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Review Article

A REVIEW: SYNTHESIS AND MEDICINAL IMPORTANCE OF 1,4-BENZOTHIAZINE ANALOGS

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ABSTRACT

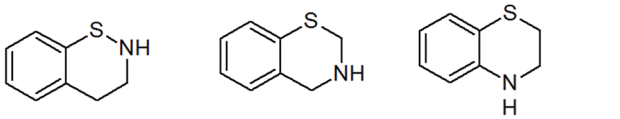
The ultimate beneficiary of scientific advances is discovering new and better therapeutic agents. 1,4-benzothiazine forms an important class of heterocyclic system, contains both N and S. Consequently, there have been various efforts for the production of novel 1,4-benzothiazine derivatives possessing various biological activities such as anti-hypertensive, anti-HIV, anti-inflammatory, antimicrobial, anti-rheumatic, ATP-sensitive potassium channel opener, cardiovascular, cytotoxic, immunomodulator, neuroprotective, antioxidant, antimalarial and aldose reductase inhibitor etc. As a part of an ongoing effort toward finding novel pharmacological active agents, it was thought worthwhile to synthesize hybrids of 1,4-benzothiazine.

Keywords: 1,4-Benzothiazine, Ring expansion reaction, Biological activity, 2-aminothiophenol.

INTRODUCTION

Several sulfur and nitrogen containing heterocyclic compounds have been studied. 1,4-various derivatives of benzothiazine derivatives can be synthesized by the various methods [1-7]. 1,4-benzothiazine derivatives are important because of their interesting biological properties such as antibacterial [8-10], antifungal [11-14], anti-hypertensive [15-18], Ca antagonist [19,20], anti-inflammatory [21,22], central nervous system activity [23,24], HCV NS5B polymerase inhibitor [25], anti-rheumatic [26], aldose reductase inhibitor [27], potassium channel opener [28,29] antioxidant [30], cardiovascular [31], antimalarial [32], anti-HIV [33], neuroprotective [34], anthelmintic [35] and N-methyl-D-aspartate receptor antagonist [36] etc. 1,4-benzothiazine forms an important class of heterocyclic system. Several studies are available for 1,4-benzothiazine formation and their application in drugs. 1,4-benzothiazine and thiazoles constitute an important class of sulfur and nitrogen heterocytes.

Benzothiazine rings are of following types depending on the position of the sulfur and nitrogen in the ring.



1,2-BENZOTHIAZINE 1,3-BENZOTHIAZINE 1,4-BENZOTHIAZINE

Thiazine is the suffix used for six membered ring containing one nitrogen and one sulfur (Table 1).

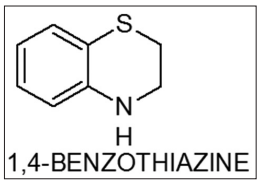
SYNTHESIS OF 1,4-BENZOTHIAZINE RING

i. From ring expansion reaction of benzothiazolines
ii. From α-haloacyl system, α-haloketon, α-haloacids, α-haliacyl chloride and haloesters
iii. From α, β-unsaturated acids and esters
iv. From maleic anhydride
v. From α-cyno α-alkoxy carbonyl epoxide.

Synthesis of benzothiazine from ring expansion reaction of benzothiazoline

Benzothiazoline obtained from *o*-aminothiophenole undergo novel ring expansion reaction to benzothiazine. Thus, *N*-acyl derivative benzothiazoline on treatment with sulfonyl chloride undergo ring expansion to benzothiazine. The reaction proceeds by the immediate formation of sulfonation ion forwarded by ring cleavage substituent intermolecular cyclization to benzothiazine [3] (Fig. 1).

Table 1: Physical properties of 1,4-benzothiazine

1	Structure	 1,4-BENZOTHIAZINE
2	IUPAC name	2,3-dihydro-1, 4-benzothiazine
3	Molecular formula	C_8H_9NS
4	Molecular weight	165.22
5	Shape	Diamond shape plate, rhombic leaflets
6	Taste	Acrid
7	Odor	Garlic
8	Uses	CNS stimulant, immunomodulator
9	Color	Slightly yellow
10	Solubility	Soluble in benzene, ether, DMSO Insoluble in water

DMSO: Dimethyl sulfoxide, CNS: Central nervous system

Synthesis of benzothiazine ring from α-halo carbonyl system

α-Halocarbonyl system reacts with α-ATP to afford benzothiazine derivatives. The reaction followed as a general pattern in which the halogen atom replaced by the thiol functional group followed by the intermolecular cyclization [4] (Fig. 2).

