medical sciences forum

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Proceeding Paper

Benzothiazole Moiety and Its Derivatives as Antiviral Agents †

Khyati Bhagdev [1,*] and Sibaji Sarkar [2]

[1] Dr. Subhash Technical Campus, Faculty of Pharmacy, Khamdhrol Road, Junagadh 362001, Gujarat, India
[2] Nobel Pharmacy College, Bhesan Road, Junagadh 362310, Gujarat, India; sibajisarkar004@gmail.com
* Correspondence: khyatiiibhupta@gmail.com; Tel.: +91-760-002-3301

† Presented at the 1st International Electronic Conference on Molecular Sciences: Druggable Targets of Emerging Infectious Diseases, online, 1–14 September 2021.

Abstract: A virus is a microorganism that uses the machinery of the host to multiply. At present, there are various species of viruses known to us that are dangerous for the health of human beings. One of such viruses has destroyed many lives nowadays and that is a coronavirus. Such other viruses like Human Immunodeficiency Virus, Poliovirus, etc., destroy one's capability to survive normally. As science progresses, we invent many antiviral drugs as per the type of virus. There are many antiviral drugs available to treat viral infections. From them, benzothiazole derivatives are potent antiviral agents. Researchers continuously work on benzothiazole moiety to get more effective benzothiazole derivatives that can be used as antiviral agents. This review article gives information about various benzothiazole derivatives that are invented during 1980 to 2021, that act against the various viruses as antiviral agents, the structure–activity relationship of benzothiazole as an antiviral agent, various schemes to synthesize benzothiazole derivatives as an antiviral agent as well as includes various methods to evaluate the antiviral activity of novel synthetic compounds against specific viruses.

Keywords: benzothiazole antiviral derivatives; schemes for synthesis; structure–activity relationship; in vitro methods to evaluate antiviral activity

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Citation: Bhagdev, K.; Sarkar, S. Benzothiazole Moiety and Its Derivatives as Antiviral Agents. *Med. Sci. Forum* **2021**, *7*, 9. https://doi.org/10.3390/ECMS2021-10839

Academic Editor: Claudiu T. Supuran

Published: 31 August 2021

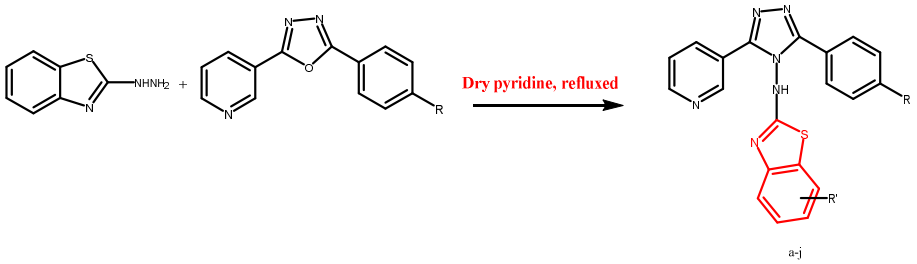
1. Introduction

Avirus is very tiny infectious agent that replicate only inside the living cells of an organism. Viruses infect all types of plants, animals and microorganisms also, like bacteria, etc. [1]. Viral infections are considered to be one of the major threats to the health of human beings. Virus infections take place due to globalization and unexpected climate change [2]. We are informed about just about 260 varieties of viruses, but the unknown varieties of viruses are responsible for 99.9% of total infection cases. These viruses come to the picture when they show some symptoms to the host [3]. Despite of the development of many molecules as antiviral, they are unable to satisfy the requirement criteria to treat the viral infection and drug resistance of current viruses. That's why there is still a need for newer vaccines, diagnostic agents and antiviral molecules [4]. Because, benzothiazole is such a versatile moiety, it shows many biological activities including antiviral effect against various species of viruses [5]. Due to feasible physical and chemical properties of benzothiazole moiety, many researchers have tried to synthesize various benzothiazole derivatives that shows potent antiviral effects against various strain of viruses [6].

