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Review paper

Chemistry and Anti-Cancer Potential of Benzotriazole (BT) Subordinates

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ABSTRACT

Benzotriazole is a bicyclic heterocyclic system consisting of three nitrogen atoms and fused benzene ring, shows wide range of biological and pharmacological activities. Benzotriazole can be synthesized using benzene-1,2-diamine, and carboxylic acid. Benzotriazole possess wide spectrum of biological activities like including anticancer, antibacterial, antifungal, antiviral, anti-inflammatory, antihypertensive, analgesic properties. The present reviews attempted to gather the various developments in chemistry, synthetic advancement, and anticancer activities of benzotriazole derivatives. This review is focused on defining the place of benzotriazole derivatives in biomedical research, highlighting their mode of action and Structure Activity Relationship (SAR) studies for anticancer drug development.

1. Introduction

Azimidobenzene generally known as benzotriazole are a class of heterocyclic organic compound having a ring system containing three nitrogen atoms and fused benzene ring shows wide range of biological activities. Being an isostere of the purine nucleus, wh-ich is found in naturally occurring nucleotides like ATP and other naturally available substances, benzotriazole is not surprising for its broad-spectrum biological activity [1]. Benzotriazole is widely used by medicinal chemists as a privileged scaffold for the identification and development of novel bioactive compounds and drug candidates. Additionally, benzotriazole is a structural motif of seven pharmaceuticals; some of these compounds are approved, commercially available medications, while others are experimental drugs still under investigation. It is synthesised by diazotization

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process using benzene-1,2-diamine with sodium nitrite and acetic acid [2-3]. Due to their properties and applications, benzo-fused azoles are a class of heterocyclic compounds of great interest in the pharmaceutical chemistry area. Benzimidazole and its derivatives have been studied for decades. and drugs having this heterocycle moiety as main element have been widely used in clinic, for instance as anthelmintic in humans. Benzo-condensed azole containing three heteroatoms, such as bezoxadiazole, benzothiazole and benzotriazole, have been extensively studied for their broad range of biological activity [4]. However, few reviews were focalized on a single nucleus. Indeed, the aim of this paper is to provide an overview of the benzotriazole based systems and their relevance in medicinal chemistry. The 1*H*-benzo[*d*] [1,2,3] triazole (BT) (Fig. 1) can be considered as a privileged structure for its several pharmacological activities. Useful as scaffold for the design of new pharmacologically active compounds, BT is undergoing rapid development in the synthesis of heterocycles. From a purely chemical point of view, the benzotriazole structure proved extremely versatile applicabilities. For instance, it is currently used as a synthetic auxiliary or as a good leaving group after reaction with a variety of carbonyl groups. It is interesting the use of the acyl benzotriazole methodology, developed by Katrizsky and co-workers. The N-acyl benzotriazole is an easy-to-handle acylating agent for advantageous N-, O-, C- and S-acylations. New peptidomimetic macrocycles were obtained from dicarboxylic benzotriazole using this methodology [5]. Benzotriazole also acts as an electron-donor or a precursor of radicals or carbanions. It is easily insertable into other chemical structures through a series of reaction, such as condensation, addition reactions and benzotriazolyl-alkylation. Some authors have also reported the synthesis of stable nitrenium ions using BT as synthon. Polymer-supported benzotriazoles were also used as catalysts for the generation of a tetrahydroquinoline library. However, the main interest on BT is focused in the pharmaceutical field, as suitably substituted benzotriazole derivatives can boast the most different biological properties, including plant-growth regulator, choleretic, antibacterial, antiprotozoal, antiviral and antiproliferative activity [6-8].

Fig. 1. Chemical structure of 1*H*-benzo[*d*][1,2,3]triazole (BT).

2. Chemistry

Benzotriazole (BT) is an aromatic heterocyclic compound that has been widely popular in organic as well as inorganic chemistry. It belongs in the general category of azoles, along with other well-known heterocyclic molecules such as pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole and tetrazole. BT contains a benzene ring that is fused with a five-membered aromatic ring which incorporates the 1,2,3-triazole moiety. Since the proton in this moiety can easily relocate between the nitrogen atoms, BT can exist in two tautomeric forms, 1H- and 2H-Benzotriazole (Scheme 1, Forms A and B respectively) [9,10]. Investigation of this phenomenon has been the subject of multiple studies throughout the years, which showed that the 1H-tautomer (**A**) is the predominant species in solution. This has been attributed to its high dipole moment (μ = 4.3 D in **A**, 0.38 D in **B**, according to theoretical calculations) which favours interactions with the solvent and therefore provides better solvation than in the case of the 2H-tautomer. These spectroscopic studies as well as X-Ray crystallography have also shown that the 1H-tautomer is the only stable isomer found in the solid state [11].

