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Tetrazole Anticancer and Antibodies

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Abstract:

Tetrazole derivatives are a prime class of heterocycles, very important to medicinal chemistry and drug design due to not only their bioisosterism to carboxylic acid and amide moieties but also to their metabolic stability and other beneficial physicochemical properties. Although more than 20 FDA-approved drugs contain 1H- or 2H-tetrazole substituents, their exact binding mode, structural biology, 3D conformations, and in general their chemical behavior is not fully understood. Importantly, multicomponent reaction (MCR) chemistry offers convergent access to multiple tetrazole scaffolds providing the three important elements of novelty, diversity, and complexity, yet MCR pathways to tetrazoles are far from completely explored. Here, we review the use of multicomponent reactions for the preparation of substituted tetrazole derivatives. We highlight specific applications and general trends holding therein and discuss synthetic approaches and their value by analyzing scope and limitations, and also enlighten their receptor binding mode. Finally.

1-1: Over view

infections has increased remarkably over the past two decades, which was mainly attributed to the increasing emergence of drug-resistant bacteria especially multidrug-resistant strains, intractable pathogens and newly arising pathogenic organisms. Tetrazoles, the bioisoster of carboxylic acid, possess considerable antibacterial property.

Hybridization of tetrazole with other antibacterial pharmacophores has the potential to enhance the efficacy against both drug-sensitive and drug-resistant pathogens. Some tetrazole hybrids such as tetrazoleoxazolidinone hybrid Tedizolid 25 and Tedizolid phosphate 26 have already been marketed for the treatment of acute bacterial skin and skin structure infections caused by various bacteria. DA-7867 (27), the amide analog of Tedizolid, also exhibited promising activities against a panel of clinically important pathogens including drug-resistant organisms, demonstrating the possible utility of the tetrazole scaffolds in the development of new antibacterial agents. Thus, hybridization of tetrazole with other antibacterial pharmacophores represents a promising strategy to develop novel antibacterial candidates. This work is attempted to systematically review the research of tetrazole hybrids in the design and development of antibacterial agents during the past two decades. The

structure-activity relationship (SAR) is also discussed to provide an insight for rational design of more effective tetrazole

1-2: Interatuer review

- Tetrazoles represent a class of five-membered heterocyclic compounds with polynitrogen electron-rich planar structural features. This special structure makes tetrazole derivatives useful drugs, explosives, and other functional materials with a wide range of applications in many fields of medicine, agriculture, material science, etc.

Derek J. McPhee2014 .

- Tetrazoles are a class of doubly unsaturated five-membered ring aromatic heterocycles, containing one carbon and four nitrogen atoms (Scheme 2.1). They do not exist in nature. The first tetrazole derivative was obtained occasionally by the Swedish chemist J. A. Bladin in 1885.1

He proposed the name “tetrazole" for this new ring structure. Base on the number of the substitution, the systems can be classified into un-, mono- and disubstituted tetrazoles**.**

Zhao, Ting2016.

- Cancer is one of the main causes of death throughout the world. The anticancer agents are indispensable for the treatment of various cancers, but most of them currently on the market are not specific, resulting in series of side effects of chemotherapy. Moreover, the emergency of drug-resistance towards cancers has already increased up to alarming level in the recent decades. Therefore, it's imperative to develop novel anticancer candidates with excellent activity against both drug-susceptible and drug-resistant cancers, and low toxicity as well. Tetrazole is the bioisoster of carboxylic acid, and its derivatives demonstrated promising anticancer activity. Hybridization of tetrazole with other anticancer pharmacophores may provide novel candidates with anticancer potency. The present review described the anticancer activity of tetrazole hybrids, and the structure-activity relationship (SAR) is also discussed to provide an insight for rational designs of tetrazole anticancer candidates with higher efficiency.

1-3: Out line

In the first chapter it was explained:

Over view

Literature review

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…....

will be explained in the second chapter:

problem statement

Challenges

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……..

Will be explained in the third chapter:

Synthesis and biological evaluation of tetrazole containing

Compounds as possible anticancer agents:

Objective

Method

Results

Conclusions

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……..