Synthesis of ring from α, β-unsaturated acid and esters

The reaction of α, β -unsaturated acid and esters with *o*-ATP displays interesting product variation depending on reaction conditions and substrates. It is generally observed that acrylic acid derivatives having strong electron withdrawing b-carbonyl substituents such as -CoAr, -COOH, $-CONH_2$ or COO-alkyl on reaction with *o*-ATP afford benzothiazine derivatives whereas acrylic acid with β-alkyl or β-aryl substituents form benzothiazipines [5] (Fig. 3).

Benzothiazine ring from maleic anhydride

1,4-benzothiazine-2-acetic acid has been prepared by the reaction of *o*-ATP with maleic anhydride in diethyl ether. This is an exothermic reaction and directly yields the corresponding benzothiazine at room temperature. This reaction is believed to proceed throughout the formation of *o*-mercaptomaleanilic acid intermediate formed from initial nucleophilic anhydride ring opening cyclize *in situ* providing 1,4-benzothiazine-2-acetic acid [6] (Fig. 4).

Benzothiazine ring from α-cyno α-alkoxy carbonyl epoxide

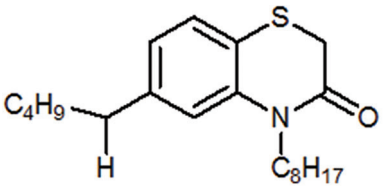
The synthesis of 1,4-benzothiazines from α-cyano α-alkoxy carbonyl epoxides is another alternative. The reactants are mixed and heated under reflux of acetonitrile. Several types of reactivity of these α-cyano α-alkoxy carbonyl epoxides are SN2 type reactions between nucleophiles and the two epoxides carbon atoms. However, when there is a steric hindrance at the level of the nucleophile, the reaction takes place in this case on the carbonyl of the ester group [7] (Fig. 5).

BIOLOGICAL ACTIVITY OF 1,4-BENZOTHIAZINE

Antimicrobial activity

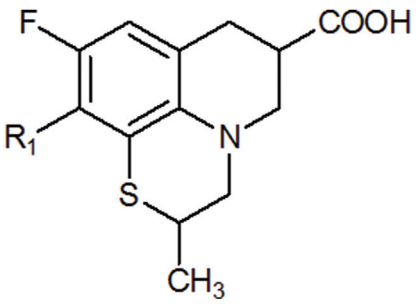
Antibacterial activity

The synthesis of 4-octyl-2*H*-1,4-benzothiazine-3-one showing antibacterial activity was reported by Guarda *et al*. (2003). The new compound was prepared by acylation or alkylation of the amino group under phase transfer catalysis condensation. Acid hydrolysis of the alkyl acylamino-2*H*-1,4-benzothiazine-3-one affords *N*-alkykamino-benzo thiazine-3-one (1) [8].



(1)

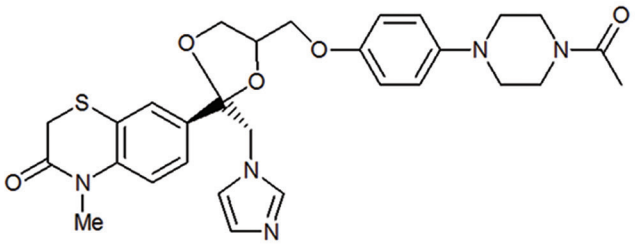
The synthesis of 2-substituted 7-oxo-2,3-dihydro-7*H*-pyridol[1,2,3-de][1,4]bezothiazine-6-carboxylic acid was prepared and its antibacterial activity were reported by Cecchetti *et al*. (1993). Among all derivatives the most active compound 2 was and rapidly absorbed and induced lasting plasma and urinary levels [9].



(2)

Antifungal activity

The novel ketoconazole analogue based on the replacement of 2,4-dichlorophenyl group with 1,4-benzothiazine moiety were design and synthesized by Schiaffella *et al*. (2006). These compounds were computationally investigated to assess whether the 1,4-benzothiazine moiety was a suitable bioisosteric replacement for the 2,4-dichlorophenyl group of KTZ in order to obtain a more potent inhibition of CYP 51 enzyme of *Candida albicans*. The best activity was observed in the racemic trans-7 analog (3) [11].



