


Electronic Features and Pharmacological Potentials of Substituted Thiazines

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Abstract: Nitrogen and sulfur-containing heterocycles are used as a potential material in a wide range of industries, such as pharmaceuticals, paint, packaging, and textiles, especially in the manufacturing of dyes, paint, agrochemicals, and medications due to their diversified properties. The medicinal potential of thiazines, a class of heterocyclic chemical compounds, is still unexplored. 1,2-Thiazine, 1,3-Thiazine, and 1,4-Thiazine are the types of thiazine nucleus. MEP data of thiazine derivatives expressed that total structure maintained a balance between electrophilic and nucleophilic regions. The HOMO orbital energies (eV) of 1,2-Thiazine, 1,3-Thiazine, 1,4-Thiazine, and Phenothiazine were -4.65, -6.06, -7.18, -4.89, respectively. The LUMO orbital energies (eV) of 1,2-Thiazine, 1,3-Thiazine, 1,4-Thiazine, and Phenothiazine were -1.03, -1.22, -0.13, and -0.32, respectively. These data confirmed that the highest gap between HOMO and LUMO orbitals was observed with 1,4-Thiazine. The maximum electrophilicity index value was observed with the 1,3-Thiazine molecule. Piroxicam, lornoxicam, sudoxicam and meloxicam are the most popular thiazine NSAID derivatives. Other than NSAID, thiazine derivatives showed antipsychotic (chlorpromazine) H1 antagonist (Promethazine) activities. Thiazine derivatives also showed antibacterial, antifungal, anti-inflammatory, analgesic, antimalarial, antineoplastic, and antiviral properties. They represent an interesting class of heterocyclic medicinal compounds deserving further research. The current review focused on nitrogen-sulfur heterocycles that could be therapeutically effective, especially when coupled with thiazine.

Keywords: Thiazine; MEP; FMO analysis; Antimicrobial; Anticancer; Analgesic.

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1. Introduction

The heterocyclic compounds are extensively distributed in nature and are necessary for all life. Nitrogen heterocycles are the most common among the many heterocycles found in nature, especially those containing oxygen or sulfur[1,2]. Heterocycles are present in more than 90% of new drugs, and synthesized heterocyclic pharmaceuticals are still more common[3,4]. Most drugs designed for therapeutic use are based on heterocyclic constituents because of their distinct chemical reactivity. In recent years, a sizable number of drugs that contain heterocyclic

compounds have been added to pharmacopeias. Among the wide variety of heterocyclic compounds studied to produce pharmaceutically relevant molecules, six-membered heterocyclic compounds have been demonstrated to be potential chemotherapeutic and pharmacotherapeutic agents [6,7]. According to a survey of the literature, six-membered heterocycles are a class of compounds with considerable biological chemistry. The current research effort will concentrate on creating novel heterocyclic compounds with improved chemical structures and biological activity. We believe that product development will also involve utilizing the already-approved drug to serve new therapeutic requirements and discover novel molecular entities [8–10].

2. Electronic Features and Pharmacological Role of 1,3-Thiazine

1,3- thiazine is a chemical structure with one nitrogen and one sulfur atom at different positions. Based on the position of nitrogen and sulfur atoms, thiazine molecules have three types: 1,2-thiazine, 1,3-thiazine, and 1,4-thiazine (1-3). Generally, thiazine possesses antibacterial, anticancer, antitubercular, antifungal, insecticidal, herbicidal, and tranquilizer activities [11-20]. The 1,3-thiazine nucleus also possesses outstanding antiradiation potential. They are used to modify reaction intermediates and a range of organic syntheses. Molecular electrostatic potential (MEP) was considered interaction energy at a certain zone of a structure involved in the electrical charge distribution from the proton, nuclei, and electrons. This electrostatic potential map showed the attractive or repulsive force observed by a fixed charge (a point positive charge, i.e., proton) at various points in space that are equidistant from a molecular surface. This map also shows the regions that are electron-rich and electron-deficient. The probable nucleophilic (blue region) and electrophilic (red region) attack sites were established. MEP was computed at the B3LYP functional and 6-31+G(d,p) level. MEP analysis data of 1,2-Thiazine, 1,3-Thiazine, 1,4-Thiazine, and Phenothiazine showed that electrophilic regions were mainly focused on the nitrogen atom and total structure maintained a balance between electrophilic-nucleophilic region (Figure1). The HOMO LUMO calculations data of 1,2-Thiazine, 1,3-Thiazine, 1,4-Thiazine, and Phenothiazine derivatives focused on the structural features and electrophilicity index values of the molecules. The electric and optical parameters of the synthesized molecules in the Frontier Molecular Orbital (FMO) theory were computed by using B3LYP/6-31+G(d,p) and B3LYP/6-311+G(d,p) basis sets. The charges of the molecules were zero with one multiplicity. FM orbitals are the important orbitals in a structure, and it is considered the lowest unoccupied molecular orbitals (LUMO) and the highest occupied molecular orbital (HOMO). The outermost orbital is occupied by electrons called the HOMO, which can act as electron donors. The energy of the LUMO is the foremost vacant innermost orbital unoccupied with electrons, which are observed as electron acceptors. The electron-donating capacity of the molecule is associated with the E_{HOMO} , and overall the greater the HOMO energy (smaller negative value), the superior the capacity to donate electrons. The energy gap (ΔE) between the HOMO and LUMO, softness, electronegativity, chemical hardness, and electrophilicity index values were put in Table 1. Here, we considered GAMESS software for FMO analysis, and WxMacMolPlt was used for data visualization.

Chemical hardness $\eta = \frac{I-A}{2}$; Softness $\zeta = \frac{1}{2\eta}$; Electronegativity $\mu = -\frac{I+A}{2}$; Electrophilicity index $\Psi = \frac{\mu^2}{2\eta}$ Where A and I are electron affinity and ionization potential. $A = -E_{LUMO}$ and $I = -E_{HOMO}$.

