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Review on Synthetic Strategies of Benzothiazole Derivatives and its Biological Activity

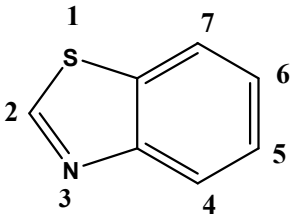
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Abstract: *Heterocycles containing nitrogen and sulphur plays a vital role in medicinal chemistry. The bicyclic heterocycles in which benzene ring fused with thiazole is known as benzothiazole. Benzothiazole is one of the important moity presents in various drug. Benzothiazoles derivatives synthesized on combination with various heterocycles exhibit a wide range of biological activities like antimicrobial, antiviral, anticancer, anti-inflammatory, anticonvulsant, cardiovascular drugs, anti-HIV, analgesic, antidiabetic making them a promising scaffold for drug development. Benzothiazole when coupled with pi conjugated system shows optical, piezoelectric, and ferroelectric properties. Benzothiazole derivatives are also used as accelerator in vulcanization of natural rubber. Naturally benzothiazole is found in grapes, human urine. In this review our aim is to summarize recent synthetic strategies and biological activities of benzothiazole derivatives in last twenty years.*

Key Words: Benzothiazole, antimicrobial, antiviral, anticancer.

1. INTRODUCTION

Heterocyclic compound plays important role in the synthesis of various drug. Benzothiazole is one of the bicyclic heterocyclic compounds containing benzene ring fused with thiazole ring which is widely used in the modern drug discovery. Benzothiazoles and its various derivatives on combination with various heterocycles exhibit a wide range of biological activities like antimicrobial [1], antimalarial, anthelmintic, diuretics [2], analgesic, antiviral, anticancer, anti-inflammatory, anticonvulsant [3], cardiovascular drugs, insecticides, fungicides, making them a promising scaffold for drug development. Benzothiazole when coupled with pi conjugated system shows optical, piezoelectric, and ferroelectric properties [4]. Benzothiazole derivatives are also used as accelerator in vulcanization of natural rubber [5]. This review serves as a guide to consolidating current knowledge to describe the path towards more efficient, selective, and sustainable chemical synthesis and its various biological activities of benzothiazole.



Benzothiazole

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II. STRUCTURE OF BENZOTHIAZOLE

Occurrence:

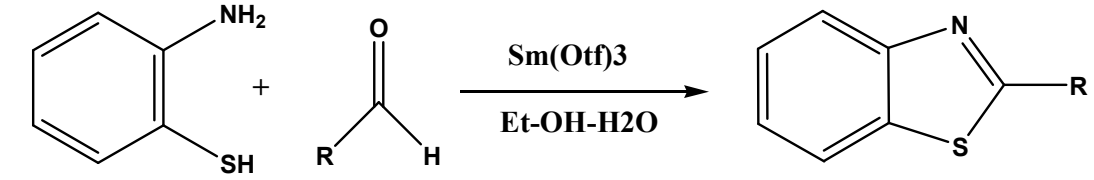
In 1967 Benzothiazole was first isolated from cranberries (Vaccinium macrocarpon) in natural compound. It is also extracted from oak leaves and tea leaves. Benzothiazole derivatives are also detected in marine organism like firefly luciferins which shows bioluminescence activity. [6]

Synthesis of benzothiazole derivatives:

Synthesis of Benzothiazole was first reported by A.W. Hofmann in the synthesis of 2-choro and 2-phenyl benzothiazole. Initially he obtained 1- mercapto benzothiazole by reaction of carbon disulfide with amino thiophenol.

Benzothiazole is mainly synthesized by reaction 2-amino thiophenol with aldehyde, acid chloride, carboxylic acid, ester, nitrile etc.

