect (IC_{50} = 34 µM) against HCT 116 cells with the highest selectivity index of 3.1 concerning the normal endothelial cells. The docking result of these compounds against hAChE showed potent activities with different binding modes. These compounds could be a promising pharmacological agent to treat cancer and Alzheimer's disease. Singh

et al. [40] designed and synthesized a series of novel Schiff bases-benzothiazole hybrids (compound **27**) for their anticancer activity by MTT assay and western blot method. Antiproliferative screening indicated that compound containing dihydroxy substituents had potent inhibitory activity with IC_{50} value 34 µg/mL against SKOV3, A2780-S and A2780-CR cell lines. It showed more potent cytotoxicity in combination with cisplatin and paclitaxel than alone in the selected cell lines (SKOV3, A2780 and A2780-CR models). The *in vitro* cytotoxicity of the compounds on IOSE 364 cell line was evaluated to establish the selectivity. Molecular docking study exhibited good binding against epidermal growth factor receptor, which was further ascertained by immuno blot assay using specific antibody against phosphorylated EGFR and thus unravelling the targeted anticancer mechanism [40].

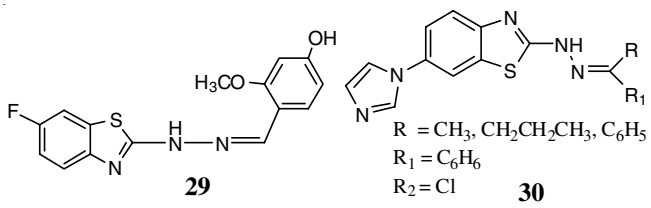


Schiff bases of 2-aminopyridine and 2-aminobenzothiazole were synthesized and evaluated for antioxidant potential using DPPH method and anti-hepatocellular carcinoma property using diethylnitrosamine (DEN) induced hepatocellular carcinoma rat model. Benzothiazol-2-ylimino)methyl)phenol could be a potential compound in fighting the oxidative damage of hepatic cells occurred due to the development of hepatocellular carcinoma induced by a chemical carcinogen, DEN. The *in silico* pharmacokinetic, rule of five and toxicity studies reveals that all the leads have an excellent intrinsic quality and sufficient structural features necessary for an oral activity. Molecular docking studies of all compounds into the ligand binding pocket of checkpoint kinase1 and vascular endothelial growth factor receptor-2 was also performed using Schrodinger software suite v8.5 and which have shown good Glide scores [41].

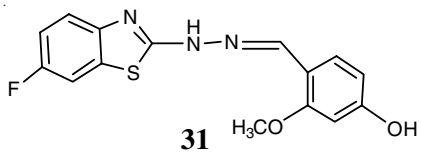
Shanthalakshmi *et al.* [42] designed and synthesized Schiff bases from *o*-vanilidine refluxing with 2-amino-6-chloro benzothiazole, 2-amino-6-bromobenzothiazole and 2-amino-6-methylbenzothiazole. The compounds were tested for DPPH radical assay and ABTS radical scavenging antoxidant activities. Among the synthesized compounds, *o*-vanilidine-2-amino-6-bromo benzothiazole shows IC_{50} value 248.82 µg/mL in DPPH assay and *o*-vanilidine-2-amino-6-chloro benzothiazole shows IC_{50} value 52.36 µg/mL in ABTS assay. Ma *et al.* [43] reported benzothiazole-Schiff base derivatives containing an *ortho*-hydroxy-*N*-acylhydrazone moiety for anti-proliferative activities and procaspase-3 kinase activation activities against five different cell lines, specifically MDA-MB-231 (human breast adenocarcinoma cell line), MNK-45 (gastric cancer cell line), NCI-H226 (human lung cancer cell line), HT-29 (human colorectal adenocarcinoma cell line) and SK-N-SH (neuroblastoma cell line). The substituted 2-hydroxybenzylidene containing semicarbazide (**28**) showed inhibitory activities against all cell lines with IC_{50} and EC_{50} values ranging from 0.24 to 0.92 mM and 0.31 mM respectively.



Gabr *et al.* [44] obtained hydrazine-based derivatives by treating 2-amino-6-fluorobenzothiazole with hydrazine hydrate which was further treated with the different aldehydes to afford benzothiazole-Schiff base derivatives. These derivatives were screened for anti-tumour activity which exhibited IC_{50} of 2.41 mM and 4.31 mM against Hela (cervical cancer) and COS-7 (kidney fibroblast cancer) cell lines as compared to reference doxorubicin having IC_{50} 2.05 mM and 3.04 mM, respectively. The SAR studies explained the effect of 2-(4-hydroxymethoxy benzylidene)hydrazino moiety (compound **29**) at the C-2 position which remarkably enhances the anti-tumour potential, whereas replacing the 4-hydroxy moiety with 4-methoxy decreased the activities against both cell lines. Synthesized compounds incorporating various structurally important moieties like benzothiazole and Schiff bases (compound **30**) were docked against CDK2 kinases protein target when BTZ 6 ligand showed two interactions and found to give a good docking score. All the synthesized compounds were screened to study their antioxidant effect comparing to the known standard drug and also produced the least IC_{50} values in DPPH 45.67 ± 1.2 and *p*-NDA 224.89 ± 0.7 exhibiting promising antioxidant activity and hence proving to be in the line of drugs used for the treatment of cancer disease [45].



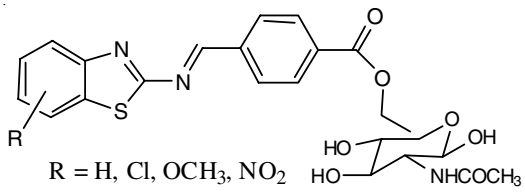
A new series of benzothiazole and pyrimido[2,1-*b*]-benzothiazole derivatives were synthesized and screened for their antitumor activity at a single dose (10 µM) against a panel of 60 cancer cell lines. Structure-based pharmacophore mapping, molecular docking, protein–ligand interaction, fingerprints and binding energy calculations were employed in a virtual screening strategy to identify the interaction between the compounds and the active site of EGFR tyrosine kinase [46]. Benzothiazole-Schiff base structures were synthesized and screened for antitumor activity against cervical cancer (Hela) and kidney fibroblast cancer (COS-7) cell lines. In addition, compound **31** displayed excellent activity against COS-7 cell line with IC_{50} value of 4.31 µm/L in comparison to doxorubicin as a reference antitumor agent with IC_{50} value of 3.04 µm/L. Based on pharmacophore mapping, molecular docking, protein-ligand interaction, fingerprints and binding energy calculations were employed



31

in a virtual screening strategy to identify the interaction between the compounds and the active site of the putative target, EGFR tyrosine kinase [47].