Chapter four

Preparation

Properties

1-4: Problems statement

Cancer is the second leading cause of death globally, and is responsible for an estimated 9.6 million deaths in 2018. Globally, about 1 in 6 deaths is due to cancer.

The most common types of cancer in males are lung cancer, colorectal cancer, prostate cancer and stomach cancer. In females, the most common types are breast cancer, colorectal cancer, lung cancer, and cervical cancer. If skin cancer other than melanoma was included in the total number of new cancers every year, that would represent about 40% of cases. In children, acute lymphocytic leukemia and brain tumors are more common, with the exception of Africa where non-Hodgkin's lymphomas occur more often. In 2012, about 165,000 children under the age of 15 were diagnosed with cancer. Cancer can affect all life stages in a person, even fetuses, but the risk of developing it increases as a person ages. Cancer causes 13% of all deaths

Use of antibiotics:

When infections persist in the body, it can lead to serious complications and many diseases, including:

1. Dermatitis, 2. Chronic infections, 3. Fatigue, 4. Burning feeling, 5. Pain in the joints and body,6. Stomach problems, 7. Enlarged lymph nodes, 8. Eye tears and runny nose, 9. Cough and sputum, 10. Gum problems, 11. Feeling anxious, 12. Belly fat, 13. Lack of sleep.

1-5: Challenges

1 _ The lack of a suitable environment for the researcher is one of the difficulties that we faced, in addition to the lack of necessary equipment, tools, and appropriate means of communication for research.

2_ Because of the Corona virus, we were not able to read more

3_ The weakness of the Internet is one of the most important problems that happened to me, as the writing of the research was delayed for a period of time.

4_ The sharing of information between us via the Internet was only due to the Corona virus, which caused the difficulty of the discussion between us

1-6: Synthesis and biological evaluation of tetrazole containing compounds as possible anticancer agents:

A series of new tetrazole derivatives are synthesized from Baylis–Hillman allyl amines in a clean, efficient and straightforward manner. The stereochemistry of the double bond is confirmed by X-ray diffraction data. These compounds are evaluated for in vitro anticancer activity against five cancer cell lines. Most of the compounds exhibited good anticancer activity in micro molar concentration out of 16 compounds synthesized and screened. Furthermore, the compound 5o has good binding affinity to calf thymus DNA (ct DNA), as assayed by UV-vis absorption and fluorescence spectroscopic methods.

Tetrazole derivatives as promising anticancer agents

Tetrazole cycle is a promising pharmacophore fragment frequently used in the development of novel drugs. This moiety is a stable, practically non-metabolized bioisosteric analog of carboxylic, cis-amide, and other functional groups. Over recent 10–15 years, various isomeric forms of tetrazole (NH-unsubstituted, 1H-1- substituted, and 2H-2-substituted tetrazoles) have been successfully used in the design of promising anticancer drugs. Coordination compounds of transition metals containing tetrazoles as ligands, semisynthetic tetrazolyl derivatives of natural compounds (biogenic acids, peptides, steroids, combretastatin, etc.), 5-oxo and 5- thiotetrazoles, and some other related compounds have been recognized as promising antineoplastic agents.

This review presents a comprehensive analysis of modern approaches to synthesis of these tetrazole derivatives as well as their biological (anticancer) properties. The most promising structure types of tetrazoles to be used as anticancer agents have been picked out.

Synthesis, molecular docking study and in vitro anticancer activity of tetrazole linked benzochromene derivatives Globally, cancer is regarded as one of the biggest health concern in humans and animals and is one of the most terrifying diseases. Therefore, there is a necessity for the discovery, development and improvement of novel antitumor drug molecules which could efficiently prevent proliferative pathways and clonal expansion of cells. Heterocyclic compounds like benzochromene play a key role in the development of current pharmaceuticals, natural resources, agriculture products, analytical reagents and dyes. Therefore, anticancer drugs show increased resistance, it is essential to designing the novel structured heterocyclic moieties to create potential anticancer

1-7: Objective

To synthesis a novel 1-(substitutedphenyl)-2-(1H-tetrazol-5-yl)-1H-benzo[f]chromene-3-amine derivatives for in vitro antitumour activity.