The popularity of benzotriazole derivatives amongst organic chemists is in no small part due to their attractive properties. BT is an odourless, non-toxic, non-sensitive chemical that shows excellent solubility in a variety of organic solvents and is almost insoluble in water. Additionally, it is inexpensive and easy to synthesize. More importantly, BT exhibits both electron donating and electron attracting capabilities; it can either act as a weak acid (pKa = 8.2) through proton loss, or as a very weak Brønsted base (pKa < 0) through accepting a proton using the lone pair electrons available on the nitrogen atoms. As such, it is also soluble in aqueous Na_2CO_3 as well as HCl, meaning that it can be easily separated from reaction mixtures. Finally, its ring system shows remarkable thermal (up to 400 °C) and chemical (in the presence of H_2SO_4, KOH, $LiAlH_4$ etc.) stability. For these reasons, benzotriazole and its derivatives have been extensively used in synthetic organic chemistry as auxiliary tools towards a great range of reactions and syntheses. Relevant work by Katritzky should be noted, as his group contributed more than 600 research papers as well as multiple reviews and books related to this field in the span of three decades. This enormous work revolving around the

synthetic utilities of benzotriazole derivatives extends well beyond the scope of this review. Characteristic examples include benzotriazole-mediated alkylation reactions or the synthesis of heterocycles, peptides, and amino-acid derivatives [12-14].

Historically, the synthesis of the first benzotriazole derivative dates to the late 19th century. A study by Zinin in 1860 reports efforts towards the nitration of azoxybenzene. One of the afforded products was 2-phenylbenzotriazole-1-oxide, although this was not recognised until 1899 by Werner and Stiasny. Other studies in that period by Hofmann and Ladenburg investigated the effect of nitrous acid on various phenylenediamines, noting that the use of o-phenylenediamines resulted in products with unique properties compared to the rest. These products were later found to be benzotriazole derivatives and the synthetic method to obtain BT remains similar today (Fig. 2), albeit with certain improvements in the reaction conditions [15-16].

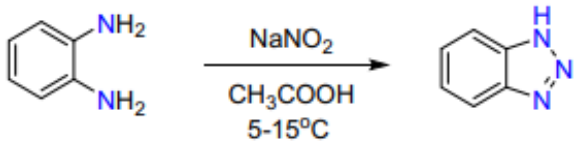

Fig. 2 Common synthetic method to obtain benzotriazole

The benzotriazole fragment is known to behave as (1) an excellent leaving group, (2) an electron-donating or an electron-withdrawing group, (3) an anion precursor, and (4) a radical precursor. It confers unique physicochemical properties to its immediate vicinity on various molecular scaffolds. This review covers the preparation and synthetic utility of versatile benzotriazole derivatives. The selected compounds are conveniently prepared from 1*H*-benzotriazole and are characterized by a huge synthetic potential (Fig. 3) [17-18].

3. Synthetic Approaches of Benzotriazole Derivatives

1,2,3-Benzotriazole has been prepared directly by the action of nitrous acid on o-phenylenediamine and by the hydrolysis of an acylated or arylated benzotriazole which has been previously prepared by the action of nitrous acid on the corresponding mono acylated or arylated o-phenylenediamine. The following procedure is the direct method and gives better over-all yields than the methods involving several intermediate steps [19]. N-Alkylation of Benzotriazole under Solvent-Free Conditions: An efficient, simple, and solvent-free method for highly regioselective N-alkylation of benzotriazole in the presence of SiO_2, K_2CO_3 and tetrabutylammonium bromide (TBAB) under thermal and microwave conditions has been described. In this method, 1-alkyl benzotriazoles were obtained regioselectivity in moderate to high yields and short reaction times (Fig. 4) [20].

