IJBPAS, July, 2023, 12(7): 3201-3214

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

THERAPEUTIC JOURNEY, SYNTHESIS AND RECENT ADVANCES IN BENZOTHIAZOLE DERIVATIVES

DUBEY B, SINGH K*, KUMAR A, KUSHWAHA SP

Faculty of Pharmacy, Integral University, Lucknow, Uttar Pradesh, India

***Corresponding Author: Dr. Kuldeep Singh: E Mail: kuldeep@iul.ac.in**

Received 12th July 2022; Revised 18th Sept 2022; Accepted 27th Oct. 2022; Available online 1st July 2023

https://doi.org/10.31032/IJBPAS/2023/12.7.7275

ABSTRACT

Benzothiazole is a heterocyclic organo-sulfur moiety which is weakly basic. Benzothiazole pharmacophore containing a benzene ring that is combined with a five membered thiazole ring at position 4 and 5. Benzothiazole and its derivatives demonstrate a huge variety of pharmacological effects such as anticancer, antimicrobial, antimalarial, antituberculosis, antidiabetic, anthelmintic, antioxidant, anti-inflammatory, anti-glutamate, antiparkinsonism, anticonvulsant, muscle relaxant activity, neuroprotective, inhibitors of numerous enzymes. In this review, we discussed benzothiazole chemistry, recent synthesis procedures and pharmacological activities of commonly developed benzothiazole derivatives in brief, as well as numerous structural modifications performed on the benzothiazole ring and privileged specificities communicated in their biological responses.

Keywords: Benzothiazole; Antimalarial; Pharmacophore; Pharmacological activities

1. Introduction:

The heterocyclic compound benzothiazole and its derivatives is a remarkable heterocyclic compound with medicinal, dyeing, and agricultural pesticide functions. Antibacterial, anticancer, anthelmintic, and anti-diabetic properties have been reported for benzothiazole and its derivatives **[1-3]**. In industry, benzothiazole and its derivatives are used as antioxidants and vulcanization accelerators. Due to their unusual structure and application as radioactive amyloid imaging agents, certain benzothiazoles, such as 2-aryl benzothiazole, have gotten a lot of attention **[4-5]**. The synthesis of benzothiazole derivatives has piqued the

interest of academics and scientists **[2-4]**. Due to its simple chemical structure ease of synthesis, and significant effects on biological responses. The tiny and easy benzothiazole moiety can be found in compounds used in studies to evaluate new products with promising biological properties **[1-5]**. In this study, we briefly covered benzothiazole chemistry, contemporary synthesis processes and pharmacological activity of widely generated benzothiazole derivatives, as well as structural modifications to the benzothiazole ring and preference specificities communicated in biological responses.

2. Chemistry:

Benzothiazole is a bicyclic structure made up of nine atoms that contain the heterocycle 1, 3-thiazole combined to a benzene ring. The ring benzothiazole has a methylene group between the sulphur and nitrogen atoms, which has pharmacological and biological effects. 2- Benzothiazole molecules with aromaticity give stability, hence benzothiazole with an electron-withdrawing moiety is thermally stable **[1-3]**. The colourless, faintly thick liquid benzothiazole has a melting point of 2ºC and a boiling temperature of 227-228°C. The concentration of benzothiazole at 25°C is 1.238 g/ml. Furthermore, it is a weak base with a huge range of biological, bioorganic, and medicinal chemistry activity, as well as drug development applications. It is relatively stable due to its aromaticity, despite the fact that it is a heterocycle with reactive sites that allow for functionalization **[1-5]**, it's employed in industry and for research, and it's quite useful for the development of numerous pharmaceutical compounds **[4-7]**. A huge number of analogs have been synthesized with different methods some are discussed below **(Figure 1)**.

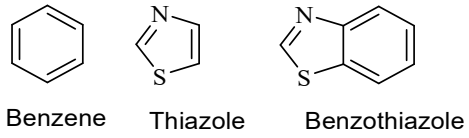


Figure 1

2.1 Conventional methods of Synthesis:

The 2-substituted Benzothiazole derivatives have been synthesized by the condensation reaction of 2-aminothiophenol and aldehyde derivatives **[8-12]**. The condensation reaction of 2-aminothiophenol and aldehydes is carried out using homogeneous or heterogeneous catalysis. Homogeneous acid catalysis is reported with using H_2O_2 / HCl in ethanol

at room temperature **[8] (Figure 2a)** and acetic at room temperature **[10] (Figure 2b)**, while homogeneous basic catalysis is reported with ammonium chloride in methanol/water as a dual solvent system at room temperature **(Figure 2c) [12]**.

