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Research paper

Tetrazolylmethyl quinolines: Design, docking studies, synthesis, anticancer and antifungal analyses

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ABSTRACT

A new series of 2,5 and 1,5-regioisomers of the tetrazolyl group *viz*., 3-[(5-benzyl/benzylthio-2*H*-tetrazol-2-yl) methyl]-2-chloro-6-substituted quinoline **6h-q** and 3-[(5-benzyl/benzylthio-1*H*-tetrazol-1-yl) methyl]-2-chloro-6-substituted quinolines **7h-q** were synthesized. Docking studies of all these compounds with DNA as target using PDB: 1AU5 and 453D revealed that the compounds **6h** and **6i** act as covalent cross linker on the DNA helix of the former and intercalate the latter both with higher C score values. Another set of docking studies in the active pocket of dihydrofolate reductase and *N*-myristoyl transferase as targets to assess antifungal activity revealed that compounds **6k**, **6l**, **6p** and **7q** (with *bromo* and *fluro* substituents) showcases different binding modes and hydrogen bonding. Further, the compounds were screened for anticancer activity (primary cytotoxicity) against NCI-60 Human tumor cell line at a single high dose (10^{-5} M) concentration assay. Among the tested compounds, **6h** has shown 99.28% of GI against Melanoma **(SK-MEL-5)** and compound **6i** has shown 97.56% of GI against Breast Cancer **(T-47D)**. Further, *in vitro* antifungal assay against *A. fumigatus* and *C. albicans* for these compounds **6h-q** and **7h-q** revealed potential to moderate activities as compared to the standard.

1. Introduction

Cancer is one of the second leading causes of mortality, which is a great concern of the current century to the mankind. Moreover, all the countries across the globe are being increasingly affected with this disease. As the populations live longer, the negative lifestyle and the food habits also increase the cancer risk, which conveys that cancer can also be termed as lifestyle disease. As per the world cancer report released by WHO in the forthcoming years the mortality rates due to cancer will increase twice its current percentage [1,2]. Therefore, discovery and development of newer anticancer agents have become the need and the key focus of many researchers and pharmaceutical companies. Although earlier reported chemotherapeutic drugs efficiently kill cancer cells, but many times this concludes to develop multi-drug resistance [3]. Prevalence of fungal infections is increasing over the past few years by an increase in cases which are susceptible to such pathogenic infections. These include patients undergoing chemotherapy for cancer, malignancies, AIDS or immunosuppressed by afflictions, with high risk of getting fungal infections [4]. However, like bacterial infections, some fungi no longer respond to the antifungal medications which were designed to cure them and most of the marketed antifungal agents have several drawbacks with respect to the potency and spectrum of activity. These factors motivate the researchers to design and develop novel targets with effective mode of mechanism, more bioactivity and least side effects [5].

Quinoline and its derivatives are considered to be versatile synthetic modules since they have shown modes of action in the inhibition of tyrosine kinases; proteasome, tubulin polymerization and DNA repair [6]. Quinoline nucleus also occurs in several natural compounds and it is one of the pharmacologically active substances displaying a wide range spectrum of biological activity. The scaffold can also be found in many classes of biologically active compounds such as antibacterials, antiprotozoic drugs [7–10], anti-tubercular

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agents [11–14], antiprion [15] and anticancer agents [16–23]. Some quinoline analogues also showed antifilarial and HIV integrase inhibitory activities [24,25] which make it to be a valuable scaffold for many biologically active compounds and several marketed drugs [26]. Tetrazole, a five membered heterocycle is considered as a bioisostere of carboxylic group and is a pharmacophore possessing wide range of biological activities. Several substituted tetrazoles have been shown to possess anticonvulsant [27], antibacterial [28,29], anti-inflammatory [30,31], antinociceptive [32,33], anticancer [34,35], cyclo-oxygenase inhibition [36] and hypoglycemic activities [37]. It has also been reported that the lipophilic nature of tetrazole moiety in a drug improves its oral bioavailability and cell penetration [38]. One of the marketed analgesic compound, Alfentanil **i** contains a tetrazolone moiety and on the other hand TAK-456 **ii** with tetrazole ring has a broad-spectrum antifungal activity [39] Fig. 1a.

