Mini-Reviews in Organic Chemistry, 2026, *23*, 147-164

MINI-REVIEW ARTICLE

Recent Advances in the Chemistry of Tetrazole Derivatives-A Quinquennial Update (Mid-2019 to date)

Mohamed Hussein[1], Ravi Varala[2,3,*], Murali Mohan Achari Kamsali[4], Vittal Seema[5], Durga Prasad Beda[6], Mastan Ali Syed[7] and Mohammed Mujahid Alam[1,*]

[1]*Department of Chemistry, College of Science, King Khalid University, Abha, 61421, Saudi Arabia;* [2]*R&D, Scrips Pharma, Mallapur, Hyderabad, Telangana, 500076, India;* [3]*Research Fellow, INTI International University, Nilai, 71800, Malaysia;* [4]*Department of Chemistry, Sri Venkateswara College, University of Delhi, New Delhi, 110021, India;* [5]*Department of Chemistry, RGUKT Basar, Mudhole, Telangana, 504107, India;* [6]*Department of Pharmaceutical Chemistry, GITAM School of Pharmacy, GITAM (Deemed to be) University, Hyderabad, Telangana, 502329, India;* [7]*Analytical R&D, LRF Pharma Pvt. Ltd., Hyderabad, India*

ARTICLE HISTORY

Received: December 19, 2024
Revised: February 18, 2025
Accepted: February 26, 2025

DOI:
10.2174/0118756298372268250522094110

Abstract: Due to their advantageous physicochemical properties, metabolic stability, and bioisosterism with carboxylic acid and amide groups, tetrazole derivatives represent a valuable class of heterocycles that play a crucial role in medicinal chemistry and drug development. Advances in chemistry have enabled the versatile synthesis of tetrazole-based compounds. Therefore, optimizing the potential of tetrazoles to produce lead compounds requires effective synthetic access to a wide range of derivatives. According to the published papers, there are several methods for preparing tetrazole and its mono- and disubstituted derivatives, including 5-substituted 1H-tetrazoles, 2-substituted 1H-tetrazoles, 2,5- and 1,5-disubstituted, fused heterocycles, tetrazole derived hybrid azaheterocycles, *etc.* The use of tetrazoles as ligands, in bridging roles, in multiple tetrazole syntheses, and in other heterocyclic ring forms is also demonstrated. Alkylation, nucleophilic and electrophilic substitution in the side chain, electrophilic substitution at the ring carbon atom, and the effect of the reagents used are among the chemical characteristics of tetrazoles that are investigated. This mini-review also examines synthetic processes and discusses their benefits and drawbacks in this field of study.

Keywords: Heterocycles, tetrazoles, azides, cyanides, multicomponent reactions, electrophilic substitution.

1. INTRODUCTION

Compared to conventional linear multistep synthesis, Multicomponent Reactions (MCRs), which combine three or more reactants into a single-step reaction, are among the most effective synthetic tools employed in organic chemistry [1]. By cutting down on the number of experimental steps and purification procedures needed to obtain a target product, MCRs speed up the exploration of chemical space [2]. MCR's atom economy further enhances the sustainability of the chemical processes.

Tetrazoles are classified as doubly unsaturated aromatic five-member heterocycles with one carbon and four nitrogen atoms, which cannot be obtained naturally. The Swedish chemist J. A. Bladin acquired the first report on the synthesis of a tetrazole derivative at the University of Upsala in 1885 [3]. He noticed that the reactions between dicyano phenylhydrazine and nitrous acid produced a molecule with the chemical formula $C_8H_5N_5$. Then, he suggested that this new ring structure is called "tetrazole."

Tetrazoles can be categorized as un-, mono-, di-, and trisubstituted based on the number of substituents. There are two tautomeric forms of 5-substituted tetrazoles with 6π-electrons: **I** and **II** (Fig. **1**). The 1*H*-tautomer is the most common form in solution, whereas the 2*H*-tautomer is more stable in the gas phase.

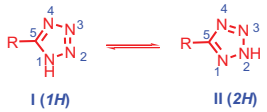

Fig. (1). Tautomerism of tetrazole derivatives.

Tetrazole chemistry has gained popularity in recent decades due to its wide range of biological applications, particularly the role it plays in medicinal chemistry (Fig. **2**), where this moiety provides a more complementary pharmacokinetic profile and a metabolically stable substitute for carboxylic acid functionalities [4-9]. The tetrazole motif has become a

*Address correspondence to these authors at the Department of Chemistry, College of Science, King Khalid University, Abha, 61421, Saudi Arabia;
E-mail: malm@kku.edu.sa; R&D, Scrips Pharma, Mallapur, Hyderabad, Telangana, 500076, India & Research Fellow, INTI International University, Nilai, 71800, Malaysia; Tel./Fax:+91-9618286529;
E-mail: ravivarala@gmail.com

1875-6298/26 $65.00+.00