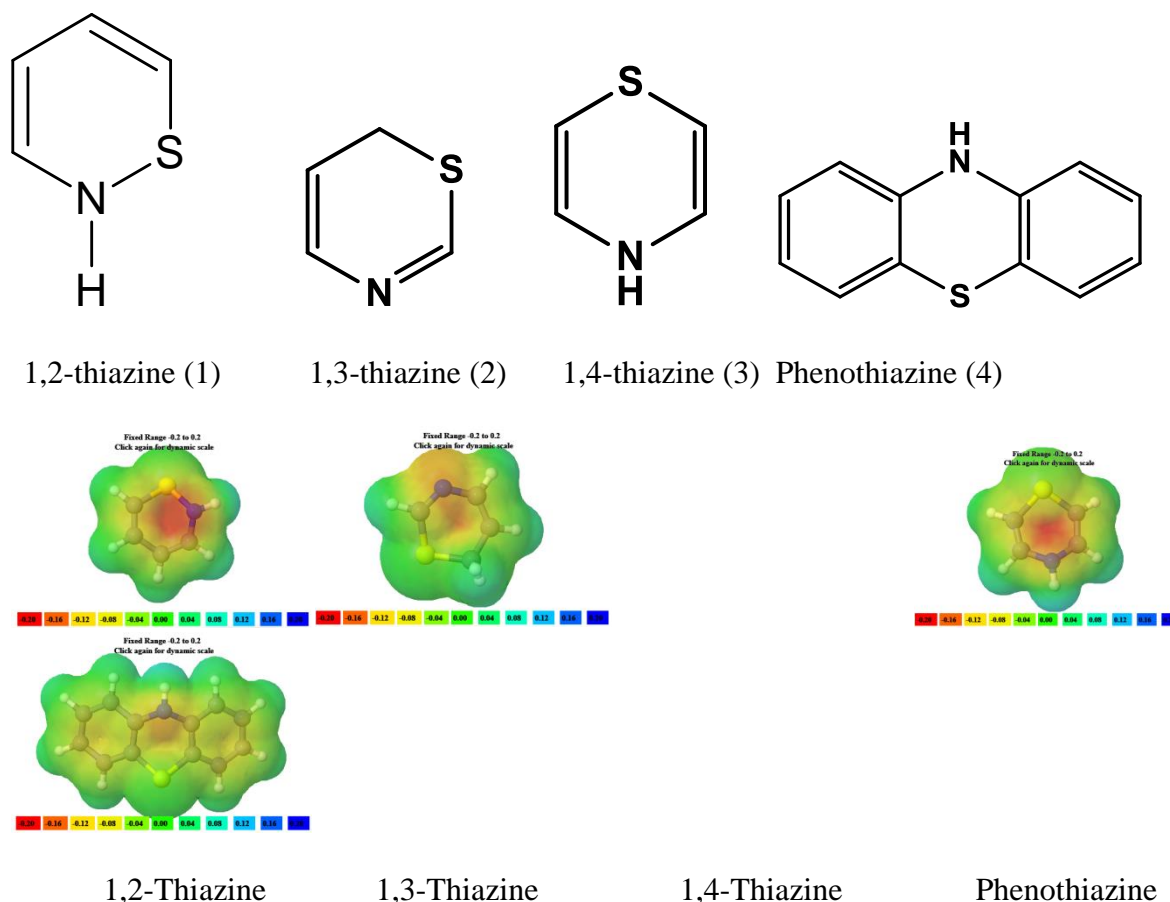


Figure 1. Structural features of different thiazine derivatives (a) 1,2-thiazine; (b) 1,3-thiazine; (c) 1,4-thiazine; (d) Phenothiazine.

Table 1. FMO calculation data of 1,2/1,3/1,4-Thiazine and Phenothiazine.

SN	MoleculeName	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE_{gap} (eV)	I	A	η	ζ	μ	Ψ
1.	1,2-Thiazine	-4.65	-1.03	3.62	4.65	1.03	1.81	0.27	2.84	2.22
2.	1,3-Thiazine	-6.06	-1.22	4.84	6.06	1.22	2.42	0.20	3.64	2.73
3.	1,4Thiazine	-7.18	-0.13	7.05	7.18	0.13	3.53	0.14	3.66	1.89
4.	Phenothiazine	-4.89	-0.32	4.57	4.89	0.32	2.29	0.21	2.61	1.48

The HOMO orbital energies (eV) of 1,2-Thiazine, 1,3-Thiazine, 1,4-Thiazine, and Phenothiazine were -4.65, -6.06, -7.18, -4.89, respectively. The LUMO orbital energies (eV) of 1,2-Thiazine, 1,3-Thiazine, 1,4-Thiazine, and Phenothiazine were -1.03, -1.22, -0.13, and -0.32, respectively. These data confirmed that the highest gap between HOMO and LUMO orbitals was observed with 1,4-Thiazine. Maximum electrophilicity index value was observed with a 1,3-thiazine molecule (Figure 2).