Structurally, benzothiazole is a fusion of two aryl rings; benzene and thiazole. As thiazole bears nitrogen and sulfur moiety, benzothiazole derivatives successfully binds to viruses and gives antiviral activity. Many articles are available for reference to develop newer antiviral agents, but this review article includes various novel synthesized antiviral compounds bearing benzothiazole moiety, the pathway to synthesize benzothiazole based antiviral agents, the structure–activity relationship of benzothiazole as antiviral agents and in vitro and in vivo methods to evaluate antiviral activity of novel synthetic compounds. That is why it is a unique article containing all the information to guide a researcher for synthesis of benzothiazole based antiviral agents.

2. Pathway to Synthesize Antiviral Drugs Bearing Benzothiazole Moiety

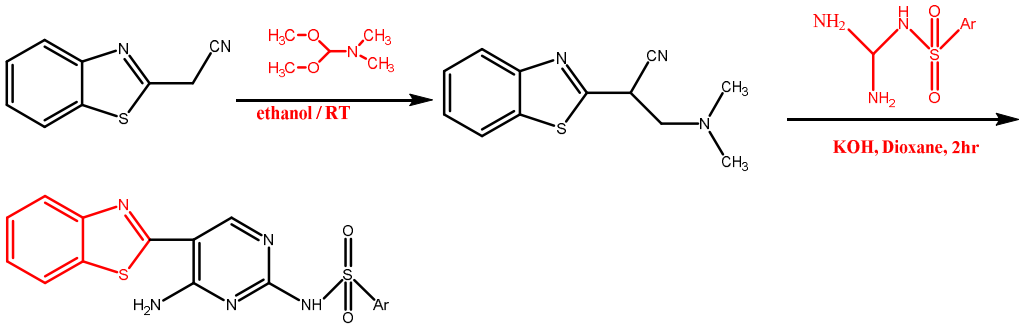
Navin B. Patel and his colleagues designed the above pathway to synthesize benzothiazole derivatives having antiviral activity. These compounds were active against Human Immuno Deficiency Virus. 2-aminobenzothiazole in dry pyridine was refluxed with 2-(4-nitrophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole or 2-(4-chlorophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole to get the respective benzothiazole derivatives [7] (Scheme 1).



R= NO_2, Cl; R′ = (a) 6-F, (b) 6-Br, (c) 6-NO_{22}, (d) 6-CH3, (e) 6-OCH_3, (f) 6-Cl, (g) 4-CH_3, (h) 4-NO_2(i) 5-Cl,6-Cl,and (j) 4-Cl

Scheme 1. Synthetic Pathway for Benzothiazole derivatives [7].

Rasha et al. synthesized benzothiazole derivatives by Scheme 2. Benzothiazole-2-yl-acetonitrile was allowed to react with *N,N-dimethylformamide dimethyl acetal* in ethyl alcohol at room temperature for 10 min to get the 2-(benzo[d]thiazol-2-yl)-3-(dimethylamino) acrylonitrile. This intermediate was further reacted with *N*-arylsulfonated guanidine in presence of potassium hydroxide and dioxane for 2 h. The resulted compounds were (4-amino-5-(benzo[d]thiazol-2-yl)pyrimidin-2-yl)-arylsulfonamides that show potent antiviral activity against Herpes Simplex Virus. They are also Hsp90α inhibitors with broad spectrum antiviral activity [8] (Scheme 2).



Ar = C_6H_5,or Ar = 4-CH_3-C_6H_4

Scheme 2. Synthetic Pathway of 4-amino-5-(benzo[d]thiazol-2-yl) pyrimidin-2-yl)- arylsulfonamides [8].

3. Various Benzothiazole Derivatives as Antiviral Agents

3.1. Anti-Hepatitis C Virus Agents

HCV is an RNA virus with six genotypes. Hepatic fibrosis is the main symptom of HCV infection. The infection of HCV spreads worldwide. Global prevalence of HCV infection has been estimated as 2–3%, which is equal to 150–170 million people with infection [9]. A few benzothiazole derivatives are discovered that show antiviral activity against HCV infection.

Using 5-fluoro-2-methylbenzo[d]thiazole, Giovanni Maga has synthesized ethyl 8-fluoro-1-oxo-2-phenyl-1H-benzo[4,5]thiazolo[3,2-a]pyridine-4-carboxylate (**1**) and ethyl 8-fluoro-1-oxo-2-phenyl-1H-benzo[4,5]thiazolo[3,2-a]pyridine-4-carboxylate 5,5-dioxide (**2**) as potent HCV inhibitors. These compounds were screened for suppression of in vitro incorporation of [3H]-UTP by recombinant HCV RNA polymerase NS5BDC21 (genotype 1b)

on a homopolymeric RNA primer/template. The non-nucleoside inhibitor aurintricarboxylic acid (ATA) was used as a reference compound in the enzymatic assay. This compound has been shown to inhibit NS5B both in vitro and in replicon assays, through binding to the benzothiadizine allosteric pocket [10].