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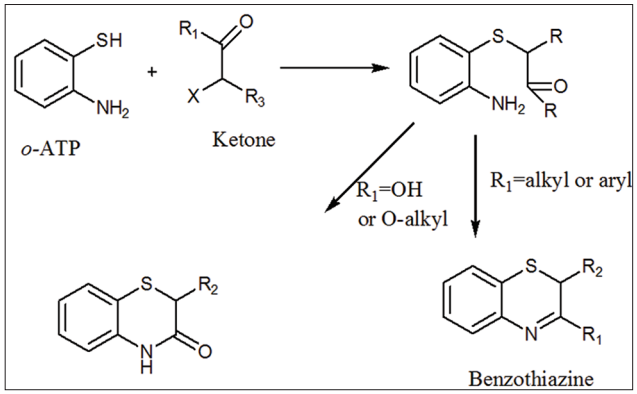


Fig. 1: Synthesis of benzothiazine from ring expansion reaction of benzothiazoline

Fig. 2: Synthesis of benzothiazine ring from α-halo carbonyl system

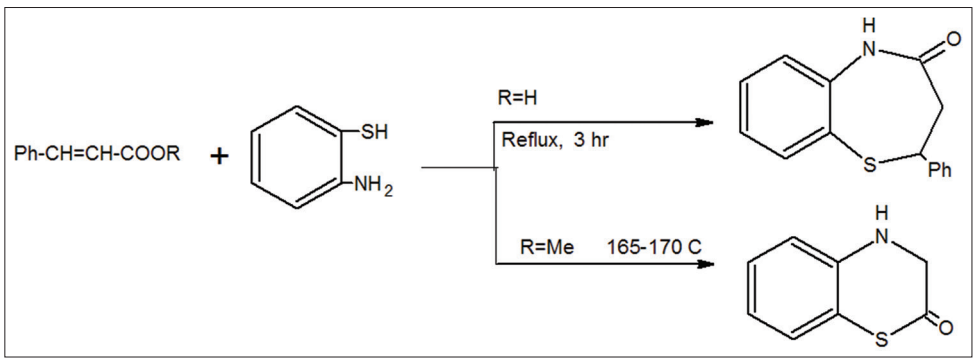
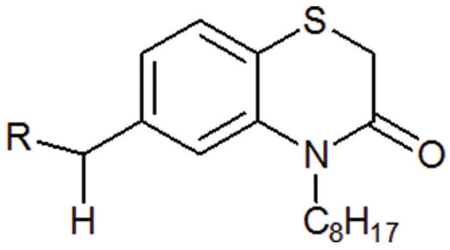


Fig. 3: Synthesis of ring from α, β-unsaturated acid and esters

The synthesis and antifungal activity of a series of 1,4-benzothiazine and 1,4-benzoxazine imidazole derivatives were studied by Macchiarulo *et al*. (2002) mainly showing antifungal activity compound shows most potent antifungal activity [12].

The synthesis and study of antimicrobial activity of 1,4-benzothiazine were reported by Deshmukh *et al*. (2007) and the compound 4 showed the highly promising antifungal activity against *Aspergillus niger* [13].

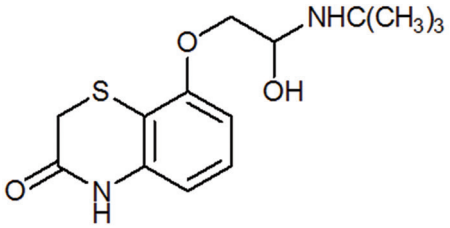


(4)

Anti-hypertensive activity

β-Adrenoreceptor blocker

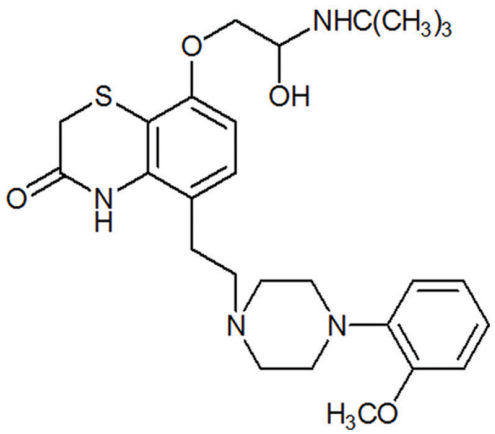
An oxypropanolamine side chain linked to an aromatic ring is the chemical features required for b-blocking activity. The alteration of these features as the intercalation of an imino group in the side chain does not abolish the interaction on b-adrenoceptors but can lead, in some cases, to potent b-antagonists. To evaluate the effect by a different type of insertion of pharmacophore oxypropanolamine chain in the 1,4-benzothiazine moiety (5) that possesses short-lived blood pressure reducing effects in experimental animals [15].



