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REVIEW ON AZAPHENOTHAIZINE ANALOGUES AND ITS BIOLOGICAL ACTIVITY.

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ABSTRACT

The azaphenothiazines are the modified structure of phenothiazines, the various types of azaphenothiazines are having its unique biological importance. This review is focused on the documentation of various azaphenothiazines and its biological activity. Based on the additional nitrogen atoms in the phenothiazines, it is classified as monoazaphenothiazines, diazaphenothiazines, triazaphenothiazines and tetraazaphenothiazines. These are the azaphenothiazines having the many biological activities such as anticancer, antimicrobial, CNS activity, antiobesity, antioxidant, anti-inflammatory, antiemetic, cytotoxic activity etc., the azaphenothiazine analogs are having various biological important so that synthesis of further substitution with this azaphenothiazine analogs are having main task for the researchers.

Keywords: Phenothiazines, CNS activity, Anticancer, Anti-inflammatory.

INTRODUCTION

The modified structure of phenothiazinesby the heteroaromaticazine ring (pyridine, pyridazine, pyrimidine, pyrazine, 1,2,4-triazine, quinoline, quinoxaline) are known as azaphenothiazines. The azaphenothiazines are to be tricyclic, tetracyclic, pentacyclic and hexacyclic. The one, two, tri and four additional nitrogen atoms in phenothiazines are known as monoazaphenothiazines, diazaphenothiazines, triazaphenothiazines and tetraazaphenothiazines. The azaphenothiazines are having important biological activities such as Neuroleptic activity, Antipsychotic activity, Schizophrenia, CNS depression, Acute-mania, Sedative activity, Hypnotic activity, Dementia, Anticholinergic, Locomotive activity, Anticonvulsant activity, Butyrylcholinesterase inhibitory activity, Acetylcholinesterase inhibitory activity, Topoisomerase IV enzyme inhibitory activity, Serotonin-antagonistic activity, Adrenolytic activity, Antiviral activity, Antibacterial activity, Antimicrobial activity, Antimalarial activity, Antimycobacterial activity, Antiparasitic effects, Antihistaminic activity, Antiasthmatic activity, Antiallergic activity, Phototoxic property, Cytotoxic activity, Radical scavenging activity, Antioxidant activity, Anticancer activity, Antiproliferative activity, Antiemetic activity, Antitussive, Irritative, Spasmodic cough, Antiobesity activity, Analgesic activity, Anti-inflammatory activity, Hypotensive activity, Antiarrhythmic activity and Antiulcer activity. This review summarizes the details about the chemical classification and biological importance of Azaphenothiazines analogs [1].

Types Azaphenothiazines analogs

The literatures, synthesis various azaphenothiazines, these are the following such as Pyridobenzothiazines, Pyridazinobenzothiazines, Pyrazinobenzothiazines, Pyrimidobenzothiazines, Tricyclic azaphenothiazines, Pyridoquinothiazines, Pentacyclicazaphenothiazines and Diquinothiazines categories.

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Pyridobenzothiazines

Pyridobenzothiazines are the monoaza phenothiazines.In this category covers 1-Azaphenothiazine, 2-Azaphenothiazine, 3-Azaphenothiazine and 4-Azaphenothiazines. The 1-Azaphenothiazine are further substituted with rothipendyl, isothipendyl, oxypendyl, cloxypendyl and pipazethate to form the compounds such as Prothipendyl, 10-(3-dimethylaminopropyl)-1-azaphenothiazine, Isothipendyl, 10-(2-dimethylamino-2-methylethyl)-1-azaphenothiazine, Oxypendyl, 10-[3-(hydroxyethyl-4-piperazinyl)propyl]-1-azaphenothiazine, Cloxypendyl, 3-chloro-10-[3-(hydroxyethyl-4-piperazinyl)propyl]-1-azaphenothiazine and Pipazethate, 2-(2-piperidinylethoxy)ethyl 1-azaphenothiazine-10-carboxylate [2].

The 2-Azaphenothiazines are10-Aminoalkyl-2-azaphenothiazines, In 3-Azaphenothiazine derivatives, the 10-Dimethylaminopropyl-3-azaphenothiazine substituted form of 1-cyano-3-azaphenothiazin-3H(2)-ones, S-oxides are also reported. Theammonium substituted in 3rd position of 3-Azaphenothiazines structure to form 10H-3-aminoalkyl-3-azaphenothiazinium chlorides 23 and it contains open and cyclic amine moieties. The 10-Benzylaminobutyl-4-azaphenothiazine S-oxide is the category of 4-Azaphenothiazines.