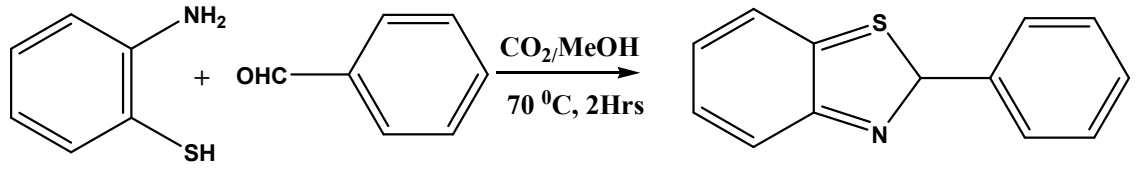
P. B. Gore-Patil et.al synthesized benzothiazole by reaction of 2-amino thiophenol with aliphatic, aromatic, and hetero aromatic aldehyde in presence of catalyst samarium triflate in an ethanol: water mixture at 60O C. [7]



2-amino thiophenol (1) | Aldehyde (2) | Benzothiazole (3)

Scheme :1

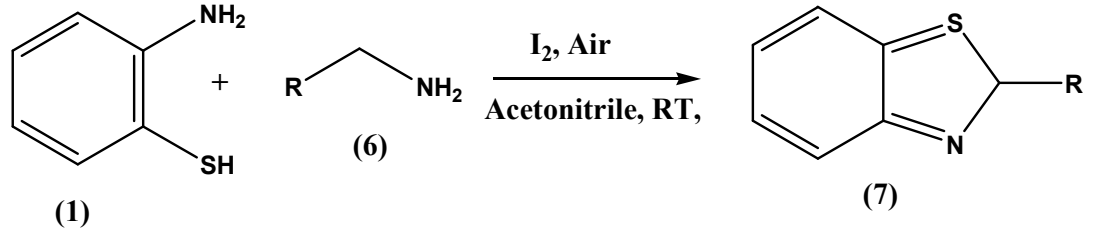
Xiao Li et. al synthesized a series of derivatives of Benzothiazole from 2-amino thiophenol with substituted benzaldehyde in presence alkyl carbonyl acid formed by CO2 and ethanol. [8]



(1) (4) (5)

Scheme :2

Naresh Gunaganti et.al synthesized derivatives of benzothiazole from 2-amino thiophenol reaction with primary amine in presence of iodine in acetonitrile. [9]



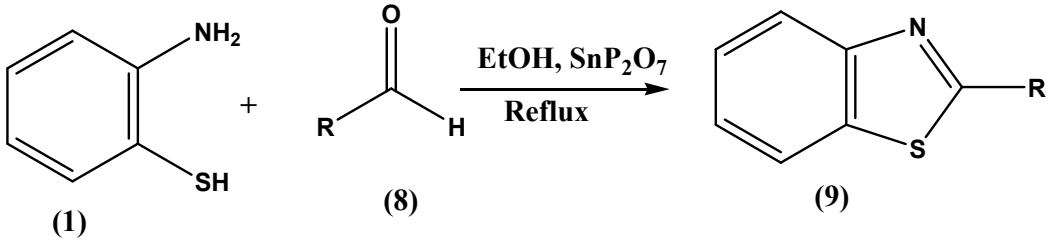
(1) (6) (7)

Scheme :3

Where R= Ph, 4-OCH3-Ph, 4-Cl-Ph, 3, 4-Cl-Ph, 4-F-Ph, 4-CH3-Ph, 4-OCF3-Ph,

Y. Merroun et. al synthesized benzothiazole derivatives by simple reflux condensation of 2-aminothiophenol with aldehyde using ethanol as solvent. [10]

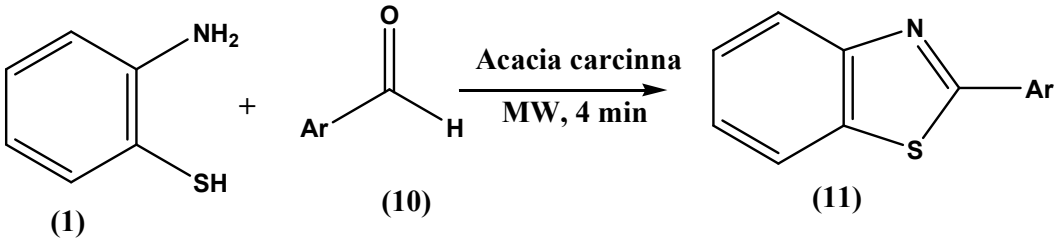
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(1) (8) (9)

