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Review of the 2-Amino Substituted Benzothiazoles: Different Methods of the Synthesis

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Abstract

Amino-benzothiazoles constitute an important class of compounds. In recent year heterocyclic compounds analogues and derivatives have attracted strong interest due to their useful biological and pharmacological properties. The small and simple benzothiazole nucleus is present in compounds involved in research aimed at evaluating new products that possess biological activities, such as anti-tumor, anti-microbial, anthelmintic, anti-leishmanial, anti-convulsant and anti-inflammatory. The present review focuses on the different methods of the substituted benzothiazoles with potential activities that are now in development.

Keywords: Benzothiazole, Different methods and Biological activities.

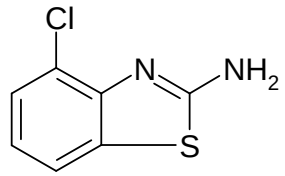
Introduction

Benzothiazoles are bicyclic ring system with multiple applications. In the 1950s, a number of 2-amino benzothiazoles were intensively studied as central muscle relaxants. Biologist's attention was drawn to this series when the pharmacological profile [1] was discovered. 6-trifluoromethoxy-2-benzothiazolamine was found to interfere with glutamate neurotransmission in biochemical, electrophysiological and behavioral experiments. After that benzothiazole derivatives have been studied extensively and found to have diverse chemical reactivity and broad spectrum of biological activity.

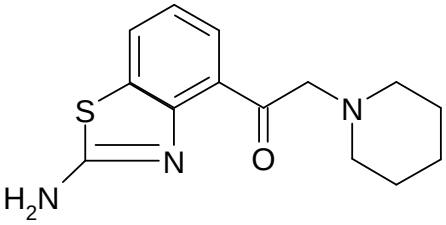
1. Synthesis and biological activity:

Several methods for the synthesis and pharmacological properties of substituted benzothiazoles reported in the literature.

Bhargava P.N. and Jose K.A. synthesized 2-amino-4-chloro-benzothiazole **(1.1)**, piperidinoacetyl-2-amino-benzothiazole **(1.2)**, 2-amino-4-methyl-benzothiazole **(1.3)**, and tested them for their local anaesthetic activity [2].



(1.1)



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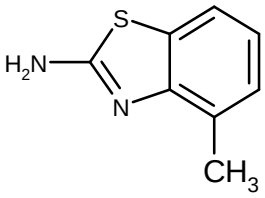
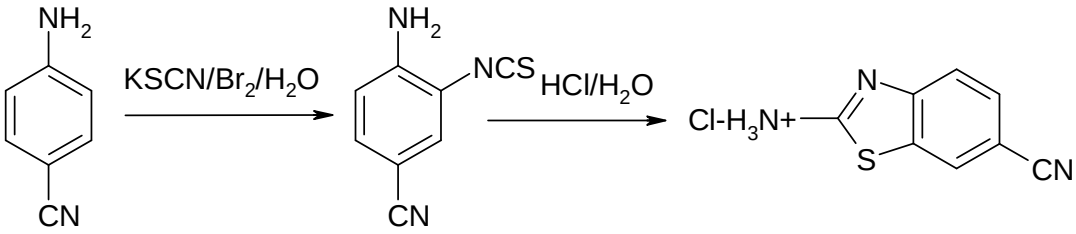


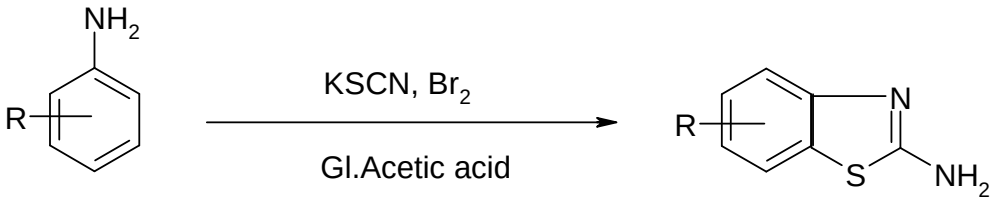
(1.3)

Caleta I. *et al.*, have reported the synthesis and antiproliferative evaluation of 2-amino-6-cyano-benzothiazole **(1.4) [**3].



(1.4)