(5)

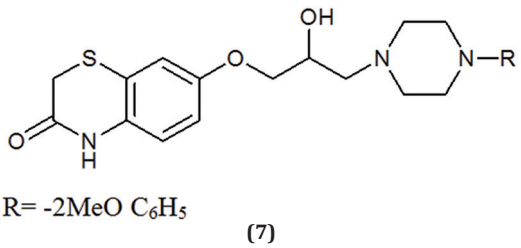
α-Adrenoreceptor blocker

To expand the investigation on benzothiazine derivatives with anti-hypertensive properties, the 1, 4-benzothiazine nucleus has been variously functionalized with phenylpiperazine or acylpiperazine (AP) moieties (6) to drive the activity toward the a-andrenoceptor (a-AR). The rational of this design is due to the high affinity for a-AR, and particularly for a1-AR, displayed by AP-containing products [16].



(6)

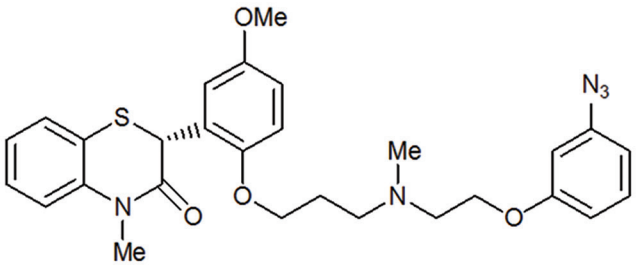
A series of compound having a piperazine moiety variously linked to the benzothiazine nucleus were synthesized and evaluated by Cecchetti *et al*. (2000) for their *in vitro* α-adrenoreceptor affinity by radiligand receptor binding assays. In the oxyproanopiperazine series shows good and selective α_1-AR affinity, which was higher for the (2-methoxyphenyl) piperazine derivatives (7) [17].



(7)

Calcium channel blocker

The aliphatic and the aromatic azido derivative of semotiadil a novel calcium antagonist with 1,4-benzothiazine skeleton were synthesized by Watanabe *et al*. (1996) for developing photoaffinity probes of L-type calcium channel. The azidophenoxy derivatives (8) proved to be a potent calcium antagonist [19].



(8)

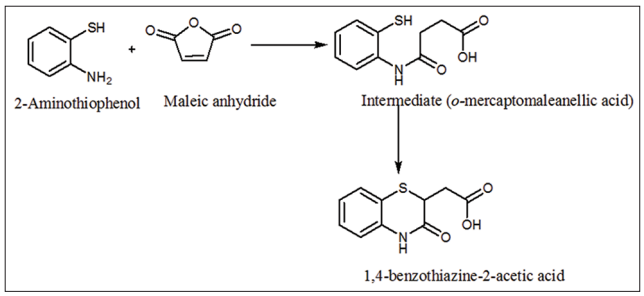


Fig. 4: Synthesis of ring from maleic anhydride

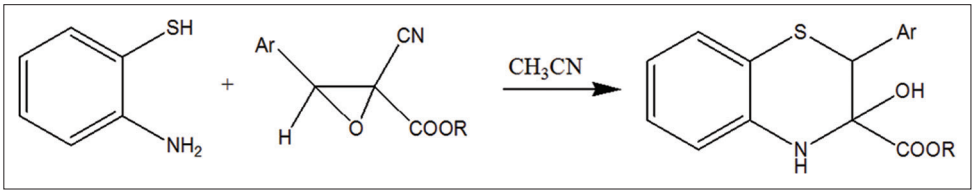
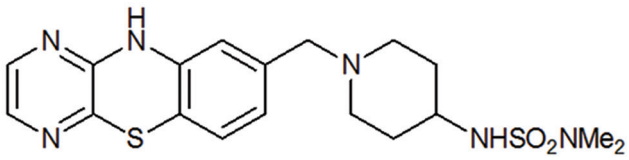


