International Journal of Scientific Research in Science and Technology
Available online at : www.ijsrst.com
Print ISSN: 2395-6011 | Online ISSN: 2395-602X
doi : https://doi.org/10.32628/IJSRST

Benzothiozole - Their Synthesis and Biological Activity : A Review

Gaurav Kumar*, Sanjay Singh, Manisha Negi, Vikrant
Siddhartha Institute of Pharmacy, VMSBUTU, Dehradun, India

ARTICLEINFO

Article History:

Accepted: 01July2023
Published:10July2023

Publication Issue
Volume 10, Issue 4
July-August-2023

Page Number
75-80

ABSTRACT

Heterocyclic chemistry has been well known for many years but in the latest years heterocyclic chemistry and heterocyclic compounds receive immense recognition. In heterocyclic chemistry, Benzothiozole is one of the most appealing moiety. Benzothiozole moiety shows a variety of application in food industry, natural products, pharmaceutical industry and many more. Benzothiozole moiety reported a diverse activities such as anti-inflammatory, antimicrobial, antibacterial, anti malarial, antifungal, antiviral antitubercular, etc. In this review we have described various synthetic methodologies and their biological activities reported by organic synthetic chemist.

Keywords: Benzothiozole, Antimicrobial, Antibacterial, Anti-Inflammatory

I. INTRODUCTION

Benzothiozole have been known for many years, but in recent years the literature review has shown appreciable activity in this field. A number of review articles were published about the reaction, application and synthesis of Benzothiozole. The Benzothiozole ring is important constituent of pharmaceuticals and biological activity 1. The motive of this review is to collect the literature dealing with the synthesis and biological activity of Benzothiozole. The vital structure of benzothiazole (Figure:1) composed of benzene merged with thiazole ring. The benzene ring is merged to the thiazole ring at 4, 5- positions and is elected as BTA 2.

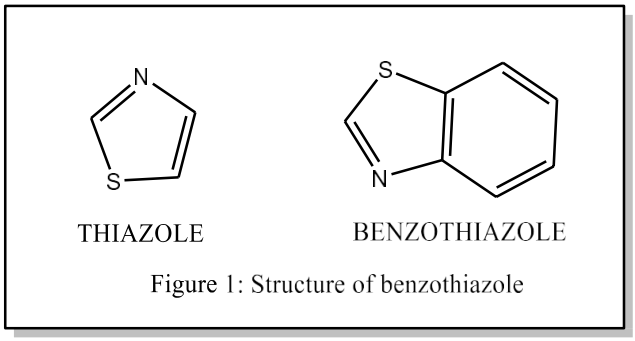
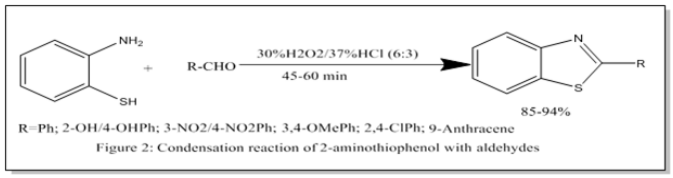


Figure 1: Structure of benzothiazole

SYNTHESISOFBENZOTHIAZOLE

AcidCatalysedCondensationreaction:Guo*et.al*demonstratethereactionof2-aminothiophenolandsubstitutedaldehydescondensationreactionutilizinghydrogenperoxide/hydrochloricacid in ethanol (Figure:2)[3]



R=Ph; 2-OH/4-OHPh; 3-NO2/4-NO2Ph; 3,4-OMePh; 2,4-ClPh; 9-Anthracene
Figure 2: Condensation reaction of 2-aminothiophenol with aldehydes

SCHEME-1

From Acid anhydride:.

By using acid anhydrides or chlorides on formic acid and amino phenols in the presence of acetic anhydride, Shivraj et al reported this scheme for the production of benzothiazole[4].