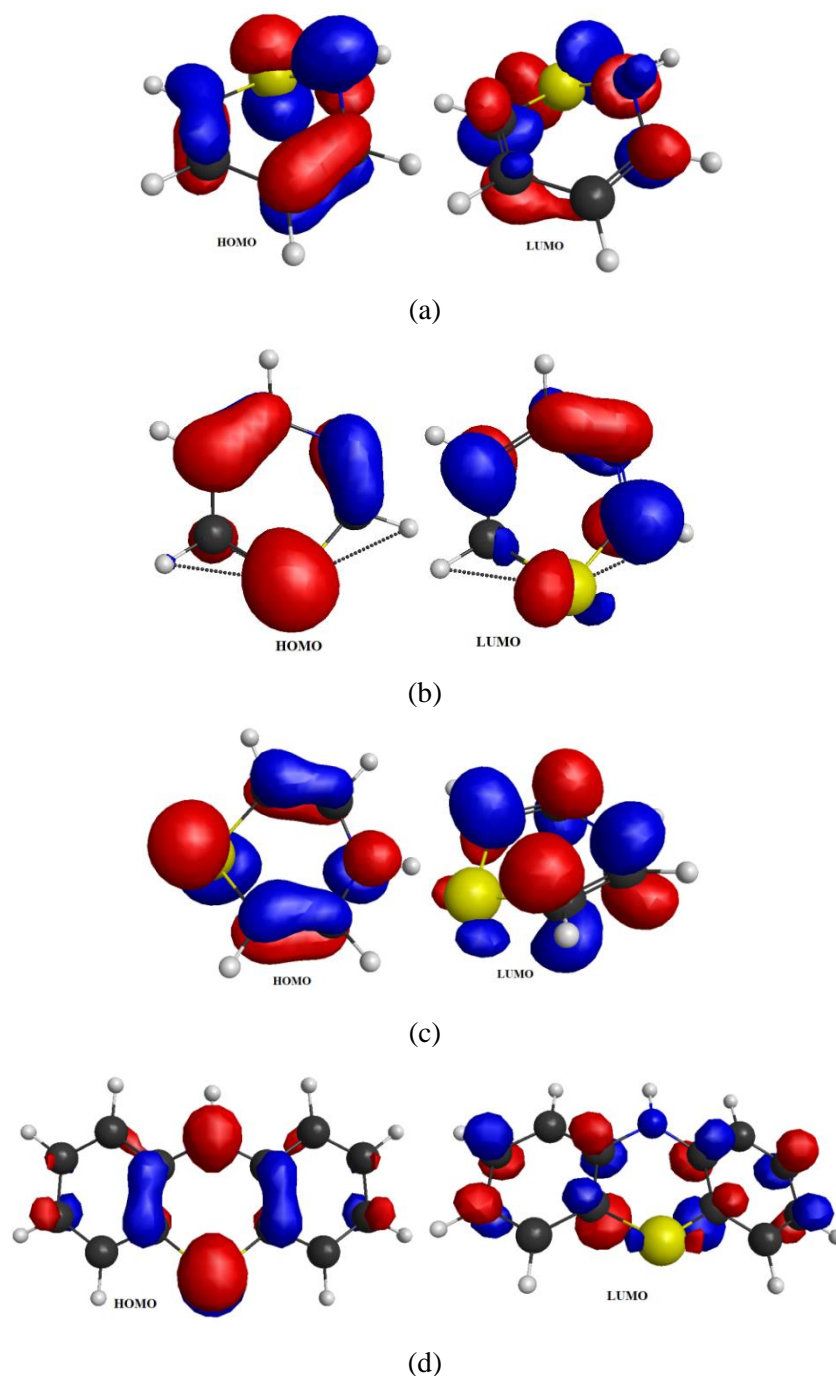


Figure 2. Frontier Molecular Orbital Analysis data of (a)1,2-thiazine; (b)1,3-thiazine; (c)1,4-thiazine; (d) Phenothiazine.

In addition to methylene blue thiazine, a vast group of dyes have a phenothiazine (4) structure. The active component of cephalosporins(5), commonly used lactam antibiotics, is the 1,3-thiazine nucleus. They lessen the amount of extra water weight the stomach is hanging onto. In medicine, 1,3-thiazine is employed as an anabolic agent, and incontinence is a very important diuretic enhancer that reduces water retention and promotes vascularity [21].

Benzothiazin-4-ones are a class of compounds that have been connected to numerous biological processes. When exposed to 2-substituted-2,4-dihydroxyphenyl derivatives, the human breast cancer T47D cell line has antiproliferative activity [22], and several gram-positive bacterial strains are adversely affected by these substances [23]. The 2-amino-4H-3,1-benzothiazin-4-ones were described as potent adenosine receptor antagonists with an affinity

for all human subtypes[24]. Inhibitors of human leukocyte elastase and cathepsin L exhibited to be 2-amino-and 2-alkylthioanalogs, respectively [25]. The decaprenyl-phosphoryl-D-ribose is the target of the other 4*H*-3,1-benzothiazin-4-one-based medications. 2-Epimerase is a unique family of pharmacological possibilities for treating tuberculosis [26-28].

Compounds with heterocyclic rings fused to the thiazin-4-one(6) were less widely explored compared to 4*H*-3,1-benzothiazin-4-one. Imidazo[4,5-*d*][1,3]thiazine-7(3*H*)-thiones were designed as acyclovir analogs, but they showed weak biological properties, and ribofuranosyl derivatives showed antibacterial activity [29-31]. 4-Acylimino-2-aminothieno[2,3-*d*][1,3]thiazin-4-ones exhibited potent antagonists of adenosine receptors[24]. 2-bromo-4chloro-6-(3,6-dihydro-6-substituted-3-phenyl-2-(phenylimino)-2*H*-1,3-thiazin-4-yl)derivatives (7) showed good antibacterial activity against several Gram-positive and Gram-negative bacteria [32]. The multi-thioether derivatives (8) exhibited antitumor activity against A-549 (human lung cancer cell) and B cap-37 (human breast cancer cell)[33].

The 2-substituted guanidino-4-(2'-amino-5'-aryl)mercapto-6-phenyl-1,3-thiazines(9) exhibited good to excellent analgesic, anti-inflammatory, and mild ulcerogenic activities comparable to indomethacin and aspirin respectively[34]. The amino-dihydrothiazine derivatives (10) were used to prevent diabetes, mainly type-2 diabetes, by selective inhibition of BACE2 [34-36].

A series of tetrahydro[1,3]-thiazine derivatives (11) were synthesized from condensation of thiocarbamide and malonyldichlorides and used as anti-inflammatory and immunosuppressive agents. Among mercaptothiazine derivatives 5,5-diallyl-2-phenylimino-3-phenyl-2,3,4,5-tetrahydro-[1,3]-thiazine-4,6-dione and 5,5-diethyl-2-phenyl-imino-3-naphthyl-2,3,4,5-tetrahydro-[1,3]-thiazine-4,6-dione (12) showed remarkable inhibition of inflammation. These compounds also showed immunomodulatory and immunosuppressive activities [37].