Girijavallabhan et al. have designed some HCV replication inhibitors bearing benzothiazole moiety. Compound (**3**) was screened for its HCV replication inhibition ability and the potent compound was found as an antiviral compound [11]. All the structures of various antiviral agents those contain benzothiazole as a parent molecule are described in Figure 1.

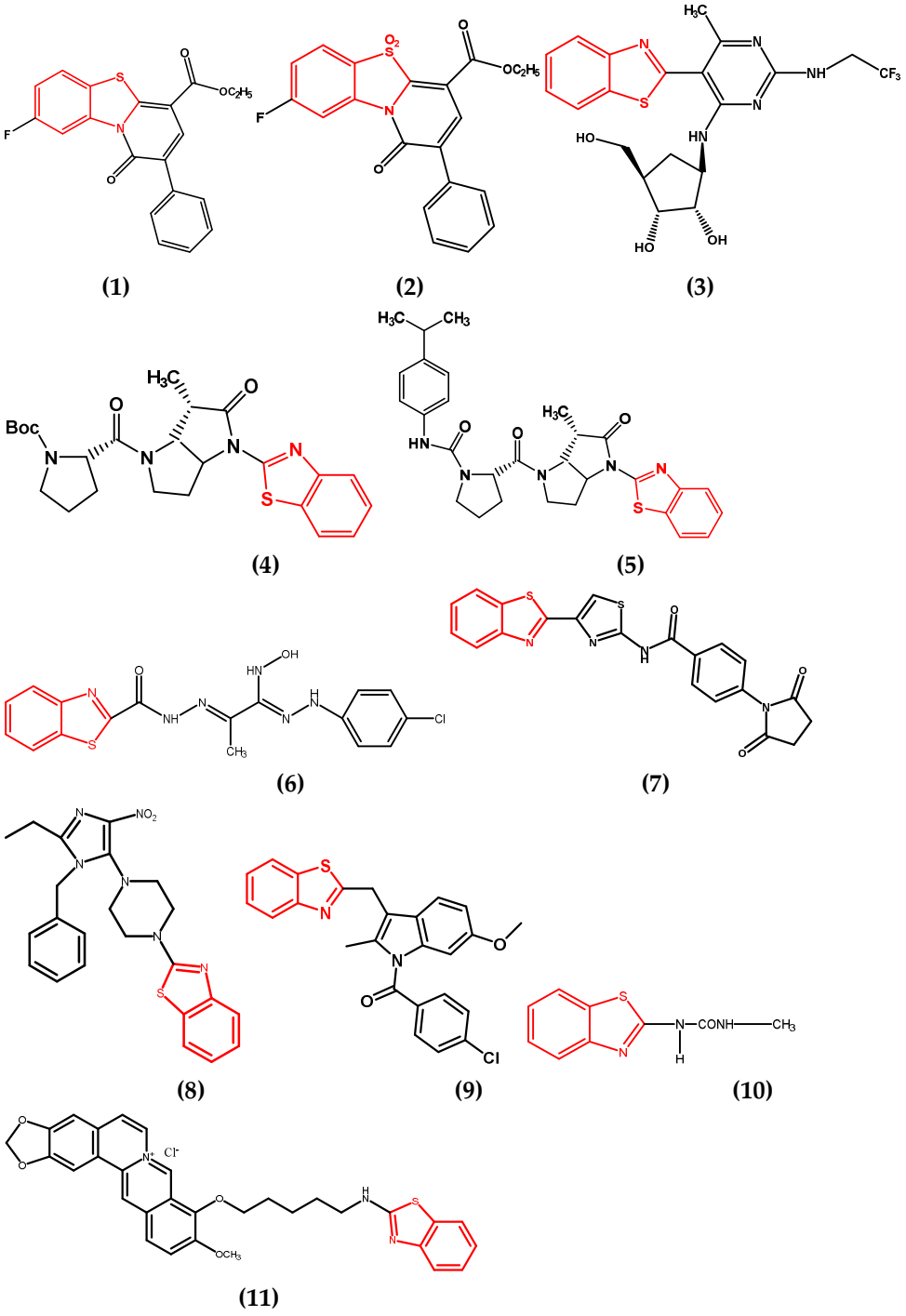


Figure 1. Structures of various Benzothiazole Derivatives as Antiviral agents [10–20].

