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Benzothiazole derivaties and its Biological activities: A Review

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ABSTRACT

Different heterocyclic compounds are made to synthesize by large number of efforts and their derivatives were found to possess anti-tumor, antidiabetic, anti-microbial, anti-convulsant and anthelmintic activities. In recent years heterocyclic compounds analogues and derivatives have attracted strong interest due to their biological and pharmacological properties. Benzothiazole moiety is very small but it posses different biological activities by not only benzothiazole but its different substituted derivatives also give different biological activities. This review was focused on the benzothiazole and its different derivatives that posses different biological activities.

Keywords: Benzothiazole, Biological activities.

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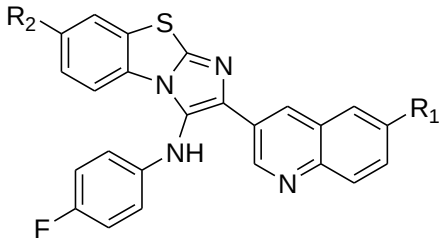
INTRODUCTION

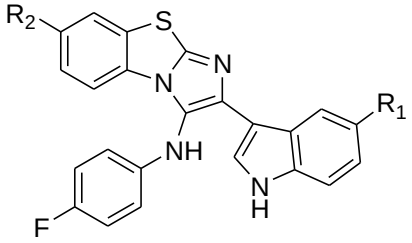
A heterocyclic compound is one which possesses a cyclic structure with at least two different kinds of hetero atoms in the ring. Nitrogen, oxygen, and sulphur are the most common heteroatoms. Benzothiazole ring made from thiazole ring fused with benzene ring. Thiazole ring is a five-member ring consists of one nitrogen and one sulfur atom in the ring. Benzothiazoles are bicyclic ring system. In the 1950s, a number of 2-amino benzothiazoles were intensively studied as central muscle relaxants and found to interfere with glutamate neurotransmission in biochemical, electrophysiological and behavioral experiments. Benzothiazole derivatives have been studied and found to have various chemical reactivity and biological activity. Benzothiazole derivatives have been studied and found to have various chemical reactivity and biological activity. Benzothiazole ring found to be possessing pharmacological activities such as anti-bacterial [1], anti- microbial [2], anti-diabetic [3], antitumor [4], anti- inflammatory [5], anthelmintic [6] activities.

ANTIMICROBIAL ACTIVITY

Al-Tel et al., [7] synthesized a series of imidazo[2,1-b][1,3]benzothiazole. The compounds **(1 a-d)** and **(2 a-e)** were tested for their in vitro antibacterial activity against Gram-positive bacteria S. aureus, E. faecalis and B. megaterium and Gram-negative bacteria E. coli, P. aeruginosa and E. aerogenes. The antifungal activity against C. albicans, C. parapsilosis, A. flavus and M. gypsuem. The compounds have shown good activity.



(1 a-d)



(2 a-e)

Comp. No.	R_1	R_2
1a	Br	F
1b	F	F
1c	OCH_3	F
1d	CH_3	F

Comp. No.	R_1	R_2
2a	Br	F
2b	F	F
2c	CH_3	F
2d	Br	OCH_3
2e	OCH_3	F

Sekar et al., [8] synthesized a series of 2-(1H-benzimidazol-2-yl)-5-(diethylamino)phenol, 2-(1,3-benzoxazol-2-yl)-5-(diethylamino)phenol, 2-(1,3-benzothiazol-2-yl)-5-(diethylamino) phenol. All compounds **(3a-i)** were evaluated for in vitro antibacterial activities against Escherichia coli and Staphylococcus aureus strains and in vitro antifungal activity against

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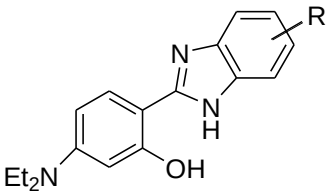
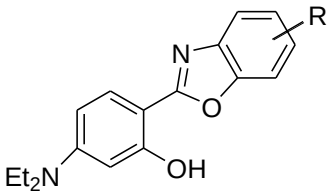
Candida albicans and Aspergillus niger strains by using serial dilution method. The compounds have shown moderate activity.