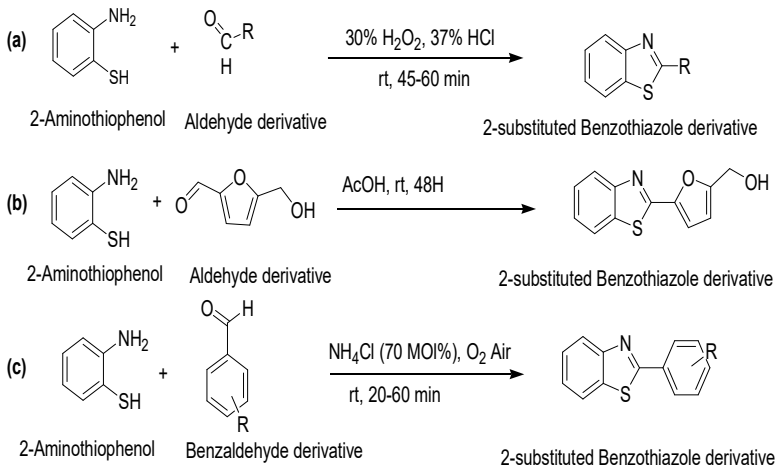


Figure 2

2.2 Microwave-assisted Synthesis:

With higher synthetic yields, systematically shorter reaction times, and one-step synthesis of numerous typical multi-step artificial processes, microwave-assisted organic synthesis improves the drug innovation and development route **[13]**. Microwave-assisted organic synthesis has forever revolutionized how scientists think about organic synthesis. This enabling technology is currently in widespread usage in industry research centers, and it has been successfully applied to a number of organic transformations **[14, 15]**, with phenyliodonium bis trifluoroacetate (PIFA) as a catalyst (an oxidant), microwave-assisted cyclo-condensation of 2-aminothiophenols among aldehyde derivatives generated a high yield of the products **(Figure 3a) [16]**. The 2-substituted benzothiazole derivatives have been synthesized via the combination of 2-aminothiophenol with aldehydes under CEM-focused microwave irradiation environment using glycerol as a green solvent **(Figure 3b) [14]**.

2.3.Green chemistry approach

In recent years, a considerable number of benzothiazole derivatives have been synthesized using green chemistry concepts for environmental protection and resource utilization **[17-19]**. Researcher's attention has been aroused by the creation of metal-free catalysts, the use of renewable reaction materials and reagents, and the realization of reactions under moderate circumstances **[17-21]**. By using p-Toluenesulfonic acid

(10 mol %) as an effective and efficient catalyst for the condensation reaction of aromatic aldehydes with 2-aminothiophenol in water with moderate to good yields **(Figure 4a) [22]** green chemistry is applied to create 2-substituted benzothiazole derivatives. A green approach to benzothiazole derivative synthesis utilizing brick-derived clay as a catalyst. These derivatives were synthesized by a four-component condensation reaction that involved benzil, aldehyde, 2-aminobenzimidazole/2-amino-6-nitrobenzothiazole, and ammonium acetate **(Figure 4b) [23]**. These methods offer an easy and effective methodology in terms of mild reaction conditions, clean reaction profiles, small quantities of catalyst, and simple workup procedure.