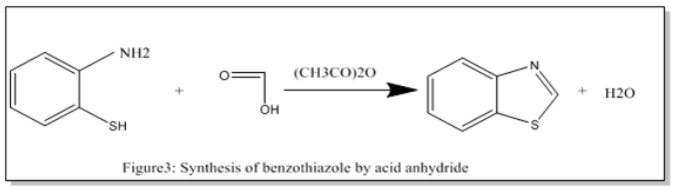


Figure3: Synthesis of benzothiazole by acid anhydride

SCHEME-1

From Acid anhydride:.

By using acid anhydrides or chlorides on formic acid and amino phenols in the presence of acetic anhydride, Shivraj et al reported this scheme for the production of benzothiazole[4].

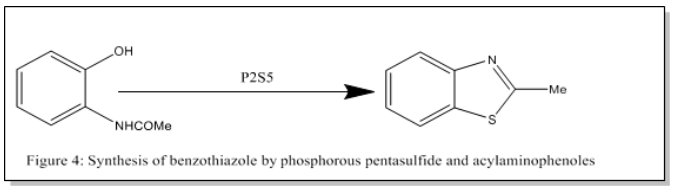
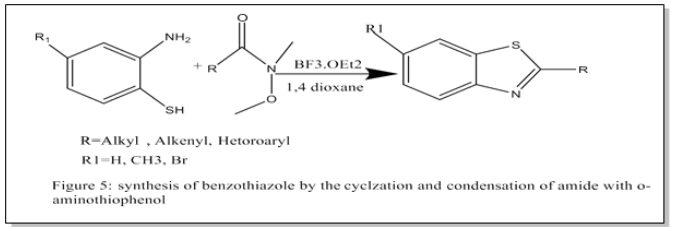


Figure 4: Synthesis of benzothiazole by phosphorous pentasulfide and acylaminophenoles

SCHEME-3

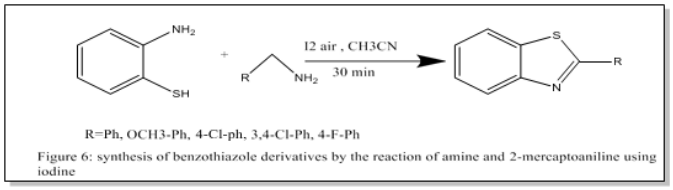
From condensation and cyclization of amide: Sadashiva et al. produced benzothiazole bycondensation and cyclization of amide with o-aminothiophenol (Figure 5) in the existence ofBF3.OEt2(borontrifluoride etherate)in the solvent 1,4-dioxane[5].



R=Alkyl , Alkenyl, Hetoroaryl
R1=H, CH3, Br
Figure 5: synthesis of benzothiazole by the cyclzation and condensation of amide with o-aminothiophenol

SCHEME-4

From amine and 2-mercaptoaniline: Narender et al. produced benzothiazole derivatives (Figure:6) from amine and 2-mercaptoaniline by reacting the two compounds with iodine 6.



R=Ph, OCH3-Ph, 4-Cl-ph, 3,4-Cl-Ph, 4-F-Ph
Figure 6: synthesis of benzothiazole derivatives by the reaction of amine and 2-mercaptoaniline using iodine

SCHEME-5

From substituted aniline and potassium thiocyanate:

Using substituted aniline and potassium thiocyanate, Trapani G. et al, reported the preparation of substituted 2-ethoxycarbonyl- imidazole benzothiazoles in presence of bromine, acetic acid, and dimethyl formamide (Figure:7)

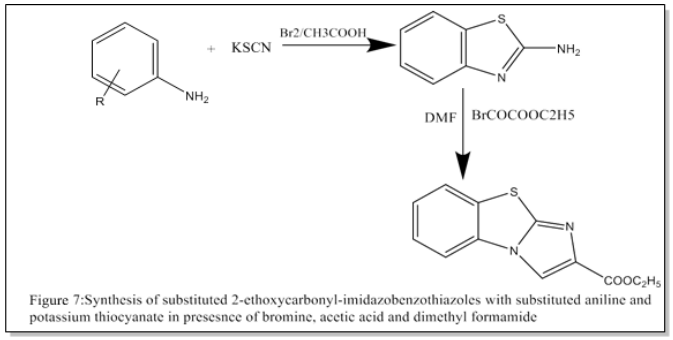


Figure 7:Synthesis of substituted 2-ethoxycarbonyl-imidazobenzothiazoles with substituted aniline and potassium thiocyanate in presesnce of bromine, acetic acid and dimethyl formamide