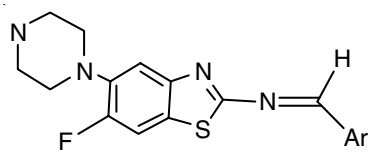
Synthesis of bioconjugates of benzothiazole, based on glucosamine (compound **32**) biocomponent showed promising *in vitro* anticancer activities. Integration of *N*-acetyl-glucosamine unit with benzothiazole increased the potency, observed as decrease in MIC value from 25 to 1.25 µg/mL against all the tested strain. The lead compound -NO_2 with MIC value 1.25 µg/mL, which also showed promising *in vitro* anticancer activities against He*p*-2 cell line and caco cell line. The results can be accounted to the enhanced interaction in bioconjugates as evident from AFM and docking studies. This bioconjugates can be highlighted as a new promising lead as future antibiotics with multi-targeted mode of action possibility [48]. Schiff bases of 2-aminobenzothiazoles were evaluated for their activity with an IC_{50} value of 2.517 µg/mL in comparison to the reference compound cisplatin and some of them also give positive result *in silico*-interactions. The antioxidant activity of the compounds was tested by DPPH assay. Assay was performed in concentrations ranging from 15.62-1000 µg/mL by using ascorbic acid as a standard. *In vitro* MTT assay was performed on HeLa cell lines to validate the cytotoxic activity against cervical cancer cells. Generally, chlorine substitution at 6th position of benzothiazole increases the activity which was further confirmed by *in silico* docking studies [49].



R = H, Cl, OCH_3, NO_2

32

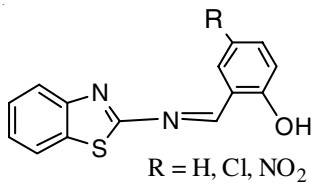
Cytotoxicity assays were performed in order to test the benzothiazole-Schiff bases for anticancer activities and to evaluate their safety to human primary non-transformed cells. Fluorine plays a role in controlling DNA gyrase and bacterial potency. Fluorine (compound **33**) shows a selective antitumor activity. Thus, initial screening of cell viability was performed for the Schiff bases at concentrations ranging from 1 µg/mL to 0.01 ng/mL, on DMS-53 human small cell lung cancer cell line and on primary human lung microvascular endothelial cells (HLMVECs) [50]. Schiff bases were synthesized from *o*-vanilidine refluxing with 2-amino-6-chloro benzothiazole, 2-amino-6-bromo benzothiazole and 2-amino-6-methyl benzothiazole. The synthesized compounds were tested for DPPH radical assay and ABTS radical scavenging antioxidant activities. All the compounds were showed good activity compare to the standard and shows IC_{50} value 248.82 µg/mL in DPPH assay [42]. Some authors [51,52] also reported a very intensive antitumor activity, especially with the fluorobenzothiazoles.



33

Uremis *et al.* [53] synthesized BTA derivatives using substituted aldehyde with bicyclo[3.2.0]hept-2-en-6-one. The nitrostyryl benzothiazole derivative and the fluorostyryl benzothiazole derivative were reported for their anticancer activity against pancreatic cancer cells having IC_{50} values of 27 ± 0.24 mM and 35 ± 0.51 mM, respectively. New-fangled Schiff bases carrying benzothiazole-1,2,3-triazole conjugates were designed and synthesized. The reported Schiff bases exhibited good to excellent anticancer activities by interacting with DNA [54]. Benzothiazole-Schiff bases containing indole moiety were screened for their cytotoxicity and antibacterial activities. Cytotoxicity screening revealed moderate activity against KB-3-1 cell line (IC_{50} = 57.7 µM) in comparison with the positive control (+)-Griseofulvin (IC_{50} = 19.2 µM) *in vitro*. Also, molecular docking study of Schiff bases was performed by molecular operating environment (MOE) program on the matrix metalloproteinase-8 (MMP-8) in an attempt to explore their mode of action as anticancer drugs [55].

Metal complexes: The structures for Schiff bases bearing benzothiazole scaffolds acts as a good ligand and binds with different metal ions to show various biological activities. The antiproliferative outcomes revealed that metal complexes of 5-chloroisatin-linked benzothiazole-moiety (compound **34**) are found to have a better prospect of acting as chemotherapeutic agents. The *in vitro* cytotoxicity of ligands and its metal complexes was screened on MCF7 (human breast adenocarcinoma), HeLa (human cervical carcinoma) and HepG2 (human hepatocellular carcinoma), cell lines and normal cells (PBMC). The antiproliferative outcomes revealed that metal complexes exhibit superior activity in general as compared to free ligands where metal complexes (Cu, Zn) of 5-chloroisatin-linked benzothiazole moiety are found to have better prospect of acting as chemotherapeutic agents, which can be explained in terms of greater biopotency, planarity and conjugation against all the tested cancer cell lines with IC_{50} [56].