Fig. 5: Synthesis of ring from α-cyano α-alkoxy carbonyl epoxides

Anti-inflammatory activity

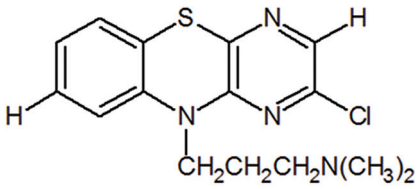
A new series of 10*H*-pyrazino [2,3-*b*] [1,4] benzothiazine derivatives were studied by Kaneko *et al*. (2002). *N*-[1-(10*H*-pyrazino [2,3-*b*] [1,4] benzothiazin-8-ylmethyl)-piperidin-4-yl]-*N'*,*N'*-dimethylsulfamide (9) showed the potent oral inhibitory activities against neutrophil migration in a murine interleukin-1 induced paw inflammation model [17,21].



(9)

Tranquilizing activity

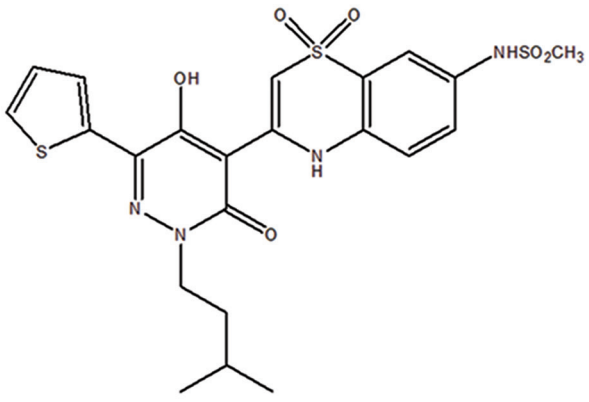
The chloro and methyl substituted 10*H*-pyrazino [2,3-*b*] [1,4]-benzothiazine were prepared and studied by Saari *et al*. (1983). Its structure was determined by C^{13} NMR and X-ray crystallographic analysis. The 2-chloro compound 10 proved to be the most effective derivative in displacing [3*H*] siperone, [3*H*] apomorphine and [3*H*] prazosin radioligands from binding sites [23].



(10)

HCV NS5B polymerase inhibitor

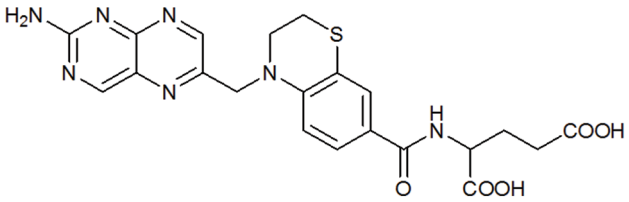
4-(1,1-Dioxo-1,4-dihydro-1k6-benzo[1,4]thiazin-3-yl)-5-hydroxy-2H-pyridazin-3-one analogs (11) were discovered by David *et al*. (2008) as a novel class of inhibitors of HCV NS5B polymerase. Structure-based design led to the identification of the compound that displayed potent inhibitory activities in biochemical and replicon assays as well as good stability toward human liver microsomes [25].



(11)

Anti-rheumatic activity

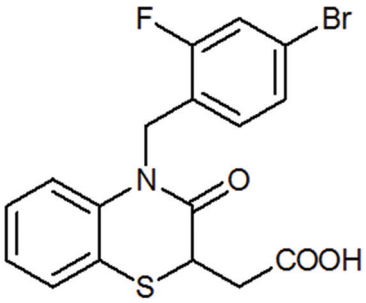
The novel methotrexate (MTX) derivatives bearing dihydro-2*H*-1,4-benzothiazine or dihydro-2*H*-1,4-benzoxazine (12) were synthesized by Matsuoka *et al*. (1997) and tested for *in vitro* anti-proliferative activities against human synovial cells and human peripheral blood mononuclear cells obtained from patients with rheumatoid arthritis (MX-68) is a potent and safe candidate anti-rheumatic agent, absent of the side-effect of MTX [26].



(12)

Aldose reductase inhibitors

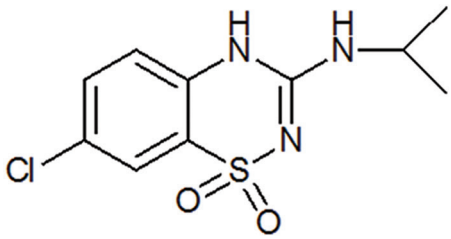
A number of 1,4-benzothiazine-2-acetic acid derivatives and their bioisosters were synthesized by Aotsuka *et al*. (1994) for the ability to inhibit aldose reductase in porcine lense. 4-(substituted benzothiazol-2-ylmethyl)-1,4-benzothiazine-2-acetic acid (13) derivative showed more potent aldose reductase inhibitory activity [27].