1-8: Method

The reaction of 3-amino-1-(substitutedphenyl)-1H-benzo[f]chromene-2-carbonitrile with sodium azide, ammonium chloride in dimethyl formamide solvent under reflux condition for 4 h afforded products (3a-k). The synthesized molecules were subjected to possible potential anti-tumour activity in vitro in four human cancer cell lines (MCF-7, Caco-2, HeLa and SKBR-3), and one human non-cancer cell line (HEK293), using the MTT cell viability assay.

1-9: Results

A novel series of products (3a-k) were synthesized with good yield and were identified with 1H NMR, 15N NMR, 13C NMR, FT-IR and HR-MS spectrum. The most potent compounds 3d, 3e, and 3f possessing the greatest cytotoxicity activity with IC50 values slightly higher (15-33 μM) than that of 5-Fluorouracil (10-17 μM), indicating their potential to be antitumor agents. The 3a, 3b, 3c, 3h, 3i and 3j compounds showed moderate activity. Additionally, a molecular docking analysis was conducted to predict the multi-drug resistance modulator behavior of synthesized compounds in the ATP binding site of P-glycoprotein.

1-10: Conclusions

We synthesized and designated eleven novel derivatives of tetrazole linked benzochromenes (3a-k) and evaluated their anti-cancer activity. Additionally, the results from the docking studies were found to be in good agreement with the results from computational profiling.

1-11: Synthesis, characterization and evaluation of anticancer activity of some tetrazole derivatives:

Tetrazole, a bioisostere of the carboxylic acid group, can replace the carboxyl group in drugs to increase the lipophilicity, bioavailability and reduce side effects. Tetrazole derivatives possess a broad-spectrum of biological properties including anti-tubercular and anti-malarial activities, and some tetrazole-based compounds have already been used in clinics for the treatment of various diseases. Therefore, tetrazole is an important pharmacophore in the development of new drugs. This review covers the recent advances of tetrazole derivatives as potential anti-tubercular and anti-malarial agents, and the structure-activity relationship is also discussed for the further rational design of tetrazole derivatives .

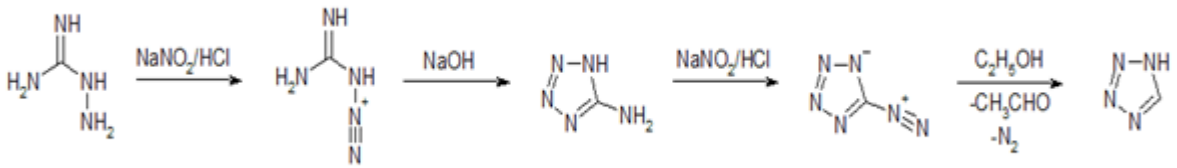
Cancer is a disease of striking significance in the world today. It is the second leading cause of death in the world after cardiovascular diseases and it is projected to beginning the primary cause of death there within the coming years [1, 2]. The identification of novel structures that can be potentially useful in designing new, potent selective and less toxic anticancer agents is still a major challenge to medicinal chemistry researchers [3]. Despite of the important advances achieved over recent decades in the research and development of various cancerostatic drugs, current antitumor chemotherapy still suffers from two major limitations− the first is the lack of selectivity of conventional chemotherapeutic agents for cancer tissues, bringing about unwanted side effects. The second is the acquisition by cancer cells of multiple-drug resistance.

Unwanted side effects of antitumor drugs could be overcome with agents capable of discriminating tumor cells from normal proliferative cells and the resistance is minimized using combined modality approach with different complementary mechanism of action [4]. The current scenario highlights the need for the discovery and development of new lead compounds of simple structure, exhibiting optimal in vivo antitumor potency and new mechanisms of action. Recent advances in clinical techniques, including large co-operative studies are allowing more rapid and reliable evaluation of new drugs. The combination of these advantages with improved preliminary screening systems is enhancing the emergence of newer and more potent.

1-12: Preparation

The compound is prepared by the reaction of anhydrous hydrazoic acid with hydrogen cyanide under pressure; Derivatives can also be prepared from the reaction of organic nitriles with sodium azide in the presence of iodine or sodium bisulfate on silica. The aryl derivatives at position 2 can also be prepared through the [2+3]cyclic addition reaction between aryl diazonium and trimethylsilyldiazomethane.