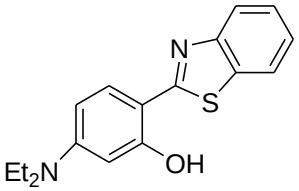
R= H, NO_2, NH_2

(3 a-c)



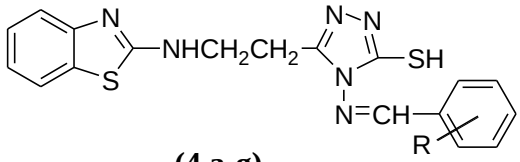
R= H, NO_2, NH_2

(3 d-h)



(3 i)

Soni et al., [9] synthesized a series of 5-[2-(1,3-benzothiazol-2-yl-amino)ethyl]-4-(arylideneamino)-3-mercapto-(4H)-1,2,4-triazoles. The synthesized compounds **(4 a-g)** were screened for their antibacterial activity against Bacillus subtilis MTCC 441, Escherichia coli MTCC 443 and Streptomyces griseus MTCC 1540 and antifungal activity against Candida albicans MTCC 227 and Aspergillus niger MTCC 282. All the compounds tested showed some degree of antimicrobial activity.



(4 a-g)

Comp. No.	R_1
4a	H
4b	4-OH
4c	2-NO_2
4d	3-NO_2
4e	2-Cl
4f	4-$N(CH_3)_2$
4g	3,4-OCH_3

Sahu et al., [10] synthesized a series of 1,3-benzothiazole-2-yl-hydrazones **(5 a-j)**. In vitro antimicrobial activity was evaluated against the four pathogenic bacterial strains, Bacillus subtilis, Escherichia coli, Klebsiella pneumoniae and Pseudomonas alkaligenes and three fungal strains Aspergillus niger, Rhizopus oryzae and Candida albicans. The compounds have shown moderate activity.

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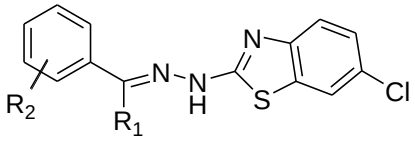
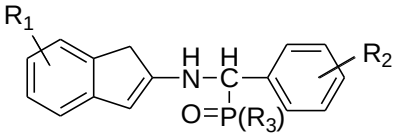


(5 a-j)

Comp. No.	R_1	R_2
5a	CH_3	No_2
5b	CH_3	Br
5c	CH_3	OCH_3
5d	CH_3	Cl
5e	CH_3	OH
5f	CH_3	NH_2
5g	C_6H_5	H
5h	CH_3	H
5i	H	F
5j	H	CH_3

ANTICANCER ACTIVITY

Song et al., [11] synthesized a series of a-Aminophosphonates containing benzothiazole and fluorine moiety, **(6 a-m)** were synthesized by Mannich-type addition in ionic liquid media with high yield and short reaction time. The newly synthesized compounds were evaluated for their anticancer activities against PC3, A431, A375, and Bcap37 cells in vitro by the MTT method. Compound **6c** is highly effective against PC3 cells and moderate to A431 cells.



(6 a-m)

Comp. No.	R_1	R_2	R_3
6a	4-CH_3	2-F	Et
6b	4-CH_3	2-F	*n*-Pr
6c	4-CH_3	2-F	*n*-Bu
6d	4-CH_3	4-CF_3	Me
6e	4-CH_3	4-CF_3	Et
6f	4-CH_3	4-CF_3	*i*-Pr
6g	4-CH_3	4-CF_3	*n*-Bu
6h	6-OCH_3	2-F	Me
6i	6-OCH_3	2-F	Et
6j	6-OCH_3	2-F	*n*-Pr
6k	6-OCH_3	2-F	*i*-Pr
6l	6-OCH_3	2-F	*n*-Bu
6m	6-OCH_3	2-F	Et

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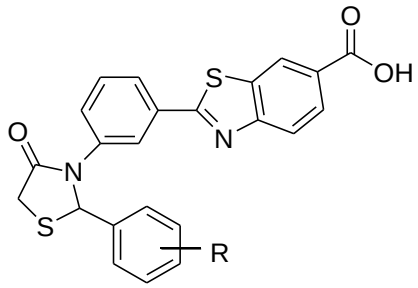
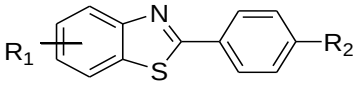
Prabhu et al., [12] synthesized a series of 2-(3-(4-oxo-2-substituted phenyl thiazolidin-3-yl)phenyl)benzo[d]thiazole-6-carboxylic acid derivatives **(7 a-h)** were synthesized by various benzothiazole Schiff's bases by reaction with thioglycollic acid. All the synthesized compounds were screened for their in vitro anticancer activity by 3-(4,5-dimethyl thiazole-2yl)-2,5-diphenyltetrazoliumbromide (MTT) assay on human cervical cancer cell line (HeLa) cell lines. Among these compound **7b** exhibited most significant activity as compared with **7e**, **7g** and **7h**. However, the activity was less as compared to the standard drug Cisplatin.