3.2. Anti-Herpes Virus Agents

Human cytomegalo virus is under the category of beta herpes virus. Once the person is infected with this particular virus, the virus remains in that person's body for their whole life. It does not affect a healthy human, but it shows symptoms in pregnant women or people with weak immunity [12]. Then, the treatment becomes necessary.

The substituted benzothiazole derivatives (**4**) and (**5**) were prepared by reacting lactam with respective substituted bromobenzothiazole under Cu catalysis using modified Goldberg conditions by Alan et al. compounds (**4**) and (**5**) were tested against HCMV virus using modified ELISA technique. The compounds show potent antiviral activity against HCMV—Human Cytomegalovirus [13].

Hatem et al. have synthesized (1Z,2E)-2-(2-(benzo[d]thiazole-2-carbonyl)hydrazineylidene)-*N*′-(4-chlorophenyl)-*N*-hydroxypropanehydrazonamide and other benzothiazole derivatives having antiviral activity. Benzoyl hydrazine was reacted with 2-oxo-*N*-arylpropanehydrazonoyl chlorides by refluxing with ethanol. The reaction was resulted in corresponding hydrazonoyl chloride which was further reacted with benzene sulfinate to have corresponding sulphones. Reaction of some hydrazonoyl chloride with hydroxylamine hydrochloride in presence of potassium carbonate, resulted in *N*-hydroxy-2-(2-(benzothiazole-2-carbonyl)hydrazono)-N9-(4-aryl)propanehydrazonamide (**6**). This compound is active against Herpes simplex type 1 virus (HSV-1) [14].

3.3. Anti-Dengue Virus Agents

The main cause of dengue is Flaviviridae virus with a carrier mosquito. This is a single-stranded RNA virus who infect almost 50 million people every year. Nowadays, no specific agents are available to treat dengue, but the effective molecules directly target the viral structural proteins [15]. Various benzothiazole derivatives have been screened for their anti-dengue activity and some of them shows potent activity against dengue.

Compound (**7**) was designed by Halim et al. for screening against dengue virus. Novel DENV NS-3 helicase inhibitor from zinc database was confirmed having antiviral activity against dengue virus by computational modelling techniques as well as in vitro and in vivo biological assays [16].

3.4. Anti-HIV Virus Agents

Human Immunodeficiency Virus is the most dangerous virus in the virus family. The resultant disorder is Auto Immunodeficiency Disorder. The current therapy against AIDS is based on six of categories drugs: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs/NtRTIs); nonnucleoside reverse transcriptase inhibitors (NNRTIs); protease inhibitors (PIs); cell entry inhibitors [fusion inhibitors (FIs) and co-receptor inhibitors (CRIs)]; and integrase inhibitors (INIs) [17]. HAART (Highly active anti-retroviral therapy) is beneficial, but it has a very high cost and severe toxicity. However, some benzothiazoles are analyzed for their anti-HIV activity, which may be at low cost and higher potency.

2-(4-(1-benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)piperazin-1-yl)benzo[d]thiazole (15) was synthesized and analyzed by Yaseen et al. for their anti-HIV activity. 1-benzyl-5-bromo-2-ethyl-4-nitro-1H-imidazole was reacted with 1-(1-benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)piperazine, and it will result in the targeted compound. The resulting compound (**8**) was assumed to act as a non-nucleoside reverse transcriptase inhibitor (NNRI) [18].

Al-Masoudi et al. have designed a series of benzothiazole derivatives. The compounds were tested for in vitro activity against HIV-1 and HIV-2 in human T-lymphocyte (MT-4) cells based on the MTT assay. From which (3-(Benzothiazol-2-ylmethyl)-6-methoxy-2-methyl-1H-indol-1-yl)(4-chlorophenyl)methanone (**9**) was found to be active against a strain of human immunodeficiency virus [19].