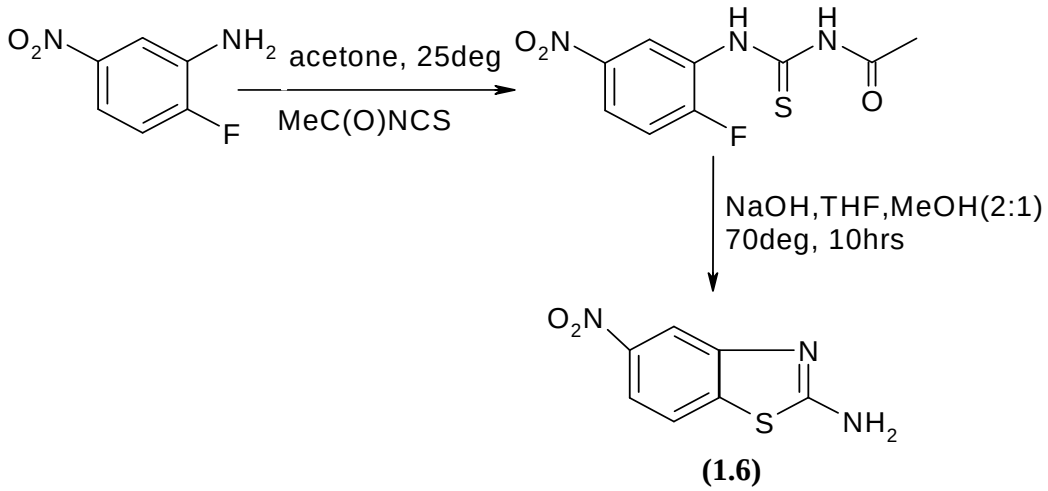
Trapani G. *et al.*, reported synthesis of substituted 2-aminobenzothiazoles **(1.5)** as anticonvulsant agents [4].



(1.5)

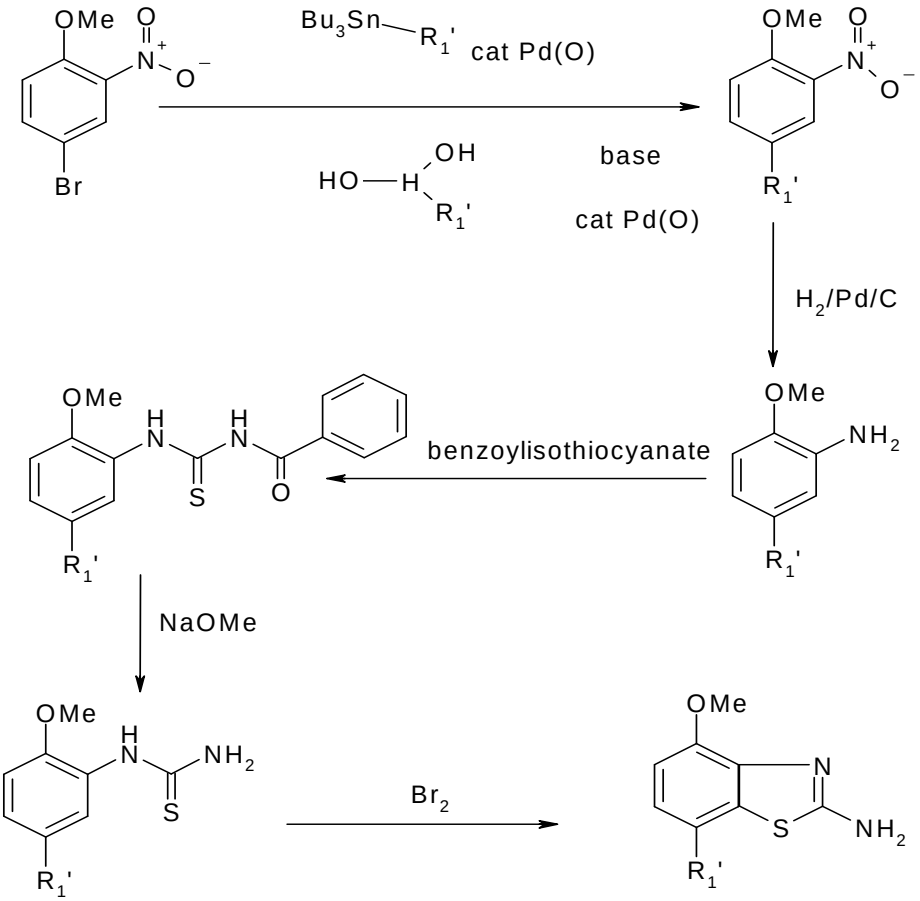
R= H, CH_3, OCH_3, Cl

Yoshida M. *et al.*, reported synthesis and biological evaluation of benzothiazole derivatives **(1.6)** as potent antitumor agents[5].



(1.6)

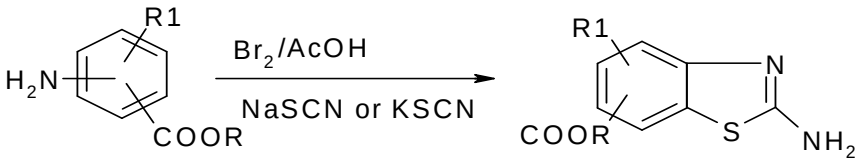
Flohr A. *et al.*, reported synthesis of 2-amino-4-methoxy-7-substituted-benzothiazoles **(1.7)** as adenosine receptor ligands[6].



(1.7)

R_1'= 3, 6-dihydro-2H-pyran-4-yl, 5,6-dihydro-4-H-pyran-3-yl, 5,6-dihydro-4-H-pyran-2-yl, cyclohex-1-enyl, or 1,2,3,6- tetrahydro-pyridin-4-yl

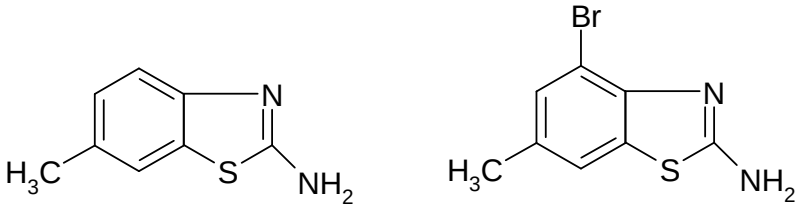
Das J. *et al.*, reported synthesis of various substituted 2-aminobenzothiazoles **(1.8)** as protein tyrosine kinase inhibitors [7].