Scheme :4

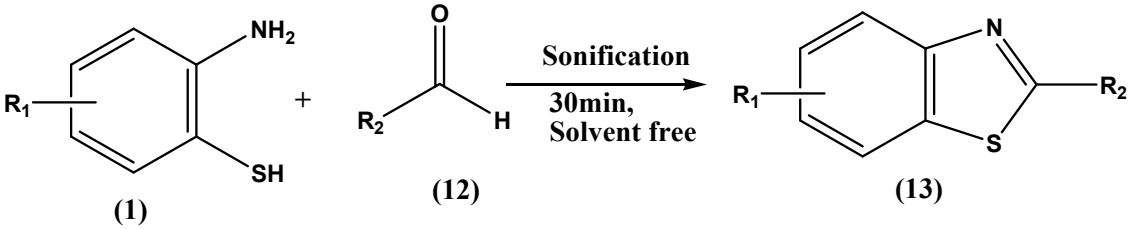
R. Bhat, et.al synthesized benzothiazole derivatives using Acacia concinna in microwave radiation as green synthesis. The time taken for synthesis is very low and that is 4 minutes, The method is fast and efficient with high yield. [11]



(1) (10) (11)

Scheme :5

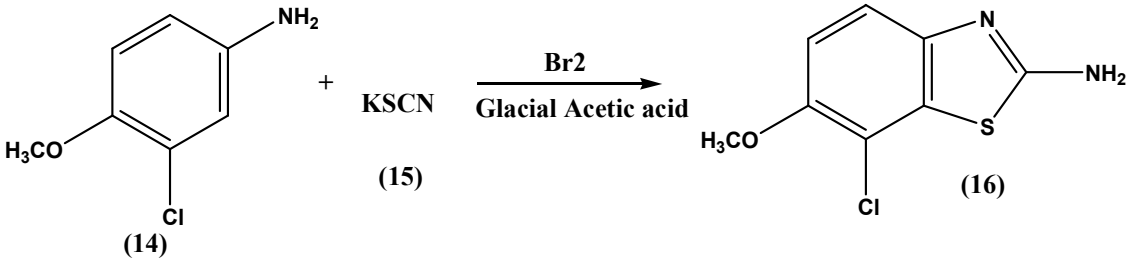
H.T. Nguyen et. al synthesize benzothiazole using sonification in absence of solvent gives good yield and less time as compared to reaction carried out in solvent. [12]



(1) (12) (13)

Scheme :6

Akhilesh Gupta synthesized a benzothiazole derivatives (16) by reaction of 3-chloro 4-methoxy aniline potassium thiocyanate in glacial acetic acid below room temperature and temperature of reaction is control by ice and salt mixture. The bromine in glacial acid is added under temperature control. [13]

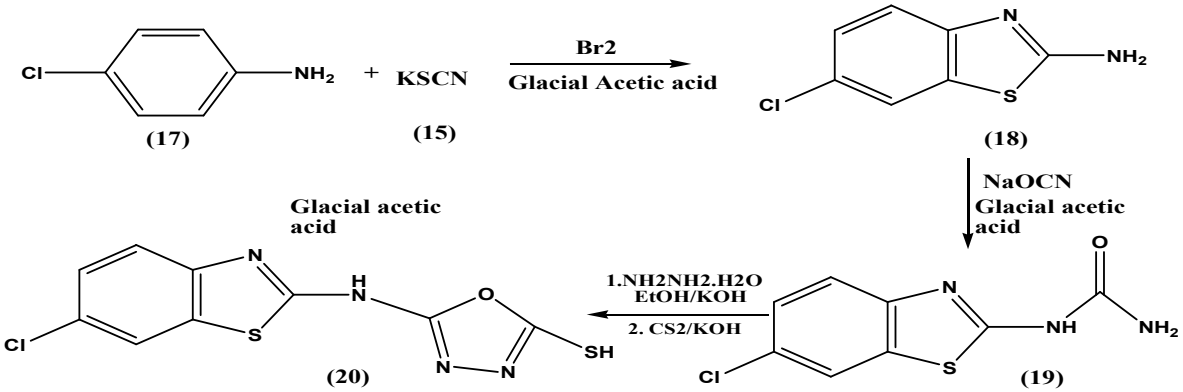


(14) (15) (16)

Scheme :7

Sadaf J. Gilani et. al synthesized benzothiazole derivatives (20) from reaction of 4-chloroaniline with potassium thiocyanate in presence of Bromine in acetic acid formed benzothiazole derivatives (18) which on further reaction with NAOCN in glacial acetic acid gives intermediate (19). This on further reaction with hydrazine followed by carbon disulfide in potassium hydroxide give 5-(6-chlorobenzo[d]thiazol-2-ylamino)-1,3,4-oxadiazole-2-thiol.[14].