Docking is a method which predicts the orientation of one macromolecule of protein to the ligand when bound to each other, thus forming a stable complex at the atomic level [40]. Actually, drug discovery program is oriented towards the search for lead structures and thus virtual screening/molecular docking program constitute a great tool to find hit which further undergoes limited optimization to identify promising lead molecule. In the present paper, we have carried out docking of the compounds **6h-q** and **7h-q** into the base pairs of DNA and active sites of *N*-myristoyl transferase (NMT) and dihydrofolate reductase (DHFR). This is because DNA being specifically taken as a molecular target for many of the clinically available drugs which is trending in cancer therapeutics and is a non-specific target of cytotoxic agents. It was noticed that smaller drug molecules which contain planar polyaromatic systems bind to double stranded DNA and exhibit more than one binding mode *ie.*, the intercalation and covalent binding. It has been oriental as a target for many antitumor as well as antibiotic drugs and hence further interaction of drug and DNA is important to study the rational designing of selective targets in pharmacology [41,42]. NMT is a cytosolic monomeric enzyme that catalyzes the transfer of

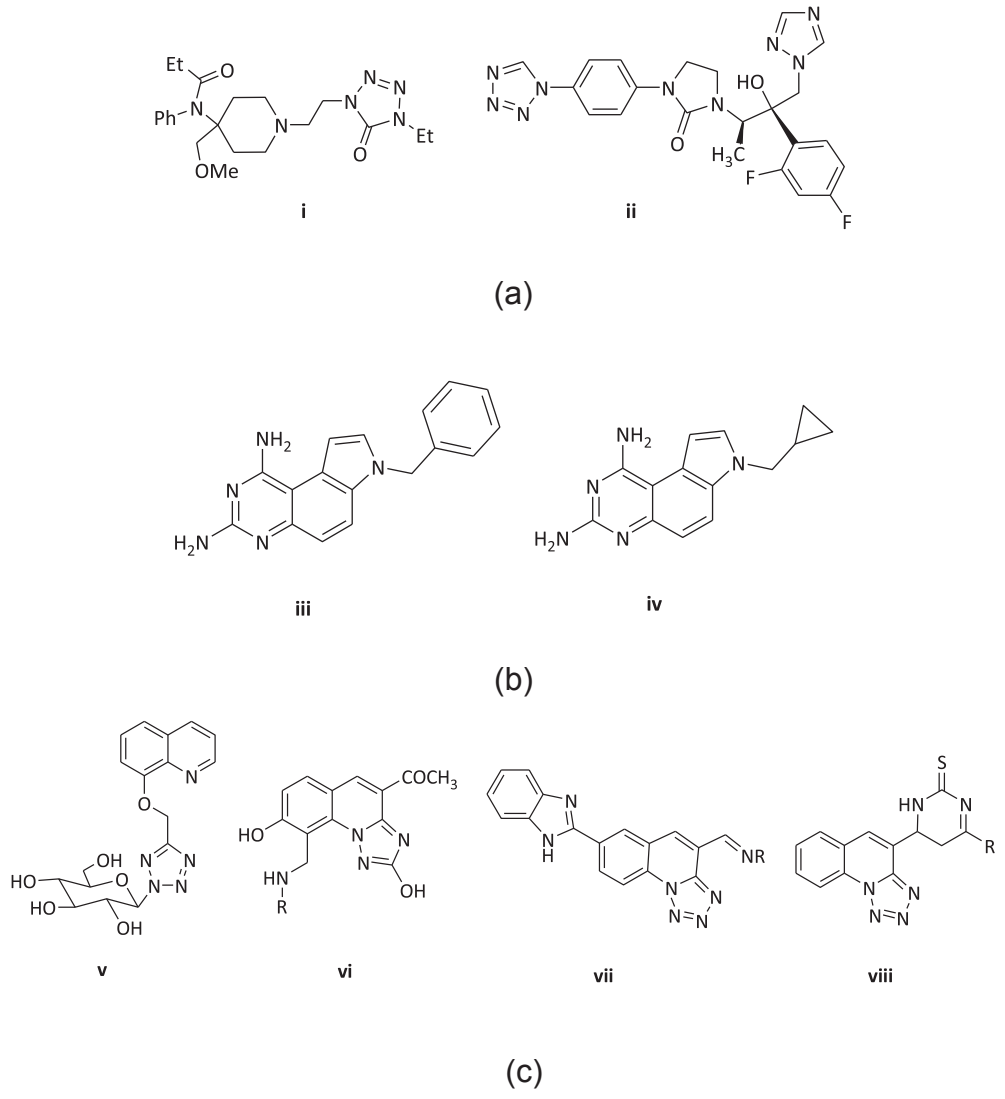

Fig. 1. (a) Marketed drugs containing tetrazole moiety. (b) *C. albicans* inhibiting Quinazolines. (c) Anticancer and antifungal azole quinolines.