(1.8)

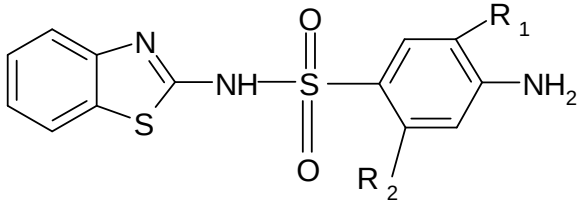
R=alkyl or aryl alkyl, R1=alkylene or alkenylene

Jung B. Y. *et al.*, reported synthesis and methods of use of 2-amino-6-methyl-benzothiazole **(1.9)** and 2-amino-4-bromo-6-methyl-benzothiazoles **(1.10)** as antifungal agents[8].



(1.9) **(1.10)**

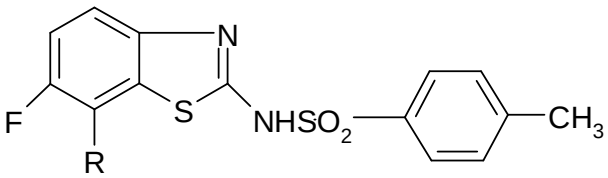
Bhusari.K.P. *et al.*, have reported the synthesis and antitubercular activity of some substituted 2-(4-aminophenylsulphonamido) benzothiazoles **(1.11) [**9].



(1.11)

R_1= CH_3, H, COOH, Cl, R_2= H, Br, NO_2, Cl

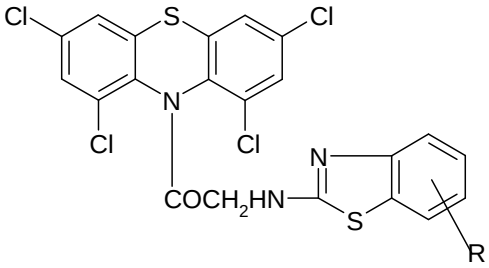
Nargund L.V.G. *et al.*, synthesized 6-Fluoro (N-p-tolyl sulphonamido)-6-fluoro-7-substituted benzothiazoles **(1.12)** and reported their antibacterial activity [10].



(1.12)

R= $HNC_6H_4mNO_2$, $HNC_6H_4pNO_2$, $HNC_6H_4mCH_3$, $HNC_6H_4pCH_3$, HNC6H5, HNC_6H_5COOH

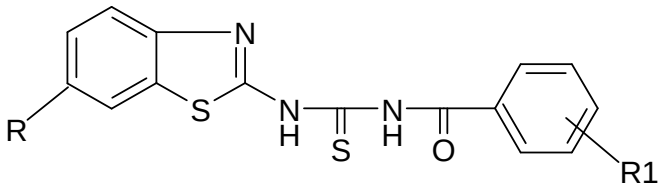
Dave A.M. *et al.*, have reported synthesis and antibacterial efficacy of halogenated phenothiazine derivatives by using substituted 2-aminobenzothiazoles **(1.13) [**11].



(1.13)

R= H, 4-Cl, 5-Cl, 6-Cl, 4, 6-$(Cl)_2$, 6-Br, 4-NO_2, 5-NO_2, 6-NO_2, 5-OCH_3, 6-OCH_3, 6-OC_2H_5, 6-OC_2H_5, 5-OH, 6-OH, 5-CH_3, 6-CH_3, 5,6-$(CH_3)_2$, 6-$COCH_3$, 6-$NHCOCH_3$

Rana A. *et al.*, have reported the synthesis and pharmacological evaluation of N-{[(6-substituted-1,3-benzothiazole-2-yl)amino]carbonothioyl}-2/4-substituted benzamides **(1.14)** as anticonvulsant agents [12].

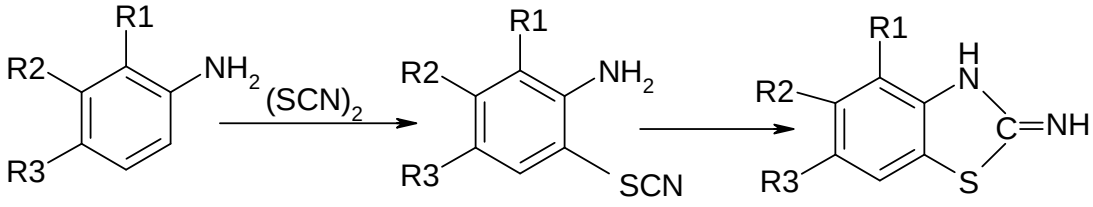


(1.14)

R= Br, Cl, F, NO_2, CH_3, OCH_3, R1= H, 2-Cl, 4-Cl, 4-OCH_3

2) Synthesis:

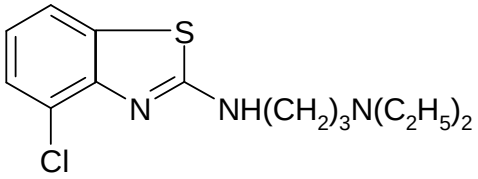
Brewster R. Q. and Dains F. B. obtained substituted 2-imino- benzothiazoles **(1.15)** by direct thiocyanogenation [13].