SCHEME-6

From 2-aminothiophenol and substituted benzaldehyde: Mortimer and his co-authors created a seriesof 2-phenylbenzothiazoles from 2-aminothiophenol and substituted benzaldehyde by reacting the twosubstancesin ethanol(Figure:8)[8].

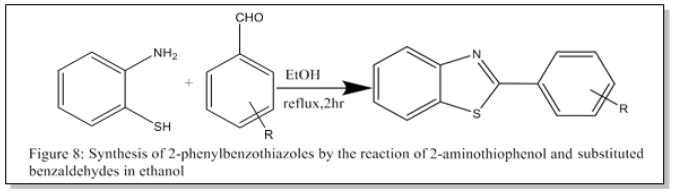


Figure 8: Synthesis of 2-phenylbenzothiazoles by the reaction of 2-aminothiophenol and substituted benzaldehydes in ethanol

SCHEME-7

From condensation of 2-amino-benzenethiol and ketone of aryl:

Aneffective 2-aryl benzothiazolehasbeendiscoveredby Dengandhisco-authors by the condensation of o-amino benzene thiol and ketone of aryl. (Figure: 9)[9]

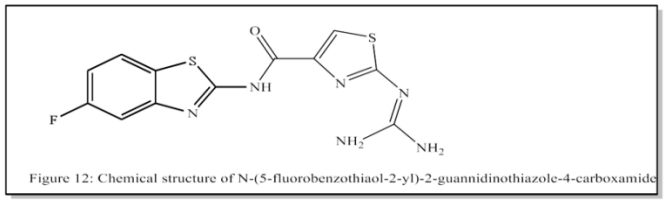


Figure 12: Chemical structure of N-(5-fluorobenzothiaol-2-yl)-2-guannidinothiazole-4-carboxamide

SCHEME-8

From N - (2-benzothiazolyl)-cynoacetamide and triethyl ortho formate inhot nitrobenzene: Stetinova and his co-authors synthesize 2-Oxo-2H-pyrimidobenzothiazole-3-carbonitrile by N -(2-benzothiazolyl)-cynoacetamide and triethyl ortho formate **(Figure:10)** inhot nitrobenzene(Onepot synthesis)[10].

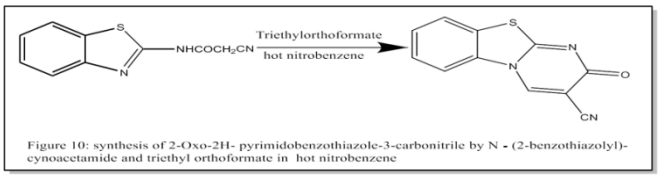
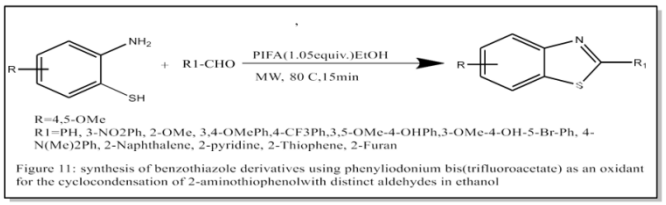


Figure 10: synthesis of 2-Oxo-2H- pyrimidobenzothiazole-3-carbonitrile by N - (2-benzothiazolyl)-cynoacetamide and triethyl orthoformate in hot nitrobenzene

SCHEME-9

Microwave induced condensation: The microwave-induced synthesis of benzothiazole derivatives is described by Praveen and his co-authors by phenyl iodonium bis (tri fluoro acetate) as an oxidant for the cyclo condensation of o- amino phenol with various aldehyde in ethan-1-ol at 800C 11.



