Ind. J. Pharm. Edu. Res., 2024; 58(3s):s704-s719.
https://www.ijper.org

Review Article

Synthesis and Pharmacological Activities of Benzothiazole Derivatives

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ABSTRACT

The Research and Development in benzothiazole-based medicinal ingredients have turn into a hastily on the rise and gradually more lively topic. Broad number of compounds having Benzothiazole (BTZ) moiety are involved in the treatment of a various number of diseases with maximum curative potency. This review is aimed to afford modern progress in the synthesis of Benzothiazole analogues associated to the green chemistry. Literature surveys on scientific national and international journals, books as well as electronic resources were performed. Benzothiazole and its moieties containing various numbers of structural multiplicities play evidence in search of different pharmacological actions. This review steadily grants an all-inclusive review in the progressive developments of Benzothiazole-based compounds of medicinal chemistry as antibacterial, Hepatitis-C virus inhibitors, anti-alzheimer's disease, anti-inflammatory and analgesic, antioxidant, anti-convulsant, anti-diabetic, anti-histaminic, anti-malarial, anti-depressant and other medicinal agents. The wide field of pharmacological activity in creature benzothiazole derivative indicates that this string of compounds is of an unquestionable curiosity. This review is also believed to be extra efficient in finding pathogenic problems and diagnostic analogues is ready to find new-fangled judgment in the chase for drawing of a reduced amount of toxic and additional active Benzothiazole-based drugs. It is projected that this knowledge would give rise and show enormous impact for the growth of synthetic pathways for benzothiazoles with expansion of novel synthetic approaches.

Keywords: Benzothiazole, Heterocyclics, Synthesis, Structure Activity Relationship, Antibacterial.

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Received: 12-03-2023;
Revised: 10-10-2023;
Accepted: 16-05-2024.

INTRODUCTION

Over a long time for the search of new drug discovery, the auspicious structure-activity relationship has materialized as a rewarding and hastily rising theme in the science of pharmaceutical chemistry. For the drawing and synthesis of new molecules, Benzothiazoles (BTZs) are the standard composition with in-house likeness of varied natural receptors, symbolize ultimate source with scaffolds on a practical time scale. For the competent binding against numerous receptors having elevated affinity, the referred formation presents course group of molecules. To hastily find out in nature lively molecules extensive choice of remedial region over limited moment of period, management of compound derivatives permits pharmaceutical chemist N and S holding heterocycles take part in a chief role in countless other built-up fields as well as in science interrelated with unique whereas in pharmaceutical chemistry.[1]

Among them, benzothiazoles exerts numerous biological activities which encompass a set of curative molecules. Fusing at 4,5-positions of thiazole with benzene is designated as Benzothiazole (BTZ) and hybridized as entirely planar.[2]

From the benzothiazole, fraction of composition of firefly, luciferin and benzothiazole also are acknowledged as fragrance component of the tea plants as well as essence amalgam produced by the fungi *Polyporus frondosus* and *Aspergillus clavatus*. In studies biological activities found in benzothiazoles, like compounds which occur in land or aquatic region. Benzothiazole derivatives have attracted continuing interest because of their varied biological activities viz. anticancer, antimicrobial, anticonvulsant, antitubercular, antimalarial, antihelmintic, analgesic and antiinflammtory, antidiabetic and fungicidal activities etc. In present, benzothiazole moieties have been estimated as budding amyloid-binding diagnostic agents in neurodegenerative disease, selective fatty acid amide hydrolase inhibitors, inhibitors of stearoylcoenzyme-Ad-9 desaturase, LTD4

DOI: 10.5530/ijper.58.3s.74

receptor antagonist, orexin receptor antagonist 2, histamine H2 antagonists and β-amyloid plaques.[3]

They are also valuable as appetite depressants, intermediates for dyes, plant protectants, imaging representative for photographic sensitizers. As a heterocyclic compound, benzothiazole derivatives come across for a chemical research, as in polymer chemistry, dyes, drugs etc.

Methabenzthiazuron (MBTU) is used as herbicide in cold season to corn crops and is a lively ingredient of two marketed accessible formula Tribunil[R] and Ormet[R], slimicides in the paper and pulp manufacturing unit. 2-Aminobenzothiazole is common in invent of various disperse azo dye. Riluzole (2-amino-6-trifluoromethoxy benzothiazole) is marketed by Rhone-Poulenc (Rilutek) for management of amyotrophic lateral sclerosis and 2-(4-aminophenyl) benzothiazole evidenced antitumor properties.[4]

Benzothiazole moieties helps in the creation of sulfide linkages (reticulation) among unsaturated elastomeric polymers in a flexible as well as elastic cross-linked material.[5]

The synthesis of benzothiazole moieties has expected an increasing thought to researchers.

Different Methods of Synthesis of Benzothiazole Heterocyclic Ring

In 1887, 2-substituted benzothiazole was first produced by A. W. Hofmann by simple cyclization mechanism used by traditional path as well as diversified activity have been reported.[6]

Established methods for research of the benzothiazole skeleton comprise 2-aminothiophenols condensation reactions with substitute aldehydes, nitriles, carboxylic acids, esters, or acyl chlorides.

Synthesis of benzothiazoles by Bouchet and co-workers have stated an well-organized tactic for best yield by the cyclization using riboflavin of thiobenzanilides as photosensitizer and potassium peroxydisulfate as oxidizing representative underneath sunlight radiation.[7]

In latest years, nonstop development of green chemistry thoughts for environmental defense[8,9] and resource exploitation, the awareness of reactions beneath gentle circumstances, the utilization of renewable reaction reagents and materials, and the expansion of metal free catalysts have paying attention of Scientist. Remarkably, in past decades a variety of nature friendly way have been out in the open for the synthesis of benzothiazole. The present editorial is planned to momentarily review current research advancement relating to the synthesis of benzothiazole compounds, which chiefly comprise the condensation reaction of acids/ketones/acylchlorides/aldehydes and 2-aminobenzenethiol. The cyclization of benzothiazole scaffolds offered thioamides. Furthermore, a string of benzothiazole scaffolds were too manufactured by cyclization of CO_2 as unprocessed resource.[10,11]

These methods suffer from restrictions for example troubles in the grounding of 2-aminothiophenols which are oxidizable possessing readable substituents.

One more familier path known to put in order that the benzothiazole shows the cyclization of thiobenzanilides by Jacobson's. Other broad methods consist of the microwave mediated reaction of β-chlorocinnamaldehydes with *o*-aminothiophenol, the rejoin of *o*-aminothiophenol with dibenzyl disulfides, arylhaloamines with S-aryl thiobenzoate, radical cyclization of benzyne intermediates, 1,2,3-benzodithiazole-2-oxides.[12] Different methods of synthesis of benzothiazole heterocyclic ring are shown in Figure 1.

Different Reported Pharmacological Activities of Benzothiazole Derivatives

In medicinal chemistry, benzothiazole and its analogues are crucial pharmacophores and grateful structures having quality in numeral of drugs. In, attendance, examination gives a wide-ranging indication in current developments of benzothiazole base in medicinal chemistry, SAR and strategies are discussed.