(1.15)

R_1= NO_2, H, R_2= CH_3, R_3= H, NO_2

Elderfield R. C. and Sort F. W. have synthesized substituted benzothiazoles **(1.16-1.17) [**14].



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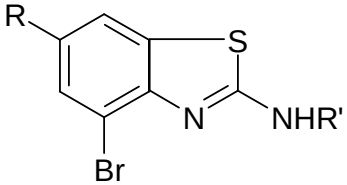
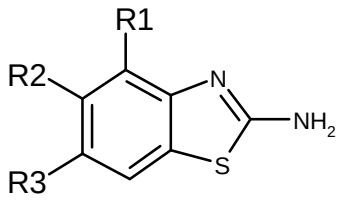


R= Br, Cl, CH_3, R'= H, CH_3

(1.17)

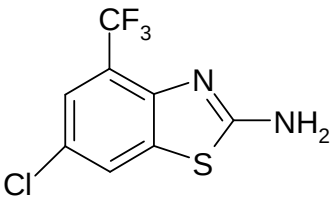
Bhargava P.N. and Baliga B.T. synthesized 2-aminobenzothiazoles by condensing arylthioureas with bromine in chloroform and studied their properties and group reactions leading to various derivatives **(1.18)** [15].



(1.18)

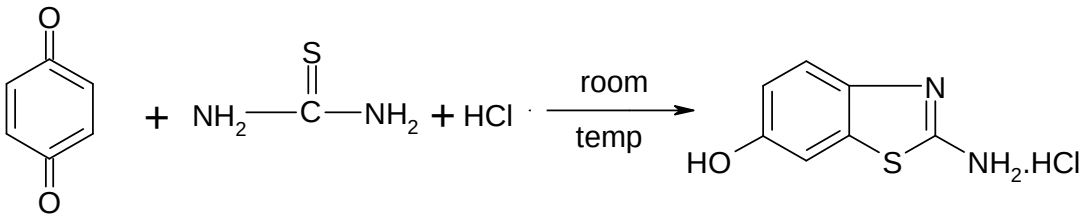
R_1= H, CH_3, R_2= H, CH_3, R_3= H, OCH_3, OC_2H_5

Thomas L, Gupta A. *et al.*, synthesized 2-amino-6-chloro-4 (trifluoromethyl) benzothiazole **(1.19)** [16].



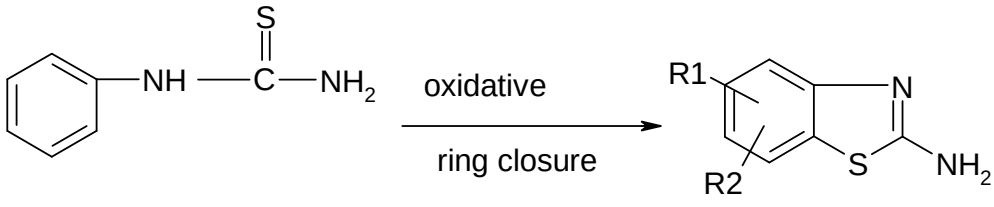
(1.19)

Lau P. T. S. and Gompf T. E. reported the synthesis of 2-aminobenzothiazoles **(1.20)** by using thiourea [17].



(1.20)

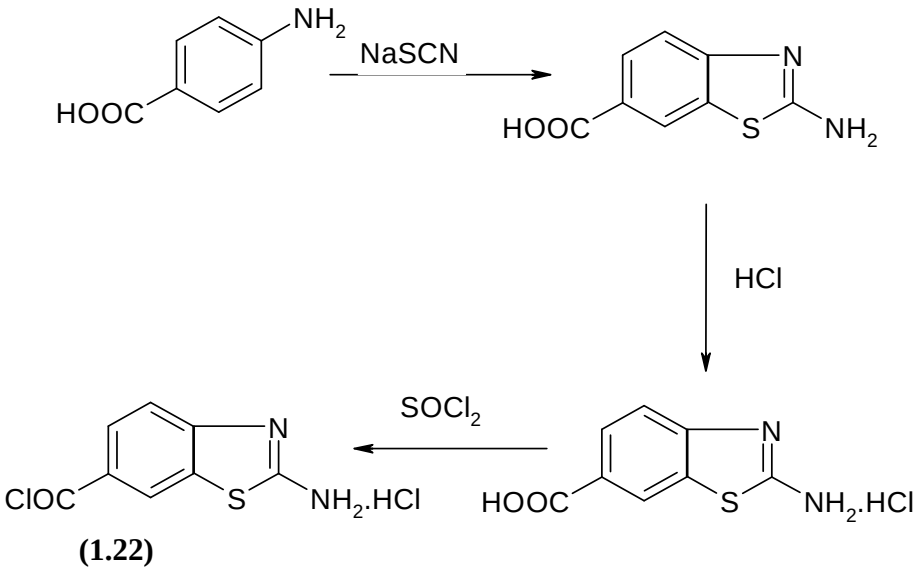
Clark R. D and Pridgen H. S. prepared 2-aminobenzothiazoles **(1.21)** by oxidative ring closure of an arylthiourea [18].