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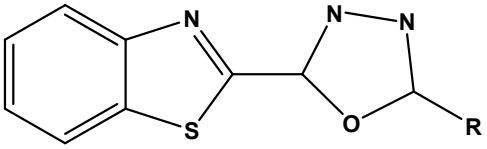


Scheme :8

III. BIOLOGICAL ACTIVITY OF BENZOTHIAZOLE DERIVATIVES

1. Antibacterial activity:

S. M. Shantikumar et. al. synthesized a new series of 2-(5-substituted 1,3,4-oxadiazole-2-yl)-1,3-benzothiazole (21) from reaction benzo thiazolyl carboxyhydrazide with various aryl acids in phosphoryl chloride which shows broad spectrum antibacterial activity against gram positive and gram-negative bacterial strain like Bacillus subtilis, Bacillus pumilus, E. coli.[15]

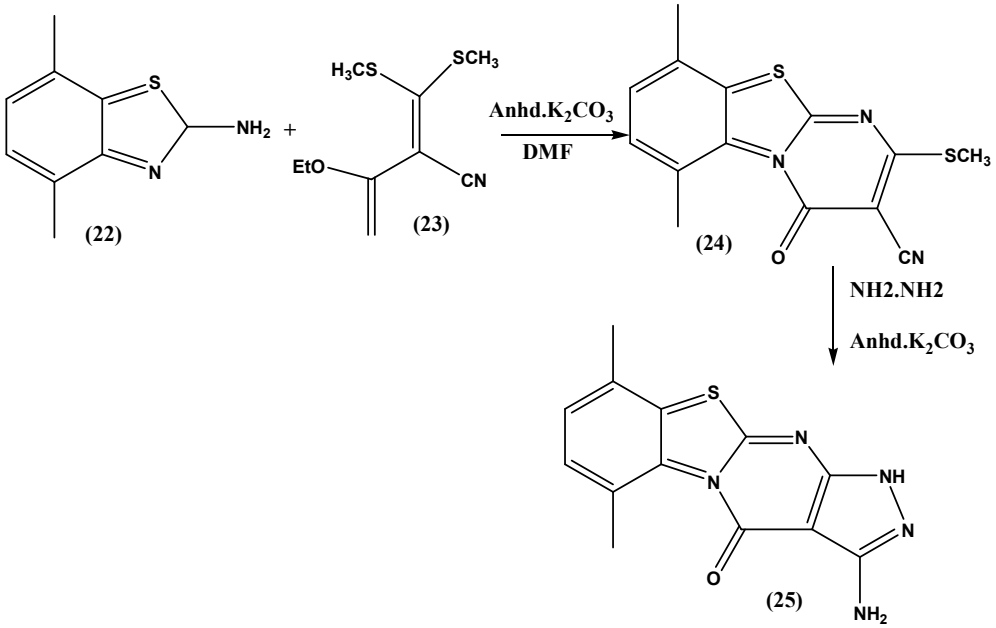


(21)

R= $C_6H_5CH_2$-, O-Br-$C_6H_5CH_2$-, O-OCH_3-$C_6H_5CH_2$-, O-Br-$C_6H_5CH_2$-, $C_5H_5NCH_2$-

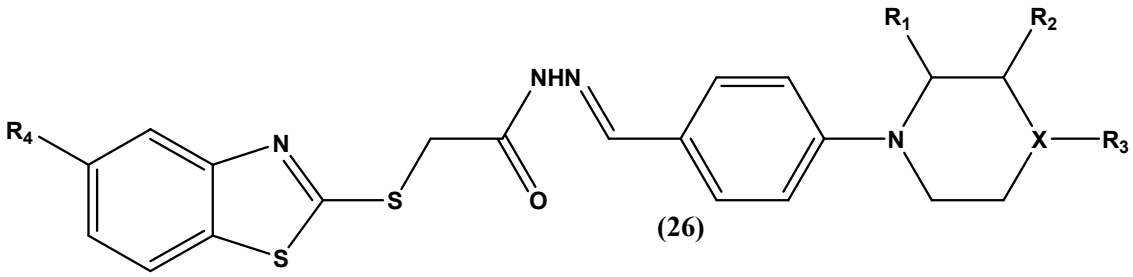
Gangadhar S. Bhopalkar synthesised a derivative of 3-amino-6,9-dimethyl-4-oxo-Pyrazolo[3,4-e] Pyrimido [2,3-b] [1,3] Benzothiazole (25) from 2-amino 4,7-dimethyl [1,3] benzothiazole on reaction with Ethyl 2-cyano 3,3' bis-methyl Thio acrylate in presence of anhydrous K2CO3 in DMF followed by reaction with hydrazine gives product, The derivatives form shows antimicrobial activity against E. coli and S. aureus.[16]