BTZ as Antimicrobial Agents

Innovation and expansion of novel anti-microbial molecules in hunt for healthier healing is core ambition for scientists.[13]

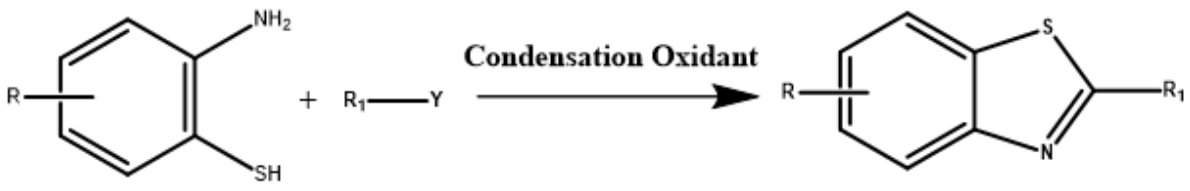
Schiff bases that contains benzothiazole-triazole complex were found and are identified for their antimicrobial behavior adjacent to a division of fungal and bacterial variant. 4-hydroxy, 4-dimethylamino and 3,4-dimethoxy group shows good anti-bacterial activity of those compounds having aromatic ring.

Structure Activity Relationship of Benzothiazoles for their Antimicrobial Activity

Antifungal activity found elevated at position 2 by chloro group and 3,4-dimethoxy (3,4-OCH_3) on aromatic ring. Decline in the property if substitution at position by 2-NO_2 or 3-NO_2 group. Most effective antifungal agents were compound 1(a-c).

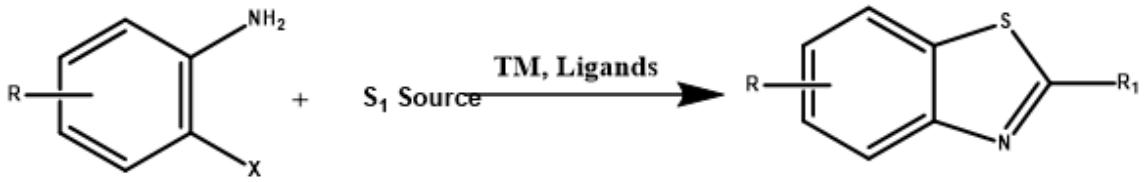
Benzothiazoles containing sulfonamide were prepared and estimated against collected bacteria. A good antimicrobial activities of compound 2 judged against Sulfamethoxazole-trimethoprim complex was identified. Decline in property found when Nitro (-NO_2) compound 2b group replaced by amino (-NH_2) group compound 2a.

2-mercapto derivatives with 2-amino ones were active against various bacteria and more potent beside fungi. Overall highlights and significance on substitution at 6-position with huge groups of 2-aminobenzothiazole derivatives for elevating anti-fungal property. An electron donating groups existence with halogens



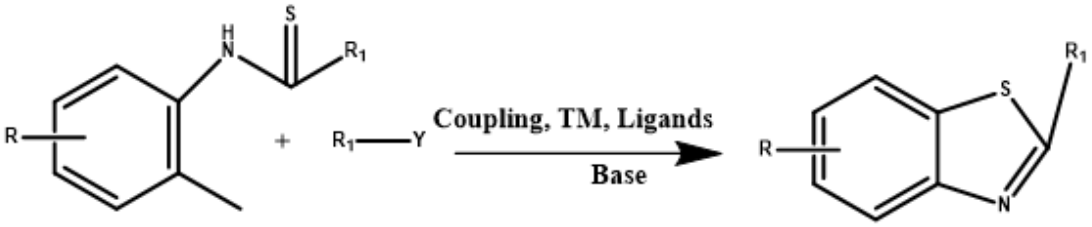
Y= CHO, COX, COOR, COOH, CN, etc

Scheme 1



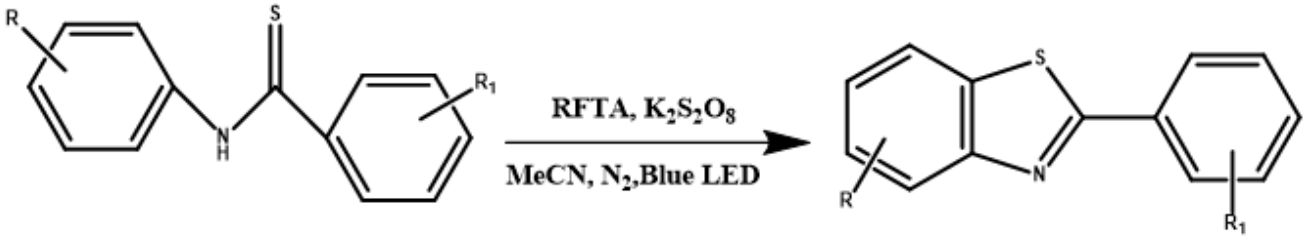
S_1 Source = CS_2, SCN, Na_2S, etc

Scheme 2

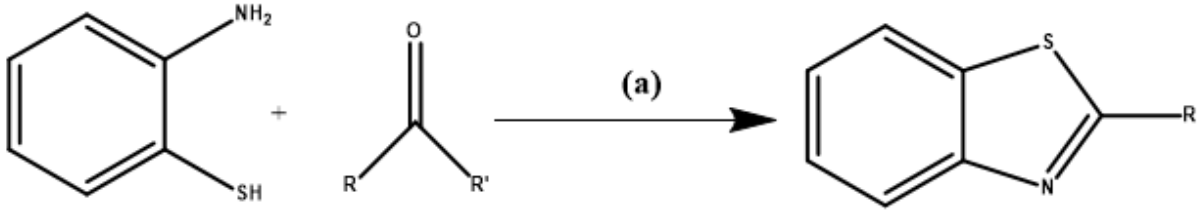


X= I, Cl, Br

Scheme 3



Scheme 4



Where R' = Acid, adldehyde, nitriles, imidates, orthoesters, anhydrides or lactones.
Reagent: a) strong acids/ milder reagents/ oxidative reagent/ different catalyst

Scheme 5

Figure 1: Different schemes of synthesis of benzothiazole heterocyclic ring.

(-Cl, -Br, -I) and methoxy (-OCH_3) in benzothiazole ring manipulate the antifungal and antibacterial property.[14]

Connecting linker occurrence and location -NHCSNH- group in between the purine ring and Benzothiazole ring look like important for antimicrobial effect. Mixed molecules possess pyrazolinone/pyrazole and Benzothiazole moieties possess antifungal activity beside *Aspergillus niger* and *C. albican* while antibacterial activity beside *S. aureus* and *E. coli*. Compound (3) having para-bromo group on the phenyl ring in pyrazolinones.

Ferruh Lafzi and co-workers identified benzothiazole/benzimidazole/indole bearing thiourea/urea derivatives as antimicrobial agents. The benzothiazole-thiourea as well as benzothiazole uera derivatives had no activity with either R or S configurations. The activity of synthesized compounds were evaluated against gram positive (*S. aureus* and *B. cereus*) and gram negative (*E. coli* and *P. aeruginosa*) bacteria by disc diffusion assay. The MIC of some compounds was determined as 62.5 µg/mL. Moreover, it was found that all the compounds were effective against gram positive rather than gram negative which may be related to low penetration of compounds to outer membrane.[15]

Thiazolidin-4-ones clubbed with azetidin-2-ones incorporated benzothiazole analogs were likely antimicrobial property was stated. All the bacteria were tested against compounds 4(a-c) and evidenced for good antimicrobial property.

From the SAR studies it is found that 2,4-dichloro, methyl and 4-nitro groups bind to the phenyl at 2nd position of the thiazolidin-4-ones ring and the presence of 2,4-dichloro and phenoxy (-OC_6H_5) groups linked at 4th position at azetidin2ones nuclei proofs fine activity beside bacterial strains of all type.

Conjugates of benzothiazole-guanidinopropanoic acid compounds were prepared and reviewed for antiproliferative and antimicrobial, activities against human cancer cell line, found superior over Ciprofloxacin alongside *P. aeruginosa* and compounds are highly active against *Salmonella paratyphyi*. A good number of potent antiproliferative properties were also showed by compound positive control, against doxorubicin.