3. Electronic Features and Pharmacological Role of 1,4-Benzothiazines and its Derivatives

It is acknowledged that 1,4-benzothiazine derivatives have medical significance and are extensively used in drug development. The primary component of the pheomelanin and trichomemelamine found in mammalian hair and feathers is 1,4-benzothiazine derivatives[38]. As a result, various variations of this molecule have been developed as potential targets for new therapeutic development. 1,4-Benzothiazines are thought to be involved in various biological processes [39–41]. Some 1,4-benzothiazines exhibit biological activity comparable to phenothiazines due to the existence of a fold along the nitrogen sulfur axis and share the same structural specificity [42–47]. 1,4-benzothiazine is used in medicinal chemistry, and the pharmacological and chemical features of 1,4-benzothiazines and phenothiazines[48]. Generally, benzothiazine derivatives have found extensive biological and chemical applications such as analgesic, anti-inflammatory [49,50], antibacterial[51], antineoplastic or anticancer [52], antiepileptic or anti-seizure [53], antidiabetic[54], antifungal [55], anthelmintic [56], anti-HCV [57], antihypertensive [58], antimalarial [59], antimicrobial [60], antiproliferative [61], anti-psychotropic [62], antithyroid [63], antitubercular [64], antiviral agents [65], vasorelaxant [66] and calcium channel antagonist [67]. In addition, 1,4-benzothiazine is the primary structural component of numerous medications, including

antibiotics and medicines that decrease blood cholesterol [68]. Particularly in many *in vivo* and *in vitro* experimental setups, 1,4-benzothiazine derivatives have been demonstrated to exhibit several biological effects[69].

1,4-benzothiazine is used as a chemical dye, ultraviolet (UV) light-absorbing medium, and free radical scavenger[70,71]. The corrosion inhibitory characteristics of 1,4-benzothiazine against mild steel in hydrochloric acid (HCl) solution[72]. The 1-(3-methyl-4H-1,4-benzothiazin-2-yl) ethanone is an effective inhibitor in the cathodic domain. Clinical research has exhibited the versatility of semotiadil fumarate (13), a 1,4-benzothiazine derivative, as a calcium channel antagonist with the added benefit of its highly selective vasodilatory actions [73,74]. To produce compounds with increased antagonist action, attempts are being made to alter and synthesize a few novel semotiadil derivatives [75,76].

3-(3,4,5-trimethoxy-phenyl)-2H-1,4-benzothiazine(14)and3-(4-nitrophenyl)-6-(trifluoromethyl)-2H-1,4-benzothiazine (15) [77,78] showed good antibacterial effect with MIC value of 25mg/ml and 2-(4-ethylbenzoyl)-7-chloro-3-methyl-5-trifluoromethyl-4H-1,4-benzothiazine(16) exhibited good antibacterial activity against five bacterial strains with (16–19) mm zone of inhibition.

The1,4-benzothiazine derivatives exhibited Hepatitis C Virus (HCV) inhibitory activity. The 4-(1,1-dioxo-1,4-dihydro-1λ6-benzo[1,4]thiazin-3-yl)-5-hydroxy-2H-pyridazin-3-ones(17) exhibited potent inhibitory activities and act as HCV-NS5B polymerase inhibitors [79]. A series of hydroxyquinolone-1,4-benzothiazine analogs (18 and 19) have sub-micromolar action against the HCVNS5B polymerase in antiviral drug search [80].

A series of phenyl-substituted pyrazole and pyrimidine benzothiazinedioxides (20&21) exhibited antimalarial action via hemoglobin hydrolysis inhibition. 1,4-Benzothiazine with biphenyl substitution on the C-2 position(22) exhibited highly anti hyperlipidemic or cholesterol-lowering activity with LD₅₀ value of 12.8 mM[81].

The2-Methyl-1,2,3,4-tetrahydro-10H-pyrido[4,3-b][1,4] benzothiazine(23) exhibited superior analgesic action, so it is an appropriate alternate for a number of presented challenging NSAIDs[82]. Benzothiazine core within the phenothiazine moiety was vital in anticancer treatment[83]. The enamionone(24) has an important synthon for the preparation of fused1,4-thiazine derivatives, like 2-(aryl-hydrazone)-6,7-dimethoxy-2H-1,4-benzothiazin-3-(4H)-ones(25),8,9-dimethoxy-11H-[1,2,4]triazolo[3,0,4:3,4][1,2,4]triazino-[6,5-b][1,4]benzothiazine(26)and10,11-dimethoxy-13H-benzimidazolo[20,10:3,4][1,2,4]triazino[6,5-b][1,4]benzothiazine(27) showed good activity against the HCT-116 cell line more than HEPG2 and MCF7 cell lines[84].

Compounds 28 and 29 showed effective inhibition of platelet aggregation activity induced by collagen, epinephrine, ADP, and platelet-activating factors[85,86].

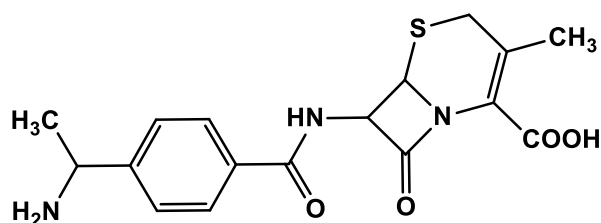
The compound (30) showed a powerful aldose reductase inhibitor activity *in vitro*, a considerable decrease in orbital accumulation in the rat sciatic nerve and lens, and antihypertensive actions[87]. Alzheimer's disease(AD) is a brain disorder that causes progressive and irreversible reduction in memory. Because HMGCoA reductase is directly associated with AD, 1,4-benzothiazine analogs such as 7-(2-aminoethyl)-3,4-dihydro-5-hydroxy-2H-1,4-benzothiazine-3-carboxylic acid(31) is an inhibitor of HMGCoA reductase and useful for preventing, treating, and delay the onset of and/or decreasing the risk of AD[88].1,4-Benzothiazine is also valuable in fighting cerebral ischemia, brain edema, brain

hemorrhage, brain infarction, and brain disorders from dementia, psychosis, injuries, neuropathy, etc [89].