(7 a-h)

Comp. No.	R_1
7a	H
7b	*p*-Cl
7c	*m*-F
7d	*p*-NO_2
7e	*p*-OCH_3
7f	*p*-F,m-OCH_3
7g	*p*-CH_3
7h	*p*-OH

Bhuva et al., [13] synthesized a series of novel 2-phenyl-1,3-benzothiazoles. All the compounds **(8 a-j)** were tested for their anticancer activity against MCF-7 breast cancer cell line with the MTT assay. Most of the compounds showed moderate to good anti-breast cancer activity. Anticancer activity varied with substitution on the benzothiazole nucleus with halogens and at 4 position, substitution of the 2-phenyl moiety with methyl and methoxy groups was also explored. Among the compounds tested with MTT assay, mono fluoro substitution on benzothiazole nucleus and 4-methyl variations at 2-phenyl position demonstrated highest percent growth inhibition of MCF-7 cells. Docking studies of the synthesised compounds was done on EGFR using GRIP batch docking method to study their observed activity.



(8 a-j)

Comp. No.	R_1	R_2
8a	6-F	Me
8b	5,6-diF	Me
8c	6-Br	OMe
8d	6-F	OMe
8e	6-Br	Me
8f	5-Br, 7-Br	OMe, OMe
8g	5-Cl, 7-Cl	OMe, OMe
8h	4-F	OMe
8i	5,6-diF	OMe
8j	4-F	Me

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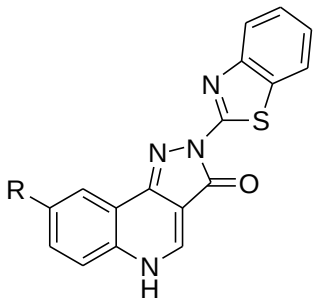
Vasconcelos et al., [14] synthesized a series of 2-(benzo[d]thiazol-2-yl)-8-substituted-2H-pyrazolo[4,3-c]quinolin-3(5H)-ones **(9 a-g)** have been synthesized and evaluated for their in vitro antiproliferative activities against four human cancer cell lines: MDA-MB-435 (breast), HL-60 (leukemia), HCT-8 (colon) and SF-295 (central nervous system). The results showed that the compounds **9b** (2-(benzo[d]thiazol-2-yl)-8-methyl-2H-pyrazolo[4,3-c]-quinolin-3(5H)-one) and **9c** (2-(benzo[d]thiazol-2-yl)-8-bromo-2H-pyrazolo[4,3-c]quinolin-3(5H)-one) exhibited good cytotoxicity for three cell lines with IC_{50} values lower than 5 µg/ml. Analysis of theoretical toxicity risks have shown medium tumorigenic and irritant risks related to **9b** and **9c** in contrast to doxorubicin, the positive control.

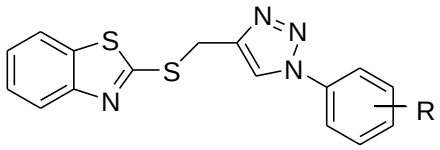


(9 a-g)

R = a: F; b: CH_3; c: Br; d: OCH_3; e: Cl; f: H; g: NO_2

ANTIINFLAMMATORY ACTIVITY

Shafi et al., [15] synthesized a series of 2-mercapto benzothiazole and 1,2,3-triazoles. The synthesized compounds have been tested for their anti-inflammatory activity by using biochemical cyclooxygenase (COX) activity assays and carrageenan- induced hind paw edema. Among the tested compounds, compound **10d** demonstrated a potent selective COX-2 inhibition with COX-2/COX-1 ratio of 0.44. Results from carrageenan-induced hind paw edema showed that compounds **10a**, **10d**, **10e** and **10f** possess significant anti-inflammatory activity as compared to the standard drug Ibuprofen.