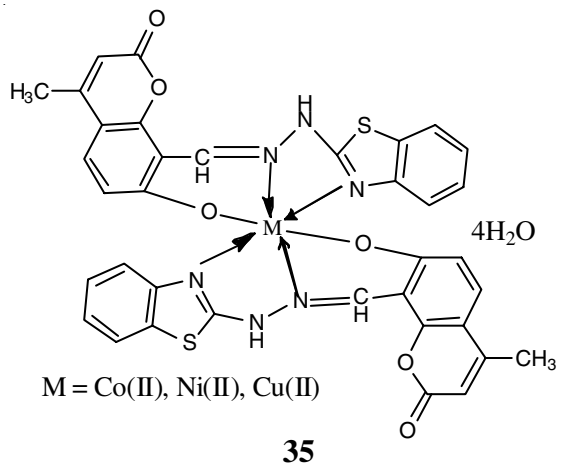
R = H, Cl, NO_2

34

Schiff bases are obtained by condensation of 2-amino-4,6-dimethyl benzothiazole with 2,5-dihydroxy acetophenone, pyridine-2-aldehyde, lanthanum(III) chloride, neodymium(III) chloride, samarium(III) chloride, gadolinium(III) chloride, thorium(IV) chloride were chosen to synthesize new complexes. All of the representative ligands and complexes were also screened for the antimicrobial activity, antibacterial activity against bacteria like *S. aureus*, *E. coli* and antifungal activity

against *A. niger* and *A. flavus* [57]. Substituted benzothiazole-Schiff base ligands and their Cu(II)/Zn(II) complexes have been synthesized with antimicrobial and anticancer properties. The introduction of the electron withdrawing substituents into hetero-aromatic core is expected to increase the hydrophobic character and lipophilicity resulting in substantial biological activity of the metal complexes. The chloro-substituted copper complexes display promising biological activities and developed as a potential antimicrobial and chemotherapeutic agent. The cytotoxicity profile indicated that chloro-substituted copper complex was found to be most active with a remarkably low IC_{50} value of 4.8 µg/mL against HeLa cancer cell line compared to other analogues. The screening data reveals high antibacterial and antifungal activity of chloro-substituted Cu(II) and Zn(II) complexes against *E. coli* and *C. albicans* in comparison with doxycycline as standard drug with maximum zone of inhibition in the range of 27-21 mm [58].

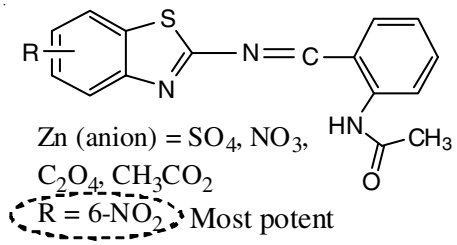
Coumarin based Schiff base-transition metal complexes (compound **35**) have been synthesized and thoroughly screened for their bacterial and fungal activity. The cytotoxic activity of the metal complexes was evaluated against the human ovarian cancer cell line (PA-1) and are found to be non-toxic against the tested cell line. These metal complexes furthermore screened for antitubercular activity [59]. A Schiff base ligand has been synthesized by the condensation of thiophene-2-carbaldehyde and 2-amino-6-methylbenzothiazole. Copper(II) complex, has been synthesized by the reacting ligand and copper(II) acetate in 2:1 molar ratio. The spectroscopic studies revealed that ligand binds with the Cu(II) ion as bidentate fashion and a distorted octahedral geometry has been assigned for the complex. The binding mode of metal complex with CT-DNA could be assigned as intercalation of the metal complex between DNA base pairs [60].



35

Binding of ligand with trasnition metals: Novel Schiff bases and their mononuclear binary Cu(II) complexes exhibited good antimicrobial activity and also bind to DNA mainly in an intercalative mode with moderate strengths. The DNA cleavage studies of complexes revealed that these complexes can effectively cleave supercoiled pBR322 DNA into nicked circular/linear form in the presence of H_2O_2 and UV light [61]. New enantiomeric Cu(II) and Zn(II) fluorobenzothiazole-Schiff base-valine complexes have been synthesized. All the metal complexes were screened for *in vitro* antimicrobial activity and exhibited varying degree of inhibitory effects on the growth of bacterial and fungal strains. L-Enantiomer of Cu(II) complex exhibits highest DNA binding propensity and cleavage activity, possessing distinct chiral preference over its D-enantiomer. Furthermore, cytotoxicity of the complexes was evaluated on the human cervical cancer cell line (HeLa) which implicated that more than 50% cells were viable at 15 µM and these results were further validated by cell imaging studies. Molecular docking studies were carried out to authenticate the spectroscopic studies which revealed that the complexes recognize the narrow minor groove region situated within the GC region of the DNA duplex [62].

Metal complexes are of type $ML_2{\cdot}(H_2O)_2$ (M = Mn, Fe, Co, Ni and Cu) derived from some heterocyclic β-diketones with 4-phenyl-2-aminothiazole. The compounds were tested for their antibacterial activity against pathogenic bacteria species (*Escherichia coli*, *Bacillus subtilis*, *S. aureus*, *A. niger* and *S. cerevisiae*). The biological activity of the complexes follow the order: Co(II) = Ni(II) > Mn(II), Fe(III), Cu(II). Spectroscopic measurements suggest that Schiff based-metal complexes show moderate antibacterial activity in the agar cup assay method [63]. Reaction of 2-acetamidobenzaldehyde with different substituted benzothiazole afforded a series of Schiff bases. These compounds have been used for complexation reactions to obtain Zn(II) chelates (compound **36**) having the same metal ion but different anions of the type $[Zn(L)_2]Xn$ [L = Schiff base derivative, X = SO_4, NO_3, C_2O_4 and CH_3CO_2 and n = 1 or 2]. The Schiff bases act tridentate and their metal complexes were proposed to possess an octahedral geometry. These compounds have been screened for antibacterial properties against pathogenic strains such as *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* [64].



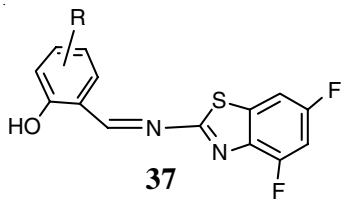
36

N-(Thiophen-2-ylmethylene)benzothiazol-2-amine and its complexes with Cu(II), Fe(III), Ni(II), Zn(II) were prepared and isolated. The IR spectra showed that the Schiff base under investigation behaves as bidentate ligand. The UV-visible spectra and magnetic moment data suggested octahedral geometry around Cu(II) and Fe(III) and tetrahedral geometry around Ni(II) and Zn(II). In view of the biological activity, it has been observed that the antimicrobial activity of Schiff base increased on complexation with the metal ion. Schiff base and its metal complexes assayed *in vitro* for antitumor activity against five human tumor cell lines furnished the significant toxicities [65]. Benzothiazole is a key component of deoxyribonucleic acid molecules and participates directly in the encoding of genetic information. Therefore, it represents a potent and selective class of antitumor compounds. The design and synthesis of chiral

antitumor chemotherapeutic agents of Cu(II) and Zn(II), L and D benzothiazole-Schiff base-valine complexes, interacted with *ct*-DNA by employing UV-vis, florescence, circular dichroic methods and cleavage studies of compound with pBR-322 plasmid, molecular docking were done in order to demonstrate their enantiomeric disposition towards the molecular drug target DNA. Interestingly, these studies unambiguously demonstrated the greater potency of L-enantiomer in comparison to D-enantiomer [66].

