Volume 1, Issue 6 (2023)
Article No. 02
PP 01-09

VIVA-TECH INTERNATIONAL JOURNAL FOR RESEARCH AND INNOVATION
ANNUAL RESEARCH JOURNAL
ISSN(ONLINE): 2581-7280

Study of potential applications of derivatives of benzothiazole for its anticancer, antimalarial, antiviral and antitubercular properties.

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Abstract : *Heterocyclic compounds exhibiting biological activity is widely established. Since then, a large number of heterocyclic derivatives have been synthesized and are now known to have wide range of essential applications in a variety of domains including medical chemistry. Another heterocyclic bicyclic class of molecules containing benzothiazole moiety has a wide range of therapeutic applications, including those for anthelmintics, anticonvulsants, analgesics, antiviral, antifungal, anticancer, anti-inflammatory, antidiabetic, antileishmanial, antitubercular, antibacterial etc. Since benzothiazole derivatives have a diverse range of pharmacological activity, demonstrating the undeniable interest of this class of compounds and also is a rapidly expanding and more active area of study. In this study we have focussed on the potential applications of benzothiazole functionalized compounds for their antiviral, anticancer, antitubercular and antimalarial properties.*

Keywords - *Applications, Biological activities, benzothiazole derivatives.*

I. Introduction

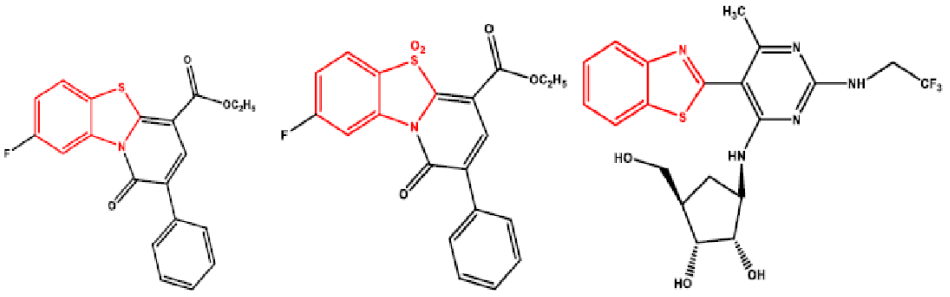
Today diseases have become the most leading problem across the globe and the most common and dreadful diseases to human life includes cancer, malaria, viral infections, tubercular diseases etc. Many humans lose their lives every year on account of getting infected by these diseases. Despite of the advancements in medical field as compared to few decades ago, still there is no permanent and complete cure for them. Hence a hunt for synthesizing newer and safer medicines with no or minimum side effects is being carried on priority basis among the researchers for benefit of mankind. Many different compounds are synthesized widely for this purpose and being tested for its biological activity against standard drugs. Heterocyclic compounds are one such class of compounds which shows potent biological activity. And among heterocyclic compounds benzothiazole derivatives has gained importance in recent time because of its effective results when compared with standard medicines. The effectiveness was observed for variety of broad range of applications in diverse fields. In medical field it had yielded promising results for anthelmintics, anticonvulsants, analgesics, antiviral, antifungal, anticancer, anti-inflammatory, antidiabetic, antileishmanial, antitubercular, antibacterial activities etc. In this study we have focussed on the potential applications of benzothiazole derivatives to enable researchers to explore and synthesise new derivatives of benzothiazole for its more potent medical applications for treatment of various diseases.

II. Biological activity of benzothiazole and it's derivatives

II.1 Benzothiazole derivatives as potent anti-viral agents

Volume 1, Issue 6 (2023)
Article No. 02
PP 01-09

Microorganisms called viruses multiply by utilising the machinery of their hosts. Numerous virus species that pose a threat to people's health have already been discovered. As a result, numerous antiviral medications are being developed and are being offered to treat viral infections. Benzothiazole derivatives are also well known to be effective antiviral agents among them. To develop more potent medications that can be employed as antiviral medicines, researchers are constantly working on the benzothiazole moiety. Here are a few effective antiviral medications that have a benzothiazole moiety and have exhibited similar and better results in comparison than the standard drugs.