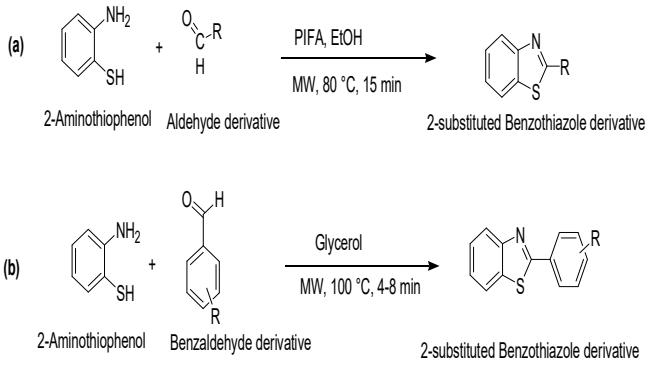


Figure 3

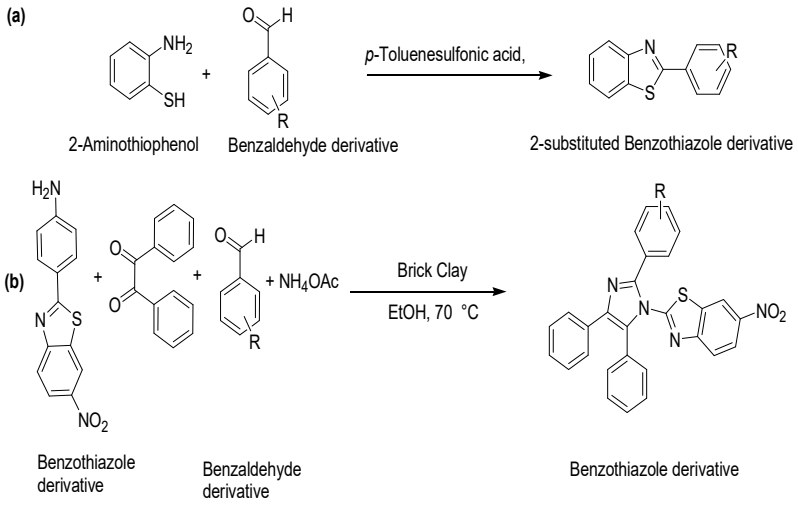


Figure 4

3. Pharmacological Activities:

The benzothiazole pharmacophore is a critical scaffold that exhibits a broad range of pharmacological actions. Anticancer, antibacterial, antimalarial, antituberculosis and a variety of other biological properties have been demonstrated for the benzothiazole and its derivatives **[1-6] (Figure 5)**.

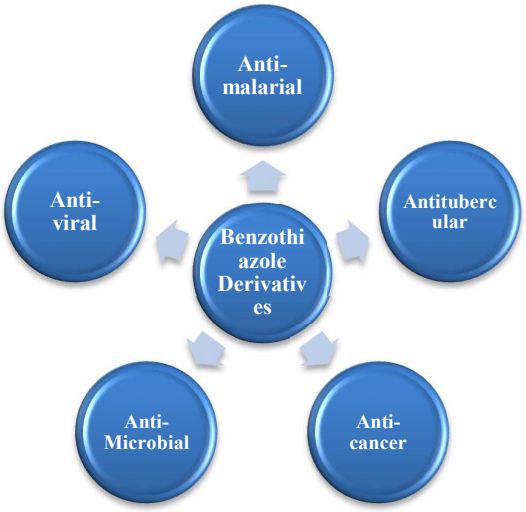


Figure 5

3.1. Anticancer activity:

Several attempts have been made to modify the benzothiazole nucleus and synthesize a large number of benzothiazole derivatives that act on a variety of molecular targets such as tyrosine kinase inhibitors, Cytochrome P-450 inhibitors, heat shock protein 90 (hsp90) inhibitors, replication and mitosis inhibitors **[1-4]**. Choi *et al*. synthesized 2-(substituted-phenyl) benzothiazoles **1** showed topoisomerase-II inhibitory response through the IC_{50} of 71.7 µM **[24]**. A series of Benzothiazole amide derivatives was discovered as a TRPC6 activator in cell based high throughput screening **[25]**. Bhuva along with Kini synthesized sequence of new 2-phenyl-1, 3-benzothiazoles **2** that showed inhibitory activity against tyrosine kinase **[26]**. Hutchinson synthesized and evaluated fluorinated 2-(4-aminophenyl) benzothiazoles **3** inhibit Cytochrome P-450 (CYP) (GI_{50}< 1nM) in human breast MCF-7 **[27]**. Synthesized thiadiazole containing thiourea, Benzothiazole and imidazole derivatives **[28]**.

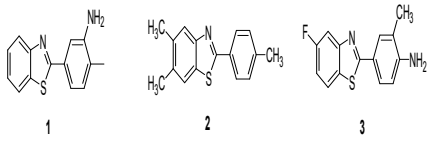
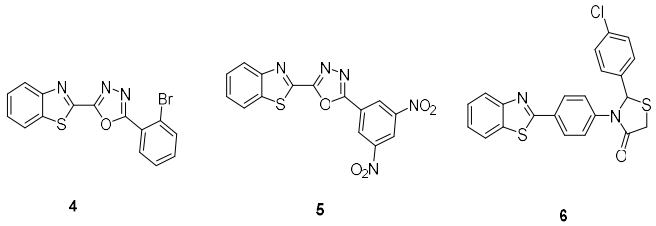