Pyridazinobenzothiazines

The Pyridazinobenzothiazines are diazaphenothiazines. In this category covers 1, 2-Diazaphenothiazines, 2 and 3-Diazaphenothiazines, 3, 4-Diazaphenothiazines. The 10-dialkylaminoalkyl-3-methoxy 1,2-Diazaphenothiazines, 10H-4-(2-aminophenylthio)-1,2-diazaphenothiazine and 10H-1,2-diazaphenothiazines are the 1, 2-Diazaphenothiazines derivatives. The 10-dialkylaminoalkyl- 2,3-diazaphenothiazinones, 10H-2,3-diazaphenothiazin-1-ones, 10H-2,3-diazaphenothiazin-4-ones, 10-Substituted 2,3-diazaphenothiazin-1-ones10H-2,3-diazaphenothiazines and 10H- and 10-substituted 2,3-diazaphenothiazin-1-one S-dioxides are the 2,3-diazaphenothiazins analogs. The 10-Dialkylaminoethyl 3,4-diazaphenothiazines3,4-Diazaphenothiazines analog [3].

Pyrimidobenzothiazines

The Pyrimidobenzothiazines are diazaphenothiazines. In this category contains 1, 3-Diazaphenothiazines and 2, 4-Diazaphenothiazines.The 10H-1,3-diazaphenothiazines, 10H-2-(pyrrolidin-1-yl)-1,3-diazaphenothiazine, 10H-1,3-diazaphenothiazin-2,4-diones, 4a-substituted 1,3-diazaphenothiazin-2,4-diones and 10-Phenylsubstituted 1,3-diazaphenothiazine S-dioxides are the 2, 4-Diazaphenothiazines analogs. 10H-2,4-diazaphenothiazin-1,3-diones, 4,6-dihydro-2,4-diazaphenothiazine- 1,3-dione, 10H-1-methyl-2,4-diazaphenothiazines, 10H-2,4-diazaphenothiazin-1,3-diones (10-thiaisoalloxazine derivatives) are the 2,4-diazaphenothiazin analogs.

Pyrazinobenzothiazines

The Pyrazinobenzothiazines are diazaphenothiazines.The 1,4-Diazaphenothiazines is under the category of Pyrazinobenzothiazines. 10-Propyl-1,4-diaza-2,3-dichlorophenothiazine, 10-Substituted 2,3-dichloro(or chloro-methoxy)-1,4-diazaphenothiazines, 10H-2,3-dichloro-1,4-diazaphenothiazine 5-oxide, 10-benzyl-2,3-dichloro-1,4-diazaphenothiazine S-oxide, 10H-and 10-substituted 1,4-diazaphenothiazines and10H-1,4-dibenzoazaphenothiazines8 position substituted with cycloamines are the 1,4-Diazaphenothiazines analogs.

Tricyclic azaphenothiazines

In Tricyclic azaphenothiazines category contains 1,6-Diazaphenothiazines, 1,8-Diazaphenothiazines, 2,7-Diazaphenothiazines, 3,6-Diazaphenothiazines, 3,7-Diazaphenothiazines and 1,3,6-Triazaphenothiazines and 1,3,9-triazaphenothiazines.

The 1,6-Diazaphenothiazines is under Dipyridothiazines (Tricyclic azaphenothiazines). The 1,6-diazaphenothiazine is having the dimethylaminopropylgroup at thiazine nitrogen atom.The 10H-1,6-diazaphenothiazine and its 10-substituted products by the alkyl, heteroaryl, amidoalkyl and dialkylaminoalkyl groups are the 1,6-diazaphenothiazine analogs. The 1,8-Diazaphenothiazinesis under Dipyridothiazines (Tricyclic azaphenothiazines). The 10H-1,8-diazaphenothiazine, andthe alkyl, heteroaryl, dialkylaminoalkyl, amidoalkyl and sulfonamidoalkyl substituted in 10th position are the 1,8-diazaphenothiazine analogs. The 2,7-Diazaphenothiazinesis under Dipyridothiazines (Tricyclic azaphenothiazines). The 10H-2,7-diazaphenothiazine and the methyl, aryl, aminoalkyl and amidoalkyl derivativessubstituted in 10th position are the 2,7-diazaphenothiazine analogs. The 3,6-Diazaphenothiazinesis under Dipyridothiazines (Tricyclic azaphenothiazines). The 10*H*-3,6-diazaphenothiazine and the alkyl, heteroaryland dialkylaminoalkylderivatives substitutedin 10th position are the3,6-Diazaphenothiazines analogs. The 3,7-Diazaphenothiazinesunder Dipyridothiazines (Tricyclic azaphenothiazines). The 10H-3,7-diazaphenothiazine and the diethylaminoethyl and dimethylaminopropylderivatives substituted in 10th position are the3,7-Diazaphenothiazines analogs.