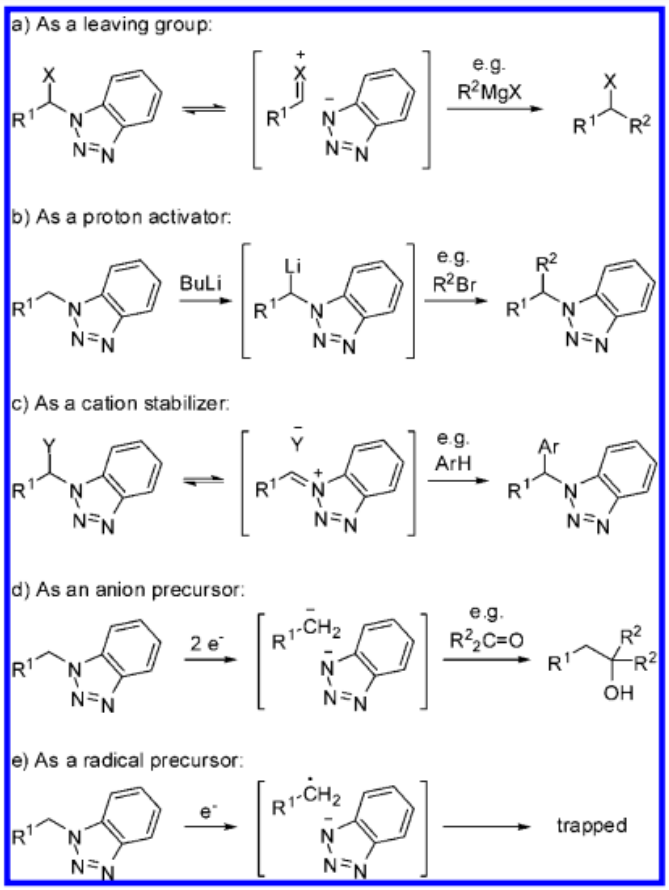

Fig. 3 Reactivity profile of benzotriazole

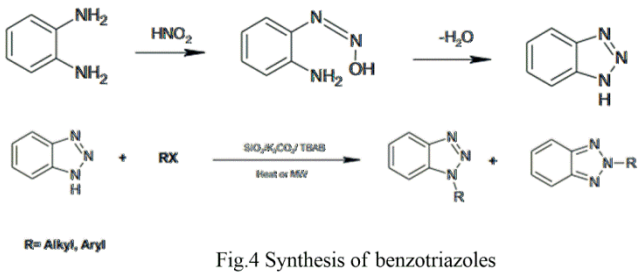

Fig.4 Synthesis of benzotriazoles

A variety of substituted benzotriazoles have been prepared by the [3 + 2] cycloaddition of azides to benzynes (Fig. 5). The reaction scope is quite general, affording a rapid and easy entry to substituted, functionalized benzotriazoles under mild conditions. Recent years have seen rapid development of the Cu catalyzed [3 + 2] cycloaddition reaction between terminal alkynes and azides, commonly referred to as "click chemistry". Such chemistry has found wide applications not only in synthetic organic chemistry and the pharmaceutical sciences [21].

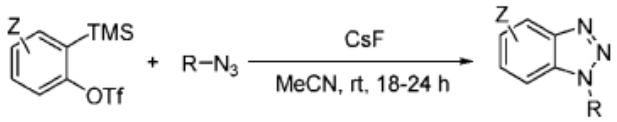

Fig. 5 Synthesis of benzotriazoles from azides

A novel protocol for the synthesis of 1-aryl1H-benzotriazole is developed via C-H activation followed by intramolecular amination employing a Pd (II) catalyst under relatively milder conditions (Fig. 6). This method features the use of Pd $(OAc)_2$ that successfully effects C-H activation followed by C-N cross-coupling to afford the cyclized products at moderate temperatures. Further study to understand the precise mechanism as well as to expand the range of substrates is currently underway in laboratory [22].

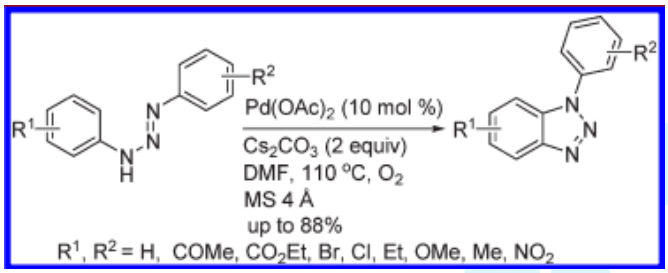

Fig. 6

Zhou et al. developed a novel 1,7-palladium migration-cyclization-dealkylation sequence for the regioselective synthesis of benzotriazoles. These reactions occurred in excellent yields with high regioselectivities. Further investigations of the mechanism and synthetic applications are underway. The coordination of palladium with the middle nitrogen of the triazene moiety would bring the C-H bond of the other aromatic ring close enough allow the 1,7-palladium migration via C-H bond activation and reductive elimination (Fig. 7) [23].