Figure 6

3.2. Antimicrobial activity:

Many problems with currently available antimicrobial drugs remain unaddressed, despite substantial efforts to develop new antimicrobial agents. Because they are still important adaptable grade of compounds opposed to microbes, benzothiazoles are promising framework in favor of future molecular research **[29]**. Synthesized 2-(5-substituted-1, 3, 4-oxadiazole-2-yl)-1, 3-benzothiazole derivatives **4, 5,** and evaluated for in-vitro antibacterial activity not in favor of gram-positive and gram-negative bacteria strain *like B. subtilis, Bacillus pummels, E. coli* in addition to initiate to acquire large spectrum of antibacterial response **[30]**. Discussed advancement in pharmacological activities of benzothiazole nucleus including antimicrobial response **[31]**. Synthesized novel benzothiazole substituted thiazolidinone derivatives **6** were estimated in support of their inhibitory capability beside *Proteus mirabilis, S. aureus, Salmonella typhi* and *K. pnuemoniae* laid out efficient inhibition regards above noticed four human microorganisms **[32]**.



4 5 6

Figure 7

3.3. Antiviral activity:

Antiviral effects of many benzothiazole analogues have been reported. Many of these compounds had desirable pharmacokinetic properties as well as a broad spectrum of antiviral activity against a variety of viruses, acting on different molecular targets such as protease, helicase, polymerase, reverse transcriptase, integrase, and neuramidase, and were used as anti-dengue, anti-hepatitis c virus, anti-HIV, anti-influenza, and anti-westnile agents **[1-5]**. Investigated a series of new benzothiazole derivatives **7** evaluated for their antiviral activity by inhibiting HIV replication **[33]**. Synthesize a series of 2, 5, 6-substituted benzoxazole, benzimidazole, benzothiazole, and oxazole (4,5-b) pyridine derivatives were evaluated for antiviral activity against HIV-I reverse transcriptase enzyme results demonstrated that compound **8** possesses good antiviral activity (IC_{50} value 0.34 µmol/L) **[34]**. Synthesized benzothiazole sulfonamide derivatives **9** as inhibitors of HIV-1 protease with improved potency and antiviral activities by replacement of the urea moiety by benzothiazole sulfonamide moiety and also possess good oral bioavailability **[35]**.

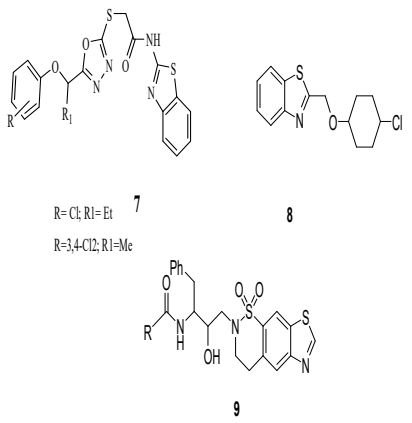


Figure 8

3.4. Antimalarial activity:

In the world's subtropical and tropical climates, malaria is foremost severe global health troubles. Malaria is originated by means of four types of malaria parasites, with *Plasmodium falciparum* being the mainly powerful moreover possibly lethal. Resistance to first-line antimalarials like chloroquine, mefloquine, and pyrimethamine is spreading quickly, necessitating the development of new antimalarial medicines that are both effective and inexpensive. Synthesized rhodacyanines derivatives **10** and evaluated them on behalf of their in-vitro and in-vivo antimalarial responses counter to Plasmodium falciparum, K1 and P. berghei in mice revealed to have extremely shows potential antimalarial responses **[36]**. Developed the benzothiazole derivative **11,** which evinced excellent activity against P. falciparum strains, K1 and W2, with IC_{50} values fluctuating from 7-22 nM **[37]**. Synthesized benzothiazole derivative **12** and estimated it beside Plasmodium falciparum (PfNMT), and displayed>25% inhibitory action in opposition to recombinant PfNMT **[38]**.

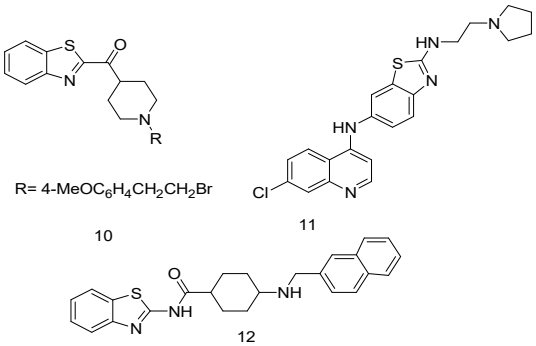
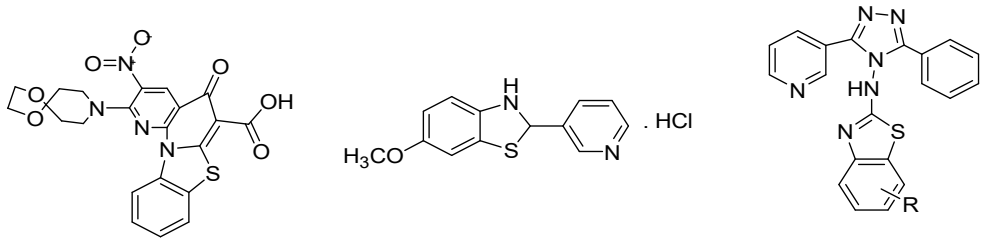