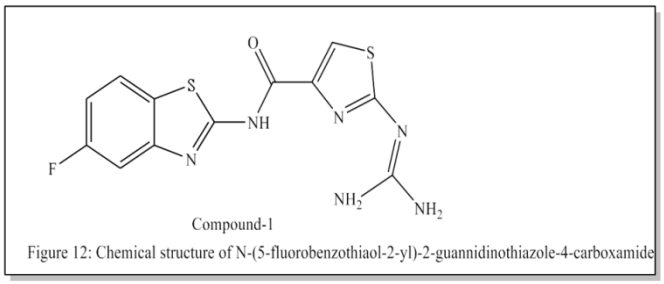
R=4,5-OMe
R1=PH, 3-NO2Ph, 2-OMe, 3,4-OMePh,4-CF3Ph,3,5-OMe-4-OHPh,3-OMe-4-OH-5-Br-Ph, 4-N(Me)2Ph, 2-Naphthalene, 2-pyridine, 2-Thiophene, 2-Furan

Figure 11: synthesis of benzothiazole derivatives using phenyliodonium bis(trifluoroacetate) as an oxidant for the cyclocondensation of 2-aminothiophenolwith distinct aldehydes in ethanol

SCHEME-10

APPLICATION OF BENZOTHIAZOLE AND ITS DERIVATIVES:

Benzothiazole as Anticancer agent: Schnur and his co-authors discus the anticancer activity of N-(5-Fluoro benzthiazole-2-yl)-2-guanidinothiazole-4-carboxamide in micro metastatic 3L.L Lewis lungs carcinoma in mice and compound 1(fig-12) shows as potent thera-peutics index when compound to the anticancer agent adriamycin.



Compound-1

Figure 12: Chemical structure of N-(5-fluorobenzothiaol-2-yl)-2-guannidinothiazole-4-carboxamide

Racane and his co-authors synthesize amidine nitro and amidine amino substituted benzothiazole (fig-13: compound 2 and 3). Racane showed the diamidino substituted 2- phenyl benzothiazole (Figure 2) and compound amino-amidine-2-phenyl benzothiazole (Figure 3) activity. While compound amino-amidine-2 phenyl benzothiazole exhibits inhibitory effect toward MCF-7 and H 460 cells, compound diamidino substituted 2-phenyl benzothiazole exhibits remarkable inhibitory activity for tumour cell proliferation, according to (13).

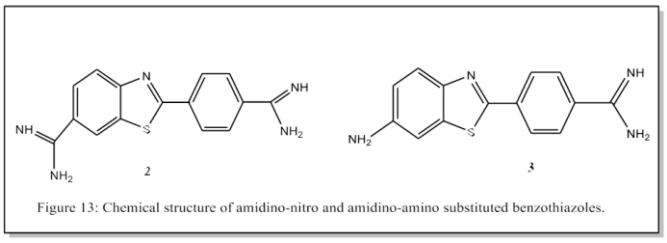


Figure 13: Chemical structure of amidino-nitro and amidino-amino substituted benzothiazoles.

2-(Substituted-Phenyl) Benzothiazoles were synthesized using a combinatorial technique by Suk-June et al. (Figure 14: Compounds 4-6) and their anti-tumor activity was reported. According to studies on SAR the BT moiety was necessary for powerful Cytotoxicity and the phenyl ring's 3-position substitution with an alkyl or halogen group improved the Cytotoxicity of antitumor BTs. Comparing these analogues IC50 values to those of the anticancer drugs etoposide, whose value is 78.4M, compounds 4 and 5 were shown to have the stronger inhibitory effect against topoisomerase II. The amino substitution-containing compound 3 & 5 exhibited strong topo II activity14.