1,3,6-Triazaphenothiazines and 1,3,9-triazaphenothiazines are Pyridopyrimidothiazines (Tricyclic azaphenothiazines). The 10H-1,3,6-triazaphenothiazines and 10H-1,3,9-triazaphenothiazines are the 1,3,6-Triazaphenothiazines and 1,3,9-triazaphenothiazines analogs.

Tetracyclic azaphenothiazines

Tetracyclic azaphenothiazines are tetraazaphenothiazines. In this category covers Quino[3,2-

b]benzothiazines (benzo[b]-1-azaphenothiazines), Quino[6,7-b]benzothiazines (pyrido[2,3-b]phenothiazines),Quino[3,4-b]benzothiazines (benzo[a]-1-azaphenothiazines), Quino[7,8-b]benzothiazines (pyrido[2,3-a]phenothiazines), 5-Alkylquino[3,4-b]benzothiazinium salts, Pyridonaphthothiazines (benzo[j]-1-azaphenothiazines)and Benzo[b]-1,4-diazaphenothiazines.

Quino[3,2-b]benzothiazines (benzo[b]-1-azaphenothiazines) are under QuinobenzothiazinesLinearly fused category (Tetracyclic azaphenothiazines). The hydrogen atom and alkyl, aminoalkyl, amidoalkyl, sulfonamidoalkyl and chloroethylureidoethyl groups in 6th position of thiazine nitrogen atom and CH3, F, Cl, Br, CF3, SCH3 additional substituents on benzene ring at 8-10 position of fused qno[3,2-b]benzothiazinesare the Quino[3,2-b]benzothiazines (benzo[b]-1-azaphenothiazines)analogs [4].

The Quino[6,7-b]benzothiazines (pyrido[2,3-b]phenothiazines)are under Quinobenzothiazines Linearly fused category (Tetracyclic azaphenothiazines). The1,4-Dihydro-11-methyl-3-carboxy-4-oxoquino[6,7-b]benzothiazine (pyrido[2,3-b]phenothiazine) with 4-quinolone-3-carboxylic acid fragment is the Quino[6,7-b]benzothiazines (pyrido[2,3-b]phenothiazines) analog.

The Quino[3,4-b]benzothiazines (benzo[a]-1-azaphenothiazines)are under Quinobenzothiazines Angularly fused category (Tetracyclic azaphenothiazines). The 12H- and 12-substituted quino[3,4-b]benzothiazines and its substituents CH3, F, Cl, Br at 9th position,12H and 12-substituted quino[3,4-b]benzothiazines its F, CF3 and SCH3 substitution at position 8-10, 12H-quino[3,4-b]benzothiazin-6-ones with 2-quinolone moiety in tetracyclic ring systemare the Quino[3,4-b]benzothiazines (benzo[a]-1-azaphenothiazines) analogs.

The Quino[7,8-b]benzothiazines (pyrido[2,3-a]phenothiazines)are under Quinobenzothiazines Angularly fused category (Tetracyclic azaphenothiazines). The 12H-quino [7,8-b]benzothiazin-4-ones with the 1-cyclopropyl-6-fluoro-4-quinolone-3-carboxylic acid moiety are the Quino[7,8-b]benzothiazines (pyrido[2,3-a]phenothiazines) analogs.

The 5-Alkylquino [3,4-b]benzothiazinium salts are exclusive category in azaphenothiazine, because of an unique production and tetracyclic ring system combined with the ammonium fragment. The 12Hquino[3,4-b]benzothiazines, 5-Methylquino[3,4-b]benzothiazinium chlorides 9-11th position CH3, F, Cl, Br, NH2 and OH substituents, 5-Methylquino[3,4-b]benzothiazinium chlorides, 9th position amino and piperidinyl groups and 9-11-substituted 5-methyl-12H-quinobenzothiazinium chlorides contains the alkoxy, amino and aminoalkoxy groups are 5-Alkylquino [3,4-b] benzothiazinium salts analogs.