(1.21)

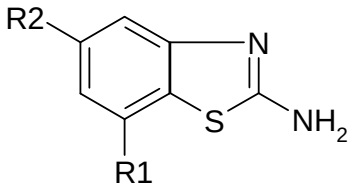
R_1= H, Cl, NO_2, R_2= H, Cl

Husam A. A. *et al.*, reported synthesis of 2-aminobenzothiazole-6-carbonyl chloride **(1.22)**[19].



(1.22)

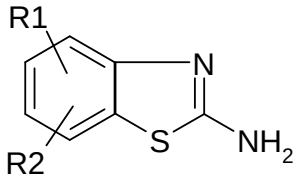
Hamprecht R. *et al.*, reported the process for the preparation of 2-amino-5,7 disubstituted benzothiazoles **(1.23)** [20].



(1.23)

R_1= H, Cl, Br, NO_2, CF_3, CN, R_2= H, Cl, Br, NO_2, CF_3, CN

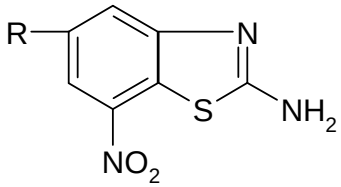
Dapperheld S. *et al.*, have reported the process of preparation of 2-amino-disubstituted benzothiazoles **(1.24)** [21].



(1.24)

R_1= H, F, Cl, Br, I, CF_3, NO_2, R_2= H, F, Cl, Br, I, CF_3, NO_2

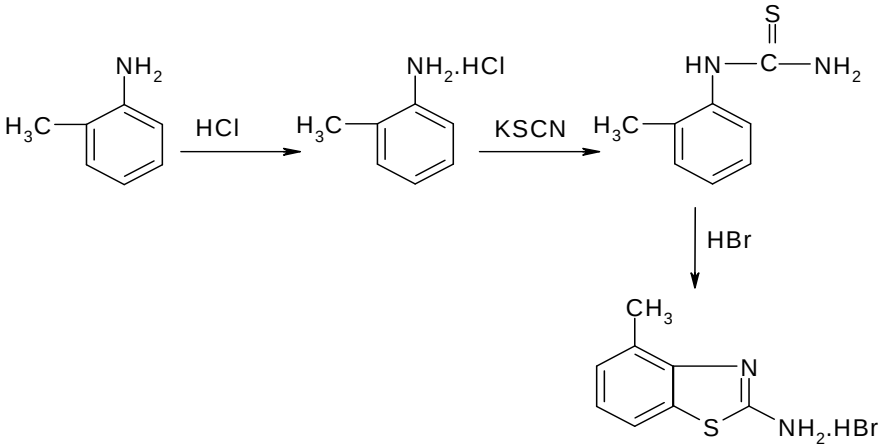
Audiau F. *et al.*, reported process for the preparation of 2-amino-4-nitro benzothiazole derivatives **(1.25)** [22].



(1.25)

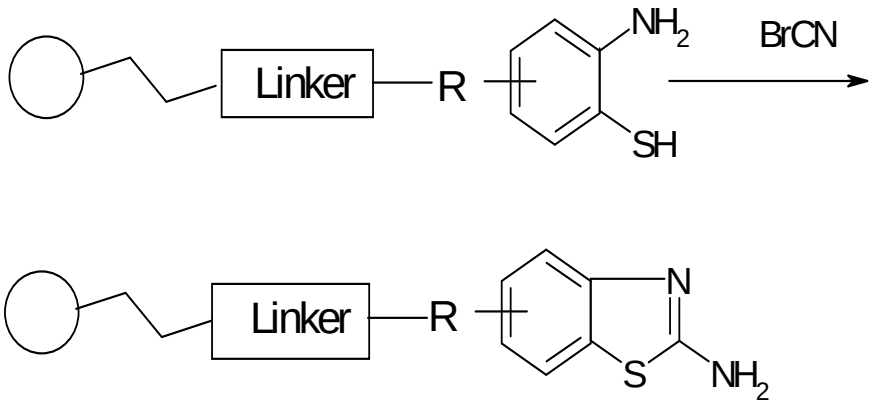
R= alkyl, alkoxy, alkylthio, polyfluoroalkyl, polyfluoroalkoxy, , alkylsulphonyl, alkoxycarbonyl, amino, cyano

Dong H. S. *et al.*, synthesized 2-amino-4-methyl-benzothiazole **(126)** [23].