Novel copper complexes of Schiff base ligands of 2-aminobenzothiazole derivatives were synthesized by the condensation of Knoevenagel condensation of acetoacetanilide and 2-aminobenzothiazole. The antioxidant activities as well as antibacterial and antifungal activity of the ligands and their complexes reveal that the complexes show higher activities than the ligands. The DNA binding constants reveal that, these complexes interact with DNA through intercalation binding mode. Thermal denaturation studies suggested the nature binding affinity of copper complexes with *ct*-DNA. Further, copper complexes also showed catalase activity. It is hoping that copper complexes were capable of decrease ROS levels or reduce oxidative stress in Alzheimer's patients [67].

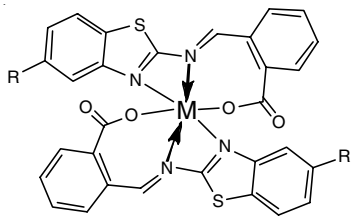
Schiff bases and their metal(II) complexes (Cu^{2+}, Ni^{2+} and Co^{2+}) tentatively adopted a square planar geometry. The binding mode of complexes with *ct*-DNA was investigated and studies reveal that, they bind through an intercalative mode. Also, they effectively cleaved supercoiled pBR322 DNA both in the presence of H_2O_2 and UV light. Further, the antibacterial activity of the synthesized ligands and their metal complexes revealed that complexes showed high antibacterial activity compared to ligands [68]. Benzothiazole-Schiff bases and their binary Cu(II) complexes (compound **37**) bind with *ct*-DNA through an intercalation mode. From the DNA cleavage studies of Cu(II) complexes, it is observed that the metal(II) complexes effectively cleave supercoiled pBR322 DNA in the presence of H_2O_2 and also UV light. *In vitro* antimicrobial activity studies of Schiff base ligands and their Cu(II) complexes revealed that the activity increases upon coordination [69].



37

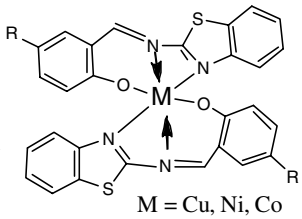
Reaction of 2-acetamidobenzaldehyde with 2-amino, 2-amino-4-methyl, 2-amino-4-methoxy, 2-amino-4-chloro, 2-amino-6-nitro and 6-(methylsulfonyl)benzothiazole afforded a series of Schiff bases. These compounds have been further used for complexation reactions to obtain Co(II) and Ni(II) chelates. The Schiff bases act as tridentate and their metal complexes possess an octahedral geometry. Additionally, they have been screened for antibacterial properties against the pathogenic species *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* [70]. The Schiff bases derived from the condensation of 2-aminobenzothiazole derivatives and 2-hydroxy-3-methoxybenzaldehyde and their silicon(IV) complexes have been shown trigonal bipyramidal geometry around the silicon atom. The ligands and their organosilicon complexes have also been evaluated for *in vitro* antimicrobial activity [71].

A couple of benzothiazole-imino-benzoic acid Schiff bases namely (*E*)-2((benzo[*d*]thiazol-2-ylimino)methyl)benzoic acid and (*E*)-2-(((5-nitrobenzo[*d*]thiazol-2-yl)imino)methyl)-benzoic acid, derived from aminobenzothiazole, 2-formyl-benzoic acid. A series of complexes (compound **38**) with Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) metal ions based on these ligands, have been synthesized. Both the ligands and complexes show good antimicrobial activity against human epidemic causing bacterial strains which causes infection in mouth, lungs breast, gastrointestinal tract and nosocomial infections [72]. Binary complexes (compound **39**) of Cu(II), Ni(II) and Co(II) were synthesized using two novel Schiff bases L_1 = 2-((benzothiazol-6-ylimino)methyl)-4-chlorophenol (BTEMCP), L_2 = 2-(-(benzothiazol-6-ylimino)methyl)-4-nitrophenol. From the analytical data, square planar geometry has been proposed for all the metal complexes. The studies revealed that the complexes showed an intercalative mode of binding to *ct*-DNA and also effectively cleaved the supercoiled pBR DNA. The synthesized compounds were evaluated for *in vitro* antibacterial activity [73].



M = Co, Ni, Cu, Zn, Cd
R = H, NO_2

38



M = Cu, Ni, Co
R = Cl, NO_2

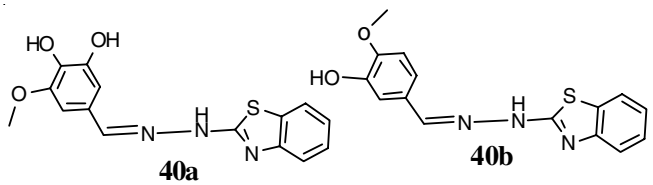
39

Two novel Schiff bases *viz*. 2-benzothiazol-6-ylimino)-methyl)-4,6-dichlorophenol and 1-benzothiazol-6-ylimino)-methyl)-6-bromo-4-chlorophenol and their bivalent transition metal complexes (M = Cu^{2+}, Co^{2+} and Ni^{2+}) strongly bound to *ct*-DNA through an intercalation mode. In addition, these ligands and their metal(II) complexes were screened for the antimicrobial activity [74]. Novel Cu(II) complexes with Schiff bases derived from 2-aminobenzothiazole and Knoevenagel condensate of β-ketoanilides showed distorted square planar geometry. Antibacterial studies of the ligands and complexes have also been evaluated which indicates that activity increases on chelation. DNA binding studies indicated that the Cu(II) complex exhibited stronger binding affinity to DNA through intercalation mode [75].