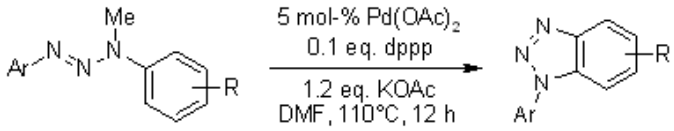

Fig. 7

1-Aryl-1,2,3-benzotriazole systems are synthesized (Fig. 8) in the high-yielding cyclocondensation of 2-(arylamino)aryliminophosphoranes under mild conditions. The reaction concludes the three-step, halogen-free synthetic route starting from simple nitroarenes and arylamines. Since the presented method enables smooth synthesis of 1-aryl-1,2,3-benzotriazoles, an efficient sequence via a 'halogen-free' way could be regarded as valuable alternative to other known methods [24].

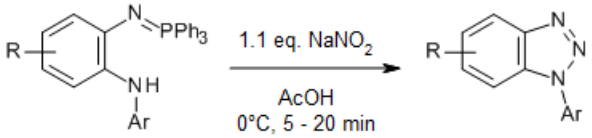

Fig. 8

4. Medicinal Chemistry of Benzotriazole (BT) derivatives as Anticancer agents

Cancer is the most prominent, notably complex, and lethal disease which became a serious concern of today's medical science. It poses a great challenge to medical scientific community for development of drugs, medicines and procedures for safer treatment and cure of cancer disease. These neoplasm tumour cells are diversified, heterogeneous cells with rapid proliferative properties. These neoplasm malignant tumours, have potential to invade or spread to other parts of body through blood stream and lymphatic system [25].

Several benzotriazole derivatives have been found to possess potent anticancer activity, for example, the antineoplastic agent vorozole that is in clinical trial, and 4,5,6,7-tetrabromobenzotriazole (TBB) (**1**) (Fig. 9) is a commercially available anticancer drug with high selective inhibition against protein kinase CK2. The successful exploration of TBB stimulates the continuous effort towards the development of novel benzotriazole-based anticancer agents targeting various kinases or receptors [26]. The special structure of benzotriazole derivatives could readily bind with different kinases via multiple non-covalent forces such as hydrogen bonds, coordination, ion-dipole, cation-π, π-π stacking, hydrophobic effect and van der Waals force, thus effectively inhibiting the activity of various kinases including protein kinases CK2 and CHK1, histone deacetylases and focal adhesion kinase and so on. The tetra Bromo substituted benzotriazole TBB is a clinical CK2 inhibitor, which is significantly selective and more effective to inhibit protein kinase CK2 in comparison to other kinases, and it could bind with CK2 in a quite different manner from other inhibitors [27, 28]. Benzotriazole substituted aminothiazole derivative **2** (Fig. 9) showed a mild inhibition against CHK1 (IC_{50}=110 nmol/mL). Its unsatisfactory activity is possibly caused by the weak ability to accept an H-bond from the Cys87 amide or weak interactions

between the nitrogen atoms of benzotriazole and carbonyl groups of nearby protein [29].

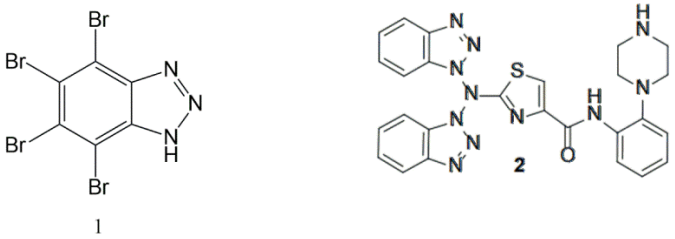

Fig. 9

Histone deacetylases (HDACs) are a type of enzymes involved in the acetylation of histones in cells, and they could catalyze the deacetylation of lysine (Lys) residues, predominantly in histones [H3] and [H4] dopamine, which is one of the key steps in the regulation of expression of target genes affecting proper cell function, differentiation, and proliferation. The abnormal recruitment of HDACs has been clearly linked to carcinogenesis. Benzotriazole based tri-methoxy benzoate **3** (Fig. 10) exhibited a considerable HDAC inhibitory activity (IC50=9.4 µg/mL) as well as a remarkable antiproliferative activity with a mean IC50 value of 1.7 µg/mL against three human cancer cell lines including oral epidermoid carcinoma KB cells, non-small-cell lung carcinoma H460 cells and stomach carcinoma MKN45 cells, which was close to the value of positive control doxorubicin. the docking study confirmed that the two oxygens of ester in compound 3 could form hydrogen bonds with the amino hydrogens of His170 and Phe198, respectively. Moreover, positive -stacking interactions were existed between two benzene rings of this molecule and Tyr264. In addition, the benzotriazole ring and benzene ring of compound 3 may form a hydrophobic interaction with Phe141, Tyr196, Leu265, Lys267, and Tyr297 of the enzyme. The different polarities and sizes of the substituents in the benzene ring and benzotriazole ring are also important factors to influence the H-bonds and π-π interactions, leading to the differences in HDAC inhibitory activity of these compounds [30].