Benzothiazole containing uanidinopropanoic acid from SAR study disclose better activities and functional groups such as in order OH>COOH> SO_2NH_2 substituted at 6th position of benzothiazole Thiazole ring play an important task for the activity.[16]

Fusarium oxysporum and *Aspergillus fumigates* were identified antifungal *in vitro* by Pyrazolo [1,5-a] pyrimidine and Thiazole. SAR study exposed, best antimicrobial activity by the integration of benzothiazole to nucleus of thiophene at 3rd position by means of carboxamide linker.

1,3,5-triazine clubbed with benzothiazole-quinoline molecules were monitor for anti-microbial property. Methoxy (-OCH_3) and Chloro(-Cl) halogen groups compounds within the phenyl ring raises the antimicrobial property.[17]

BTZ as Anticancer Agents

After heart diseases, it characterize the second top cause of death, the most life threatening disease arresting impact in the humanity at present.[18]

Among them, benzothiazole derivatives towards anticancer research attracted extensive consideration, and numerous shots were made for transforming the Benzothiazole nucleus to get better antitumor properties. Transformations on the benzothiazole nucleus results assorted pharmacological properties. With polymerized benzothiazoles and imidazobenzothiazoles in addition other benzothiazoles like 2-(3,4-dimethoxy phenyl)-5-fluoro benzothiazole (PMX 610) have been revealed to displays gracefully potent and discriminating *in vitro* anticarcinogenic property in individual tumor cell lines.[19]

Expansion of new benzothiazole-based antitumor derivatives, more importantly, drawn unbroken efforts which has been directed towards targeting a range of receptors or enzymes such as microtubule, topoisomerases, Rapidly Accelerated Fibrosarcoma (RAF) kinases, cytochrome P_{450} enzyme, farnesyltransferase, and Deoxy Nucleic Acid.

BTZ as Topoisomerase Inhibitors

Results of essential task, topo-isomerases are crucial for competence of creatures from unicellular microbes to human being.

By solid phase combinatorial method synthesized 2-(substitutedphenyl) benzothiazoles with trityl resin and assesses their capacity to reduce topoisomerase II properties. The supreme inhibitory activity showed by the compound 5 which were like the anticarcinogenic mediator was found etoposide and also more over the identical compound illustrated selectively cytotoxic beside myeloid leukemia carcinogenic cells which measure up to another carcinogenic cells.[20]

Benzothiazole analogues having 2-(Substituted phenyl/benzyl) related analogues were manufactured and tested for eukaryotic Deoxyribonucleic Acid topo-isomerase II and I. 2-bromobenzyl benzothiazole of *N*-amino tosylated salt form was established most successful derivative and etoposide has notably less lively than salt.[21]

A Benzothiazole derivatives substituted and manufacture as well as experienced for inhibitory activity against DNA topo-isomerase II in cell structure and the standard drug was used etoposide. Reference drug were bring into being less active than the 2-Phenoxymethyl benzothiazole. Many compounds having solo two merged ring system in the formation and has been affirmed that such as benzothiazole, derivatives put on view

noteworthy inhibitory activity against topoisomerase II. Synthesis of Hydroxybenzoyl-2-amino benzothiazole derivatives and their inhibitory properties deliberate beside topoisomerase II and I.[22]

Dihydroxy and Trihydroxybenzoyl-2-aminobenzothiazole derivative demonstrated 8.2 and 16.9 mM IC_{50} value, but had no topo I inhibitory properties by monohydroxy derivatives. Structures of compounds 1a to 5c are shown in Figure 2.

Structure Activity Relationship for Topoisomerase Activity

From SAR, get better properties and a smaller amount hydroxy groups turn down their activities.[23]

BTZ as Microtubule Polymerization Inhibitors

The potential microtubule inhibitor is a beautiful tactic discovery for carcinogenic therapy. Additionally, molecules i.e., tubulin-targeting counting taxanes, combretastatins and vinca alkaloids that have been extensively worn to cure many cancer. Multi drug resistance and fateful bioavailability of those molecules induce scholars to utilize fresh inhibitors towards microtubule polymerization with good oral activity, medicine resistance and low side effect.[24]

Chalcone-amido benzothiazole conjugates confirmed anticarcinogenic drugs having apoptotic and inducing G2/M arrest properties. Some compounds demonstrate potent activity in the range of 0.85-3.3 mM with an IC_{50} values beside dissimilar tumor cell line.

Some compounds revealed capable immuofluorescence analysis and tubulin polymerization illustrated to restrain micro-tubular assembly by these compounds at mutually, cellular and molecular levels.[25]

Imidazole clubbed with 2-Phenyl benzothiazole were manufactured and estimated for anticarcinogenic property beside unlike individual cancer cell. G2/M cell cycles arrested by some molecules are the most successful in causing in different cell lines. G2/M cell cycle seize is related with inhibiting tubulin disrupt touching mitotic spindle formation and chromosome segregation.[26]

Benzothiazole clubbed with 2-Phenylimidazo [2,1-b] analogs were measured with means of catalyst palladium acetate, and estimated for antitumor property.

Structure Activity Relationship for Microtubule Polymerization Inhibitors Activity

Molecules (**6a-c**) show signs of good antiproliferative property, with the range 0.19-83.1 mM GI_{50} values. 60 individual cancinogenic cell line, compound (**6c**) being evidence for potent anticancer efficacy and some compound induces cell cycle capture in G2/M phase and kept back tubulin polymerization. Level of caution for molecule (6d) is illustrated by high-throughput tubulin polymerization assay found to be parallel to combretastatin A-4.[27]

BTZ as Cytochrome P_{450} Enzyme Inhibitors

A great number of endogenous molecules especially by the cytochrome P_{450} enzymes are heme-thiolate enzymes drawn in metabolism of exogenous molecules.[28]

Fluorinated 2-(4-aminophenyl) benzothiazoles compound (6e, f) were potently cytotoxic *in vitro* sensitive human breast and MDA 468 cell lines. Benzothiazole clubbed with 2-(4-Amino-3-m ethylphenyl)-5-fluoro compound (6g) has new generation of anticarcinogenic benzothiazoles. Benzothiazoles anticarcinogenic specificity stimulated by cytochrome P_{450} CYP1A1 is a crucial event.[29]

Metabolism and accumulation of observed in cell lines only, rate of metabolism in sensitive cells is good. 2-(4-amino-3-methylphenyl) benzothiazole as anticancer agent with growth inhibitory property beside individual tumor cell lines.[30]

Other BTZ-based Anticancer Agents

Synthesis of Triazolo [1,5-b][1,2,4]benzothiadiazine clubbed benzothiazole molecules and tested beside 60 individual carcinogenic cell lines for their cytotoxicity. Study revealed good inhibitory effect by some compounds against chosen cancer cell lines. Some compounds inhibit more than 90% the growth of leukemia cell lines and lung. Few compound were shown as the largest part as lively member amongst series of compounds which exhibit noteworthy development inhibition revealed cytotoxic potency cell lines of breast, renal, melanoma.[31]

The S-atom in benzothiazole ring system and an increase of the linker length to a five-carbon chain significantly enhances the binding ability of DNA in the minor groove binders with DNA sequence.[32]

The benzothiazole thiourea clubbed compound (7) was originated effective and derivatives illustrated the fair property.

Structure Activity Relationship for Anticancer Activity

Strong electronegative atom, from SAR, substitution such as Cl/Br at position para in ring enhanced the lipophilicity of compounds and answerable as well as improved cytotoxicity.