Pyridonaphthothiazines (benzo[j]-1-azaphenothiazines) and Benzo[b]-1,4-diazaphenothiazinesare under the category of other tetracyclic azaphenothiazines. The chlorine and pbromophenylgroups at 6th position substituted pyridonaphthothiazin-5-ones are the Pyridonaphthothiazines (benzo[j]-1-azaphenothiazines) analogs. The dialkylaminoalkyl groups substituted at 11- and 12th position in benzo-1,4-thiazines are the Benzo[b]-1,4-diazaphenothiazines analogs.

Benzo[a]-3,6-diazaphenothiazinesand Benzo[a]-3,6-diazaphenothiazinium saltsare under the category ofPyridoquinothiazines. The dimethylaminopropyl and piperidinylethyl groups 12H- and 12-substituted in benzo-3,6-diazaphenothiazines 86a-c at the position of thiazine nitrogen atom are theBenzo[a]-3,6-diazaphenothiazines analogs. The 5-Methyl-12H-benzo-3,6-diazaphenothiazinium chloride is the Benzo[a]-3,6-diazaphenothiazinium salt analogs.

Pentacyclicazaphenothiazines

Pyridonaphthothiazines (benzo[j]-4-azaphenothiazines) are the category of Pentacyclicazaphenothiazines. The rifampicin moiety with Furanonaphthopyridothiazine is the Pyridonaphthothiazines (benzo[j]-4-azaphenothiazines) analogs. The Quinonaphthothiazinesdibenzo[b,h]1-azaphenothiazines and dibenzo[b,j]1- azaphenothiazines are the angularly condensed Isomericquinonaphthothiazines.

The Diquino[3,2-b;2',3'-e]thiazines (dibenzo[a,i]-1,9-azaphenothiazines) are the linearly fushedDiquinothiazines. The diquinothiazines, diethylaminoethyl, dimethylaminopropyl, chloroethylureidoethyl and p-toluenesulfonylaminoethyl are substituted in 6th position are Diquino[3,2-b;2',3'-e]thiazines (dibenzo[a,i]-1,9-azaphenothiazines).

The Diquino[3,2-b;6',5'-e][1,4]thiazine (benzo[b]pyrido[3,2-h]-1-azaphenothiazine) and Diquino[3,4-b;4',3'-e][1,4]thiazine (dibenzo[a,j]-3,7-diazaphenothiazine) are the angularly fushed Diquinothiazines. The 7H-Diquinothiazine is the Diquino[3,2-b;6',5'-e][1,4]thiazine (benzo[b]pyrido[3,2-h]-1-azaphenothiazine). 14H-Diquinothiazineis the Diquino[3,4-b;4',3'-e][1,4]thiazine (dibenzo[a,j]-3,7-diazaphenothiazine). The Pyrazolonaphthyridobenzothiazine are linearly condensed 11H-pyrazolonaphthyridobenzothiazine [5].

Hexacyclicazaphenothiazines

The 5,6-Ethylenediquinothiazinium chloride are the Hexacyclicazaphenothiazines. Hexacyclic 5,6-ethylenediquinothiazinium chloride and Substituted 17H-quinazolinoquinobenzothiazin-6-ones, The benzoxazino, pyrimidoxazino and benzothiazino derivatives of benzophenothiazines, pyridonaphthothiazines and

pyrimidonaphthothiazines(benzoxazinona phthoben zothiazines, benzoxazinona phthopyridothiazines, benzoxazinonaphthopyrimidothiazines, pyrimidoxazino naphtha benzothiazines and pyrimidoxazinonaphthopyridothiazines), benzothiazino, pyridothiazinoand pyrimidothiazino derivatives of pyrido naphtha thiazines and pyrimido naphtha thiazines(benzothiazinonaphthopyridothiazines, benzothiazinonaphtha pyrimidothiazines, pyridothiazinonaphthopyridothiazines and pyrimidothiazino naphtha pyrimidothiazines), are the Hexacyclicazaphenothiazines [6].

Biological activities of Azaphenothiazines analogs

The various biological activities of Azaphenothiazines analogs are shown in Table 1. The biological activities with chemical structures are mentioned.