(13)

ATP-sensitive potassium channel opener

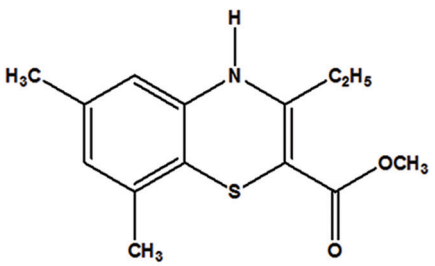
The synthesis and pharmacological evaluation of 4*H*-1,4-benzothiazine-2-carbonitril 1,1-dioxide and *N*-(2-cynomethyl sulfonyl phenyl) acylamide derivative were studied by Schou *et al*. (2005). 1, 2, 4- thiadiazine derivatives (14) like BPDZ-73 are potent opener ATP-sensitive potassium channel opener [28].



(14)

Antioxidant

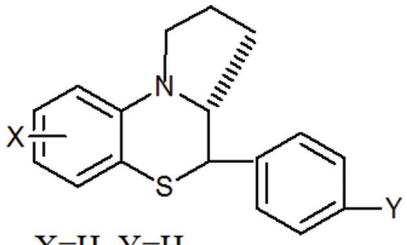
The synthesis and pharmacological evaluation of substituted 4H-1,4-benzothiazine,1,1-dioxides (sulfones) and N-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)benzothiazine derivative were studied by Gautam *et al*. (2012). Substituted 4H-1,4-benzothiazine,1,1-dioxides derivative (15) was found as a potent antioxidant by DPPH radical scavenging assay [30].



(15)

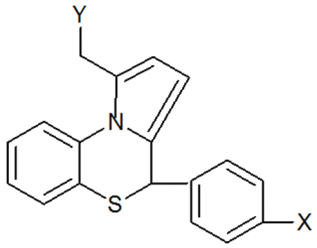
Cardiovascular activity

The synthesis and pharmacological evaluation of a series of pyrol [1,4]-benzothiazine derivatives were studied by Campiani *et al.* (1995). The compounds related to diltiazem have been shown to be representative of a novel series of calcium channel antagonist. Prerequisite for *in vitro* calcium channel blocking activity is the presence of two pharmacophore namely the substitution at C-4 and on the pyrrol ring. Two of the tested compounds (16 and 17) and were identified as potent calcium antagonist selective for cardiac over vascular tissues [31].



X=H, Y=H

(16)

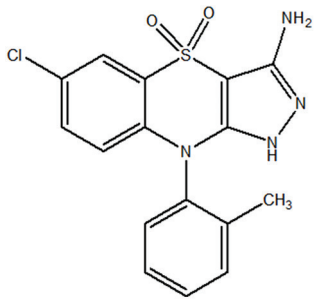


X=4'-OMe, Y=$(Me)_2$ N

(17)

Antimalarial activity

A series of phenylsubstituted pyrazolo and pyrimido benzothiazine dioxide derivatives were synthesized by Barazarte *et al.* (2008) and investigated for their abilities to inhibit b-hematin formation, hemoglobin hydrolysis and *in vivo* for their antimalarial efficacy in rodent *Plasmodium berghei*. Compounds 3-amino-7-chloro-9-(20-methylpheyl)-1,9-dihydropyrazolo -[4,3-b]benzothiazine 4,4-dioxide and 2,4-diamino-8-chloro-10H- phenyl-pyrimido-[5,4-b]benzothiazine 5,5-dioxide (18) were the most promising as inhibitors of hemoglobin hydrolysis [32].



(18)

CONCLUSION

The present review highlights that the 1,4-benzothiazine constitutes an important class of sulfur and nitrogen heterocytes. There are various methods available for formation of 1,4-benzothiazine and Its derivatives. They show various biological activities such as anti-hypertensive, anti-HIV, anti-inflammatory, antimicrobial, anti-rheumatic, ATP-sensitive potassium channel opener, cardiovascular, cytotoxic, immunomodulator, neuroprotective, antioxidant, antimalarial and aldose reductase inhibitor, etc. They may be used for the development of new drugs as an antimicrobial and anti-hypertensive agents by researchers.

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