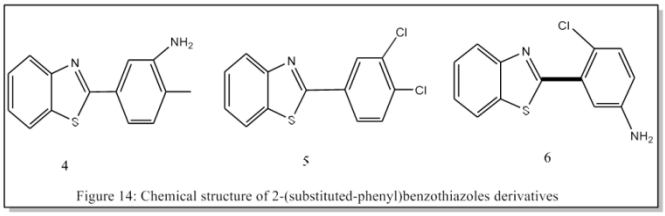


Figure 14: Chemical structure of 2-(substituted-phenyl)benzothiazoles derivatives

By using modified anilines and potassium thiocyanate, Singh et al. show the production of imidazole-based benzothiazoles and investigate their anticancer properties. (Figure 15: Compound 7) exhibited outstanding anticancer activity in comparison to doxorubicin15.

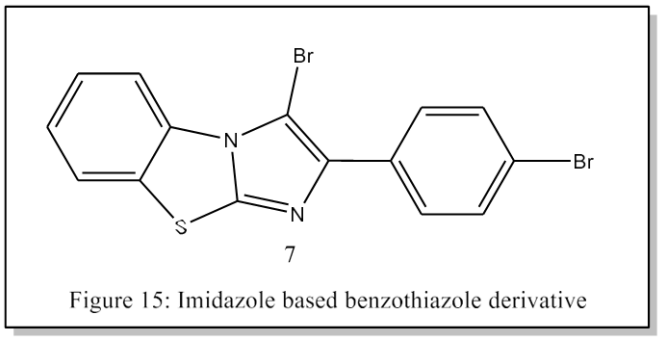


Figure 15: Imidazole based benzothiazole derivative

Benzothiazole as Anti-microbial agent:. Benzothiazole moiety based thiourea derivatives was reported by Saeed et al. with good anti-microbial action (Figure 16: Compound 8-12). Each compound exhibits strong antimicrobial activity 16.

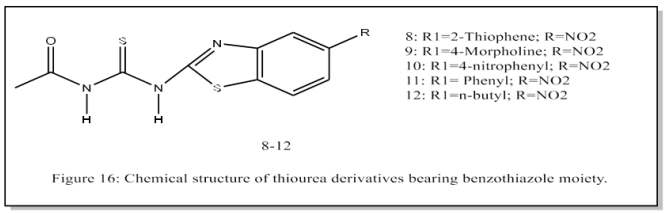


Figure 16: Chemical structure of thiourea derivatives bearing benzothiazole moiety.

The antibacterial activity of benzothiazole derivatives was investigated against Gram+ and Gram- microorganisms by Waghamode KT and his co-authors (Figure:17 Compound-13). Every synthetic substance exhibits excellent antibacterial activity 18.

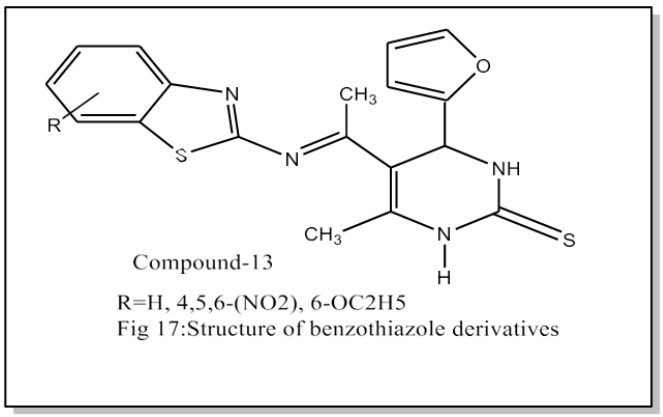


Fig 17:Structure of benzothiazole derivatives

BTA as anti-diabetic agent:

A number of substituted 3-(benzo (d) thiazol-2-yl amino) phenyl prop-2-ene, 1-one are synthesized by Patil V.S and co- authors (fig:18, compound-14) was created by combining sodium hydride, 2 aminobenzothazole & 1-aryl, 3,3-di-(methyl sulfanyl)-2- propen-1-one in THF. The anti-diabetic activity of novel synthesized compound was examined.