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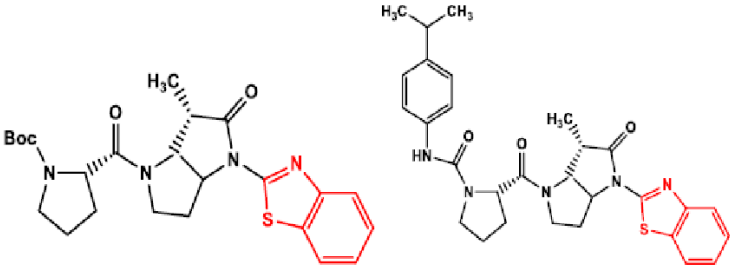

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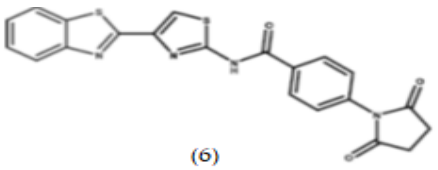

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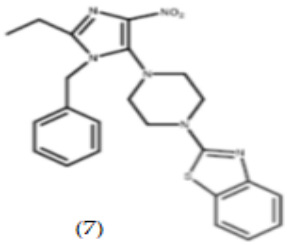

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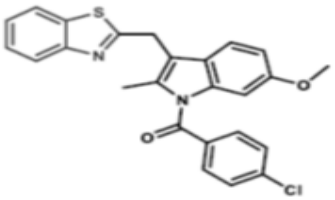

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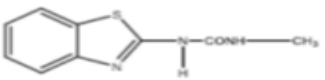

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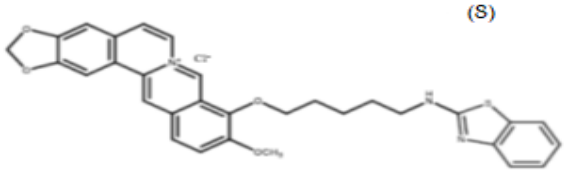

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Volume 1, Issue 6 (2023)
Article No.02
PP 01-09

2.1.1. Anti-Hepatitis C Virus (HCV) Agents

Giovanni Maga synthesized Compound (1) and compound (2) as potent HCV inhibitors. This compound has been shown to inhibit NS5B both in vitro and in replicon assays through binding to the benzothiadizine allosteric pocket [1].

Girijavallabhan et al. have designed some HCV replication inhibitors bearing benzo-thiazole moiety. Compound (3) was screened for its HCV replication inhibition ability and it was found the potent compound as an antiviral compound [2].

2.1.2. Anti-Herpes Virus Agents

Human cytomegalovirus (HCMV) comes under the category of beta herpes virus. The substituted benzothiazole derivatives (4) and (5) were prepared by Alan et al. Compounds (4) and (5) when tested against HCMV virus showed potent antiviral activity against HCMV - Human Cytomegalovirus [3].

2.1.3. Anti-Dengue Virus Agents

Many benzothiazole derivatives have been tested for their ability to combat dengue, and some of them have exhibited potent activity.

Halim et al. had designed compound (6) for screening against dengue virus, and in vitro and in vivo biological assays as well as computational modelling approaches had confirmed the compound's antiviral activity against dengue virus. [4]

2.1.4. Anti-HIV Virus Agents

The most harmful virus in the virus family is the human immunodeficiency virus. Auto Immunodeficiency Disorder is the resulting illness. No specific medication is yet available for the treatment of AIDS. Some of the benzothiazole derivatives have been screened for anti-HIV activity that may be both inexpensive and potent. Yaseen et al. developed compound (7) and evaluated its anti-HIV efficacy. And the outcomes demonstrated that it functioned as an inhibitor of non-nucleoside reverse transcriptase (NNRI) [5].

A series of benzothiazole derivatives have been designed by Al-Masoudi et al. Based on the MTT assay, the compounds were examined in human T-lymphocyte (MT-4) cells for in vitro activity against HIV-1 and HIV-2. Among the series the compound (8) was active against a strain of human immunodeficiency virus

2.1.5. Anti-Influenza Virus Agents

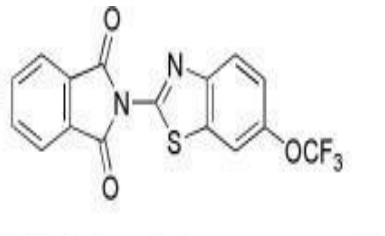
The Influenza A virus or Influenza B virus is primarily responsible for the infection of Influenza also referred to as the flu. The following benzothiazole derivatives were found to be effective against influenza virus.
The Benzothiazole derivatives that act against influenza virus are compound 9 and compound 10.[7].