The meta-substituted compound having phenylene-bisbenzothiazole of diamidinyl reserved development at submicromolar concentration of the cell lines. The para-substituted phenylene of Di-imidazolinyl bis-benzothiazole compound (8) has not shown any binding abilities of DNA.

Benzothiazole-2-thiol analogs were synthesized by *in vitro* method and checked against anticarcinogenic effects by Shi *et al.*, on individual cervical cancer cell line (Hela), individual

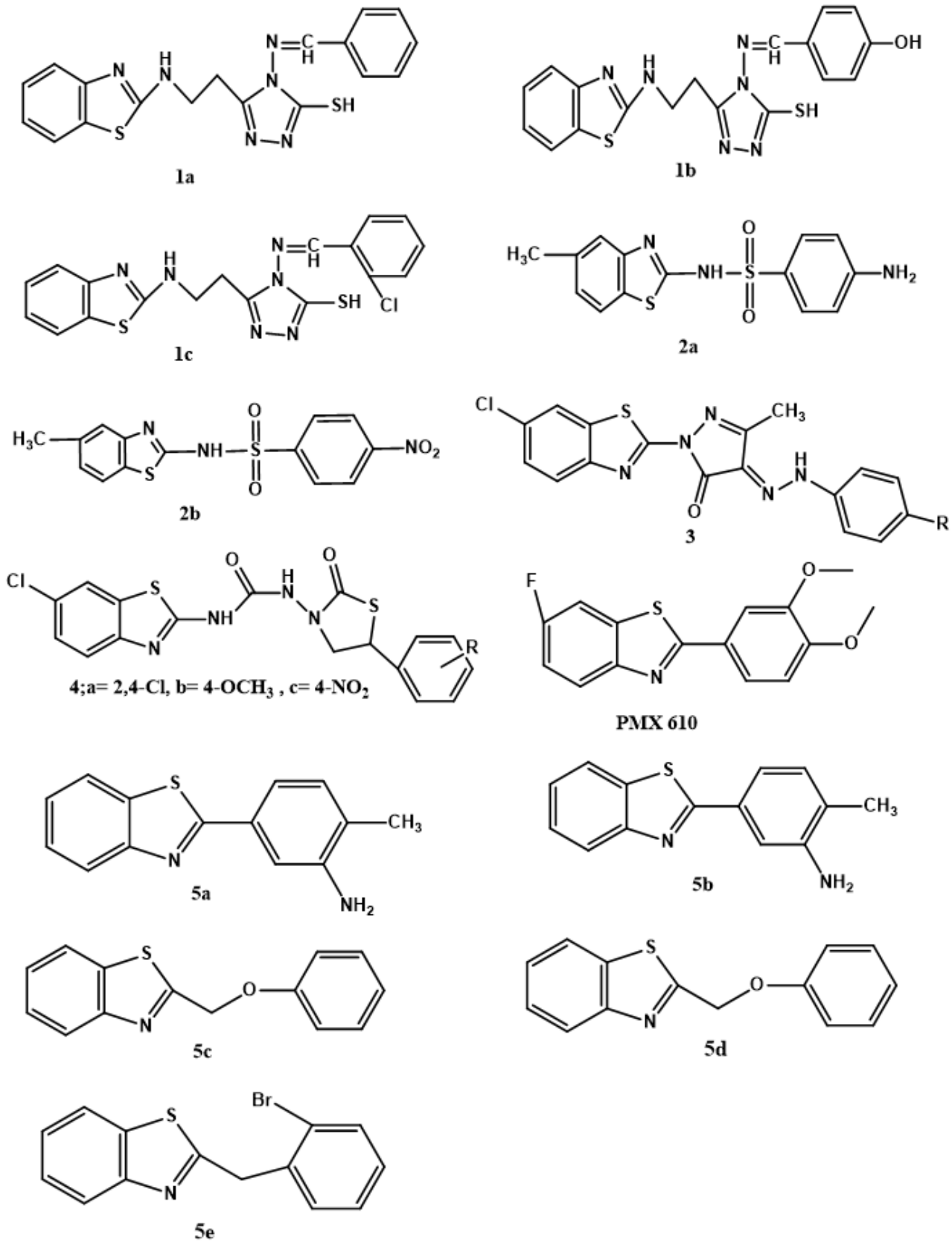


Figure 2: Structures of compounds 1a to 5e are shown.

hepatocellular carcinoma (HepG2) and individual colon adenocarcinoma (SW480). Some compounds displayed good number potent antitumor activities and some compound demonstrated potent anticarcinogenic activity.

SAR study reveals that compounds benzothiazole-2-thiol clubbed with pyridin-2-amine have shown anticarcinogenic activity. Phenylpyridopyrimidinones clubbed benzothiazole manufactured and estimated activity by using MTT assay besides diverse carcinogenic cell lines, B-16 (melanoma), DU-145(prostate cancer) and ME-180(cervical). Compound show signs of significant property with IC_{50} value 4.01 mM in ME-180 cell line that is as good as 5-flurouracil which is standard.[33]

Combretastatin clubbed-amidobenzothiazole complex synthesis further reported as anticarcinogenic agents. Compound made known for potent cytotoxicity at 4 mM against MCF-7 cells.[34]

Phenyl thiazolidinbenzothiazole-6-carboxylic acid analogs manufactured and evaluated against carcinogenic cell line.

From SAR study, the point at which substituted assembly on phenyl ring becomes visible to control on anticarcinogenic activity. In contrast, para-chloro derivative revealed superior antitumor property than that of *p*-OCH_3, *p*-OH and *p*-CH_3 derivatives.[35]

Another anticarcinogenic activity shown by benzothiazole analog were manufactured by Xie *et al*., and displayed against sixty human tumor cell lines for anticancer property. Some compounds show signs of anticarcinogenic property.

SAR study reveals 2 rings over and above having *N*-methyl piperazine functional group for budding anticarcinogenic activity. 2 phenyl rings put on analogs to symmetries the physic-chemical properties.[36]

BTZ as Hepatitis C Virus Inhibitors

Hepatitis C Virus (HCV), being a global chief cause never-ending liver failure, cirrhosis, and carcinoma. Contamination of about approximately 1700 crore citizens having HCV-1 and for viral resistance.[37]

That is why, here is serious therapeutic necessity for novel therapy. Benzothiazole and analogs, discussed as Hepatitis C Virus inhibitors in this.

5-azabenzothiazole-pyrimdine was synthesized by Verma and co-workers and validated these conjugates as HCV inhibitors.

Some molecules possess C-2 at ether, possesses excellent plasma coverage and bioavailability in rodent in addition to other superior genus.

Structure Activity Relationship for Hepatitis C Virus Inhibitors Activity

From SAR studies, C5' position lead as optimal functionality by installation of the dimethyl group.[38]

Moreover, benzothiazole replaced 5-azabenzothiazole identify HCV inhibitors. In recognition of compound the C-2 position resulted in wonderful selectivity and replicon potency. Plasma level concentration and oral bioavailability are displayed as good in dogs.[39]

Benzothiazole moiety clubbed with complex pyridothiazole molecules lead by amendment to yield selective profiles and fine potency for demonstrating fine PK in various genus.[40]

Few accessible dye like as primuline and Thioflavine S were estimated by Li *et al.*, as a HCV inhibitors. Benzothiazole tetramer introverted the wind down >50% at 2 mM, repressed at 10 mM by subgenomic HCV replicon and has no lethal effect. Compound (9) inhibits the helicase by 50%. Structures of compounds 6a to 9 are shown in Figure 3.

BTZ as Anti-alzheimer Agents

In the treatment of AD, medicinal researchers build up anti-AD agents having benzothiazole analogs show signs of AD activity.