The preparation process can also be done from the aminoguanidine compound by treating with sodium nitrite .

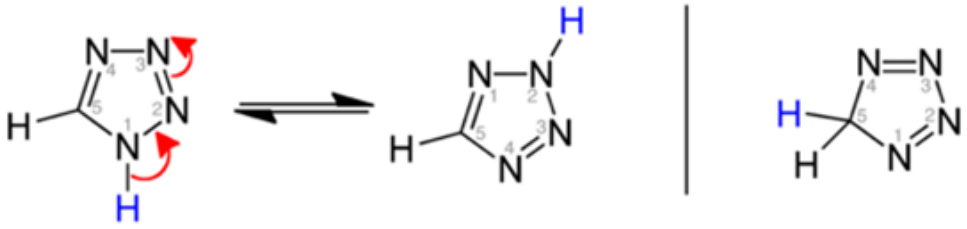


1-13: Properties

The compound exists at standard conditions as a solid that is easily soluble in water and ethanol; But it is difficult to dissolve in ether.

Tetrazol shows weak acidic properties in solutions, and has a pKa value of the acid dissociation constant (4.89) close to acetic acid.

There are resonant formulas of the compound, one of which is anti-aromatic (right image):



1-14: Derivatives

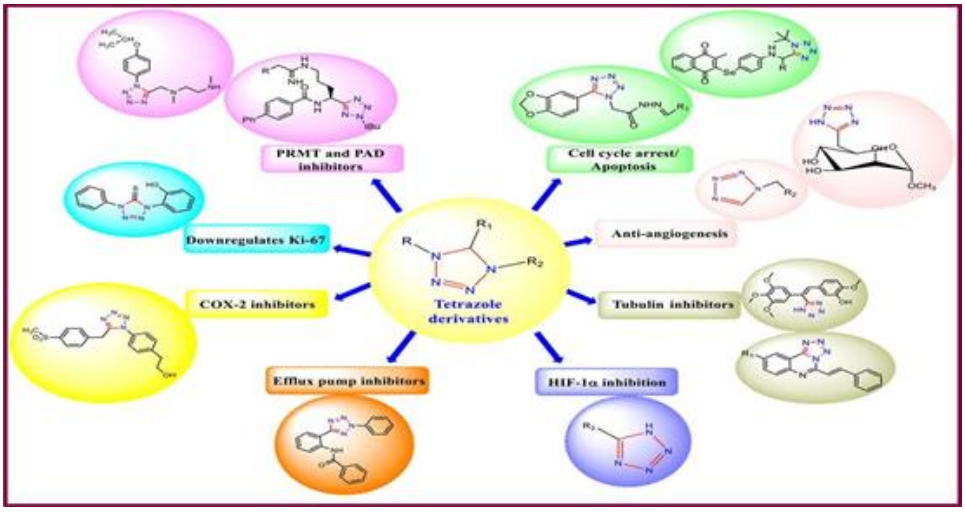


Fig.. 3/ derivatives of tetrazole

References:

1. Constantinos G Neochoritis, Ting Zhao, Alexander Dömling Chemical reviews 119 (3), 1970-2042, 2019
2. Jingyu Zhang et al. Eur J Med Chem. 2019.
3. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents) 17 (3), 464-470, 2017
4. Sridevi Gorle, Suresh Maddila, Surya N Maddila, Kovashnee Naicker, Moganavelli Singh, Parvesh Singh, Sreekantha B Jonnalagadda
5. Elena A Popova, Aleksandra V Protas, Rostislav E Trifonov Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents) 17 (14), 1856-1868, 2017
6. J. Optoelectron. Biomed. Mater. 2, 249-259, 2010
7. Dye, C. (2014). After 2015: infectious diseases in a new era of health and development. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *369*(1645), 20130426.
8. Weiss, R. A., & McMichael, A. J. (2004). Social and environmental risk factors in the emergence of infectious diseases. *Nature medicine*, *10*(Suppl 12), S70-S76.
9. Shaw-Taylor, L. (2020). An introduction to the history of infectious diseases, epidemics and the early phases of the long-run decline in mortality. *The Economic history review*, *73*(3), E1-E19.