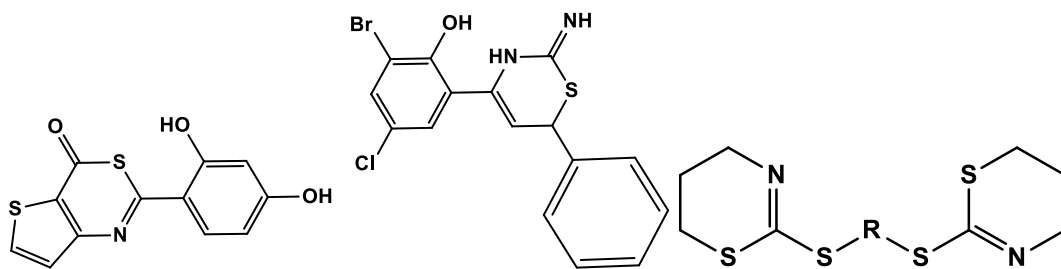
Benzothiazine derivatives showed both CNS exciting and muscle relaxant potentials. The neuropsychological outline of centrally acting skeletal muscle relaxant, the triazolo-benzothiazine analog, 2,4-dihydro-1,2,4-triazolo[3,4-c][1,4]benzothiazin-1-one(32) and activity was compared to the mephenesin, a muscle relaxant drug. Compound(32) was safer and had a longer duration of action than mephenesin[90]. A benzothiazine analog, Rifamycin(33), is effective against *Mycobacterium tuberculosis* and is used in the treatment of tuberculosis (TB), leprosy, and complex infections of *M. avium*[91].

4. Electronic Features and Pharmacological Role of 1,2-Benzothiazine and its Derivatives

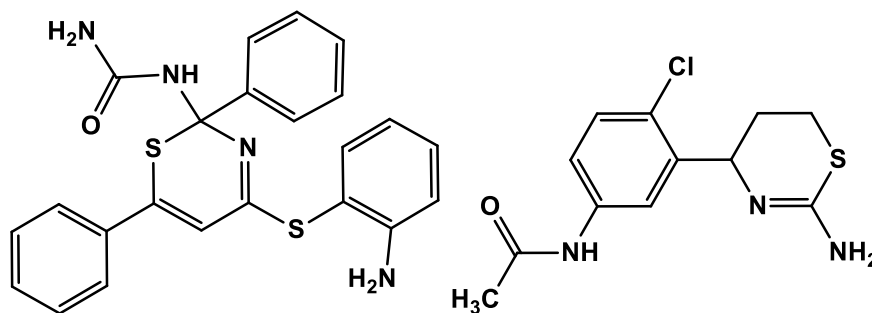
1,2-Benzothiazine 1,1-dioxide nucleus, first synthesized by Braun et al., and is familiar for its various benzothiazine derivatives like Ampiroxicam®, Lornoxicam®, Meloxicam®, and Sudoxicam®[92](Figure3). These are known as oxicams and are used as non-steroidal anti-inflammatory drugs(NSAIDs)[93]. Benzothiazine derivatives are known for their diversified pharmacological activities, e.g., 3,4-dihydro-1,2-benzothiazine-3-carboxylate 1,1-dioxide- α -ketomide and P(2)–P(3) peptide mimetic aldehyde compounds as potent calpain-I inhibitors[94] while 1,2-benzothiazin-3-yl-quinazolin-4(3*H*)-ones possess antibacterial activities [88], antioxidants[95], and used for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, rheumatic and non-rheumatic disorders[96]. The biological activity of several thiazine derivatives, such as those that are antifungal, antiviral, bacteriostatic, anti-parasitic, anti-tuberculous, and insecticidal, as documented in the literature. It has been discovered that several commonly synthesized thiazines and related chemicals have a wide range of functions[97]. A new generation benzothiazine derivative (6,7-dimethoxy-1,1-dioxido-2*H*-benzo[e][1,2]thiazin-3-yl)(4-fluoro-phenyl)methanone was developed using chalcone sulfonylamide showed antimicrobial efficacies against Gram-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus* [98]. 4-hydroxy-3-(4-methoxybenzoyl)-2-[2-(4-phenyl-1-piperazinyl)-2-oxoethyl]-2*H*-1,2-benzothiazine 1,1-dioxide, 4-hydroxy-3-(4-methoxybenzoyl)-2-[2-[4-(2-pyrimidyl)-1-piperazinyl]-2-oxoethyl]-2*H*-1,2-benzothiazine 1,1-dioxide, 4-hydroxy-3-(4-methoxybenzoyl)-2-[2-[4-(2-methoxyphenyl)-1-piperazinyl]-2-oxoethyl]-2*H*-1,2-benzothiazine-1,1-dioxide showed effects against *Staphylococcus aureus*, and *Enterococcus faecalis* [99]. All the structures are put in Figure 3.