Novel paramagnetic ruthenium complexes, *cis*-Cl, *trans*-P-[$RuIIICl_2$(carboim)(PPh_3)$_2$] with bidentate chelating carbohydrazide Schiff bases were reported. The DPPH and NO radical scavenging capabilities of ruthenium(II) complexes were investigated. The *ct*-DNA binding capabilities were explored using electronic spectroscopy and gel electrophoresis. *In vitro* anticancer studies showed that they were toxic to HCC70 breast carcinoma cells and showing promising IC_{50} at 3.4 mM [76]. Coordination behaviour of new (bidentate N,O-chelating) Schiff bases towards copper(II) and nickel(II) metal ions were studied for their *in vitro* antibacterial activities against some

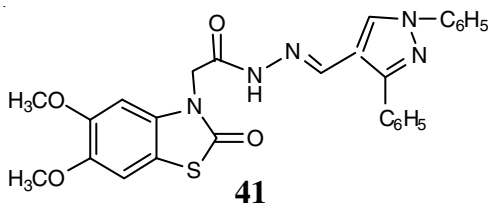
selected Gram-positive and Gram-negative bacteria, using agar well diffusion. The fluoro-substituted compounds showed better antibacterial activity compared to the methyl substituted compounds. Furthermore, the antioxidant potentials of the compounds were ascertained using DPPH radical scavenging and ferrous chelating assay. The copper complexes had the best antioxidant properties of all the tested compounds [77].

Other therapeutic activities: Benzothiazole-hydrazones derivatives (**40**) were reported for exploring their antioxidant, cytoprotective properties, such as their scavenging effect DPPH radical and the inhibition of superoxide anion (O^{2-}) generation. The catechol derivative (**a**) exhibits the best DPPH radical scavenging activity (6.8 mM) and compound (**b**) showed good radical superoxide anion scavenging activity (41.7%) than chlorogenic acid (35.5% and Trolox (22.2%). From SAR, the phenolic frame is not the only condition for antioxidant activity but N-methylbenzothiazole hydrazone moiety magnifies the dual required properties in two most interesting derivatives. The cytoprotective efficacy was also evaluated by measuring the cell viability in the presence of cytotoxic oxidized LDL [78].



40a **40b**

Benzoisothiazole, benzothiazole and thiazole Schiff bases were synthesized and tested *in vitro* against emergent and re-emergent human and cattle infectious diseases (AIDS, hepatitis B and C, tuberculosis, bovine viral diarrhoea) against drug-resistant cancers (leukaemia, carcinoma, melanoma, MDR tumors) for which no definitive cure or efficacious vaccine is available at present. The benzo[*d*]isothiazole compounds showed a cytotoxicity (CC_{50} = 4-9 mM) against the human CD4+ lymphocytes (MT-4) that were used to support HIV-1 growth. For this reason, the most cytotoxic compounds were evaluated for their antiproliferative activity against a panel of human cell lines derived from haematological and solid tumors [79]. It is worth mentioning that the attachment of Schiff base of benzothiazole with diphenyl pyrazole nucleus (compound **41**) is important in order to gain dual anti-inflammatory and antinociceptive activity. Also, the conjugation of benzothiazole ring with the triazolo-thiadiazine system led to the obtaining of high antinociceptive activity, even more than the potent tramadol reference drug [80].



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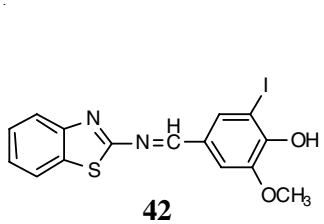
Novel thiazolyl/thiazolinyl/benzothiazolyl Schiff bases have been designed and screened for their reducing activity with the stable free radical 1,1-diphenyl-2-picryl-hydrazyl, DPPH and for inhibition of soybean lipoxygenase (LOX). Anti-inflammatory activity was also examined *in vivo* using the carrageenin induced mice paw edema (32.6/75%). Compound **42** possessed the highest inhibition 75% [81]. Cycloalkylthiopheneimine derivatives containing benzothiazole synthesized and evaluated for their antiviral activities. Compound **43** shows highest antiviral activity, which was better than the control compound ribavirin. Compound **a** exhibited high potent anti-virus activities against CVB5, ADV7 and EV71 virus with the EC_{50} values of 5.4, 10.8 and 2.0 mg/mL. SAR studies revealed, compounds having a 2-OH-Ph unit showed comparatively good antiviral activities [82].



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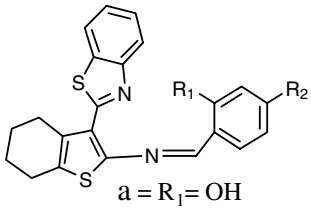
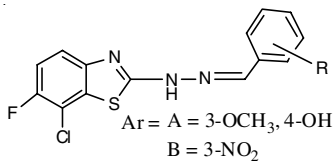


a = R_1= OH
b = R_2= F

43

Various substituted benzothiazole derivatives containing 7-chloro-6-fluoro-*N*-(substituted hydrazones)benzothiazole (**44**) was evaluated for anti-inflammatory activity using carragennan induced paw edema method. The selected compounds have shown significant anti-inflammatory activity as compared to the standard drug diclofenac sodium [83]. Several thiazolyl/benzothiazolyl/benzoisothiazolyl Schiff bases and hydrazones have been tested as anti-inflammatory agents. The anti-inflammatory activity was examined *in vivo* using the carrageenin induced mice paw edema test (inhibition 16.3-64%). The compounds were tested for antioxidant activity as hydroxyl scavengers and for their ability to interact with the stable free radical 1,1-diphenyl-2-picryl-hydrazyl (DPPH). Both anti-inflammatory and antioxidant activities depended on some structural characteristics of the synthesized compounds [84].

