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Short Communication

Recent Advancements for Triazoles as Anticancer Agents

Yashwant[1,*], B.K.Sharma[2], B.Srivastava[1], Vandana Sharma[1]

[1]*School of Pharmaceutical Sciences, Jaipur National University, Jaipur, 302025, India*
[2]*Department of Chemistry, S. K. Government College, Sikar-332 001, India*

ABSTRACT
Cancer is one of the leading causes of death in the world. The present work gives the recent advancements for triazoles as anticancer agents. Triazoles are known to have a large spectrum of potential anticancer, antimitotic and antifungal properties. With an improved understanding of the genes and pathways responsible for cancer initiation and progression, cancer drug development has undergone a paradigm change in recent years, from predominantly cytotoxic agent-based therapy to therapy aimed at molecular and genetic targets

Keywords: Anticancer, triazoles, antitumor, C-nucleoside.

INTRODUCTION

Triazoles are known to have a large spectrum of potential anticancer, antimitotic and antifungal properties. With an improved understanding of the genes and pathways responsible for cancer initiation and progression, cancer drug development has undergone a paradigm change in recent years, from predominantly cytotoxic agent-based therapy to therapy aimed at molecular and genetic targets

RECENT ADVANCEMENTS

In 1999: Fucheng Qu, Joon H. Hang, Jinfa Du, M. Gary Newton Chung K. Chu reported Asymmetric Synthesis of (2'R,4'R) and (2'S,4's)- 1,3-Dioxolanyl Triazole C-Nucleosides as potential antiviral and anticancer agents. They synthesized four new optically pure D- and L-1,3-dioxolanyl triazole C-nucleosides The stereochemical assignments of synthesized compounds were unambiguously made based on NMR studies as weh us X-ray crystallographic studies[1]. C-Nucleotides contain a C-C bond instead of the C-N bond between the heterocyclic moiety and the carbohydrate which stabilizes the glycosyl bond of the nucleosides. Synthetic as well as naturally occurring C-nucleosides exhibit interesting biological activities. The substances which focused main attention as potent anticancer agents include tiazofurin[2], 1,2,3-triazole C-nucleoside[3] and selenazofurin[4]. A number of structural modifications of the ribosyl moiety of tiazofurin have also been reported[5,6,7].

In 2001, Bentval Shivarama Holla et. al. synthesized some halogen containing 1,2,4-triazolo-1,3,4-thiadiazines and performed their anticancer screening which found to be good for further investigation[8]. 1,2,4-Triazoles and N-bridged heterocycles derived from them are found to be associated with diverse pharmacological activities[9-12].

Corresponding author
Email: yash99yash@gmail.com

Synthesis and reactions of 4-amino-5-mercapto-3-substituted-1,2,4-triazoles have been reviewed by Temple Jr. [13]. The 1,2,4-triazole nucleus has been incorporated into a wide variety of therapeutically important drugs.

In 2002, B.Shivram Holla synthesized and screened new bis-aminomercaptotriazoles and bis-triazolothiadiazoles as possible anticancer agents[14]. It was observed that incorporation of aryloxymethyl substituent and the halogen atom into the heterocyclic ring systems augments the biological activities considerably. They designed the synthesis of a series of novel 1,4-bis-[4-amino-5-mercapto-1,2,4-triazol-3-yl-ethoxy]phenylenes and their triazolothiadiazole derivatives starting from hydroquinones.

In 2004, Najim A. Al-Masoudi and coworkers synthesized and performed antitumor and antiviral properties of some 1,2,4-triazole derivatives[16]. In 2005, Ashis K.Saha carried investigations on novel triazole based inhibitors of Ras farnesyl transferase[17] The zinc-metalloenzyme farnesyl transferase (FTase) catalyzes the transfer of a farnesyl group to a cysteine thiol group contained in the C-terminal tetra peptide signal sequence of Ras, frequently referred to as a CAAX motif. Farnesylation causes membrane localization of Ras which, in turn, determines the switch from an inactive to an active Ras-GTP-bound form. [18] Among the Ras isoforms H-ras, N-ras, and K-ras, mutations in the K-ras isoform are most relevant to human cancers in particular pancreatic, colon, and lung cancers, which exhibit approximately 90, 40, and 25% incidence of Kras mutations, respectively. Inhibitors of FTase prevent membrane localization of the Ras oncogene and have the ability to revert the transformed phenotype, providing the rationale for the development of farnesyl transferase inhibitors (FTIs) as anticancer drugs[19].