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2. Anticancer activity:

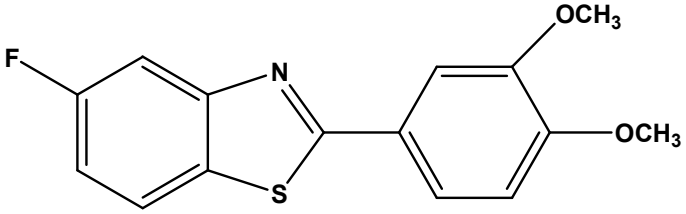
Derya Osmaniye et.al synthesized a series of acetohydrazide derivatives of 2-((5-substitiuted benzothiazole-2-yl) thiol) (26) from the reaction of 4-flurobenzaldehyde and secondary amine. The synthesized derivatives show selective anticancer activity against C6 cellines.[17]



(26)

R_1= H,CH_3, R_2=H, CH_3
R_3=H, CH_3, R_4=Cl, OCH_3

Catriona G. Mortime synthesized a series of 2-(3,4-dimethoxy phenyl)5-fluro benzothiazole (27) from reduction of o-aminothiphenol disulfide with benzaldehyde. The author observed that synthesized derivatives of benzothiazole shows potent activity against lungs, colon and breast cancer cell.[18]



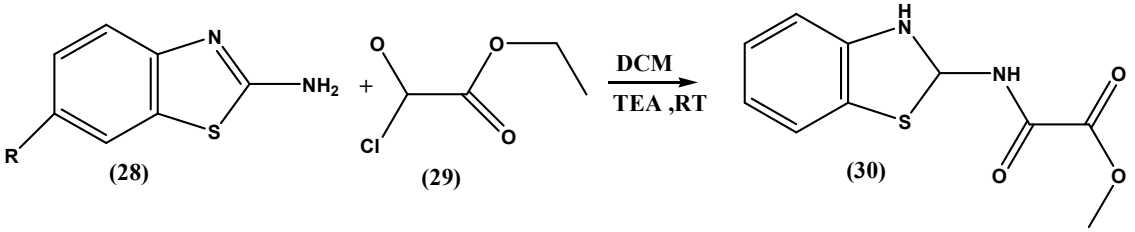
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3. Antidiabetic activity:

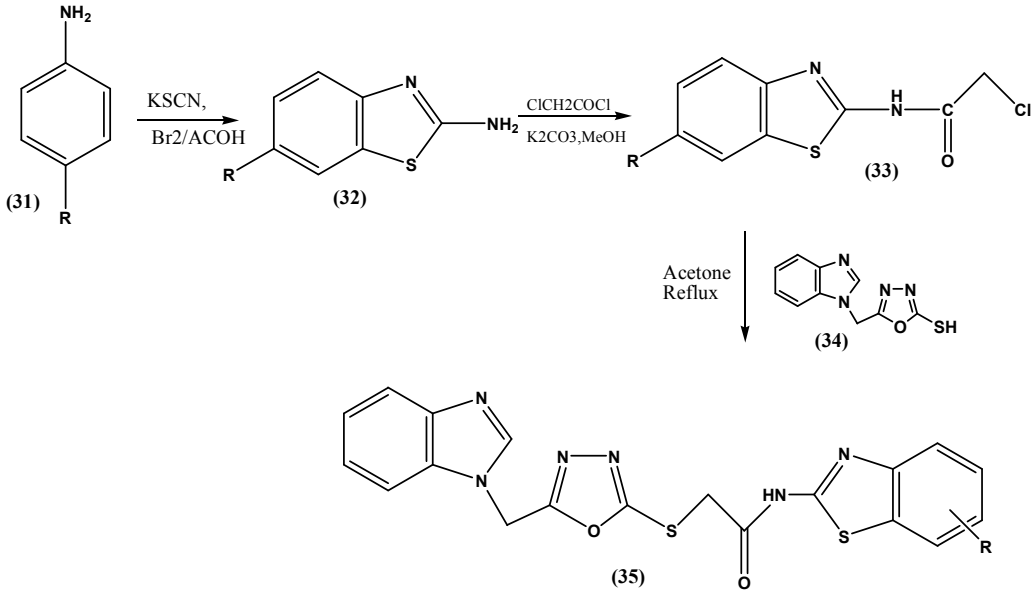
Navarrete-Vazquez et al synthesized ethyl 2-(6-substituted benzo[d]thiazol-2-ylamino)-2-oxoacetates (30), which shows hypoglycaemic activity lowering glucose concentration in acute normoglycemic model and oral glucose tolerance test in vivo. [19]