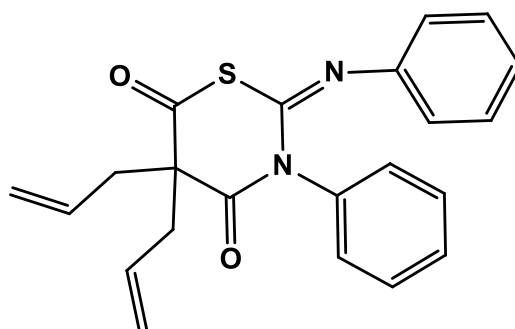
Cephalosporin (5)



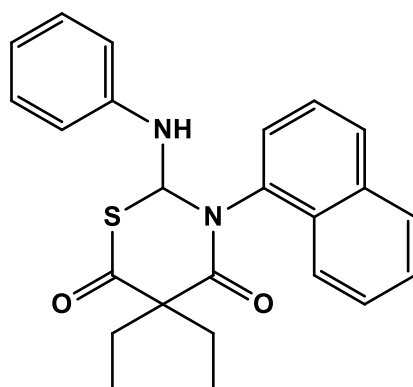
Benzothiazin-4-one (6) 1,3-thiazin-4-yl derivatives (7) Thioether compound (8)



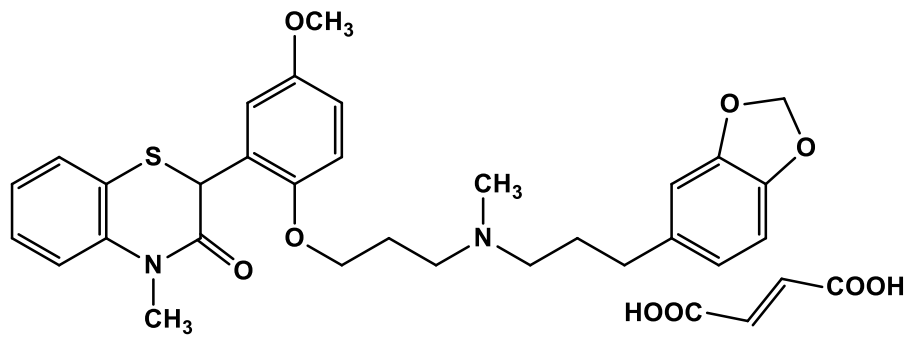
Mercapto-6-phenyl-1,3-thiazine (9) Aminodihydrothiazines (10)



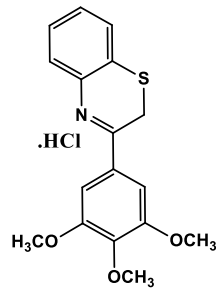
**(E)-5,5-diallyl-3-phenyl-2-(phenylimino)-1,3-thiazinane-4,6-dione
(11)**



**5,5-diethyl-3-(naphthalen-1-yl)-2-(phenylamino)-1,3-thiazinane-4,6-dione
(12)**

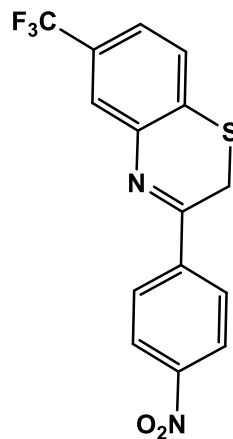


Semotiadil fumarate (13)



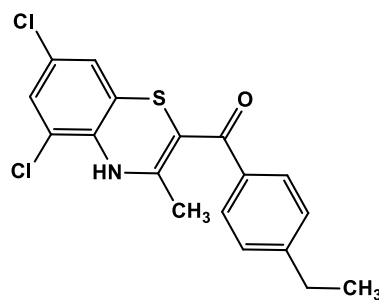
3-(3,4,5-trimethoxyphenyl)-2H-benzo[b][1,4]thiazine hydrochloride

(14)



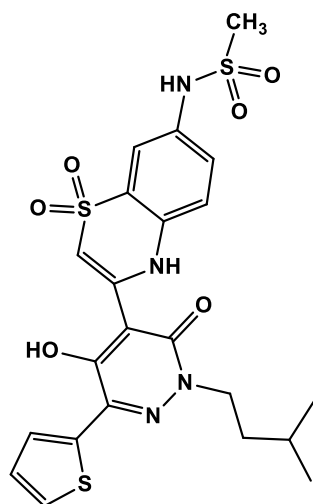
3-(4-nitrophenyl)-6-(trifluoromethyl)-2H-benzo[b][1,4]thiazine

(15)

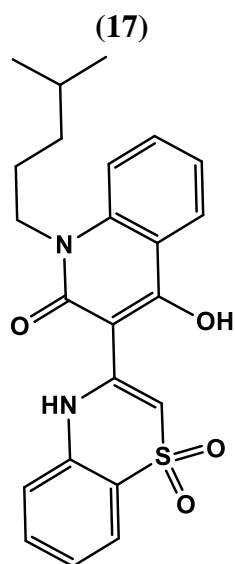


(5,7-dichloro-3-methyl-4H-benzo[b][1,4]thiazin-2-yl)(4-ethylphenyl)methanone

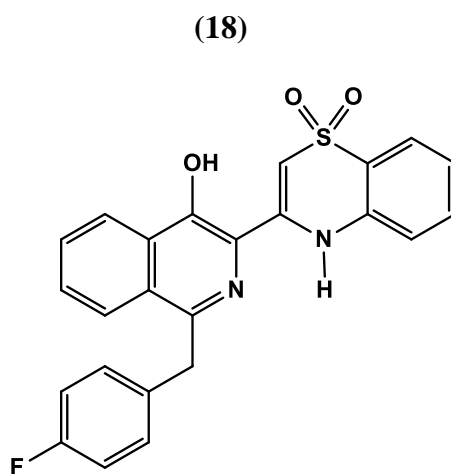
(16)



N-(3-(5-hydroxy-2-isopentyl-3-oxo-6-(thiophen-2-yl)-2,3-dihydropyridazin-4-yl)-1,1-dioxido-4*H*-benzo[*b*][1,4]thiazin-7-yl)methanesulfonamide

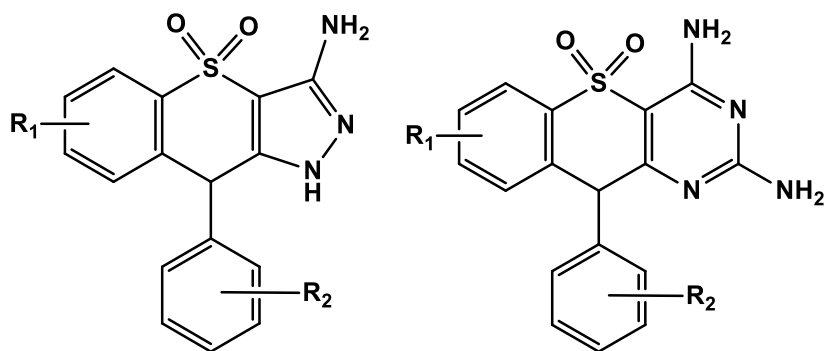


3-(1,1-dioxido-4*H*-benzo[*b*][1,4]thiazin-3-yl)-4-hydroxy-1-(4-methylpentyl)quinolin-2(1*H*)-one