II.2 Benzothiazole derivatives as potent anti-cancer agents

The research carried out on anticancer activity of benzothiazole derivatives has shown a very good activity results against various cell lines of various organs of the human body like colorectal carcinoma

Volume 1, Issue 6 (2023)
Article No. 02
PP 01-09

colon cancer (HCT-116), as MDA-MB-468 (mammary gland/breast tissues), human breast cancer (MCF7), B16F10, MCF7, PANC1, HepG2 cell line, hepatocellular carcinoma (HEPG-2).



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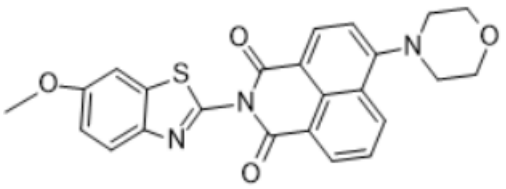

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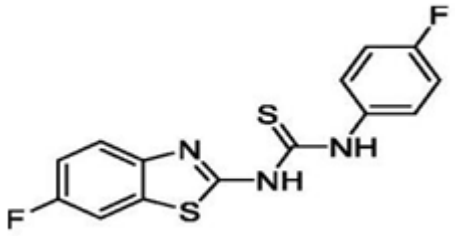

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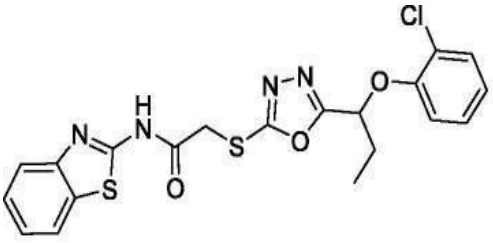

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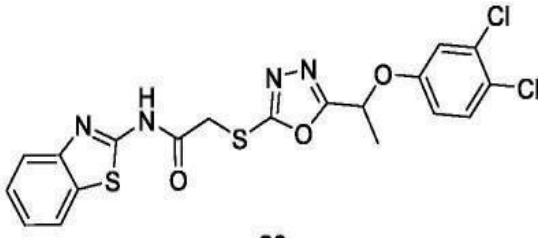

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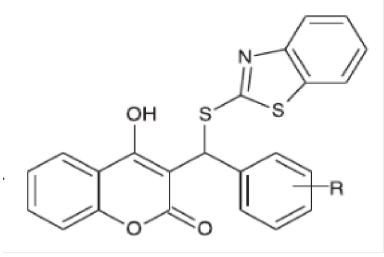

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Volume 1, Issue 6 (2023)
Article No. 02
PP 01-09

In 2008, Stanton Hon LungKok etal found that in vitro cytotoxic potential on human cancer cell lines was exhibited by phthalimide derivatives of benzothiazole (compound 1) [8].

Pramod D. Jawale Patil Synthesised of naphthalimide derivatives bearing benzothiazole as parent moeity, compound 2 shown a very good anticancer activity against B16F10, MCF7, and PANC1 [9].

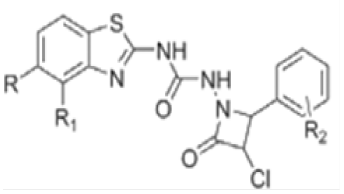
Anti-tumour activities against cancer cell lines such as MDA-MB-468 (mammary gland/breast tissues) was evaluated for synthesised fluoro benzothiazole derivatives by Aiello et al. The IC_{50} values of compound 3 were higher (4847.73 ± 2.39 μM)), (16.23 ± 0.81 μM)) and (34.58 ± 1.73 μM)) as compared to standard compound etoposide IC_{50} values (18.69 ± 0.94), (17.94 ± 0.89) and (2.16 ± 0.11 μM) against B16-F10, U-937 and THP-1 cell lines respectively [10].