Schiff bases containing benzothiazole unit were evaluated for *in vitro* antibacterial activities on four different strains (*S. aureus*, *Bacillus*, *E. coli* and *K. pneumoniae*) and antifungal activity on one strain (*C. albicans*) by using micro-broth dilution method (MIC in µg/mL). Compound **45** showed an excellent antibacterial activity for *S. aureus*, *E. coli* and *K. pneumoniae* strains, as well as an antifungal activity for *C. albicans*, compared to standard ciprofloxacin and fluconazole, respectively. Molecular docking studies were carried out to get more insight into the binding mechanism. Henceforth, it was further assessed for DNA cleavage and against MCF-7 breast cancer cell. VS5-e reveals 85.82% inhibition of cancer cells at a concentration



Ar = A = 3-OCH_3, 4-OH
B = 3-NO_2
C = 2,3,4-OCH_3

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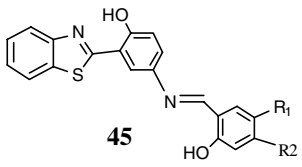
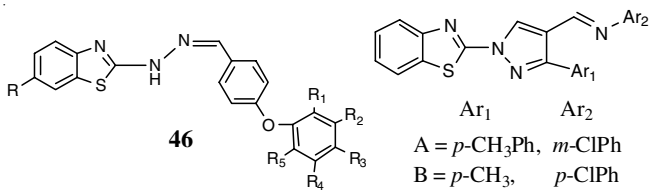


45

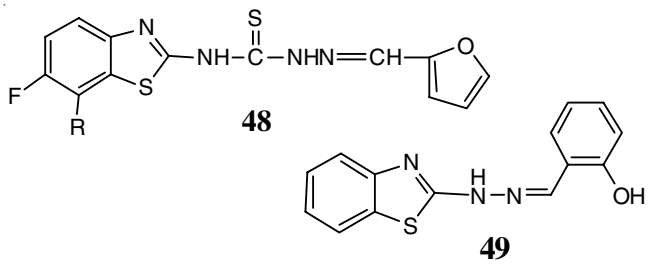
of 200 µg/mL. Compound VS5-e showed less toxicity to normal cells at the concentration required to produce an anticancer effect (with high IC_{50} = 973 µg/mL) [85].

Synthesized phenylsulfonyl of benzothiazole and benzimidazole moiety-containing pyrazolo[5,1-*c*]-l,2,4-triazine derivative, arylhydrazone derivatives and pyridazine derivative was carried out for antimicrobial and anticancer activity. The synthesized compounds containing pyrazolo[5,1-*c*]-l,2,4-triazine derivative exhibited higher activity against *Staphylococcus aureus* compared with control drug chloramphenicol. While arylhydrazones were found to be equal to the control drug. The anticancer activity on hepatocellular carcinoma (HEPG2) exhibited excellent activities, more potent than the reference drug [86]. Fragment based quantitative structure activity relationship (QSAR) analysis reported 2-(2-(4-aryloxybenzylidene)-hydrazinyl)benzothiazole dataset as antitubercular agents were carried out. Dataset of benzothiazole revealed the importance of presence of halogen atoms on is essential requirement [87].

Substituted 2-(2-(4-aryloxybenzylidene)hydrazinyl)-benzothiazole derivatives (**46**) incorporating 2-hydrazinyl benzothiazole and 4-(aryloxy)benzaldehyde were designed and synthesized using molecular hybridization approach. All the synthesized compounds exhibited promising activity (MIC 1.5-29.00 µg/mL) against *Mycobacterium tuberculosis* H37Rv strains of using REMA. Five of the evaluated compounds exhibit MIC < 3.0 µg/mL. Compound (*E*)-6-chloro-2-(2-(4-(2,4-dichlorophenoxy)benzylidene)hydrazinyl)benzothiazole showed MIC of 1.5 µg/mL [88]. Novel pyrazole-Schiff base hybrid (**47**) showed significant *in vitro* antimalarial activity against CQS strains of *P. falciparum*. Among all compounds, **A** and **B** were found to be potential molecules with EC_{50} 1.95 µg/mL and 1.98 µg/mL, respectively. The molecular modeling studies revealed that the pyrazole Schiff base analogues completely occupy the site of PfFP-2 with different modes. The ascertained ADME parameters for the synthesized compounds showed good pharmacokinetic properties. This outcome shows that the pyrazole Schiff base hybrids may be promising leads and provide a significant model for further structural as well as biological optimization [89].

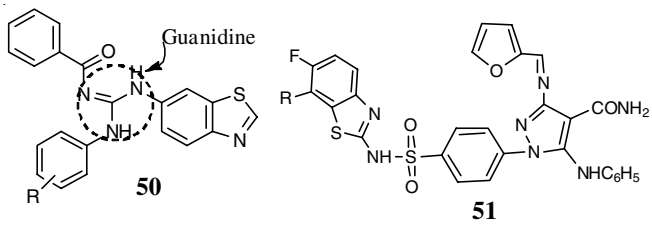


N-[6-Fluoro-7-substituted benzothiazol-2-yl]-2-(furan-2-yl methylene)hydrazine carbothioamide (**48**) were treated for anthelmintic activity against earthworms (*Perituma posthuma*) nearly equal size had shown significant activity at different concentrations compared to standard [90]. Derivatives of 2-hydrazinobenzothiazole and 2-hydrazinobenzoxazole have been synthesized for testing as antituberculous agents by Katzis (**49**) an ATP-phosphoribosyl transferase (ATPPRTase) that catalyzes the first step in the biosynthetic pathway for histidine. In addition, four compounds containing benzothiazole nucleus and capable of complexing cupric ions have been synthesized.

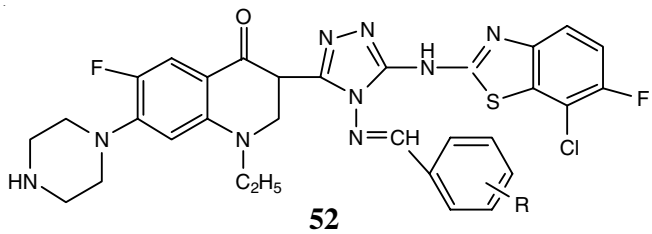


Although none of the compounds possessed outstanding anti-tuberculosis properties the derivatives of 2-hydrazinobenzo-xazole had significant antifungal activity [91].