Figure 9

3.5. Antitubercular activity:

Tuberculosis is an infectious disease among an elevated mortality rate that is presently the foremost cause of death among young people, women, and AIDS patients worldwide. Treating mycobacterial

infections, notably tuberculosis, has grow to be a severe difficulty owing to the appearance of single drug and poly drug-resistant strains of *Mycobacterium tuberculosis* **[39, 40]**. Synthesized new 3-nitro-2-(sub)-5,12-dihydro- 5-oxobenzothiazolo[3,2-a]-1,8-naphthyridine-6-carboxylic acids **13** and estimated in favor of their antitubercular responses in vitro and in-vivo beside *M. tuberculosis* H37 Rv (MTB) establish to be the mainly dynamic compound in vitro among MIC of 0.19 and 0.04 μM beside MTB and MTR-TB, correspondingly **[41]**. Evaluated a sequence of benzothiazoline derivatives designed for antimicrobial activity in opposition to gram-positive and gram-negative bacteria, dermatophytes, Entamoeba histolytica, and in favor of in vitro and in vivo action in opposition to *M. tuberculosis*. Results confirmed that compound **14** have the maximum activity in case of *M. tuberculosis* **[42]**. Synthesized BTA-triazole-pyridine conjugated analogs **15** and estimated in favor of their in vitro antitubercular action in case of Mtb H37Rv strain exposed adequate antimicrobial activity, and the compound displayed preferable anti-TB action analyzed to rifampicin **[43]**.



13 14 15

Figure 10

3.6. Anticonvulsant activity:

Benzothiazole were initially noticed in 1978 as anticonvulsant agents in opposition to pentylenetetrazole actuated seizures on 2-(-4-arylthiosemicarbazidocarbonylthio) benzothiazoles and then numerous benzothiazoles carrying sulphonamide derivatives synthesized, benzothiazolamines were synthesized and evaluated for their action in opposition to MES (maximum electroshock method) used in grandmal type of epilepsy and pentylenetetrazole which create clonic form of seizures be similar to petitmal type of epilepsy. Kale reviewed on Recent Development in Substituted Benzothiazole as an Anticonvulsant Agent **[44]**.

In the explore of novel anticonvulsant agents having benzothiazole phamacophore, **[45]** synthesized a bunch of Benzothiazole coupled sulphonamide derivatives.

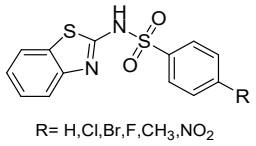


Figure 11

3.7. Anti-inflammatory activity:

Several novel 2- (4'-butyl-3', 5'-dimethylpyrazol-1'-yl) -6- substituted benzothiazole were establish to enlist anti-inflammatory response **[46]**. A sequence of 2-(2-alkoxy -6-pentadecylphenyl) methylthio-1H- Benzimidazoles / benzothiazoles and benzoxazoles from an anacardic acid **[47]**, Synthetically- tailored and nature-derived dual for their capability to hinder human cyclooxygenase and enzyme (COX-2 and LOX-5) **[48]**.

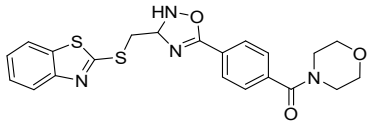


Figure 12

3.8. Miscellaneous activities:

The benzothiazole derivatives has been demonstrated antidiabetic, anthelmintic, antioxidant, anti-glutamate and antiparkinsonian, muscle relaxant activities, neuroprotective, inhibitors of several enzymes **[1-6]**.