(1.26)

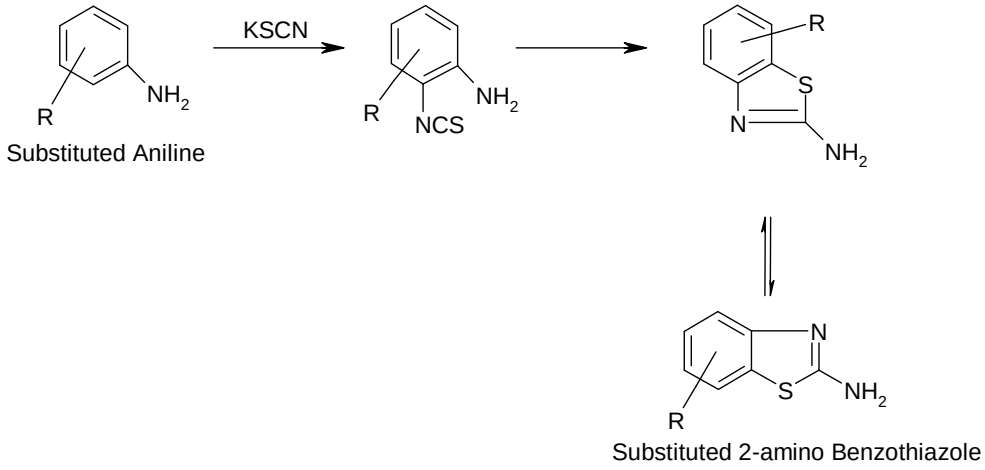
Laborde *et al.*, reported methods for the solid phase synthesis of combinatorial libraries of 2-aminobenzothiazles and their derivatives **(1.27)** [24].



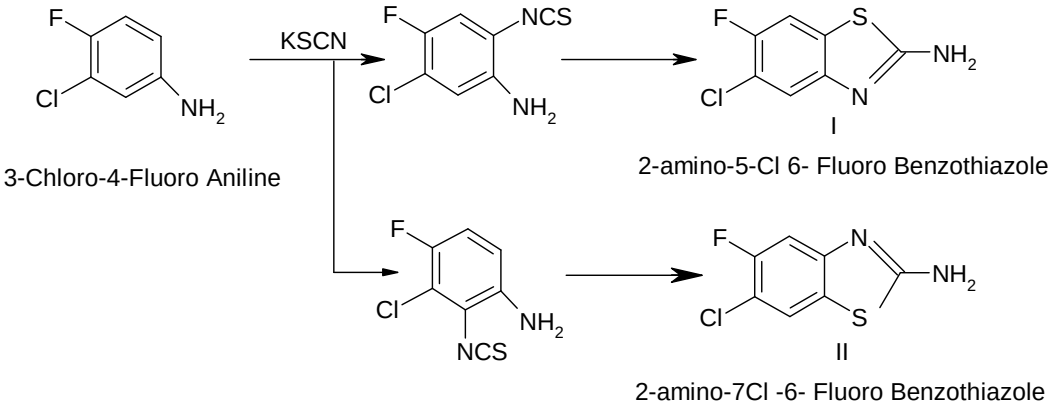
(1.27)

R= alkyl, HetAr

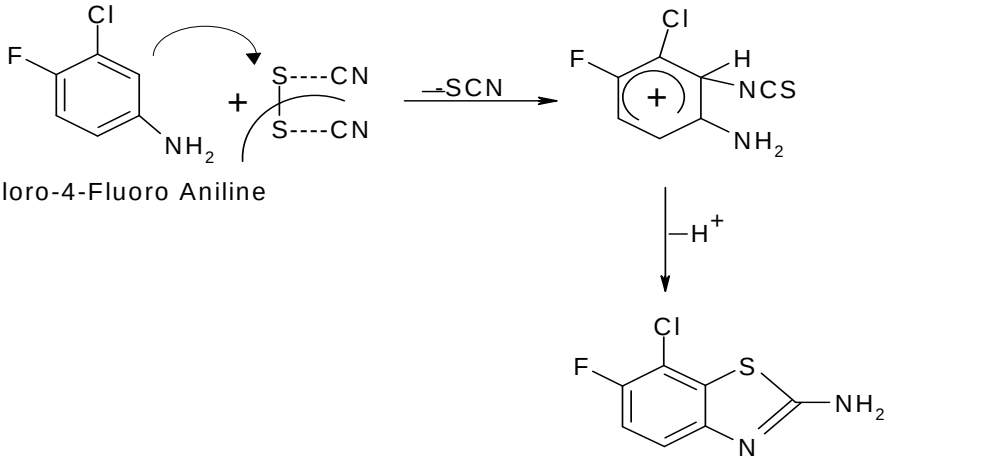
Method for synthesis of substituted benzothiazole [25]
Substituted aniline was treated with KSCN in presence of glacial acetic acid and bromine to get 2-aminobenzothiazole. The synthetic sequence is represented as.



Iso merization of the 2and 4 thiocyanato derivatives will leads to 2-amino -5-chloro -6-fluoro benzothiazole (I) and 2-amino-7-chloro-6-fluoro benzothiazole (II).