A series of *N*-phenyl-substituted and disubstituted guanidinyl-benzothiazole derivatives (**50**) were synthesized and characterized as novel antimicrobial and antioxidant agents. The *in vitro* antioxidant activities of these compounds were evaluated and using ascorbic acid and employing 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay and 2,2-azino-*bis*(3-ethyl-benzthiazoline-6-sulphonic acid (ABTS) assay. In addition, the *in vitro* antimicrobial activities of these compounds were evaluated and the results demonstrated that the compounds exhibited excellent antimicrobial activities [92]. A number of sulfonamido pyrazole derivatives of fluorobenzothiazoles (**51**) were prepared and examined for anthelmintic activity against earthworm *Perituma posthuma* [93].

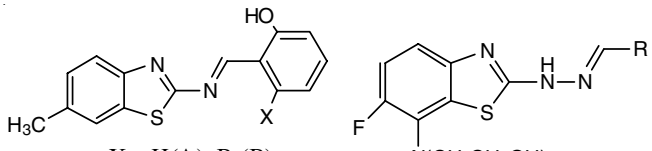


3-Substitued-5-(2′-imino-7-chloro-6-fluorobenzothia-zolyl)-1,2,4-triazolo Schiff bases (**52**) were screened for analgesic and anti-inflammatory activities using rat hind paw method. The study revealed that triazolo-Schiff base derivatives bearing substituted benzothiazole moiety showed weak to moderate anti-inflammatory activity. Substituents like 3,4-dimethoxy phenyl, 4-hydroxy phenyl, 4-cholorophenyl may contribute to enhance the anti-inflammatory activity of triazolo derivatives in presence of substituted benzothiazole moiety at 5th position. Perhaps these compounds exhibit activity through inhibition of cyclooxygenase I and II enzymes depending on the position and type of the substituent group present at the 1,2,4-triazole system [94].

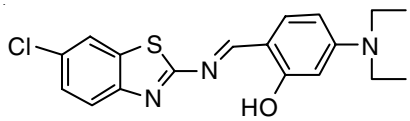


Schiff bases derived from aminobenzothiazole derivatives with salicylaldehyde/bromosalicylaldehyde (**53**) namely 2-[6-

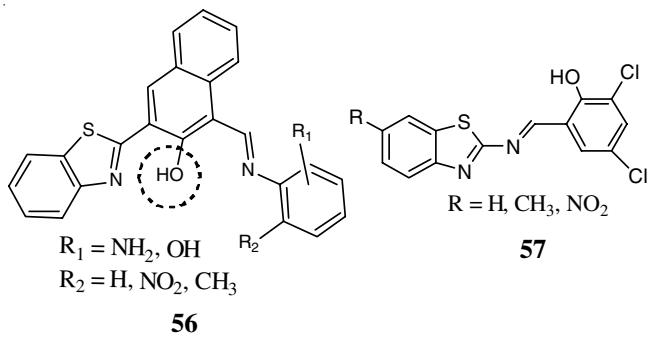
methylbenzothiazol-2-ylimino)methyl phenol (**A**) and 3-bromo-2-[6-methylbenzothiazol-2-ylimino)methyl phenol (**B**). The antimicrobial activity was carried out by the well-diffusion method. The anticancer activity of the compounds was carried out for the MCF-7 cell line (breast cancer) using MTT assay and the antituberculosis activity of the compounds was carried out using micro plate alamar blue assay [95]. {7-[*Bis*(2-hydroxyethyl)amino]-6-fluoro-1,3-benzothiazol-2yl}hydrazone (**54**) was screened for antibacterial (agar diffusion method) and antioxidant activity (ferric ion reduction method) and inhibition of denaturation of protein [96].



Miscellaneous: The silica gel modified with benzothiazole calix[4]arene *via* Schiff base reaction was applied as a sorbent [97]. The hydrated form of (*E*)-2-(((6-chlorobenzo[*d*]thiazol-2-ylimino)methyl)-5-diethylamino)phenol (CBMDP) (**55**) shows very weak fluorescence in aq. media, while on encapsulation in biomimetic media is converted back to highly fluorescent. Overall, this fluorescence "turn off-turn on" of the polarity-sensitive probe can find potential applications in fluorescence imaging for elucidating chemical and physical information in microstructures of biological cells and materials [98].

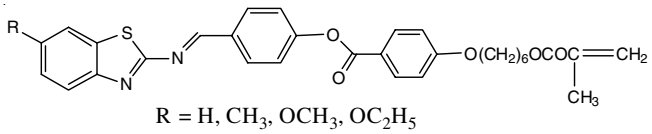


The presence of hydroxyl group *ortho* to the benzothiazolyl group as well as imine linkage (compound **56**) lead to the occurrence of excited state intramolecular proton transfer process and shows good thermal stability. The computational strategy was used to study the ESIPT process of the synthesized Schiff bases, which revealed that the keto-form predominantly exists in the ground state contradicting the ESIPT process [99]. Azo dyes and their corresponding Schiff bases (**57**) were prepared in order to obtain some high performance disperse red dyes. Electronic spectra of the dyes demonstrate that the presence of N=N and C=N bond chromophore units as well

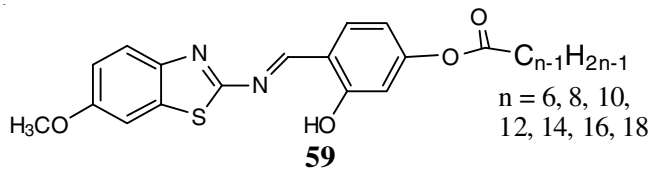


as substituent effects of different auxochrome groups in the benzothiazole backbone leads to significant alterations of bathochromic and hypsochromic shifts [100].