4. CONCLUSION

Benzothiazole is a heterocyclic organo-sulfur moiety which is weakly basic. Benzothiazole pharmacophore containing a benzene ring that is fused with a five membered thiazole ring at position 4 and 5. Benzothiazole has been the subject of a considerable and massive volume of study with multiple exceptional successes revealing its broad potential applicability as medicinal chemistry. A large number of benzothiazole and its derivatives demonstrate a wide variety of pharmacological effects such as anticancer, antimicrobial, antimalarial, antituberculosis, antidiabetic, anthelmintic, antioxidant, anti-inflammatory, anti-glutamate, antiparkinsonian, anticonvulsant, muscle relaxant activities, neuroprotective, inhibitors of numerous enzymes, and have formerly been fruitfully progressed, marketed, and enormously used in the health center in the prevention and treatment of a variety of diseases with little toxicity, high level bioavailability, and superior biocompatibility and healing effects. All of this clearly suggests that benzothiazole compounds have limitless therapeutic potential. Excitingly, a growing amount of benzothiazole derivatives have been identified as potential clinical therapeutic contenders under active

research and development. This interesting moiety has the potential to be a variety of molecular targets, and more research into this scaffold might lead to even more promising medical results. This knowledge is expected to lead to the creation of new synthetic techniques as well as the production of better molecules with improved biological characteristics and selectivity.

Acknowledgement

The authors gratefully acknowledge the Faculty of Pharmacy, Integral University and Saroj Institute of Technology & Management, Lucknow for providing the essential amenities to bring out the study.

Authors acknowledge the research committee of the Integral University for providing the manuscript communication number (MCN) – IU/ R&D/2022MCN0001462.

REFERENCES

[1] Keri RS, Patil MR, Patil SA, Budagumpi S., "A comprehensive review in current developments of benzothiazole-based molecules in medicinal chemistry". Eur J Med Chem. 2015 Jan 7;89:207-51.

[2] Sharma PC, Sinhmar A, Sharma A, Rajak H, Pathak DP., " Medicinal significance of benzothiazole scaffold: an insight view". J Enzyme Inhib Med Chem. 2013 Apr;28(2):240-66.

[3] Gao X, Liu J, Zuo X, Feng X, Gao Y., "Recent Advances in Synthesis of Benzothiazole Compounds Related to Green Chemistry". Molecules. 2020 Apr 5;25(7):1675.

[4] Shaista A and Amrita P "Benzothiazole - A magic molecule". Int J Pharm Sci Res 2017; 8(12): 4909-29.

[5] Asiri YI, Alsayari A, Muhsinah AB, Mabkhot YN, Hassan MZ. "Benzothiazoles as potential antiviral agents". J Pharm Pharmacol. 2020 Nov;72(11):1459-1480.

[6] Patel VK, Singh A, Jain DK, Patel P, Veerasamy R, Sharma PC, Rajak H, "Combretastatin A-4 based thiophene derivatives as antitumor agent: Development of structure activity correlation model using 3D-QSAR, pharmacophore and docking studies", Future J. Pharmaceutical Sci., 2017;3:71-78.

[7] Ahmad K, Malik MS and Syed MAH: "Therapeutic potential of benzothiazoles A patent review" 2010-2014.

[8] 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

[9] 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. J. Medicinal Chem., 2006; 49: 179-185.

[10] Sattler L, Zerban F, Clark G and Chu CC (1951). The Reaction of 2-Aminobenzenethiol with Al-doses and with Hydroxymethyl furfural. J American Chem Soc.73: 5908-5910.

[11] Green and Perkin: "Polythiosulphonic acids of p-diamines". J. Chcmical Society 1903; 70: 1201-1212.

[12] Maleki B and Salehabadi H: "Ammonium chloride as a mild and efficient catalyst for the synthesis of some 2-arylbenzothiazoles and bisbenzothiazole derivatives". European J. Chem., 2010; 1: 377-380.

[13] Rajak H, Jain DK, Dewangan PK, Patel V, Agrawal N. "Application of microwaves in organic synthesis: speeding up the process of drug discovery". RGUHS J. Pharm. Sci. 2013;03:14-20.

[14] Zhang X-Z, Zhou W-J, Yang M, Wang J-X, Bai L. "Microwave-Assisted Synthesis of Benzothiazole Derivatives using Glycerol as Green Solvent". J. Chemical Res. 2012; 36(8):489-491.

[15] Appukkuttan P, Mehta VP, Van der Eycken EV. "Microwave-assisted cycloaddition reactions". Chem Soc Rev. 2010 May; 39(5):1467-77.

[16] Praveen C, Nandakumar A, Dheenkumar P, MuralidharanD and Perumal P: "Microwave-assisted one-pot synthesis ofbenzothiazole and benzoxazole libraries as analgesicagents". J. Chemical Sci., 2012; 124: 609-624.