In 2006, De-Chang Zhang and coworkers found Carboxyamido-triazole inhibits proliferation of human breast cancer cells via G2/M cell cycle arrest and

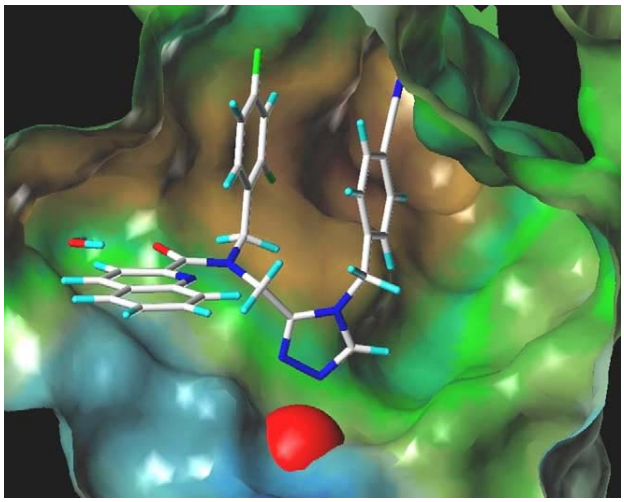

Figure: Docking model of a compound within the FTase catalytic site. The inhibitor and the structured water molecule are represented in capped sticks, the HFP ligand in wire, and the zinc atom by a red sphere. The molecular lipophilic potential has been mapped onto the Connolly surface of the cavity (blue coloring represents polar regions and brown represents hydrophobic regions). The two benzyl substituents point backward; the quinoline moiety is oriented toward the reader

apoptosis[20]. Carboxyamido-triazole (CAI) is an inhibitor of transmembrane calcium influx and intracellular calcium-requiring signal transduction pathway. CAI inhibits the proliferation and invasive characteristics of several tumor cell lines in vitro, including human breast cancer cells. CAI also demonstrates antiangiogenic activity in the chick chorioallantotic membrane assay, as well as the activity of inhibiting the proliferation of human umbilical vein endothelial cells in vitro. The antiproliferative activity of CAI has been proposed to be cytostatic and correlate with calcium-mediated signal transduction pathways.

In 2008, Krzysztof Sztanke et al. Synthesized and determined the lipophilicity, anticancer and antimicrobial properties of some fused 1,2,4-triazole derivatives[21].They reported an easy and useful method to synthesize antitumour and antimicrobial active imidazotriazole aryl derivatives containing the phenoxymethylene formation or the sulfanyl group. The identified analogues, in particular 3-phenoxymethyl-7-aryl-5H-6, 7-dihydroimidazo triazole derivatives, demonstrated antiproliferative and apoptotic properties justifying their further investigation as potential anticancer agents. Moreover, one compound was found to exhibit efficiency for DNA strand breakage and may be promising for the development of novel antitumour agents that induce the DNA strand breakage. Also significant viability decreases in human leukaemic RPMI 8226 cells treated with different concentrations of two compounds were observed, suggesting their antiproliferative properties. Two compounds can serve as novel templates for bacterial infection chemotherapy, whereas one other may be potential candidate for new antifungal agents. Further optimization of these identified chemical leads can possibly lead to more active molecules. Since all the reported examined compounds have shown promising results, studies to establish their in vivo efficacy and safety was being planned for their further development. From their work, it may be concluded that the fusion of 4,5-dihydroimidazole and 1,2,4-triazole nuclei in the case of the examined bicycles might result in bioactive molecules of high potency, particularly if the substituents are designed with optimum toxophoric requirements.

In 2009, Boja Poojary along with B.Shivarama Holla and coworkers synthesized some new fused 1,2,4-triazole derivatives carrying 2,4-dichloro-5-fluorophenyl moiety This study demonstrated the significant antitumor property of one compound against all the sixty cancer cell lines screened[22]. Further, for the first time they reported a new class of potential antitumor agents, with potential for structure activity studies and toxicological profiling. Therefore, it was concluded from their study that 1,2,4-triazole derivatives with 2,4-dichloro-5-fluorophenyl moiety at position 3 is an excellent synthon for further study. In the same year, Frank Wuest et. al. synthesized various (aryl-1,2,3-triazole-1-yl)-methanesulfonylphenyl derivatives and reported their inhibitory action on cyclooxygenase.[23]

In 2010, Qin-Pei Wu et al. synthesized and evaluated antitumor activity of novel 2’3’-dideoxy-2,3’-diethane thionucleosides bearing 1,2,3-triazole residues[24] László Somsák et al synthesized 1-(D-glucopyranosyl)-1,2,3-triazoles and evaluated them as glycogen phosphorylase inhibitors[25]

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