Scheme :9

4. Antituberculosis Activity:

Rahul V. Patel et.al synthesized series of benzothiazolyl-1,3,4-oxadiazol-2ylthio-N-phenyl acetamides (35) of which some derivatives show antituberculosis activity against Mycobacterium tuberculosis H37Rv.All the newly synthesized derivatives show activity at MIC ranging from 25 to 500 mg/m. [20]

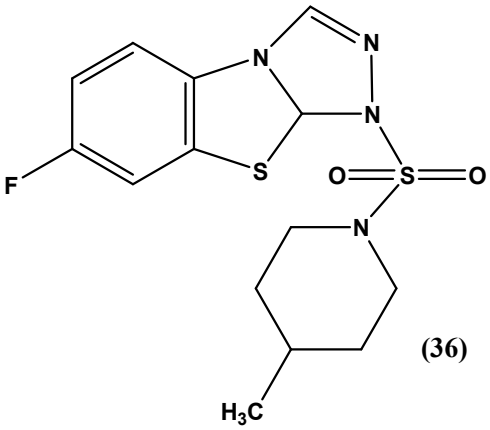


Scheme :10

5. Antimitotic activity:

Podila N et.al. synthesized 6 -fluoro-triazolo -benzothiazole derivatives (36) which shows antimitotic activity against tubulin protein. The mitotic study shows that inhibition of cancer cell by promoting microtubule formation. [21]

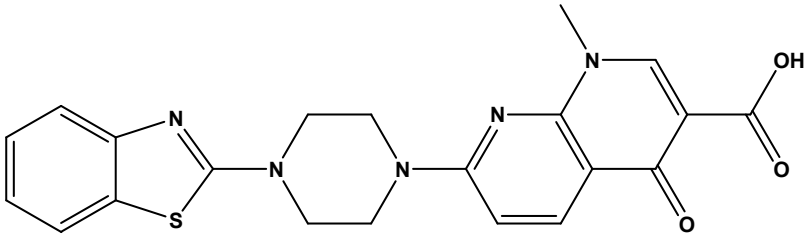
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(36)

6. Anti-HIV activity:

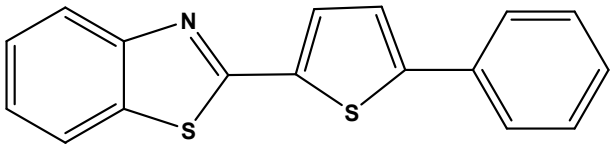
Serena Massari et.al. synthesized 7-[4-(1,3-Benzothiazol-2-yl) piperazin-1-yl]-1-methyl-4-oxo1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid Hydrochloride (37) which shows anti-HIV 1and anti-HIV 2 activity on MT 4 cells. [22].



(37)

7. Optical properties:

Rosa M. F. Baptista, et.al. studied the photophysical, piezoelectric and ferroelectric properties of a benzothiazole derivative (38) bearing an aryl thiophene π-conjugated bridge both in solution and observed that the embedded nanocrystalline phenyl thienyl-benzothiazole derivative, with crystal sizes of about 1.4 nm resulted in a good piezoelectric response from these functionalized electros spun Fibers. [23]



(38)

IV. CONCLUSION

Benzothiazole derivatives are very useful in the synthesis of different derivatives. They are used as precursors in synthetic chemistry. It has many applications across different industries, showing their versatility and significance in various fields. We concluded that this review plays an important role in synthesizing benzothiazole derivatives using reaction. There is further scope to study different benzothiazole & their Derivatives using green synthetic methods.

V. ACKNOWLEDGEMENT

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