(10 a-j)

R = a: *o*-Cl; b: *m*-Cl; c: *p*-Cl; d: *p*-F; e: *p*-Br; f: *p*-NO_2; g: *m*-NO_2; h: p-OEt; i: *o*-Me; j: H

Raghavendra et al., [16] synthesized a series of N-(benzo[d]thiazol-2-yl)-2-(piperazin-1-yl)acetamide analogs. These compounds **(11 a-l)** were evaluated for anti-inflammatory activity

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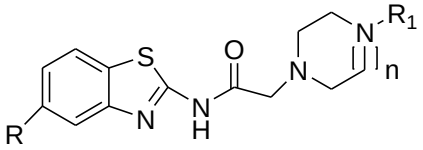
by carragenan induced paw oedema method. Promising compounds were screened for toxicity by evaluating the ulcerogenic potential. Molecular docking experiments were carried out against COX-2 enzyme using Surflex-Dock GeomX programme of Sybyl software on Dell T-1500 workstation to confirm the mechanism of action of active compounds among the series. In silico study reveal the binding interactions of N-(benzo[d]thiazol-2-yl)-2-(piperazin-1-yl)acetamide analogs with COX-2 protein and is in agreement with the in vivo anti-inflammatory activity.



(11 a-l)

Comp. No.	R	R_1	n
11a	H	H	1
11b	H	C_2H_5	1
11c	H	H	2
11d	H	C_6H_5	1
11e	OCH_3	H	1
11f	OCH_3	C_2H_5	1
11g	OCH_3	H	2
11h	OCH_3	C_6H_5	1
11i	NO_2	H	1
11j	NO_2	C_2H_5	1
11k	NO_2	H	2
11l	NO_2	C_6H_5	1

CYTOTOXIC ACTIVITY

Kumbhare et al., [17] synthesized a series of N-bis-benzothiazole derivatives. All the synthesized compounds were evaluated for cytotoxic activity against two human monocytic cell lines (U 937, THP-1) and a mouse melanoma cell line (B16-F10). Based on their IC_{50} values, the majority of the benzothiazolyl thiocarbamides and N-bis-benzothiazoles had significant antiproliferative activity on U 937 and B16-F10 cells, the compounds **12b**, **12e**, **12f**, **12k**, **13c** and **13h** were found to be the most active. The present findings indicate clearly that the compound 3e exhibited more antiproliferative activity on U 937 cells than the standard molecule, etoposide. Nevertheless, these compounds have shown comparatively less cytotoxicity towards THP-1 cells.

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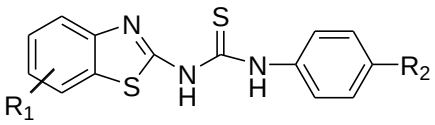
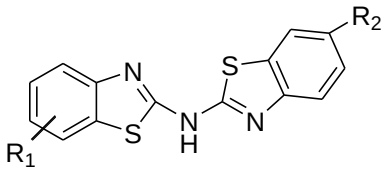


(12 a-l)

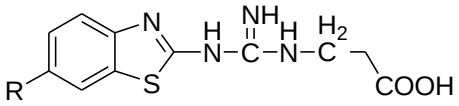
Comp. No.	R_1	R_2
12a	H	H
12b	H	F
12c	H	Cl
12d	6-F	H
12e	6-F	F
12f	6-F	Cl
12g	4-Cl	H
12h	4-Cl	F
12i	6-Me	H
12j	6-Me	F
12k	6-OEt	H
12l	6OEt	F



(13 a-l)

Comp. No.	R_1	R_2
13a	H	H
13b	H	Cl
13c	6-F	F
13d	6-F	Cl
13e	4-Cl	F
13f	6-Me	H
13g	6-OEt	H
13h	6-OEt	F
13i	6-F	H
13j	4-Cl	H
13k	H	F
13l	6-Me	H

Venkatesh et al., [18] Two series of Benzothiazole, Quinazolinone derivatives bearing guanidinopropanoic acid (38 compounds including 27 intermediates) and one series of Schiff base derivatives (14 compounds) were synthesized. All compounds were evaluated for their cytotoxicity against human cervix cell line (HeLa) by MTT assay. Compounds **(14 a-f)** showed significant activity against HeLa with IC_{50} range of 2–550 µM. Compound 3-(3-(6-hydroxybenzo[d]thiazol-2-yl)guanidino)propanoic acid **14f** showed potent activity against human HeLa cell line with the half maximal inhibitory concentration (IC_{50}) values of 1.8 µM which was close to the value of the positive control, doxorubicin.