Table1. Biological activities of Azaphenothiazines analogs

S. No	**Biological Activity**	**Activity Model**	**Name of Azaphenothiazines analog**	**Reference**
1.	Neuroleptic activity	Mammalian Brain	1-Azaphenothiazine, Cloxypendyl, 3-chloro-10-[3-(hydroxyethyl-4-piperazinyl)propyl]-1-azaphenothiazine, 1,4-diazaphenothiazines	[7]
2.	Antipsychotic activity	-	Prothipendyl, 10-(3-dimethylaminopropyl)-1-azaphenothiazine 10-Aminoalkyl-2-azaphenothiazines	[8]
3.	Schizophrenia	-	Prothipendyl, 10-(3-dimethylaminopropyl)-1-azaphenothiazine	[9]
4.	CNS depression	mice, dogs and monkeys	10 (Diisopropylaminoethylthio)carbonyl-1-azaphenothiazines	[10]
5.	Acute-mania	Human clinical trail	Prothipendyl 10-(3-dimethylaminopropyl)-1-azaphenothiazine	[11]
6.	Sedative activity	Swiss albino mice	10-carbamoylmethyl-1-azaphenothiazines	[12]
7.	Hypnotic activity	-	10-Dimethylaminopropyl-3-azaphenothiazine	[8]
8.	Dementia	-	Prothipendyl, 10-(3-dimethylaminopropyl)-1-azaphenothiazine	[13]
9.	Anticholinergic	-	Isothipendyl, 10-(2-dimethylamino-2-methylethyl)-1-azaphenothiazine	[14]
10.	Locomotive activity	Swiss albino mice	10-carbamoylmethyl-1-azaphenothiazines with the dialkylamino	[12]
11.	Anticonvulsant activity	(PTZ)-induced convulsions in mice	2,3-dihydro-3-oxo-5Hpyrido[3,4-b][1,4]benzothiazine-4-carbonitriles	[15]
12.	Butyrylcholinesterase inhibitory activity	In silico	6-Substituted diquinothiazines	[16]
13.	Acetylcholinesterase inhibitory activity	In silico	6-Substituted diquinothiazines	[16]
14.	Topoisomerase IV enzyme inhibitory activity	Docking modeling	Quino[7,8-b]benzothiazines (pyrido[2,3-a]phenothiazines)	[17]
15.	Serotonin-antagonistic activity	-	Benzo[b]-1,4-diazaphenothiazines	[18]
16.	Adrenolytic activity	-	Benzo[b]-1,4-diazaphenothiazines	[18]
17.	Antiviral activity	Chikungunya virus (CHIKV); HIV virus	Prothipendyl 10-(3-dimethylaminopropyl)-1-azaphenothiazine; 10H-2,4-diazaphenothiazin-1,3-diones	[19]
18.	Antibacterial activity	E. coli, B. subtilis and S. aureus	10H-3-nitro-1-Azaphenothiazines	[20]
19.	Antimicrobial activity	S. aureus, E. coli, A. flavus, A. niger, F. moniliformae and C. lunata	10H-3-nitro-1-azaphenothiazines	[21]