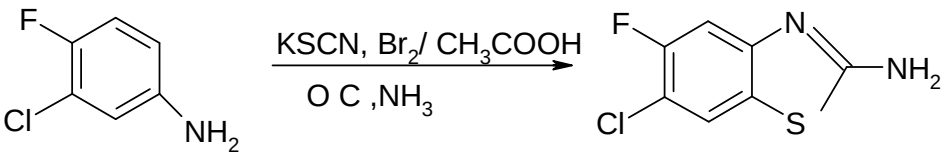
For 3-chloro -4fluoro aniline the 6th position is the most positive center .As the attack however was on the 2nd position, which is the electrophilic center , it is probable that thiocyanogen being as pseudo halogen, behaves as an electrophile by attacking this electrophilic center (2nd position). It is equally possible to consider the second position as mounting a nucleophilic attack on thiocyanogen as the substrate. Thus the reaction sequence can be as follows.



3-Chloro-4-Fluoro Aniline

2-amino-7Cl -6- Fluoro Benzothiazole

Method 1:-



3-Chloro-4-Fluoro Aniline

2-amino-6- Fluoro 7-Cl Benzothiazole

General procedure:-

To glacial acetic acid (20ml)cooled below room temp were added 8gm (0.08mole)of KSCN and 1.45gm(0.01mole)of fluoro chloro aniline .The mixture was placed in freezing mixture of ice and salt and mechanically stirred. 1.6ml of bromine in 6ml of glacial acetic acid was added from a dropping funnel at such a rate that temp. never rose beyond 0°C. After all the bromine was added (105min) the solution was stirred for 2hr below room temp and at room temp for 10hr. It was then allowed to stand over night, during which period and orange ppt settled at the bottom, water (6ml) was added quickly & slurry was heated to 85°C on a steam bath & filtered hot. The orange residue was placed in a reaction flask & treated with10ml of glacial aacetic acid heated again to 85°C. The combined filtrate was cooled & ppt was collected. recrystallization from benzene : ethanol {1:1} after treatment with charcoal gave yellow crystal of 2-amino -6- fluoro -7- chloro benzothiazole. After drying in a oven at 80°C the dry material melted at 210-211°C.The yield was found to be 75%.

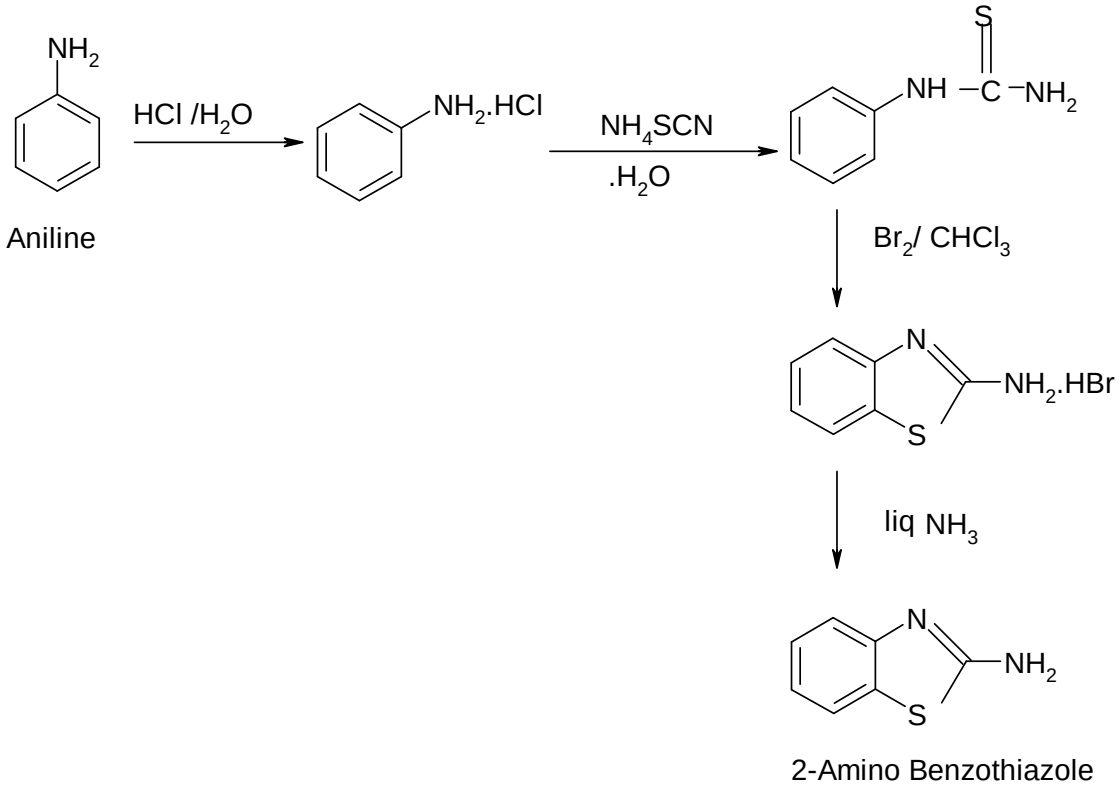
Method 2:-

A solution of substituted aniline (9gm,0.085mol)in 95% acetic acid (50ml) was added to a solution of KSCN(30gm,0.308mol) in 95% acetic acid (100ml) .The mixture was cooled to 0°C & a solution of Br_2 (7.5ml) in acetic acid (30ml) was added slowly with stirring so that temp between 0&10°C. After addition was complete, the stirring was continued for 1hr at 5°C & then the mixture was poured into water .The solid was collected & re-crystallized from ethanol. The product (6.3gm, 0.036mol) conc. HCl (27ml) and water (54ml) were refluxed for 2hr. The solution was cooled and the product was filtered off, washed with water & re-crystallized from

ethanol to yield (mp-216 to 218°C).