A pair of isomeric heterocyclic compounds, 3-amino-5-nitro-[2,1]-benzisothiazole and 2-amino-6-nitrobenzothiazole, are used as the diazonium components to couple with two N-substituted-4-aminobenzene derivatives. Both benzisothiazole and benzothiazole based dyes show planar molecular structures and offset π-π stacking interactions, solvatochromism and reversible acid-base discoloration [101]. Imine-ester linked benzothiazole mesogen based liquid crystalline monomers, having polymerizable methacrylate functional group as terminal (**58**) were designed. These monomers were differentiated from each other by varying the terminal substituents (-H, -CH_3, -OCH_3 and -OCH_2CH_3) at the sixth position on the benzothiazole moiety. The ethoxy substituted monomer showed higher thermal stability compared to other monomers [102].

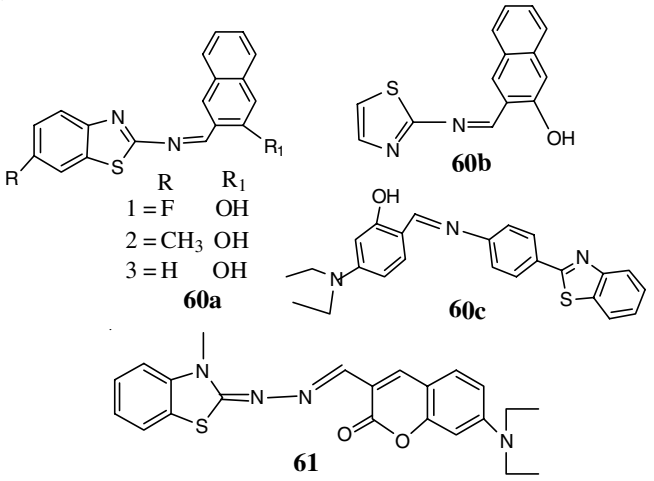


A homologous series of Schiff base-esters, 6-methoxy-2-(2-hydroxy-4-alkanoyloxybenzylidenamino)benzothiazole (**59**), comprising a benzothiazole moiety as a core, exhibited an enantiotropic nematic phase. A azomethine linkage along with the lateral hydroxyl and terminal methoxyl groups were found to exert an effect on the mesomorphic properties [103]. Crystal structure and hirshfeld surface analysis of (*E*)-*N*-(4-propyloxybenzylidene)benzothiazol-2-amine was synthesized by a condensation reaction between 2-aminobenzothiazole and 4-*N*-propoxybenzaldehyde. The benzothiazole ring system is nearly planar and makes a dihedral angle of 3.804 (12)º with the phenyl ring. These dimers are additionally linked by weak π-π stacking interactions between the phenyl rings, leading to a layered arrangement parallel to (010). Hirshfeld surface analysis of the crystal structure indicates that the most important contributions for the packing arrangement [104].



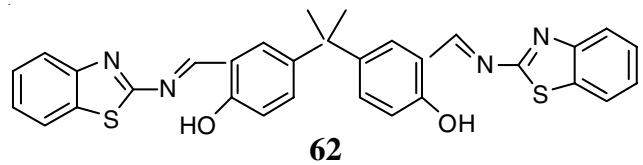
Schiff bases containing a hydroxynaphthyl ring and substituted benzothiazolyl groups exhibited thermochromism (compound **60**) in the solid-state have been synthesized. High resolution NMR spectra confirmed that these anils exist as enol-keto tautomers in solution [105].

A novel coumarin-derivative (compound **61**) was designed and synthesized by Schiff base reaction, shows fluorescent chemosensor, which was connected by 7-(*N,N*-diethylamino)-coumarin-3-aldehyde and 3-methyl-2-benzothiazolinone hydrazone through C=N. An X-ray single crystal structure analysis indicated that two aromatic groups of the compound



was almost in the same plane. It displayed enhancement of the fluorescent intensity and absorbance when the sensor interacted with Hg^{2+} ions. This chemosensor compound exhibited a good sensitive and selective recognition towards Hg^{2+} ions in the presence of other important relevant metal ions [106]. Three AIE (aggregation induced emission)-ESIPT (excited-state intramolecular proton transfer) active 2-(2′-hydroxyphenyl)benzothiazole derivatives could act as fluorescence, chemosensors to detect Cu^{2+} and Zn^{2+} ions *via* the "turn off" mode in THF/HEPES media [107].

Pyrrolopyrrole aza-BODIPY (PPAB) developed from diketopyrrolopyrrole by $TiCl_4$-mediated Schiff-base formation reaction with heteroaromatic amines is a highly potential chromophore due to its intense absorption and fluorescence in the visible region and high fluorescence quantum yield, which is greater than 0.8. After identifying a suitable PPAB molecule for application in organic photovoltaic cells based on evaluation using time-resolved microwave conductivity measurements, a maximized power conversion efficiency of 1.27% was achieved [108]. A novel, effectively selective and sensitive colorimetric and fluorescent sensor based on a benzothiazole-bisphenol A (BBA), compound **62** acts as a both colorimetric and fluorescent OFF-ON sensor selective for fluoride ion in MeCN. BBA has displayed a remarkable fluorescence enhancement (over 40-fold) and naked-eye detection at room temperature for F^- anion. The reversibility of BBA has been demonstrated by the titration of F^- followed by Ca^{2+} for several cycles. This reversibility indicates that BBA could be reused with proper treatment. The fluorescence and absorbance responses have been also utilized as output to build an INHIBIT logic gate by using F^- and Ca^{2+} as inputs. These properties make BBA suitable for the direct and rapid detection of biologically important fluoride anion [109].



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Conclusion

From the above discussions, it is clear benzohiazole-Schiff base scaffold plays a significant role in medicinal chemistry and the related research has been being remarkably active subjects. A large amount of work has been made towards medicinal chemistry. Numerous outstanding achievements revealed that benzohiazole-Schiff base scaffold possess extensively potential application as medicinal drugs and diagnostic agents. In particular, a large number of Schiff base compounds used as clinical anticancer, antibacterial, antifungal, anti-inflammatory, analgesic, anti-HIV, antioxidant, anticonvulsant, antitubercular, antidiabetic, antileishmanial, antihistaminic agents and soon have been successfully developed, marketed and extensively used in preventing and treating various types of diseases with low toxicity, high bioavailability and good biocompatibility effects. It is expected that this information would give rise to design of better molecules with enhanced biological properties and higher specificity and together with development of novel synthetic strategies.

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