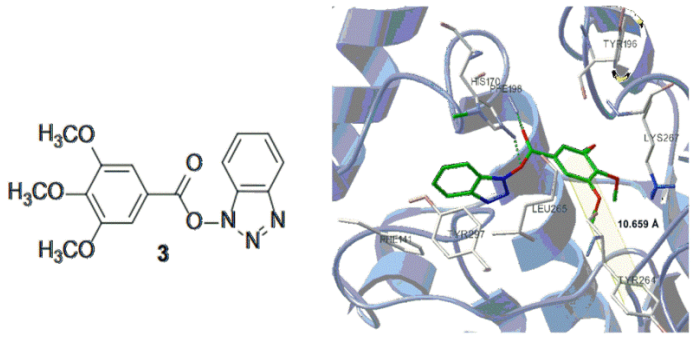

Fig. 10 Binding Model of Compound **3**

1,3,4-Oxadiazole derivatives have drawn continuing interest over the years because of their varied biological activities. In order to search for novel anticancer agents, we designed and synthesized a series of new 1,3,4-oxadiazole derivatives containing benzotriazole moiety as potential focal adhesion kinase (FAK) inhibitors. All the synthesized compounds were firstly reported. Among the compounds, compound 4 shows the most potent inhibitory activity against MCF-7 and HT29 cell lines with IC50 values of 5.68 µg/ml and 10.21 µg/ml, respectively. Besides, all the compounds were assayed for FAK inhibitory activity using the TRAP-PCR-ELISA assay. The results showed compound **4** (Fig. 11) exhibited the most potent FAK inhibitory activity with IC50 values of 1.2±0.3 µM. Docking simulation by positioning compound 4 into the FAK structure active site was performed to explore the possible binding mode. Apoptosis which was analyzed by flow cytometry, demonstrated that compound **4** induced apoptosis against MCF-7 cells. Therefore, compound **4** may be a potential anticancer agent against MCF-7 cancer cell [31].

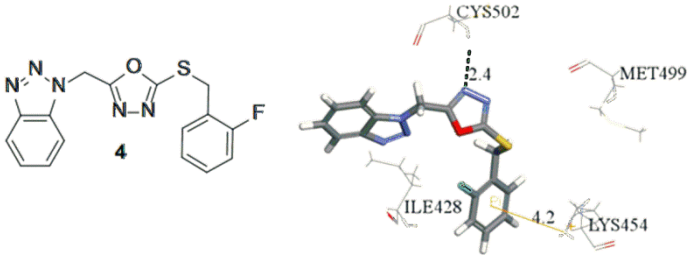

Fig. 11 Binding model of compound 4

Benzotriazole derivative **5** was designed and synthesized to enhance the chemo sensitizing activity to combat drug resistance. The in vitro evaluation indicated that compound **5** could inhibit 29.9% of cell growth in murine lymphocytic leukemia cell line P388, which was higher than the standard drug Verapamil (9.3%) at the concentration of 80 µg/mL The lipophilicity of benzotriazole and its ability to act as a hydrogen bond acceptor may improve its anticancer efficiency. Further researches are worthwhile to focus on the design of new structural anticancer benzotriazole derivatives to reduce their inherent cytotoxicity and increase the chemo sensitizing activity [32]. Benzotriazole acrylonitrile **6** exhibited stronger anticancer activities in comparison to the standard drug etoposide and greater potential than 6-mercaptopurine against a series of human cell lines including splenic B-lymphoblastoid cells, acute B-lymphoblastic leukemia, skin melanoma and breast