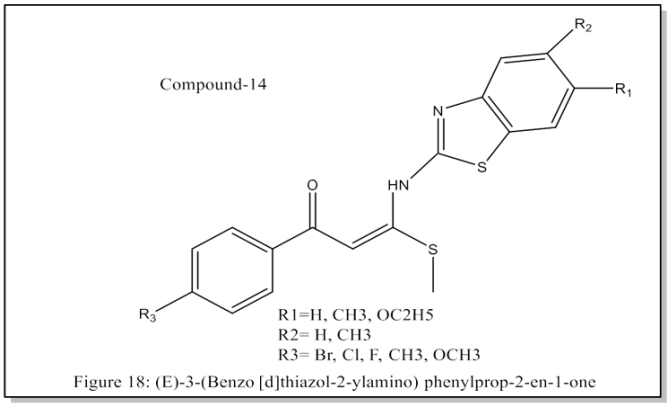


Figure 18: (E)-3-(Benzo [d]thiazol-2-ylamino) phenylprop-2-en-1-one

A few 2-((benzothiazole-2-yl thio) methyl), 5-phenyl-1,3,4 oxadiazoles were synthesized in 2016 & tested for their anti-diabetic action by Kumar S et al They Discovered that the substances. 2-(((6-nitro-benzo [d] thiazole-2yl) thio) methyl)-5-(4-nitro phenyl)-1,3,4-oxadiazole (fig-19, compound-15) possess outstanding anti diabetic action in their investigation.

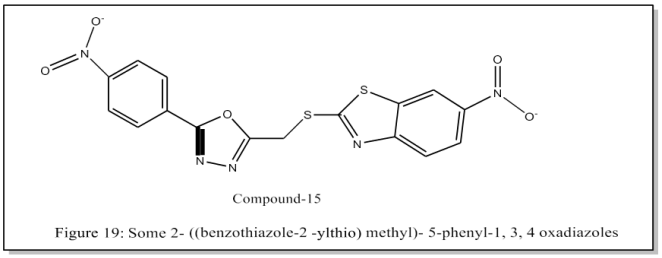


Figure 19: Some 2- ((benzothiazole-2 -ylthio) methyl)- 5-phenyl-1, 3, 4 oxadiazoles

With the help of in vitro experiment, Tuylu et al created derivatives of 2-aryl substituted (2-hydroxy, 3- Methoxy o-nitro phenyl (fig-20, compound 16-20 and evaluated mutagenicity, it was observed that they all significantly increased the number of revertant colonies, although compound 14 had the strongest mutagenic effects on TA98 and the weakest effects on TA10021.

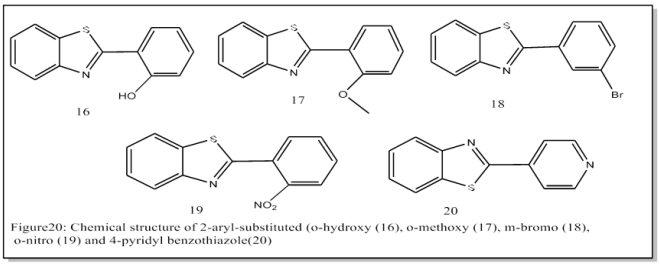


Figure20: Chemical structure of 2-aryl-substituted (o-hydroxy (16), o-methoxy (17), m-bromo (18), o-nitro (19) and 4-pyridyl benzothiazole(20)

BTA as anthelmentic agent:

Fluorobenzothiazole, which is composed of sulfonamide pyrazole derivatives, is created by Sreenivasa and his colleagues, and they demonstrate its anthelmentic activity. They note that some of these derivatives or compounds (Figure 21: Compound 21-28) exhibit significant activity in comparison to the standard drug albendazole against perituma posthuma and earthworms 22.