1,3,4-oxadiazole-2-thione benzothiazole derivatives were Synthesized by Akhtar et al. Compounds 4 and 5 have CC50 values ($CC_{50} = 12 \pm 2$ μM and 8 ± 1 μM respectively) that were compared with standard drug to Doxorubicin. [11]

According to Priya R. Kadam et al., compound 6 (R= OCH_3) demonstrated good cytotoxic anticancer activity against the HepG2 cell line with an IC50 value of 22.79 μg/mL in comparison to all other produced derivatives and standard drug.[12]

Bis-thiazole derivatives of benzothiazole were synthesized by Ibrahim Taha Radwan et al and on analysis they found potent anticancer activity for human breast cancer (MCF7), hepatocellular carcinoma (HEPG-2) and colorectal carcinoma colon cancer (HCT-116) for one of the derivatives. The results showed that strong antitumor activity against HCT-116, MCF7 and HePG2 with IC50 values of 12.67, 9.94, and 6.89 μM for and 24.86, 7.31, and 8.37μM respectively, when compared to the standard reference drug, doxorubicin (IC50 =8.87, 5.23 and 5.50 μM, respectively).[13]

II.3 Benzothiazole derivatives as potent anti-tubercular agents



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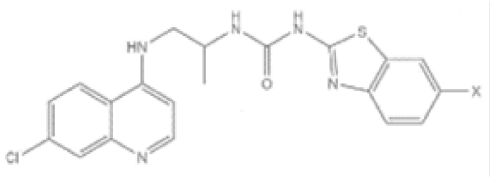

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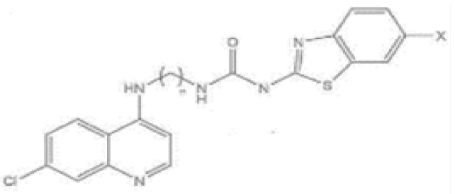

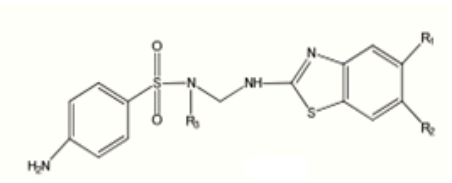

Volume 1, Issue 6 (2023)
Article No. 02
PP 01-09

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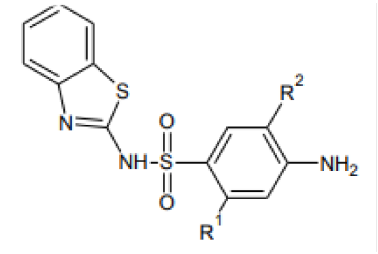

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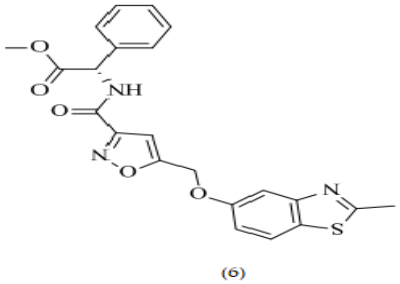

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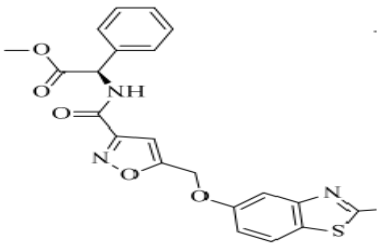

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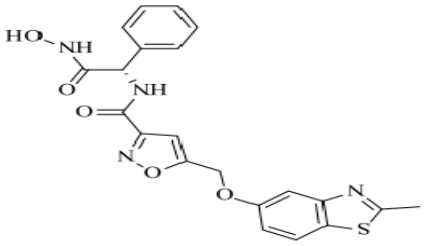

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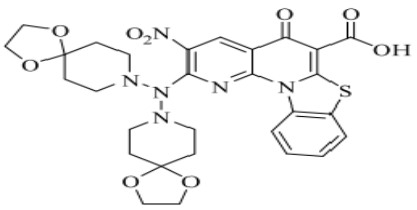