adenocarcinoma with the median cytotoxic concentrations (CC50 values) ranging from 0.05 to 0.8 µmol/L. Further molecular docking model investigations once more confirmed the ability of compound 6 to inhibit the polymerization of tubulin, thereby preventing the formation of spindle cells by blocking cell replication in its metaphase. In order to further deduce the structure activity relationship, a series of benzotriazole derivatives were synthesized and the results showed that the replacement of methoxy moiety by methyl group, chlorine or bromine atom on the benzene ring reduced the antiproliferative ability (Fig.11) [33]. Benzotriazole derivatives have been shown to be able to induce growth inhibition in cancer cells. In the present study, Zhang et al. synthesized bioactive compound, 3-(1H-benzo [d] [1,2,3] triazol-1-yl)-1-(4-methoxyphenyl)-1-oxopropan-2-yl benzoate (BmOB) **7a, 7b**, which is a novel benzotriazole derivative. BmOB displayed anti-proliferative effects on several human tumor cell lines. Human hepatocarcinoma BEL-7402 cell line was selected as a model to illustrate BmOB's inhibition effect and its potential mechanism, since it was the highest susceptible cell line to BmOB. It was shown that treatment with BmOB resulted in generation of reactive oxygen species, disruption of mitochondrial membrane potential (DeltaPsim), and cell death in BEL-7402 cells. BmOB induced cytotoxicity could be prevented by antioxidant vitamin C and mitochondrial permeability transition inhibitor cyclosporine A. cyclosporine A could also protect the BmOB induced collapse of DeltaPsim in BEL7402 cells, while vitamin C did not show similar effects. The results suggest that BmOB could inhibit BEL-7402 cell proliferation, and the cell death may occur through the modulation of mitochondrial functions regulated by reactive oxygen species (Fig. 12) [34].

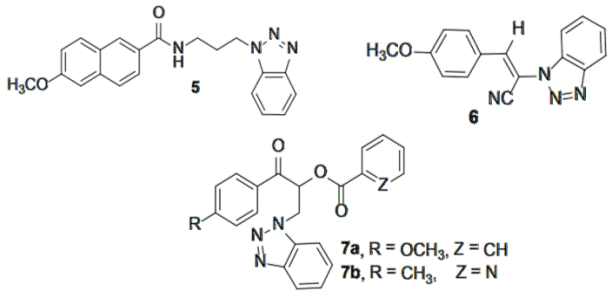

Fig. 12

The designed novel benzotriazole-oxadiazole hybrid compounds were synthesized using both conventional method and ultrasound sonication (US) as an environmentally friendly method. It was observed that the US method provided an increase in reaction yields by reducing the reaction time approximately 3-fold. The synthesized compounds were investigated against PANC-1 cell line. The compounds **8** exhibited very promising anticancer activity results with IC_{50} values of 87.82 ± 4.319 µM, respectively. Further, molecular docking studies to suggest how the synthesized compounds interact with the kinase domain of human DDR1 in complex of pancreatic Cancer proteins (PDB ID: 6HP9), and the crystal structure of PDEd of pancreatic Cancer proteins (PDB ID: 5E80). It was concluded from the docking studies that the compound **8** demonstrated the highest binding score values for active site of both proteins. Afterwards, ADME calculations were performed to examine the drug properties of benzotriazole-oxadiazole hybrid compounds [35].

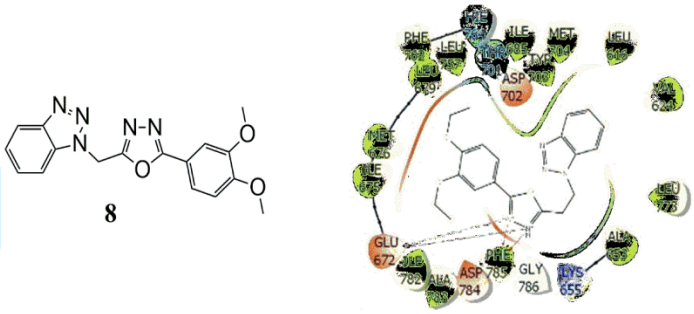

Fig. 13 Structure of compound **8** and binding Pattern

A series of benzotriazole (BTA) derivatives were synthesized as tyrosine protein kinase inhibitors using fragment-based design strategy. All desired compounds were synthesized with the reaction of benzotriazole, chloro acetonitrile and aromatic aldehyde using Ultrasonic-Microwave method and characterized by IR, ^{1}H and ^{13}C-NMR, mass spectrometry (MS) and elemental analysis. The anticancer activity of these compounds was evaluated by CCK-8 method against carcinoma VX2, lung cancer A549, stomach cancer cell lines MKN45 and MGC *in vitro*. The results showed that all compounds showed good antiproliferative activity. Compound **9** showed the most prominent inhibition of VX2 cell lines with IC_{50} of 3.80 ± 0.75 µM. Compound **10** exhibited highly potent anticancer activity of stomach MGC cell lines with IC_{50} of 3.72 ± 0.11 µM. A549 and MKN45 cell lines were sensitive to compound **11** with IC_{50} of 5.47 ± 1.11 and 3.04 ± 0.02 µM, respectively [36].