[17] Qi, Y.; Ma, J.; Chen, X.; Xiu, F.R.; Chen, Y.; Lu, Y. "Practical aptamer-based assay of heavy metal mercury ion in contaminated environmental samples: Convenience and sensitivity". Anal. Bioanal. Chem. 2020, *412*, 439–448.

[18] Kumar G, Singh N.P., "Synthesis, anti-inflammatory and analgesic evaluation of thiazole/oxazole substituted benzothiazole derivatives", Bioorganic Chem., Volume 107, 2021, 104608.

[19] Strus P, Borensztejn K, Szczepankiewicz AA, Lisiecki K, Czarnocki Z, Nieznanska H, Wojcik C, Lukasz P. Bialy, Mlynarczuk-Bialy I, "Novel podophyllotoxin and benzothiazole derivative induces transitional morphological and functional changes in HaCaT cells", Toxicology in Vitro, Volume 73, 2021, 105144.

[20] Xiu, F.R.; Lu, Y.; Qi, Y. "DEHP degradation and dechlorination of polyvinyl chloride waste in subcritical water with alkali and ethanol: A comparative study". Chemosphere. 2020, *249*, 126138.

[21] Chen, Y.; Gao, X.; Liu, X.; Ji, G.; Fu, L.; Yang, Y.; Yu, Q.; Zhang, W.; Xue, X. "Water collection from air by ionicliquids for efficient visible-light-driven hydrogen evolution by metal-

free conjugated polymer photocatalysts". Renew. Energ. 2020, *147*, 594–601.

[22] Azizi, N., Amiri, A.K., Baghi, R. *et al.* "PTSA catalyzed simple and green synthesis of benzothiazole derivatives in water". Monatsh Chem., 140, 1471 (2009).

[23] Pandey H, Shrivatsva S. P. "One Pot Synthesis, Characterization of Benzothiazole/ Benzimidazole Tethered Imidazole Derivatives using Clay as Catalyst". Orient J. Chem 2021;37(3) 583-588.

[24] Choi SJ, Park HJ, Lee SK, Kim SW, Han G, Choo YP. "Solid phase combinatorial synthesis of benzothiazoles and evaluation of topoisomerase II inhibitory activity". Bioorg. Med. Chem. 2006,14, 1229–1235.

[25] Wei Y, Zhang M, Lyu Z, Yang G, Tian T, Ding M, Zeng X, Xu F, Wang P, Li F, Liu Y, Cao Z, Lu J, Hong X, Wang H. "Benzothiazole Amides as TRPC3/6 Inhibitors for Gastric Cancer Treatment". ACS Omega. 2021 Mar 24;6(13):9196-9203.

[26] Bhuva HA, Kini SG. "Synthesis, anticancer activity and docking of some substituted benzothiazoles as tyrosine kinase inhibitors". J Mol Graph Model 2010; 29:32–37.

[27] Hutchinson I, Chua MS, Browne HL, Trapani V, Bradshaw TD, Westwell AD *et al*. "Antitumor benzothiazoles. Synthesis and *in vitro* biological properties of fluorinated 2-(4-aminophenyl) benzothiazoles". J Med Chem., 2001;44:1446–1455.

[28] Avvaru SP, Noolvi MN, More UA, Chakraborty S, Dash A, Aminabhavi TM, Narayan KP, Sutariya V. "Synthesis and Anticancer Activity of Thiadiazole Containing Thiourea, Benzothiazole and Imidazo[2,1-b][1,3,4]thiadiazole Scaffolds". Med Chem. 2021; 17(7):750-765.

[29] Sharma PC, Jain S, "Synthesis and in vitro antibacterial activity of some novel N-nicotinyl-1-ethyl-6-flouro-1,4-dihydro-7-piperazine-1-yl-4-oxoquinoline-3-carboxylates". Acta Pol Pharm Drug 2008, Res; 65:551–586.

[30] Rajeeva B, Srinivasulu N, and Shantakumar SM. Synthesis and Antimicrobial Activity of Some New 2-Substituted Benzothiazole Derivatives. J. Chem 2009, 404-596 .

[31] Kumar G, Singh N.P., 'Synthesis, anti-inflammatory and analgesic evaluation of thiazole/oxazole substituted benzothiazole derivative", Bioorganic Chem., 2021, Volume 107, 104608.

[32] Nagarajan A.S., Kamalraj S., Muthumary J., Reddy BSR. (2009). "Synthesis of biologically active benzothiazole substituted thiazolidinone derivatives via cyclization of unsymmetrical imines". Indian J chem; **157**7-1582

[33] Akhtar T, Hameed S, Al-Masoudi NA, Loddo R, La Colla P. "*Invitro* antitumor and antiviral activities of new benzothiazoleand 1,3,4-oxadiazole-2-thione derivatives". Acta Pharm 2008;58:135–149.