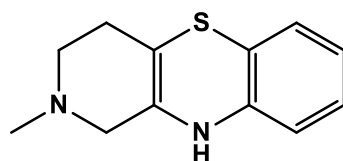
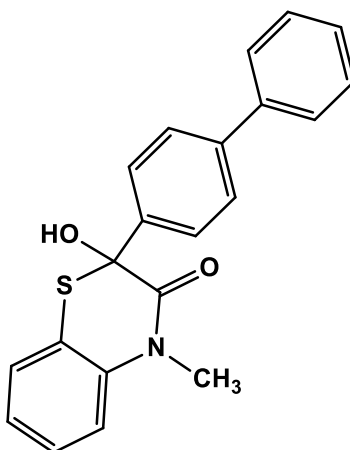


3-(1-(4-fluorobenzyl)-4-hydroxyisoquinolin-3-yl)-4*H*-benzo[*b*][1,4]thiazine 1,1-dioxide

(19)

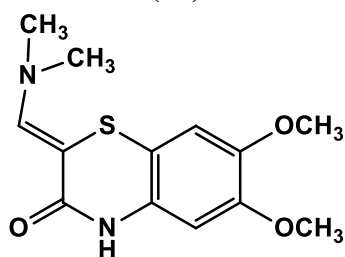


(20) $R_1 = 7Cl, R_2 = 2CH_3$ (21) $R_1 = 8Cl, R_2 = H$ (22)



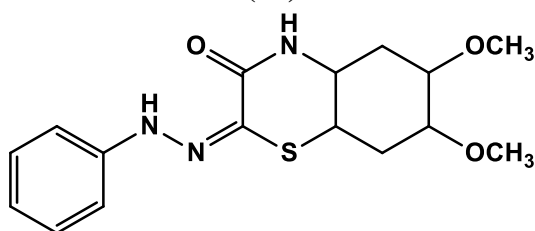
2-methyl-2,3,4,10-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]thiazine

(23)



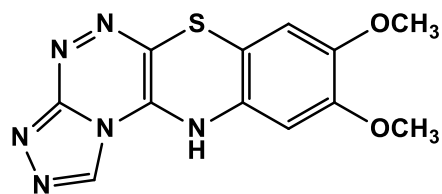
(Z)-2-((dimethylamino)methylene)-6,7-dimethoxy-2H-benzo[b][1,4]thiazin-3(4H)-one

(24)



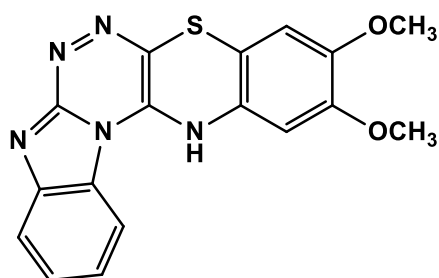
(E)-6,7-dimethoxy-2-(2-phenylhydrazono)hexahydro-2H-benzo[b][1,4]thiazin-3(4H)-one

(25)



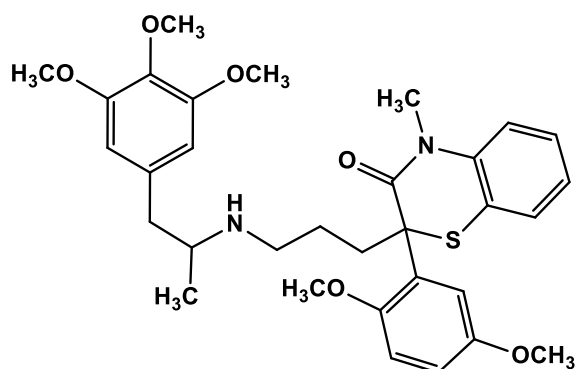
8,9-dimethoxy-11*H*-benzo[5,6][1,4]thiazino[3,2-*e*][1,2,4]triazolo[3,4-*c*][1,2,4]triazine

(26)

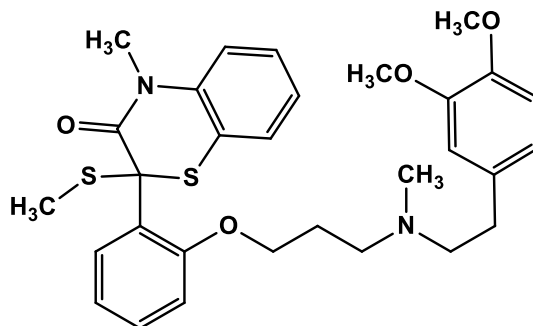


2,3-dimethoxy-14*H*-benzo[4,5]imidazo[2,1-*c*]benzo[5,6][1,4]thiazino[3,2-*e*][1,2,4]triazine

(27)

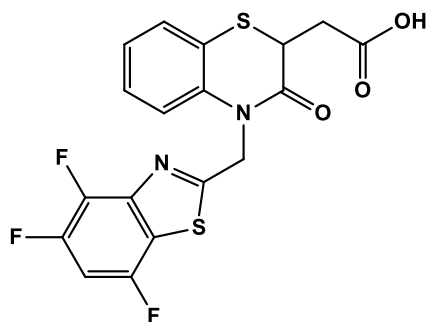


2-(2,5-dimethoxyphenyl)-4-methyl-2-(3-((1-(3,4,5-trimethoxyphenyl)propan-2-yl)amino)propyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one