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Sibaji Sarkar carried out anti tuberculosis test on synthesized compound (1). In DMSO, each chemical was dissolved. Using an in vitro assay, the ability of the compound (1) to inhibit the growth of M. tuberculosis was determined. The results of the in vitro screening showed that all analogues had significantly comparable antitubercular activity than that of the standard reference medicines, isoniazid and rifampicin. [14]

Over the course of seven days of incubation in two slightly different mediums, Rashmika et al. produced new hybrid compounds 2 and 3 and assessed their potential for in vitro antitubercular activity against the H37Rv strain. The MIC90 (minimum inhibitory concentration required to suppress 90% of the Mtb growth) is the lowest concentration of a substance that results in no discernible mycobacterial growth. The assays employed rifampicin (RIF) as a positive control or standard reference. [15]

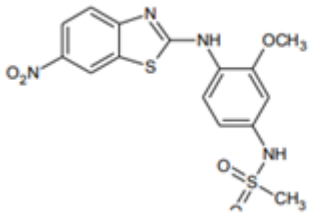
Naira Nayeem et al, tested the antitubercular activity of compound 4. The tested derivatives results inhibited the growth of Mycobacterium tuberculosis and were potent at 50µg/ml also a similar result was observed with the standard INH at 0.1 µg/ml. [16]

According to Sukhbir L. et al compound 5 (R^1= Cl, R^2 = COOH) exhibited effective in vitro antituberculosis activity against the H37Rv strain of Mycobacterium TB among all 4-Amino-N-(1,3-benzothiazol-2-yl) benzene sulphonamide derivatives synthesized. [17]

Huangand et al synthesised BTA-isoxazole carboxamide derivatives and on screening it was observed that they exhibited antitubercular and antiprotozoal activities against Mtb H37Rv and four protozoan parasites. Contrarily, compounds 6 and 7 with MIC values of 1.4 and 1.9 mM, respectively, demonstrated significant action and inhibited Mtb growth at micromolar doses. The hydroxamate compound 8, when tested against T. b. rhodesiense, had encouraging results. In vitro and in vivo anti-TB activity of benzothiazolonaphthyridone carboxylic acid derivatives against M. tuberculosis H37Rv and multi-drug resistant MT (MDR-TB). Compound 8 was the most effective compound in vitro, having MICs against Mtb and MTR-TB of 0.19 and 0.04 mM, respectively. Compound (8) was 208 and 1137 times more potent than gatifloxacin and isoniazid, and it had potential action against MDR-TB (INH). [18]

II.4 Benzothiazole derivatives as potent anti-malarial agents

Malaria is one of the most lethal and widely distributed diseases in the world. According to the World Health Organization, malaria affects around 40% of the world's population and has grown to be a serious public health issue in developing nations too.



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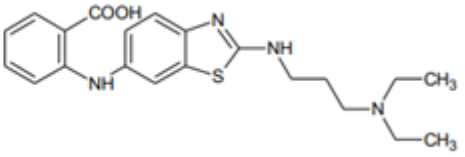

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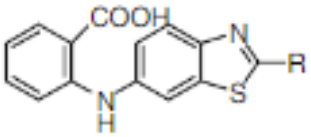

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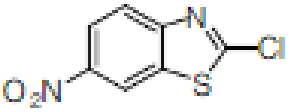

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Hout S et al carried out Antimalarial activity on W2 and 3D7 strains of P. falciparum for their 2-substituted -6-nitro and 6-amino benzothiazoles and their anthranilic acids were carried out. The

results revealed the potency of compounds 1 and 2 better than the standard antimalarial agents. The findings demonstrated the effectiveness of compounds 1 and 2 as antimalarial medications in both clinical and biological studies. The majority of chemical compounds were found to be able to prevent the proliferation of human malignant cells when tested for antiproliferative action on human cells. Compared to anthranilic acids, nitro- and amino-benzothiazoles displayed stronger antiproliferative effects. It was demonstrated by compounds 3 and 4 that these chemical structures may support significant antiproliferative activity on human cells when a piperidino-group was added. [19]

III. Conclusion

From the above study it has been observed that benzothiazole possess very potential medicinal properties which can be useful to the society. so there is a wide scope for synthesizing new derivatives of benzothiazole for exploring its more potent biological properties such as antiviral, anticancer, antitubercular, antimalarial etc.

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