The benzothiazole HCl salt was prepared from a suspension of 2-amino benzothiazole (0.25gm) in a dry toluene (25ml). The suspension was cooled to 0°C & saturated with dry HCl gas. After 5hr white solid ppt & was collected filter & washed with ethanol.[26]

Method 3rd:-



2-Amino Benzothiazole

The aniline (0.1mol) was taken in a R.B.F. fitted with condenser & a mixture of HCl (9ml) & water (25ml) was added & then it was heated for about 30min. The solution of aniline HCl obtained was cooled down to room temp & ammonium thio cyanate (0.1mol) was added. The reaction mixture was refluxed for 4 hr .The solid separated out on cooling was filtered, washed with water, dried and crystallized from ethanol.

In 2nd step phenyl thio urea [0.1mol] was taken in a two necked round bottom flask equipped with mechanical stirrer &dropping funnel along with chloroform [100ml].To his reaction mixture bromine [0.1mol] in chloroform [100ml] was added with stirring over a period of 2hr .During the addition of bromine, a temp of reaction mixture was maintained below 5°C. After completion of total addition of bromine the stirring as continued for a period of 4hr. It was refluxed until the evaluation of HBr ceased [about 4hr] chloroform was removed by filtration & resulting solid was treated with sulphur dioxide water & filtered .The filtrate was neutralized with aq. ammonia .The ppt of 2-amino benzothiazole was filtered washed with water & recrystallized from ethanol.[27]

Although they have been known from long ago to be biologically active [28] their varied biological features are still of great scientific interest. Benzothiazoles show antitumor activity, especially the phenyl-substituted benzothiazoles, while condensed pyrimido benzothiazoles and benzothiazolo quinazolines exert antiviral activity. Recently, have described the synthesis of bis-substituted amidino benzothiazoles as potential anti HIV agents Substituted 6-nitro-and 6-amino benzothiazoles show antimicrobial activity. Given below is a brief account of various alterations conducted on benzothiazole ring and their associated biological activities.[29]

Miscellaneous:

The synthesized original derivatives of 2-piperazinyl benzothiazoles and studied as mixed ligands for serotoninergic 5-HT $_{1A}$ and 5-HT $_{3}$ receptors [30]. The studied compounds exhibited significant affinities for these two serotoninergic receptor subtypes. The pharmacological profile of these ligands was agonist for 5-HT $_{1A}$ receptors and antagonist for 5-HT $_{3}$ receptor sub sites. Compounds with such a pharmacological profile are of clinical relevance in the treatment of psychotropic diseases. e.g., anxiety, depression and schizophrenia.

A series of pyridazinylpiperidinyl capsid-binding compounds with novel bicyclic substituents and screened against human rhinovirus (HRV) [31]. HRV cause approximately one-half of all cases of respiratory tract infection (colds). Several 2-alkoxy and 2-akylthio-benzoxazole and benzothiazoles derivatives showed excellent anti HRV activity. When tested against a panel of 16 representatives HRV types, the 2-ethxoy-benzooxazole derivatives, was found to have superior HRV activity (median EC $_{50}$ 3.88 ng/mL) to known capsid-binders pleconaril and pirodavir.

A series of structurally novel benzothiazoles based small molecule inhibitors of p56 ^{lck} was prepared to elucidate their structure-activity relationships (SAR), respectively and cell activity in the T-cell proliferation assay. p56 ^{lck} (Lck), a member of the Src family of non-receptor protein tyrosine kinase is expressed primarily in T-lymphocytes and natural killer cells.[32]

Conclusions

The reviewed new class of 2-substituted amino-benzothiazoles has shown a wide spectrum of biological activities. The substituted benzothiazolylimino dithiazolidines and the 2-(2'-aryl-1, 3, 4-oxadiazol-5-yl)mercaptomethyl benzothiazoles are having significant antibacterial activity. Significant anti-inflammatory activity is displayed by some new 2-(4'-butyl-3'-5'-dimethylpyrazol-1-yl)-6-substituted benzothiazoles and 4-butyl-1-(6'-substituted-2'-benzothia -zolyl)-3-methylpyrazol-5-ones.

Potent anti-tumor activity was demonstrated by a number of 2-(4-aminophenyl) benzothiazoles. The 2-(4-acetamido-2-bromo-5-methylphenyl sulfonamide) benzothiaole is found to be effective as anti-tuberculor agents, whereas ethoxazolamide and o-acyl derivatives of 6-hydroxybenzothiazole-2-sulfonamides are found to show the carbonic anhydrase inhibitory action. The biological profiles of these new generations of benzothiazoles represents much progress with regard to the older compounds.

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