20.	Antimalarial activity	Infected mice with P. berghei ANKA	10-Phenylsubstituted 1,3-diazaphenothiazine S-dioxides	[22]
21.	Antimycobacterial activity	-	12H-quino[3,4-b]benzothiazin-6-ones	[23]
22.	Antiparasitic effects	-	10-dialkylaminoalkyl-2,3-diazaphenothiazinones	[24]
23.	Antihistaminic acyivity	-	10-Dialkylaminoethyl 3,4-diazaphenothiazines	[25]
24.	Antiasthmatic activity	Asthmatic rat assay	10H- and 10-substituted 1,4-diazaphenothiazines	[26]
25.	Antiallergic activity	insect bites and radiation sickness	10-Substituted 2,3-diazaphenothiazin-1-ones	[27]
26.	Phototoxic property	ultraviolet A (UVA)	Isothipendyl, 10-(2-dimethylamino-2-methylethyl)-1-azaphenothiazine	[28-29]
27.	Cytotoxic activity	Lung fibroblast MRC5 cell lines; human peripheral blood mononuclear cells; SNB-19, melanoma C-32 and breast cancer MCF-7 cell lines; C-32 and SNB-19 cell lines	1-Azaphenothiazine; 1,8-Diazaphenothiazines; 3,6-Diazaphenothiazines; 5-Methylquino[3,4-b]benzothiazinium chlorides	[30-33]
28.	Radical scavenging activity	DPPH, ABTS, GSH, LPO.	1-Azaphenothiazines	[34]
29.	Antioxidant activity	Swiss albino mice	Quino[3,4-b]benzothiazines	[35]
30.	Anticancer activity	leukemia, melanoma, non-small cell, colon, CNS, ovarian, renal, prostate and breast cancer	Diquino[3,2-b;2',3'-e]thiazines (dibenzo[a,i]-1,9-azaphenothiazines)	[36]
31.	Antiproliferative activity	Human peripheral blood mononuclear cells (PBMC)	Diquino[3,2-b;2',3'-e]thiazines (dibenzo[a,i]-1,9-azaphenothiazines)	[37]
32.	Antiemetic activity	-	10-[3-(hydroxyethyl-4 piperazinyl)propyl]-1-azaphenothiazine	[38]
33.	Antitussive	-	Pipazethate, 2-(2-piperidinylethoxy)ethyl 1-azaphenothiazine-10-carboxylate	[39]
34.	Irritative	-	Pipazethate, 2-(2-piperidinylethoxy)ethyl 1-azaphenothiazine-10-carboxylate	[40]
35.	Spasmodic cough	-	Pipazethate, 2-(2-piperidinylethoxy)ethyl 1-azaphenothiazine-10-carboxylate	[41]
36.	Antiobesity activity	Mouse model	1-Azaphenothiazine	[42]
37.	Analgesic activity	Writhing test in rats	10-aminoalkyl 3-azaphenothiazines	[43]
38.	Anti-inflammatory activity	Carrageen-induced edema test in mice	10H-2,3-diazaphenothiazines	[44]
39.	Hypotensive activity	Mice, dogs and monkeys	10-(Diisopropylaminoethylthio)carbonyl-1-azaphenothiazines	[26]
40.	Antiarrhythmic	CHCl3-induced	10-Substituted 2,3-diazaphenothiazin-1-ones	[27]

	activity	arrhythmia in mice		
41.	Antiulcer activity	Rat model	10H- and 10-substituted 2,3-diazaphenothiazin-1-one S-dioxides	[45]

Fig 1. Pyridobenzothiazines (Monoazaphenothiazines)

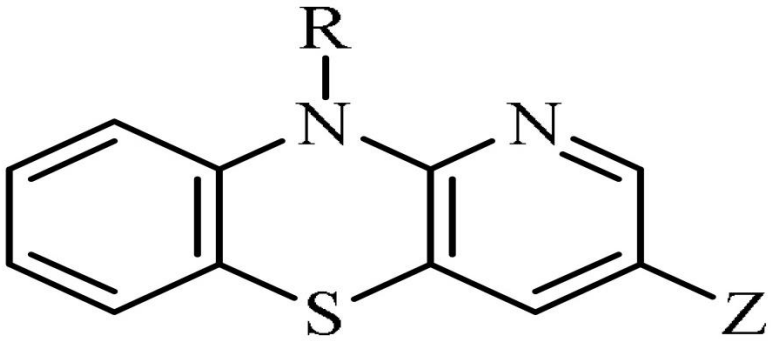


Fig 2. Pyridazinobenzothiazines (Diazaphenothiazines)

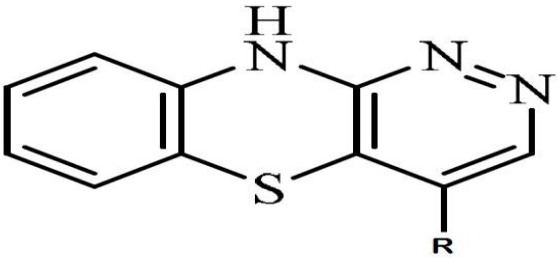


Fig 3. Pyrimidobenzothiazines (Diazaphenothiazines)

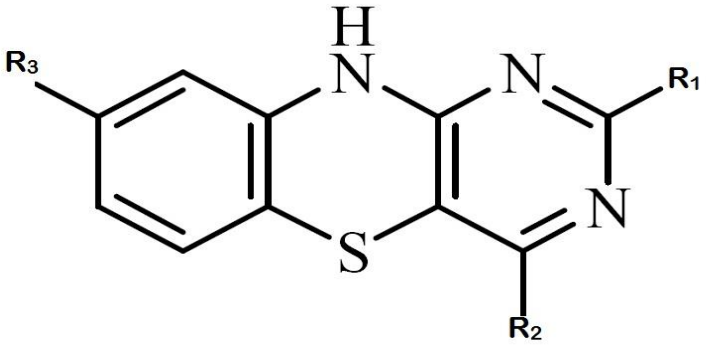


Fig 4. Pyrazinobenzothiazines (Diazaphenothiazines)