Sequence of benzothiazole clubbed with tacrine complex molecules were validated against acetylcholinesterase and aggregation on beta-amyloid (Ab). All benzothiazole clubbed tacrine complexes put on view elevated *in vitro* properties, with the low micromolar to submicromolar concentration of IC_{50} values. Compound (10), found the smallest connector, be evidence for shows potential inhibitory property of acetyl cholineesterases (AChE), whereas maximum property as anti-Ab42 self-aggregation, for compound (11).[41]

Another tacrine clubbed phenyl benzo heterocyclic complex were validated by huang *et al*., and estimated as anti-Alzeihmer's agents. Compound (12), tacrine coupled by 3-carbon spacers with phenyl-benzothiazole, a good number of potent AChE inhibitor of 0.017 mM with an IC_{50} value and Ab aggregation inhibitory property at 20 mM 52.1%, signifying, and this mixture is a superb multifunctional drug entrant for Alzheimer's Disease.[42]

6-Fluoro benzothiazole derivatives were manufactured and assessed. Some of the derivatives of compounds illustrate the highest BChE inhibition as well as some illustrates highest AChE-inhibiting activity.

Structure Activity Relationship for Anti-alzeihmer's Disease Activity

SAR study reveals, long alkyl chain having replacement of carbamate ester which boost the BChE inhibitors and *n*-propyl chain for both of AChE as well as BChE inhibitors.[43]

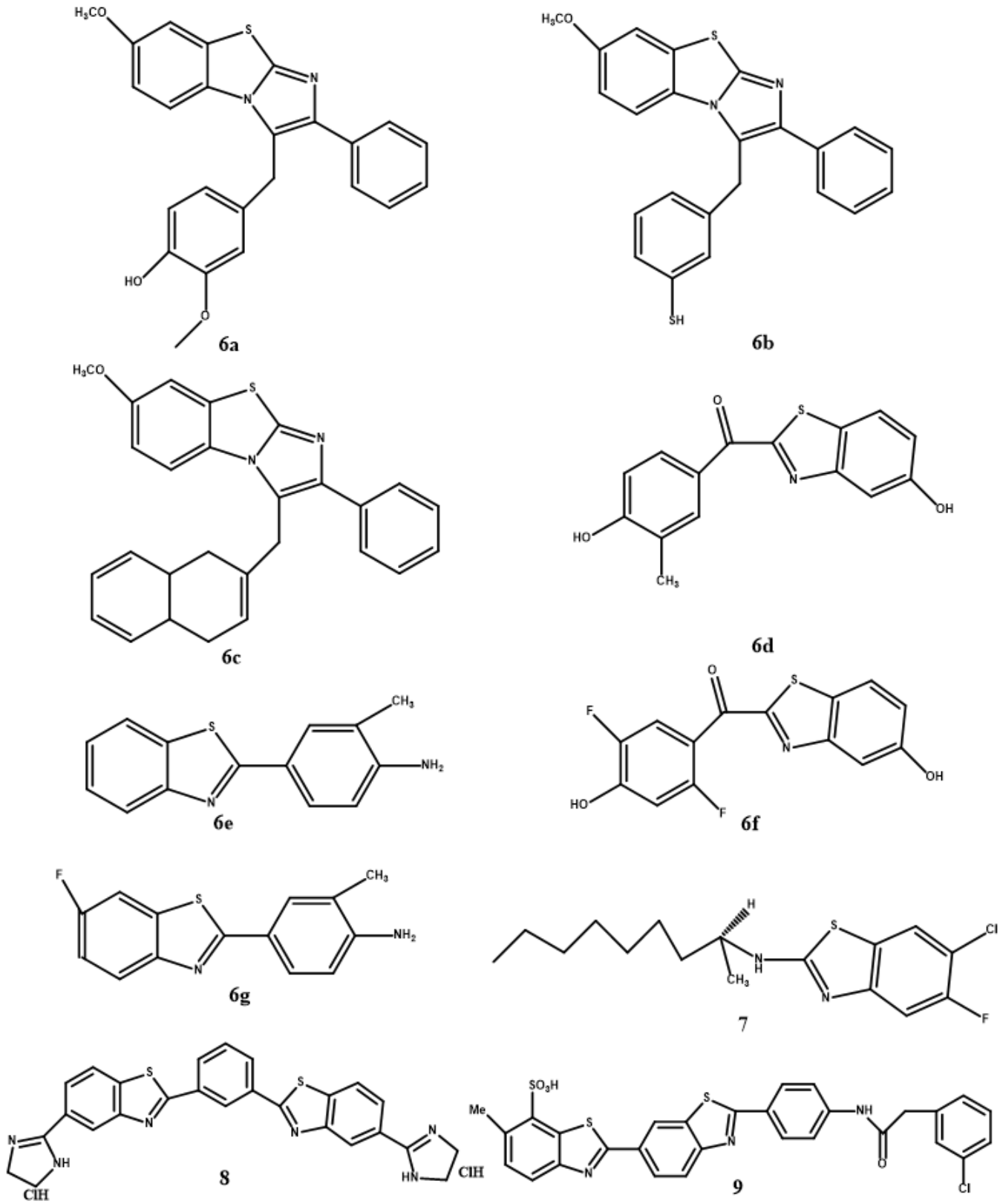


Figure 3: Structures of compounds 6a to 9 are shown.

Fluoro-ethoxy clubbed benzothiazole analogs were validated by Neumaier *et al.*, as a flexible probable entrant for 18 F-fluoro-ethylation labeling. From their study 2 derivatives i.e., fluoro as well as ethoxy at 20th and 30th aromatic ring position proves low attraction against Ab (1-40) amyloid-plaque. SAR study reveals, replacement of fluoro as well as ethoxy at 20th and 30th position it is found moderately charged under neutral binding circumstances augments pKa of amino group leftovers aniline.[44]

BTZ as Anti-inflammatory and Analgesic Agents

The new non-steroidal anti-inflammatory agent advancement follows various strategies against inflammation is a chief contributing factor in morbidity and mortality. These inflammatory chaoses include atherosclerosis, osteoarthritis, retinitis, psoriasis.

Benzothiazole clubbed with Mannich bases were prepared and evaluated against inflammatory as well as analgesic activity. It is found that compounds (13, 14) put on view remarkable anti-inflammatory and analgesic than the previously marketed standard drugs (aspirin and naproxen).[45,46]

Benzothiazole clubbed with isatin complex compound demonstrated a superior quality of anti-inflammatory property when matched up to with marketed standard indomethacin.

Correspondingly, 6-fluorobenzothiazole-pyarzole compounds (15, 16) analogs demonstrated good property. The o-, m-toulidines having beta-phenyl ethyl amine, illustrated a superior anti-inflammatory property.[47]

Bis-hetero cycles surrounding 2-mercaptobenzothiazole compound (17) and 1, 2, 3- triazoles manufactured by a approach of click chemistry by Shafi *et al.*, and experienced against anti-inflammatory property with help of carrageenan induced hind paw edema and biochemical Cyclo Oxygenase (COX) activity assays.