3.5. Anti-Influenza Virus Agents

Influenza virus is commonly known as "flu", and the main cause of this infection is influenza A or influenza B virus. The machinery that the virus contains is single-

stranded RNA virus. It affects the upper respiratory tract, therefore, the symptoms involve common cold and fever.enzothiazole derivatives that act against influenza virus are 1-(benzo[d]thiazol-2-yl)-3-methylurea37 (**10**) and 9-((5-(benzo[d]thiazol-2-ylamino)pentyl)oxy)-10-methoxy-[1,3]dioxolo[4,5-g]isoquinolino[3,2-a]isoquinolin-7-ium (**11**) [20].

4. Structure Activity Relationship of Benzothiazole Derivatives as Antiviral Agents

- Amine or amido linkage at the 2nd position of benzothiazole gives anticancer activity of compound.
- Second position of benzothiazole is active to attach substituents.
- Methyl group substitution at the 5th or 6th position of benzothiazole increases potency of antiviral compounds.
- Aryl moieties like pyrazole, pyridine, phenyl, imidazole, benzothiazole, thiazole, etc., at the 2nd position gives antiviral activity of the compound. Directly attached or through amine or amide linkage, aryl moiety at 2nd position of benzothiazole gives potent antiviral compounds.
- Fourth position of benzothiazole is also important for substitution in 2-aminobenzothiazoles to derive antiviral moieties.

5. Methods to Evaluate Antiviral Activity of Benzothiazole Derivatives

The antiviral activity of a novel synthetic compound can be measured by the four following methods in vitro.

5.1. Inhibition of Virus Induced Cytopathic Effect

A quantal assay can be used to determine effectiveness of those viruses that induce cytopathic effect, but do not cause plaque reduction. Here is the procedure to follow the assay method: Prepare a series of one fourth of cell cultures in culture tubes that are infected with a constant dose of 100 TCID50 (Median Tissue Culture Infectious Dose). The series should be kept at 37 °C for 1–2 h.Add antiviral agent with maintenance media to that series after completion of 1–2 h.Concentration range of antiviral agent should be from a minimal dose that does not show any antiviral activity to the maximum dose of inhibition. Virus induced cytopathic effects will be recorded each day until all the samples and blank cultures show cytopathic effects. ED50, that is, the 50% of the effective dose of antiviral drug, is the concentration that inhibits cytopathic effect in half of the culture tubes [21,22].

5.2. Plaque Reduction Assay

This method is applicable to all viruses that form plaque in suitable cells. This method is performed in corresponding cell monolayers infected with a constant concentration of virus depending on the size of monolayer. The monolayers are kept at 37 °C for 1–2 h and after those nutrients and antiviral agent with 1–2% methylcellulose is added. The infected culture is kept for rest for incubation for a respective period of time for different species of viruses. At the end of incubation period, all the cultures are stained for examination of plaque number. Plaque numbers in the culture without antiviral agent and with different concentration of antiviral agents are compared for results [23].

5.3. Virus Yield Reduction Assay

This method is used when long time determination of antiviral agent becomes necessary. Here, the cultures are infected with a fixed dose of virus and kept for 2 h at 37 °C then the unabsorbed viruses are removed by washing with Hanks' Balanced Salt Solution and the antiviral drug of various concentrations are added. After the incubation period, the cultures are tested for total virus yield. ED90 (Drug concentration 90% of the virus yield) in comparison with virus control is determined from dose response curves [24,25].

5.4. Assay Systems Based on Measurement of Specialized Functions and Viral Products

Certain viruses do not produce plaque or cytopathic effect, but perform some specific functions so we can use them as evaluation parameters. The specific functions could be hemagglutination, hemadsorption, extent of viral replication, reduction of virus specific polypeptides, synthesis of viral nucleic acids, reverse transcriptase activity, by dose response curve, etc., from these all measurements, one can derive ED50 value of antiviral agent and can compare it with virus control to evaluate antiviral activity of the compound [26,27].

Author Contributions: Schemes for synthesis—S.S., Remaining—K.B.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: All the data has been taken from the sources or articles available on internet.

Acknowledgments: We are very thankful to Subhash Technical Campus staff for contribution in this work.

Conflicts of Interest: The authors declare no conflict of interest.

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