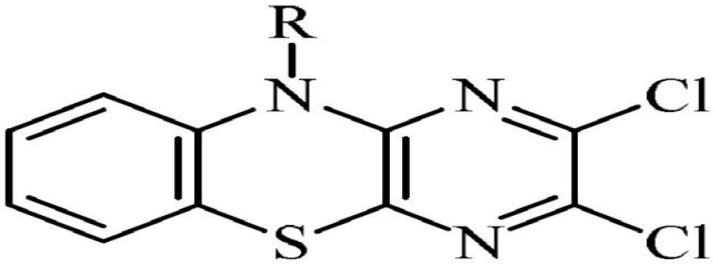


Fig 5. Tricyclic azaphenothiazines

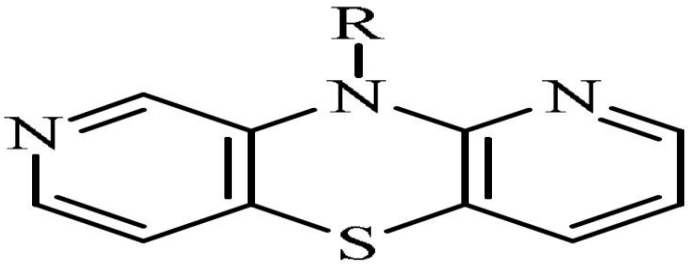


Fig 6. Quino[3,2-b]benzothiazines

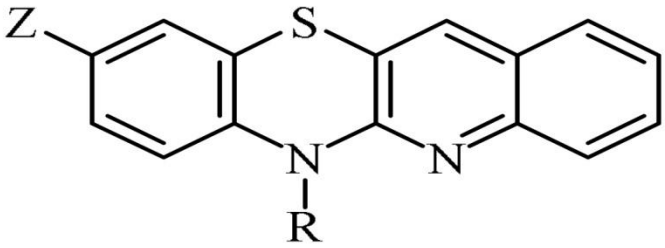


Fig 7. Pentacyclicazaphenothiazines (Pyridonaphthothiazines (benzo[j]-4-azaphenothiazines)

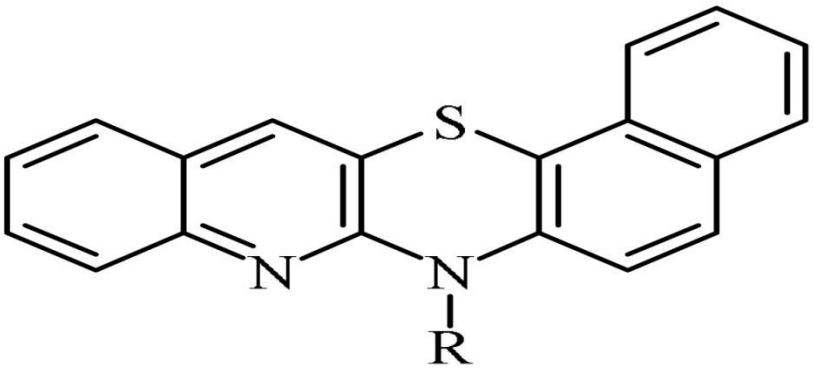
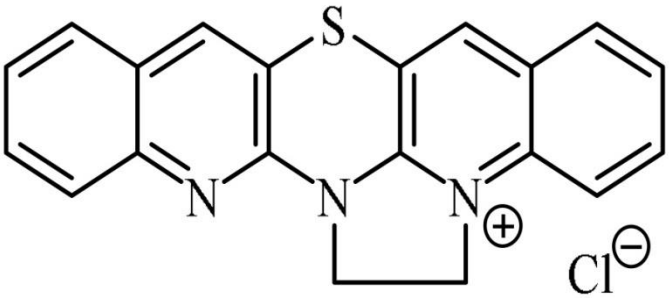


Fig 8. Hexacyclicazaphenothiazines (5,6-Ethylenediquinothiazinium chloride)



CONCLUSION

The azaphenothiazines and its analogs are having various biological activities so that synthesis of further substitution with this azaphenothiazine analogs are plays important task for the future researchers.

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