Structure Activity Relationship for Inflammatory and Analgesic Activity

SAR study reveals that the groups having electron withdrawing substitutions like -F, -Br, -NO_2 conferred the greater activity over electron donating groups such as -CH_3, -OEt, Fluoro and chloro replacements give extensively superior property at 3 hr +2 at 5 hr.[48]

Benzothiazole analogs clubbed with triazolo-thiadiazole and 1, 3, 4-oxadiazole were manufactured for anti-inflammatory as well as analgesic activity. Analogs having at position 6th phenoxy group at own utmost property than marketed standard drug ibuprofen.[49]

Benzothiazole scaffolds having thio-substitution were manufactured by Baylis-Hillman, and assessed for COX-2 and COX-1 inhibitory property. Greater part scaffolds originated as to be the enormously against selective COX-2 inhibitors.[50]

Benzothiazole analogs having alkoxy group were manufactured and examined for their aptitude to restrain human COX 2 enzyme. Some compounds are more selective 470 times towards COX-2 inhibition than that of COX-1.[51]

BTZ as Antioxidant Agents

An ability to entrap the free radicals is the main attribute of an antioxidant that is why antioxidant composite foodstuff played imperative responsibility in protecting health factors. Lot of papers of scientist advises the evidence for antioxidants that can shrink various life-threatening diseases.

Amino benzothiazole clubbed with thiosulfonic acid portrayed by scientist Cressier and his co-workers. Analogs of respective molecules were used in the direction of antioxidant property by ABTS or DPPH free radical hunting. Free radical hunting activity towards DPPH did not display by amines and amides scaffolds. The low activity of amine and amide scaffolds is almost certainly due to the disability.[52]

Benzothiazole clubbed with thiazolidine-dione-2 acetamides were manufactured and estimated for various types of anti-oxidant activity like as DPPH radical forage potential and many more. With the help of this, it found these molecules were good as compared to other marketed standard drugs. These molecules were also good in superoxide anion scavenging activity, inhibition of lipid per-oxidation.[53]

Also, respective these benzothiazole analogs show signs of excellent DPPH radical forage potentials with EC_{50} values as matched up to standard ascorbic acid. Compound (18) showed excellent EHI and LPI in conjunction and 6-methoxy benzothiazole-2-amine (19) demonstrated excellent IL-1b inhibitory property.[54] Structures of compounds 10 to 19 are shown in Figure 4.

Benzothiazole clubbed with 2 Hydrazino manufactured by Scientist Suresh and his coworkers and these were assesed for antioxidant property. Good antioxidant activities illustrated by all compounds ranging with 6.8-12.93 mM IC_{50} values.

Free radical forage activity exemplify by compounds (20, 21) at the highest percentage.[55]

Bis-Benzothiazole-pyrazoline derivatives were clued-up and reviewed. Presence of 2 benzothiazole with pyrazoline ring improves antioxidant property. Electron donating substitution at the phenyl ring 4th position improved the property.[56]

Coumarin clubbed with benzothiazoline were produced and tested as radical scavenging activities.

Structure Activity Relationship for Anti-oxidant Activity

From the SAR study, it exposes that -OH functional group having coumarin nucleus augment the scavenging property next to that of free radicals.[57]

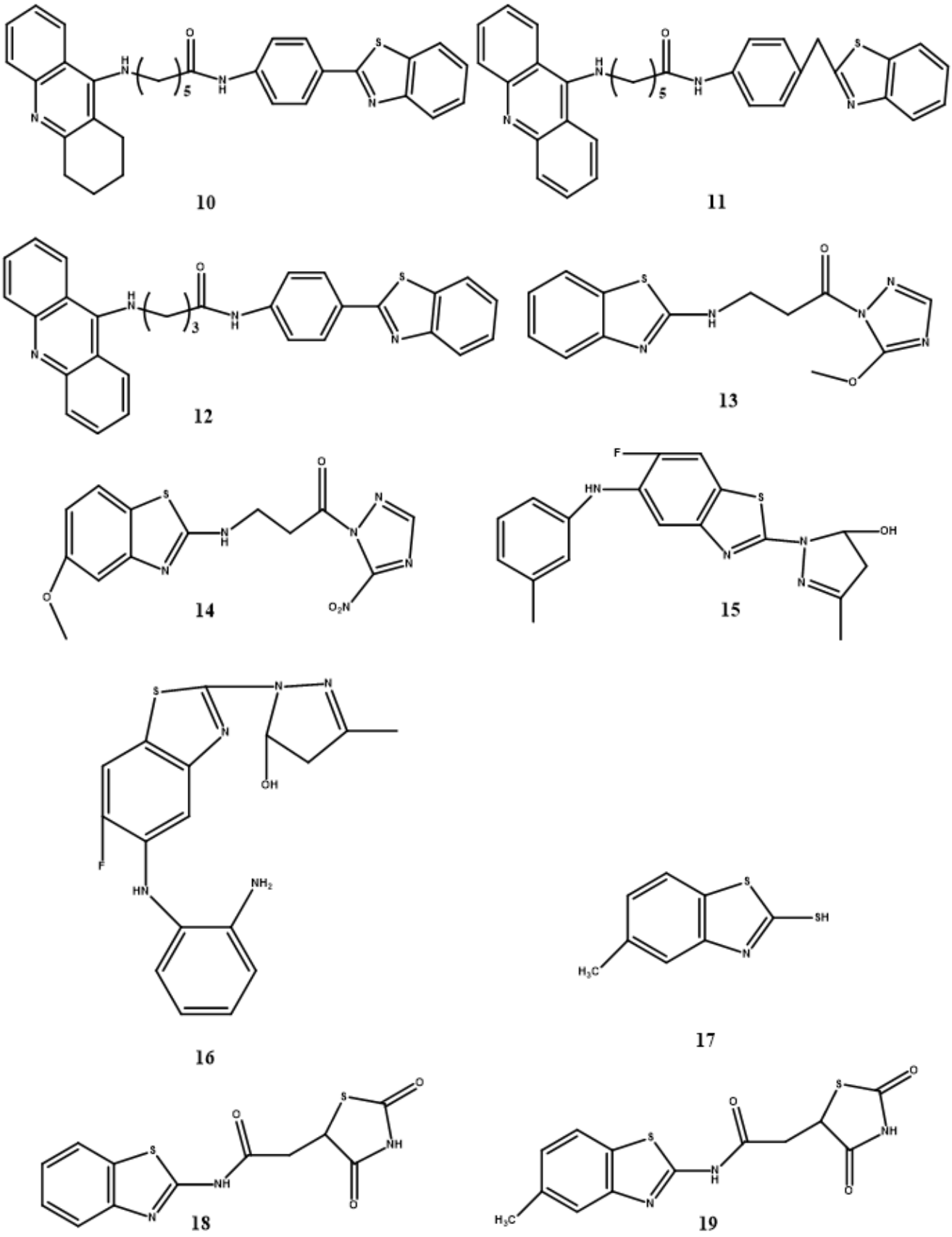


Figure 4: Structures of compounds 10 to 19 are shown.

Pyrazolyl clubbed benzothiazole analogs put on showed first-class free radical antioxidant activity, with specially substituents of trihydroxy compounds were found as effective antioxidant.[58]

Benzothiazole-pyrazole compounds of Mannich bases explained first-class anti-oxidant property. Compounds in the company of electron withdrawing substitution attach in N-methyl-benzenamine nucleus at the para position of conveyed impresive antioxidant property.[59]

Benzothiazole clubbed with hydrazones analogs was stated for various activities such as antioxidant as well as many cytoprotectives. SAR studies reveals that the phenol substitution which is frames as not only pre-condition for antioxidant property.[60]

BTZ as Anticonvulsant Agents

For the safer AEDs, an innovative efficient, hunt remains to find out fresh chemical entities is neccessary. The tri-fluoromethoxy functional group in benzothiazole moiety in compound (22) take part in a fundamental role, also the para chloro functional group attached in benzothiazole ring of (23) amplified in antagonistic AMPA neuro-transmission as imagined and identified standard marketed riluzole drug as anticonvulsant drug at GABA.[61]

Some Quinazolino clubbed benzothiazole compound confirmed considerable property adjacent to tonic seizure by clonic seizure and MES model, by PTZ tempt model, respectively. To get anticonvulsant effect substitution at 3rd position with groups having electron withdrawing property on benzothiazole moiety is valuable for anticonvulsant property.[62]

Some *N*-(substituted benzothiazole) (24) amide scaffolds were manufactured and tested for neuroprotective effect as a good number valuable anticonvulsant at median doses. Also, compound showed accomplished with neuroprotective property.