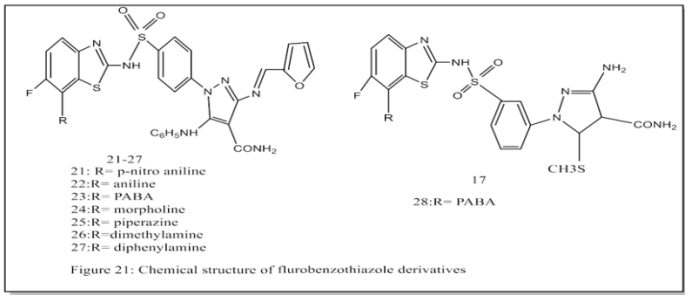


Figure 21: Chemical structure of flurobenzothiazole derivatives

Anti-inflammatory activity:

When synthesising 2-amino benzothiazole derivatives (Figure 22: Compound 29-31) for their anti-inflammatory studies, Venkatesh and his co-author Pandeya noticed that certain of the compounds (Figure:22 Compound 29-31) were more effective than the reference medication diclofenac sodium 23.

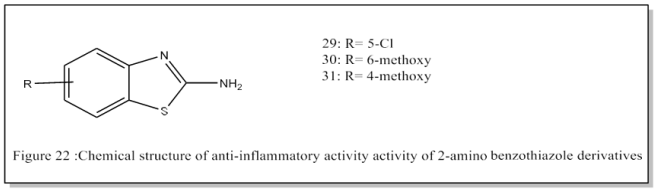


Figure 22 :Chemical structure of anti-inflammatory activity activity of 2-amino benzothiazole derivatives

Cite this article as :

Gaurav Kumar, Sanjay Singh, Manisha Negi, Vikrant, "Benzothiozole - Their Synthesis and Biological Activity : A Review", International Journal of Scientific Research in Science and Technology (IJSRST), Online ISSN : 2395-602X, Print ISSN : 2395-6011, Volume 10 Issue 4, pp. 75-79, July-August 2023.
Journal URL : https://ijsrst.com/IJSRST523103193

REFERENCES:

1. Gao X: Recent advances in synthesis of benzothiazole compounds related to green chemistry. molecules 2020; 25(7):1675: 1-16.
2. Shaista A and Parle A," Benzothiozle- A magic molecule, International journal of pharmaceutical sciences and research 2017; 8(12): 4909-4929
3. Guo HY, Li JC and Shang YL: A simple and efficient synthesis of 2-substituted benzothiazoles catalyzed by H2O2 /HCl. Chinese Chemical Letters 2009; 20: 1408-1410
4. Shivraj H: Synthesis and biological evaluation of some benzothiazole derivatives. Asian J Research Chem-2010; 3(2): 421-427
5. Sadashiva and Lingaraju: Weinreb amide as an efficient reagent in the one pot synthesis of benzimidazoles and benzothiazoles. Tetrahedron Lett-54(2013); 2693– 2695
6. Narender T and Naresh G: Molecular iodine promoted divergent synthesis of benzimidazoles, benzothiazole and 2-benzyl-3-phenyl-3,4-dihydro2H-benzo[e][1,2,4]thiadiazines. J. Org. Chem 79(2014); 3821-3829
7. Trapani G and Franco M: Synthesis and benzodiazepine receptor binding of some 4Hpyrimido [2, 1-b]benzothiazol-4-ones. European journal of medicinal chemistry 1992; 27: 39-44
8. Mortimer CG, Wells G, Crochard JP, Stone EL, Bradshaw TD, Stevens MF and Westwell AD: Antitumor benzothiazoles. 26(1) 2-(3, 4-dimethoxyphenyl)-5-fluorobenzothiazole (GW 610, NSC 721648), a simple fluorinated 2-arylbenzothiazole, shows potent and selective inhibitory activity against lung, colon, and breast cancer cell lines. Journal of Medicinal Chemistry 2006; 49: 179-185
9. Deng G.P, Liao Y, Qi H, Chen S, Jiang P, Zhou W: Efficient 2-Aryl Benzothiazole Formation from Aryl Ketones and 2-Aminobenzenethiols under Metal-Free Conditions. Org. Lett. 2012; 14: 6004–6007.