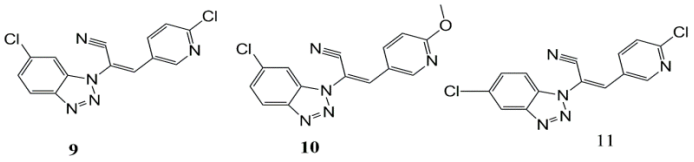

Fig. 14 Structure of compound 9,10, 11

Different series of benzotriazole-1,2,3-triazole hybrids (carrying different pharmacophores) have

been designed and synthesized **12** (Fig. 15) (by both conventional and microwave syntheses) through the Cu(I)-catalyzed click 1,3-dipolar cycloaddition reaction of the propargylated BT with the appropriate aliphatic, aromatic and phenyl/benzyl acetamide azides. These compounds were characterized by proper spectroscopic methods. The anticancer activities with A549 and H1299 lung cancer cell lines were in the range of 70.0 to 90.0%. The reported compounds showed good DNA binding constants in the range of 1.3×10^3 to 11.90×10^5 M^{-1}. The docking results suggested strong DNA bindings of the reported compounds in the minor grooves of DNA; through hydrogen bonding and hydrophobic interactions. The quite good anticancer activities and high DNA binding constants have indicated that the reported molecules may be future for anticancer drug development [37].

A series of novel benzotriazole N-acyl aryl hydrazone hybrids **13** was synthesized according fragment-based design strategy. All the synthesized compounds were evaluated for their anticancer activity against 60 human tumor cell lines by NCI (USA). Some of them exhibited significant to potent anticancer activity at low concentrations, most active compound showed prominent broad-spectrum anticancer activity against 34 tumor cell lines, with mean growth inhibition percent of 45.80%. It exerted the highest potency against colon HT-29 cell line, with cell growth inhibition 86.86%. Additionally, it demonstrated lethal activity to MDA-MB-435 belonging melanoma and exhibited the highest anticancer activity against leukemic CCRF-CEM and HL-60(TB) cell lines, with cell growth inhibition 86.69% and 86.42%, respectively. Moreover, it exerted marked potency against ovarian OVCAR-3 cancer cell line, with cell growth inhibition 78.24%. The anti-proliferative activity of potent compound appeared to correlate well with their ability to inhibit FAK at nano-molar range between 44.6 and 80.75 Nm and was a potent, inhibitor of FAK and Pyk2 activity with IC_{50} values of 44.6 and 70.19 nM, respectively. Inhibition of FAK enzyme led to a significant increase in the level of active caspase-3, compared to control (11.35 folds), accumulation of cells in pre-G1 phase and annexin-V and propidium iodide staining in addition to cell cycle arrest at G2/M phase indicating that cell death proceeded through an apoptotic mechanism [38].