(14 a-f)

R = a:NO_2; b: Br; c: COOH; d: Cl; e: SO_2NH_2; f: OH

ANTICONVULSANT ACTIVITY

Siddiqui et al., [19] synthesized a series of 1,3-benzothiazol-2-yl semicarbazones **(15 a-o)**. All the synthesized compounds were evaluated for anticonvulsant activity. Majority of the compounds were active in MES screen. Results indicate that the compounds possessed marked

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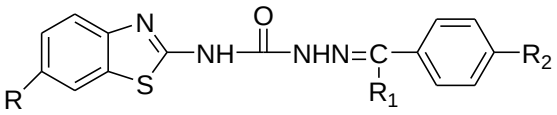
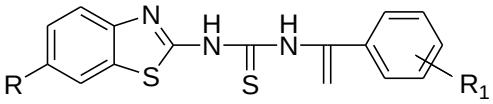
anticonvulsant activity as indicated by their prevention of the effects of maximal electroshock induced seizures in comparison with standard drug.



(15 a-o)

Comp. No.	R	R_1	R_2
15a	Cl	CH_3	H
15b	Cl	CH_3	OH
15c	Cl	CH_3	NO_2
15d	Cl	CH_3	OCH_3
15e	Cl	C_6H_5	H
15f	CH_3	CH_3	H
15g	CH_3	CH_3	OH
15h	CH_3	CH_3	NO_2
15i	CH_3	CH3	OCH_3
15j	CH_3	C_6H_5	H
15k	CH_3O	CH_3	H
16l	CH_3O	CH_3	OH
15m	CH_3O	CH_3	NO_2
15n	CH_3O	CH_3	OCH_3
15o	CH_3O	C_6H_5	H

Rana et al., [20] synthesized a series of 1,3-benzothiazol-2-yl benzamides. All the synthesized compounds were evaluated for anticonvulsant activity. Majority of the compounds were active in MES and scPTZ screen and showed the decrease in the immobility time.



(16)

R = Br, Cl, F, No_2, CH_3, OCH_3
R_1 = H, 2-Cl, 4-Cl, 4-OCH_3

ANTIOXIDANT ACTIVITY

Guzel et al., [21] synthesized a series of 3H-Spiro[1,3-benzothiazole-2,30-indol]-20(10H)-ones **(17 a-h)**. The new compounds were screened for their antioxidant activities such as the Fe^{3+}/ascorbate system induced inhibition of lipid peroxidation (LP) in liposomes, trolox equivalent antioxidant capacity (TEAC), scavenging effect on diphenylpicryl hydrazine (DPPH), and reducing power. These compounds showed potent scavenging activities against DPPH and 2,20-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) ($ABTS^+$) radicals, reducing powers, and strong inhibitory capacity on lipid peroxidation. Compound **17d** incorporating methyl both at R_1 and R_2 was found to be the most potent antioxidant.

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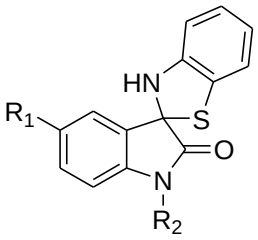
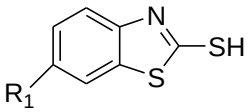


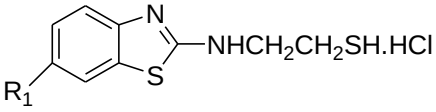
(17 a-h)

Comp. No.	R_1	R_2
17a	CH_3	H
17b	Cl	H
17c	NO_2	H
17d	CH_3	CH_3
17e	CF_3O	CH_3
17f	Cl	CH_3
17g	Br	CH_3
17h	NO_2	CH_3

Rima et al., [22] synthesized a series of new compounds derived from benzothiazoles and thiadiazoles. All the synthesized compounds were screened for anticonvulsant activity. The majority of these compounds were subjected to antioxidant activity screening by determining the DPPH or ABTS free radical scavenging using simple UV spectroscopic methods. The compounds have shown good activity.



(18 a-c)



(19 a-c)

R_1 = a: H, b: CH_3, c: CH_3CH_2O

ANTI-LEISHMANIAL ACTIVITY

Delmas et al., [23] synthesized a series of (1,3-Benzothiazol-2-yl) amino-9-(10H)-acridinone derivatives. All the synthesized compounds were screened for their in vitro antileishmanial and anti-HIV activities. Antileishmanial activity was assessed on the referenced strain L. infantum (MHOM/FR/78/LEM75). L. infantum promastigotes in late log-phase were incubated in RPMI medium supplemented with 12% fetal calf serum. The addition of a benzothiazole group on a parent amino-9-(10H)-acridinone ring could enhance antileishmanial abilities.