[34] Akbay A, Oren I, Temiz-Arpaci O, Aki-Sener E, Yalcin I. "Synthesis and HIV-1 reverse transcriptase inhibitor activity of some 2,5,6-substituted benzoxazole benzimidazole benzothiazole and oxazolo(4,5-b) pridine derivatives". Arzneim-forsch/Drug Res., 2003;4:266–271.

[35] Nagarajan AS, crescendo GAD, Getman DP, Lu HF, Sikcrski JA, Walker JL, Mcdonald JJ, houseman KA, Kocan GP, Kishore N., Mehta P.P., Shippy C.L.F.. "Discovery of novel benzothiazole sulphonamides as potent inhibitors of HIV -1 protease". Bio org med chem. 2003,11(22):4769-77.

[36] Takasu K, Pudhom K, Kasai K, Terauchi H, Inoue H, Kaiser M, Brun R, Ihara M. "Synthesis of three classes of rhodacyanine dyes and evaluation of their in vitro and in vivo antimalarial activity". Bioorg. Med. Chem 2006, 14 8550–8563.

[37] D.S.B. Ongarora, J. Gut, P.J. Rosenthal, C.M. Masimirembwa, K. Chibale, "Benzoheterocyclic amodiaquine analogues with potent antiplasmodial activity: synthesis and pharmacological evaluation", Bioorg. Med. Chem. Lett. 22 (2012) 5046e5050

[38] Bowyer PW, Gunaratne RS, Grainger M, Withers-Martinez C, Wickramsinghe SR, Tate EW *et al*. "Molecules incorporating a benzothiazole core scaffold inhibit the N-myristoyltransferase of *Plasmodium falciparum"*. Biochem J 2007;408:173–180.

[39] Karali N, Gürsoy A, Kandemirli F, Shvets N, Kaynak FB, Ozbey S *et al*. "Synthesis and structure anti-tuberculosis activity relationship of 1H-indole-2,3-dione derivatives". Bioorg Med Chem 2007;15:5888–5904.

[40] Aridoss G, Amirthaganesan S, Kim MS, Kim JT, Jeong YT. "Synthesis, spectral and biological evaluation of some new thiazolidinones and thiazoles based on t-3-alkyl-r-2,c-6-diarylpiperidin-4-ones". Eur J Med Chem 2009;44:4199–4210.

[41] Dinakaran M, Senthilkumar P, Yogeeswari P, Sriram D. "Antitubercular activities of novel benzothiazolonaphthyridone carboxylic acid derivatives endowed with high activity toward multi-drug resistant tuberculosis". Biomed Pharmacother 2009;63:11–18.

[42] Palmer PJ, Trigg RB, Warrington JV. "Benzothiazolines as antituberculous agents". J Med Chem 1971;14:248–251.

[43] N.B. Patel, I.H. Khan, S.D. Rajani, "Pharmacological evaluation and characterizations of newly synthesized 1,2,4-triazoles", Eur. J. Med. Chem. 45 (2010) 293-299

[44] Kale A, Rajendra K , Smita P, Rutuja T, (2021). "Recent Development in Substituted Benzothiazole as an Anticonvulsant Agent". Mini-Reviews in Med Chem; 21(8)**1017**-1024.

[45] Khokra L Sukhbir, Arora K, Khan AS, Kaushik P, Saini R, Husain A, "Synthesis, Computational Studies and Anticonvulsant Activity of Novel Benzothiazole Coupled Sulfonamide Derivatives" Iranian J. Pharmaceutical Res., 2019 Winter; 18(1): 1–15.

[46] Junior.VC, Danuello. A, da Silva Bolzani. V, "Molecular hybridization: a useful tool in the design of new drug prototypes", Curr Med Chem. 2007, 14 (17), 1829-1852.

[47] Xie L, Zhai X, Ren L "Design, Synthesis and Antitumor Activity of Novel Artemisinin Derivatives Using Hybrid Approach, Chemical and Pharmaceutical Bulletin" (Tokyo) 2011. 59,984-990.

[48] Meshram MA, Bhise OU, Makhal NP, Kaki RV, "Synthetically-tailored and nature-derived dual COX-2/5-LOX inhibitors: Structural aspects and SAR", Euro J of Med Chem Volume 225, 5 December 2021, 113804