Structure Activity Relationship for Anticonvulsant Activity

From the SAR study reveals, scaffold containing groups having electron releasing nature possess extra activity.[63]

Hydrazones of benzothiazol-2-yl gives us a thought about the first-class anticonvulsant agents, some compounds, which showed 50% safety and 75% protection in mice at different doses. The 1,3-benzothiazol-2-yl aceto-hydrazones containing 4- bromo phenyl proves good property.[64]

Benzothiazole comprising acetamide compound 25(a-c) derivatives confirmed better guard indices in ScPTZ and MES screen for carbothiomide association without any neurotoxicity effect. The anticonvulsant agents such as imadizolyl and morpholino analogs have excellent anticonvulsant property.[65]

Benzothiazole-1,3,4-thiadiazole complex (26) were stated and tested for anticonvulsant property within scPTZ and MES models. From SAR study reveals, the electron donating functional groups on the 6th position on benzothiazole nuclei showed better activity.[66]

BTZ as Antidiabetic Agent

As diabetes, the world facing lot of damage in due course causes micro-vascular damage in tissues which may result in various conditions such as, nephropathy and retinopathy. It related with condensed expectation, considerable morbidity due to definite diabetes- related microvascular hurdles amplified problem (stroke, peripheral vascular disease and ischemic heart disease), and reduced eminence of life.

Synthesis of 2-arylsulfonylaminobenzothiazole scaffolds have been reported by Navarrete Vazquez *et al*., and tested for protein tyrosine phosphatase-1D inhibitory property. Considerable PTP-1D inhibitory property showed by several derivatives of this group, in picky. Compound 27 shows sign of capable property as a mixed inhibitors of PTP-1D.

In study, it is also found PTP-1B inhibitory property of Benzothiazol-2-oxoacetate scaffolds demonstrated good quality in lesser micro molar range. The reversible inhibitors of PTP1B have non slow binding by some compounds as well as with mixed type.[67]

Another benzothiazole-benzimidazole having (*S*)-isothiazolidinone were manufactured by Scientist sparks and his co-worker and checked against inhibitors such as PTP1B, especially few of them showed excellent inhibition against PTP1B. These derivatives are potent, competitive, and reversible inhibitors of PTP1B. Benzimidazole and Benzothiazole substitution gave improvement in potency.[68]

Aldose reductase inhibitions were checked by some novel benzothiazole indole n-alkanoic acid which were synthesized. Some compounds hamper aldose reductase and being 5400 times less active with IC_{50} of 5 nM, against enzyme related to aldehyde reductase.[69]

BTZ as Anti-histaminic Agent

H_1 receptor antagonists have provided evidence for being valuable agents for healing allergic rhinitis. So H_1 receptor has an intention for finding drug for several years.[70]

However, a lot of limitations which complicate clinical use of classical antihistamine agents have quite non-selective pharmacological activity. H_1 antagonists (cyclazine, promethazine) express property like as a muscarine receptor antagonist, that generate side effects of anticholinergic.[71]

A reduced sedative burden has a spotlight on H_1 antagonists having sedative property which is connected to cerebral H_1 receptors. New highlighted agents were used in diseases like hay fever, rhinitis, and asthma.[72]

Benzothiazoyl clubbed with piperidines were manufactured as well as tested by Maynard and his co-workers against anti-histaminic property. Derivative having 4-methoxy-phenethyl *N* having the greatest activity.[73]

Diazepinebenzothiazole derivatives were manufactured and evaluated as H_1 and H_3 receptor antagonists. Analogs containing alkyl clubbed piperazine compounds (28) are the most and effective antagonist of H_3 receptor.[74]

BTZ as Antimalarial Agents

Rhodacyanines class was manufactured by benzothiazole-pyridine scaffolds (29) of amodiaquine manufactured and antiplasmodial property was resolute for atleast 2 resistant strains of *Plasmodium falciparum* by chloroquine, W^2 and K^1. Benzothiazole analogs illustrated superb property for the both strains. Scaffolds that have little point of annoyed resistance having with benzothiazole analog.[75]

Benzothiazole functional group clubbed with substituted cyanine dye manufactured by scientist Ge and his co-workers and then tested against *Trypanosoma cruzi*, K1, *Lishmania donovani* and for *in vitro* antiprotozoal properties. Numerous benzothiazolyl groups holding trimethine cyanines put on display tough activities against *T. cruzi* and *P. falciparum*.

Fluorinated trimethine having cyanines demonstrated no completely effective and safe treatment exists.[76]

Scaffolds of lively non-peptidic clubbed with diazole as well as benzothiazole compound (30) string manufactured and tested for inhibitor of cysteine proteases and falcipain of malaria parasite especially *P. falciparum*. Some compounds derivatives in addition put on show property besides with corresponding polar residues lacking homologous mammalian cysteine proteases, and signifying not as much of significance of these remainder in the blueprint of choosy inhibitors adjacent to FPs.[77]

BTZ as Antidepressants Agents

Depressive disorders influence lot of people specially adults in a year. This comprises of chief disorder, depressive disorder and dysthymic disorder.

Antidepressant activities were assessed with the help of 2 methods such as forced swimming test and tail suspension test by benzothiazole-2,3-dihydro-benzo[b][1,4] dioxine scaffolds which were manufactured and tested for their binding affinity on 5 HT_2A and 5 HT_1A receptors.

Some compounds exhibited moderate binding affinity being use as a means to recognize a progressed candidate for capable antidepressant.[78]

Benzothiazole based derivatives, informed by Zhu *et al.*, having dual performing SERT inhibitors and $5HT^1A$ receptor as a novel anti-depressants. Two compounds showed reasonable binding affinity at SERT site and $5HT_1A$ receptor and they have budding to additional search as dual acting reagents. Also, one compound connects with little affinity to $5HT^2C$ receptor, Norepinephrine Transporter (NET) and Dopamine Transporter (DAT).[79]

BTZ as Miscellaneous Activities

Benzothiazole as antihistaminic compounds and anti-parkinsonian agents are talk about in this section.

Substituted benzothiazole clubbed piperazine compound was manufactured by scientist Dossetter *et al.*, for inhibitors of Cathepsin K. Cathepsin K is vastly articulated in osteoclasts. Benzothiazole derivatives established as the edge to hERG ion channel inhibition and also have potent inhibitor of Cathepsin K possess fine quality dog PK and was considered much short for clinical aspirant.[80]

Conjugates of benzothiazole-thiazole imidazole analogs were manufactured and tested ALK5 inhibitors in an enzyme assay.

An Smad2 phosphorylation inhibitory activity was shown by analogs compound have selective and potent ALK5 inhibitor.[81]

Benzothiazole scaffolds which were new one manufactured and their *in vitro* b-glucuronidase latent has been tested by scientist Khan *et al.* i.e. b-Glucuronidase which is known for catalyzing the cleavage of glucuronosyl O bonds. These enzymes are in attendance to body fluids and many organs like bile, kidney, and many more.

Structure Activity Relationship for Beta-glucuronidase Activity

SAR study reveals that the functional groups at second position by a ring having imidazole have solubility in a base of lotion.[82]

Monte *et al.*, estimated Glycogen Synthase Kinase-3 (GSK-3) inhibitors and manufactured some heterocyclic moieties. The GSK-3 is concerned with numerous pathogenesis of Alzheimer's Disease (AD).