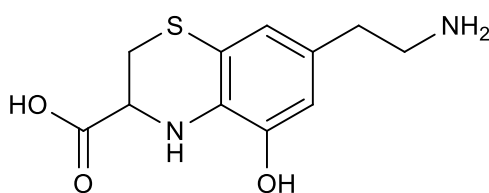
2-(2-(3-((3,4-dimethoxyphenethyl)(methyl)amino)propoxy)phenyl)-4-methyl-2-(methylthio)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one

(29)



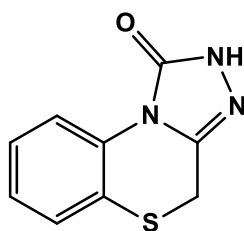
2-(3-oxo-4-((4,5,7-trifluorobenzo[*d*]thiazol-2-yl)methyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazin-2-yl)acetic acid

(30)



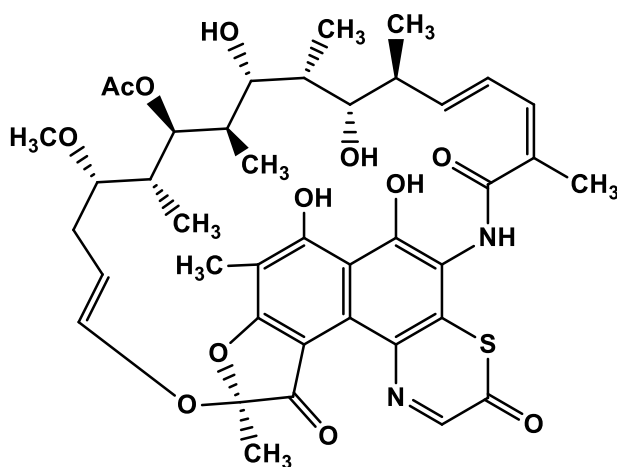
7-(2-aminoethyl)-5-hydroxy-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine-3-carboxylic acid

(31)



2,4-dihydro-1*H*-benzo[*b*][1,2,4]triazolo[4,3-*d*][1,4]thiazin-1-one

(32)



(33)

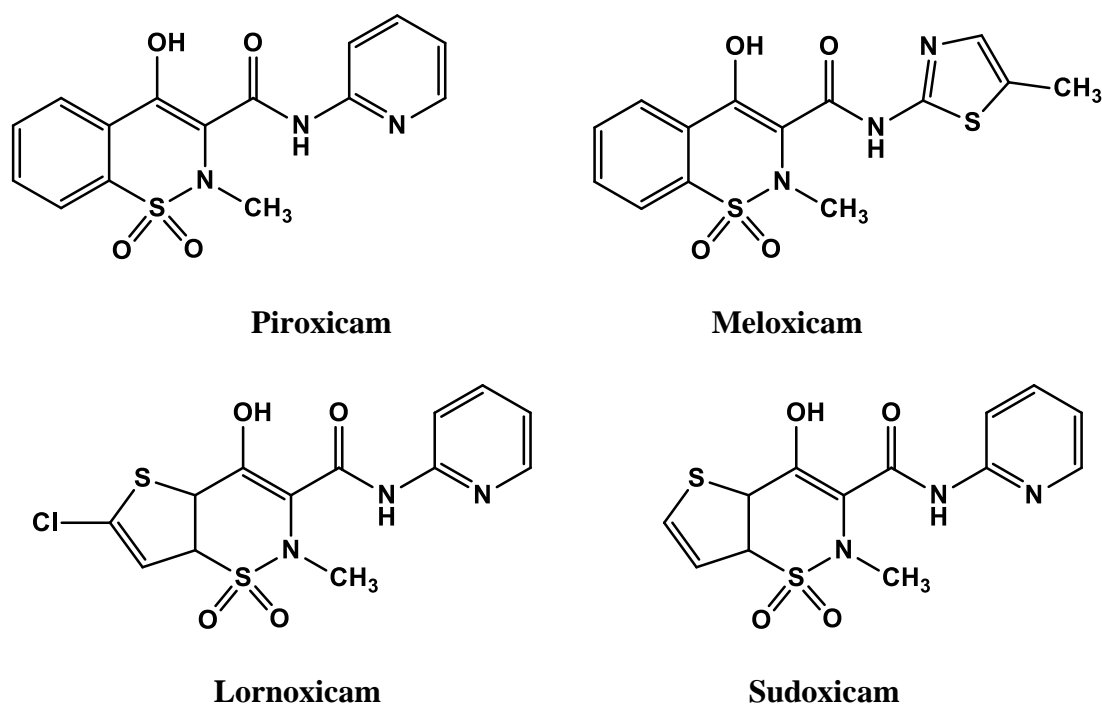


Figure 3. Chemical structures of biological potent Thiazine derivatives.

5. Conclusion

According to the literature, heterocyclic ring systems containing nitrogen and sulfur are beneficial to the evolution of humans and associated societies. These heterosystems are necessary to treat deadly diseases affecting human and animal species. Thiazines are a class of heterocyclic compounds that are highly significant and have prospective applications in the treatment of a wide range of illnesses and disorders, according to information published in the literature. Many thiazine derivatives that are physiologically active against different diseases were listed in this review. Thiazine research has also attracted the curiosity of medicinal and biochemical chemists and shown that this powerful molecule has the potential to be exploited to make bioactive drugs, which has considerably sparked their interest. This review offers information that will be extremely helpful to medicinal chemists in creating better and more effective, affordable, and widely accessible thiazine derivatives. We can also conclude that many other thiazine compounds may have potent pharmacological effects. The review aims to talk about how vital it is to have access to significant commercial compounds in the quest for a brighter future, particularly innovative and structurally varied heterocycles of possible medicinal interest, such as thiazine derivatives. According to the study, the biological activities of thiazine derivatives were discovered to be diverse, and they could serve as a model for future development by being modified or derivatized to create more potent and physiologically active compounds. If tested, the novel skeleton might also have additional biological functions similar to the parent ring systems.

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Conflict of interest

None.

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