Fig. 15 Structure of Pharmacophore 12 and their modification

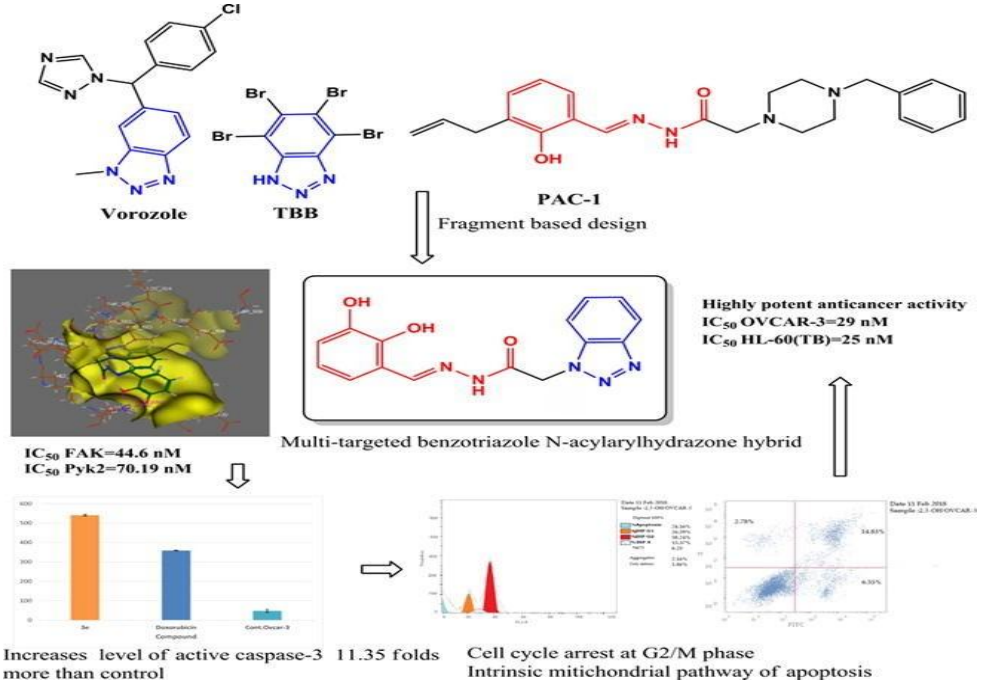

Fig. 16

Recently, a compound derived from recent scientific advances named **14** has emerged as the focus of this research, the aim of which is to explore its potential impact on solid tumor cell lines. Using a combination of bioinformatics and biological assays, this study conducted an in-depth investigation of the effects of **14**. The results of this study have substantial implications for cancer research and treatment. 14 has shown remarkable efficacy in inhibiting the growth of several cancer cell lines, including those representing prostate carcinoma (PC3) and cervical carcinoma (HeLa). The high sensitivity of these cells, indicated by low IC_{50} values, underscores its potential as a promising chemotherapeutic agent. In addition, 34 has revealed the ability to induce cell cycle arrest, particularly in the G2/M phase, a phenomenon with critical implications for tumor initiation and growth. By interfering with DNA replication in cancer cells, **14** has shown the capacity to trigger cell death, offering a new avenue for cancer treatment. In addition, computational analyses have identified key genes affected by 14 treatments, suggesting potential therapeutic targets. In conclusion, this study highlights the different mechanisms of **14** that inhibit cancer cell growth and alter the cell cycle. These promising results suggest the potential for more effective and less toxic anticancer therapies [39].

Fig. 17 (*E*)-2-(1*H*-benzo[*d*][1,2,3] triazol-1-yl)-3-(4-methoxyphenyl) acrylonitrile (14)

5. Future Direction

In recent years, drug discovery and development with significant biological profiling have gained lot of importance in research. Even though, there is considerable adverse effects, the medicinal chemists have always tried to design drug molecules possessing maximum therapeutic activity and minimal toxicity. Benzotriazole nucleus, whether from the natural origin or synthesized in the laboratory, has been explored widely anticancer drug development. Many benzotriazole-based molecules have been approved by FDA and are being marketed as therapeutics. The potential of BT scaffold should be more explored through extensive research. This review incorporates the anticancer potential of chemically modified BT-based molecules along with their activity profile. We also tried to include chemistry and synthetic approaches of different BT containing molecules for the design and development of clinically relevant drug candidates.

Benzotriazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities. Therefore, this nucleus appears a very interesting scaffold in the drug discovery and development processes. Isosteric modifications done through the introduction of benzotriazole moieties were sometimes successful, lowering activity at nanomolar concentration. More than one hundred molecules have reported as virtually hit and lead compounds for further drug development. However, despite the active, exhaustive, and target-based research on development of many compounds as anticancer molecules. No molecule has made its way to the market and clinic. It can be probably due to lack of molecular targets knowledge through which most of those compounds exert their biological actions, but it can be also due to lack of a comprehensive compilation of various research reports in each activity capable of giving an insight into the SAR of the compounds.

The therapeutic approach for the treatment of cancer diseases is different and includes surgical treatment, radiation therapy, immunotherapy, or chemotherapy. Polychemotherapy therefore provides the use of virtually toxic drugs, which selectively operate in respect of cancerous cells, thus saving the host healthy cells. Unfortunately, these cells are very similar to each other and due to the difficulty in discriminating between tumor and healthy cells the drugs selectivity is unattainable. In conclusion, even healthy somatic cells are exposed to toxic effects, especially those continuously in mitosis, such as hair follicles, intestinal epithelium, and bone marrow. For this reason, the research for new molecules able to selectively target tumor cells is still active. Particularly, nitrogen heterocycles, attracted the attention of researchers as possible isosteres of structural components of natural nucleotides, and also BT has been reported as possible antiproliferative agent.

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