10. Stetinova j, Kada R, Lesko j: Synthesis and reaction of some 2-aminobenzothiazoles. Molecules 1996; 1: 251-254
11. Praveen C, Nandakumar A, Dheenkumar P, Muralidharan D and Perumal P: Microwave-assisted one-pot synthesis of benzothiazole and benzoxazole libraries as analgesic agents. Journal of Chemical Sciences 2012; 124: 609-62
12. Schnur RC, Fliri AF, Kajiji S and Pollack VA: N-(5-flurobenzothiazol-2-yl)-2-guanidinothiazole-4-carboxamide. A novel, systemically active antitumor agent effective against 3LL Lewis lung carcinoma. J Med chem. 1991;34: 914-918.
13. Racane L, Kralj M, Suman L, Stojkovic R, Tralic-kulenovic V, Karminski-Zamola G: Novel amidino substituted 2-phenylbenzothiazoles:Synthesi , antitumor evaluation invitro and acute toxicity testing invivo. Biorg Med Chem 2010;18:1038-1044.
14. Choi SJ, Park HJ, Lee SK, Kim SW, Han G, Ch oo HY. Solid phase combinatorial synthesis of benzothiazoles and evaluation of topoisomerase II inhibitory activity. Bioorg Med Chem 2006;14:1229–1235.
15. Singh Y, Kaur B, Kaur A: spectral studies and biological activity of 2, 3-disubstituted imidazo [2, 1-b] benzothiazole derivatives. Indian J Pharmaceut Biol Res 2018; 6: 1–8
16. Saeed S, Rashid N, Jones GP: Synthesis, characterization and biological evaluation of some thiourea derivatives bearing benzothiazole moiety as potential antimicrobial and anticancer agents. Eur J Med Chem 2010; 45: 1323–31.
17. Bele D.S, Kothari H and Singhvi I: Synthesis and antimicrobial activity of some benzothiazole derivatives. Inter. J. Pharm. and Chem. Sci 2012; 4: 1238-1242.
18. Shinde PK and Waghamode KT: Synthesis, characterization and antibacterial activity of substituted benzothiazole derivatives. International Journal of Scientific and Research Publications 2017; 8: 365-370.
19. atil VS, Nandre KP, Ghosh S: Synthesis, crystal structure and antidiabetic activity of substituted (E)-3- (Benzo [d] thiazol-2-ylamino) phenylprop-2-en-1-one. European Journal of Medicinal Chemistry 2013; 59: 304–309.
20. Kumar S, Rathore DS, Garg G, Khatri K, Saxena R and Sahu SK: Synthesis and evaluation of some 2- ((benzo thiazol-2-ylthio) methyl)-5-phenyl-1, 3, 4- oxadiazole derivatives as antidiabetic agents. Asian Pacific Journal of Health Sciences, 2016; 3(4): 65-74.
21. Tuylu B.A, Zeytinoglu H.S, Isikdag I: Synthesis and mutagenicity of 2-aryl-substitute (o-hydroxy-, m-bromo-, o-methoxy-, o-nitro phenyl or 4 pyridyl)benzothiazole derivatives on salmonella typhimurium and human lymphocytes exposed in vitro 2007; 62(5): 626-632.
22. Sreenivasa GM, Jayachandran E, Shivakumar B, Jayaraj KK, KumarV:Synthesis of bioactive molecule fluoro benzothiazole comprising potent heterocyclic moieties for anthelmentic activity. Arch Pharm Sci Res 2009;1: 150–157.
23. Venkatesh P, Pandeya SN: Synthesis, characterisation and antiinflammatory activity of some 2-amino benzothiazole derivatives. Int J Chem Tech Res 2009;1: 1354–1358.
24. Wada J, Suzuki T, Iwasaki M, Miyamatsu H, U eno S, Shimizu M: A new nonsteroidal antiinflammatory agent. 2-Substituted 5- or 6-benzothiazoleacetic acids and their derivatives. J Med Chem 1973;16:930–934.