ANTI-DIABETIC ACTIVITY

Moreno-Diaz et al., [24] synthesized a series of N-(6-Substituted-1,3-benzothiazol-2-yl)benzenesulfonamide derivatives **(24 a-h)**. These compounds were evaluated for their in vivo antidiabetic activity in a non-insulin-dependent diabetes mellitus rat model. Several compounds synthesized showed significant lowering of plasma glucose level in this model. As a possible mode of action, the compounds were in vitro evaluated as 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitors. The most active compounds **24c** and **24d** were docked into the crystal structure of 11β-HSD1. Docking results indicate potential hydrogen bond interactions with catalytic amino acid residues.

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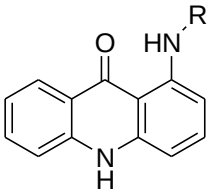
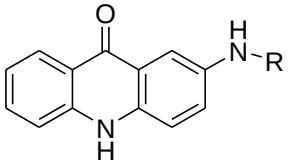
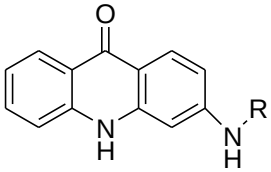


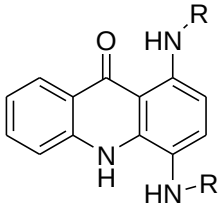
(20 a-d)



(21 a-d)

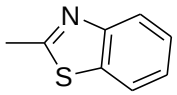


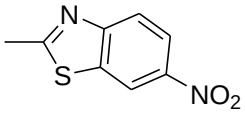
(22 a-d)

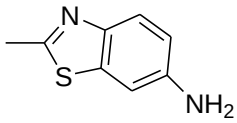


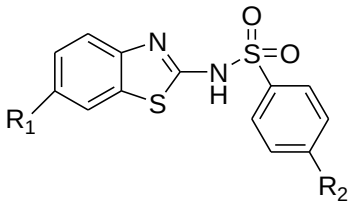
(23 a-d)

R = a: H, b: R_1, c: R_2, d: R_3

R_1 = 

R_2 = 

R_3 = 

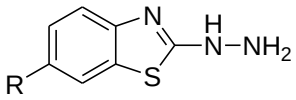


(24 a-h)

Comp. No.	R_1	R_2
24a	NO_2	OCH_3
24b	NO_2	$NHCOCH_3$
24c	OCH_3	H
24d	OCH_3	NO_2
24e	OCH_2CH_3	NO_2
24f	OCH_2CH_3	CH_3
24g	CH_3	Cl
24h	CH_3	NO_2

ANTHELMENTIC ACTIVITY

Munirajasekhar et al., [25] synthesized a series of 6-substituted-2-hydrazino-1,3-benzothiazoles **(25 a-e)**. All the synthesized compounds were evaluated for anthelmintic activity against Eudrilus eugeniea species and Megascoplex konkanensis.



(25 a-e)

R = a: H, b: CH_3, c: OCH_3, d: Cl, e: F

Suresh et al., [26] synthesized a series of 3-(2-hydrazino benzothiazoles)-substituted Indole-2-one. All the synthesized compounds were screened **(26 a-f)** and **(27 a-f)** for anthelmintic activity by using Indian adult earthwarms (pheretima postuma). The compounds **26d**, **26f**, **27d** have showed good paralytic time, compared to standard albendazole drug.

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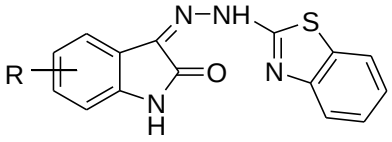
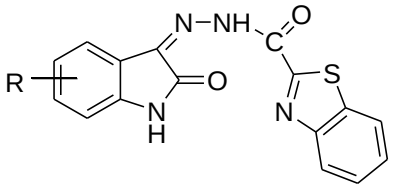


(26 a-f)



(27 a-f)

R = a: H, b: 5-COOH, c: 5-CH_3, d: 5-Cl, e: 5-NO_2, f: 5-Br

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