Benzothiazolylurea of 140 nM IC_{50} values for GSK3b was merely one capable to hold back all the kinases tested (CKIe, Cdk5/p35, PKCa and AurKA), put on show 2-3 fold improved activity versus the reference.[83]

Cyclin dependent kinase 5 (cdk5)/p25 inhibitors of benzothiazole-thiophene-2-sulfonamides were manufactured and tested. Benzothiazoles substituted with halogens confirms decline in selectivity alongside cdk2, but amplified potency against cdk.[84]. Structures of compounds 20 to 30 are shown in Figure 5.

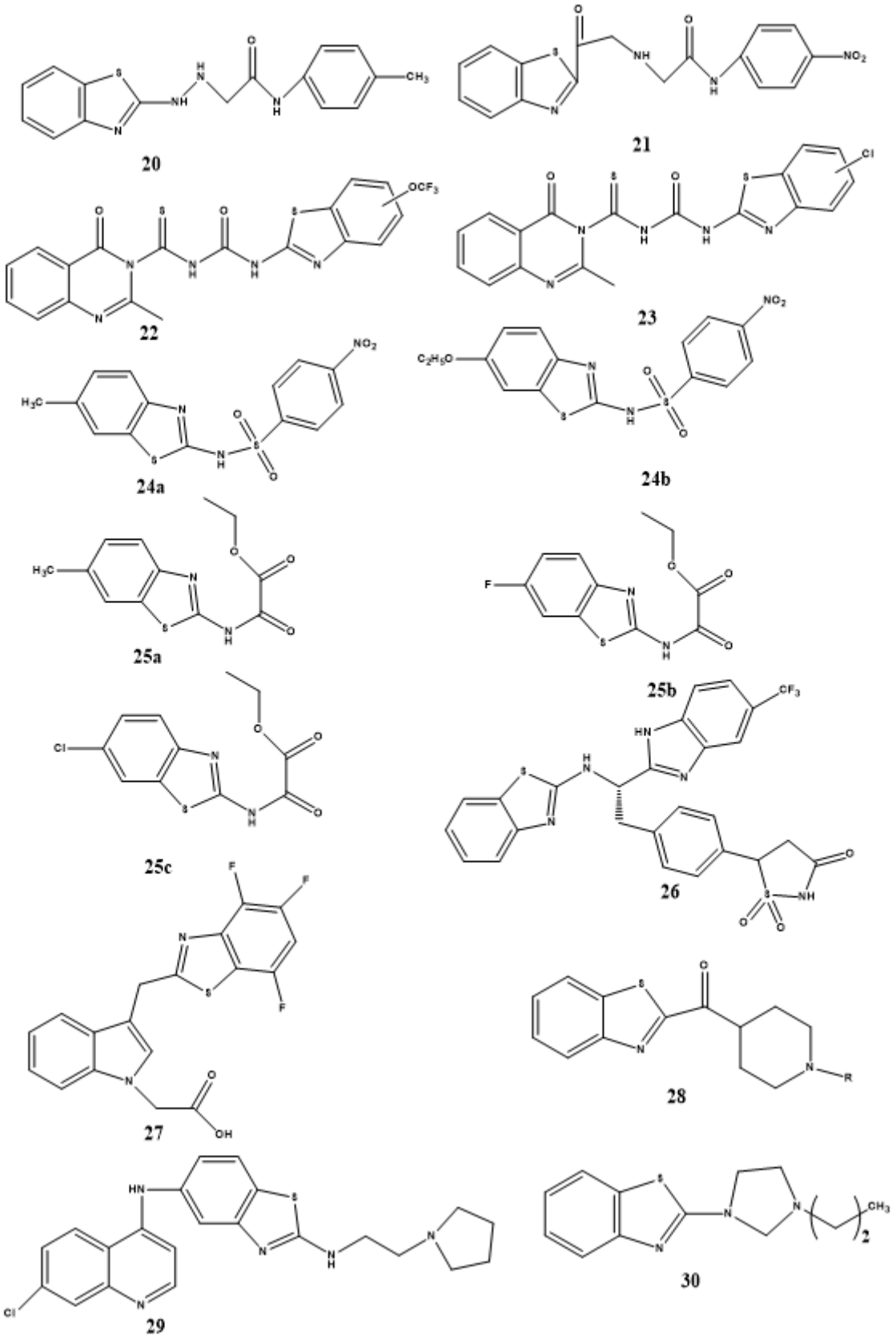


Figure 5: Structures of compounds 20 to 30 are shown.

DISCUSSION

The above discussions, in medicinal chemistry clearly describe that the benzothiazole scaffolds that has a significant character and being research related hit upon the unusual active area under discussion. Benzothiazole-based medicinal chemistry, outsized amount of work has been done and, on the way, too.

A huge digit having benzothiazole supported amalgam as antibacterial, anti-inflammatory, anti-HIV, anticonvulsant, antidiabetic, and antihistaminic agents.

Exaggeratedly, raise in amount of benzothiazole scaffolds which have been fetching entrant is actively unending R and D. In medicinal field, these benzothiazole analogs possess powerfully recommended the endless potentials. That is why there is much more scope in hopeful analog as quantity of molecular targets, upcoming survey of these analog which could suggest several other cheering outcomes in medicine field. It is anticipated that this statistics would furnish augment to plan of superior compounds with elevated specificity and better biological properties and in conjunction with progress of fresh synthetic strategies.

CONCLUSION

In conclusion, this review article has gone over modern progress in synthesis of benzothiazole scaffolds linked to green chemistry and its moieties. In precedent decades, Benzothiazole have take part in more and further important character in medicinal chemistry. It is projected that this knowledge would give rise and shows enormous impact for the growth of green chemistry synthetic pathway for benzothiazoles and also to draw of improved scaffolds with higher specificity and superior biological properties, and collectively with expansion of fresh synthetic approaches.

ACKNOWLEDGEMENT

The authors are grateful to the management of Integral University Lucknow, India. (Manuscript Communication Number is IU/R&D2023-MCN0001892).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

BTZ: Benzothiazole; **LTD4:** Leukotriene; **MBTU:** Methabenzthiazuron; **RAF:** Rapidly accelerated fibrosarcoma; **HCV:** Hepatitis C virus; **AChE:** Acetyl choline esterases; **DPPH:** 2,2-Diphenyl-1-picrylhydrazyl; **ABTS:** 2,2′-Azi no-bis(3-ethylbenzothiazoline-6-sulfonic acid); **AMPA:** α-Amin o-3-hydroxy-5-methyl-4-isoxazolepropionic acid; **GABA:** Gamma-aminobutyric acid; **MES:** Maximal electroshock seizure; **PTZ:** Pentylenetetrazole; **SERT:** Serotonin reuptake transporter; **NET:** Norepinephrine transporter; **DAT:** Dopamine transporter; **hERG:** Human ether-a-go-go-related gene; **ALK-5:** Activin receptor-like kinase 5; **GSK-3:** Glycogen synthase kinase-3; **AD:** Alzheimer's disease; **cdk5:** Cyclin dependent kinase 5; **PTCA:** Percutaneous transluminal coronary angioplasty; **CKIs:** Cyclin-dependent kinase inhibitors; **5-HT:** 5-Hydroxy-tryptamine.

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Cite this article: Nishad RK, Singh KA, Rahman MA. Synthesis and Pharmacological Activities of Benzothiazole Derivatives. Indian J of Pharmaceutical Education and Research. 2024;58(3s):s704-s719.