Recent Progress in the Synthetic Methods of Pyrazoloquinoline Derivatives (Part I)

Rita M. Borik1 , Mohamed S. Mostafa1 , Mohamed S. Behalo2 and Rizk E. Khidre3,* 1 Department of Physical Sciences, College of Science, Jazan University, Jazan 45142, P.O. Box 114, Kingdom of Saudi Arabia; 2 Chemistry Department, Faculty of Science, Benha University, Benha, P.O. Box 13518, Egypt; 3 Chemical Industry Research Institute, National Research Centre, Dokki, Giza, P.O. Box 12622, Egypt

Abstract:

The focus of this review is on the synthetic routes available for different types of pyrazoloquinoline derivatives. There are three types of synthetic methods: i) from pyrazole derivatives; ii) from quinoline derivatives; and iii) miscellaneous methods. The position of the linkage between pyrazole and quinoline rings determines the seven isomers of pyrazolo□quinolines. The purpose of this review is to provide a guide for both synthetic and medicinal chemists to discover and design new pyrazoloquinolines for medical purposes.

A R T I C L E H I S T O R Y Received: November 03, 2023 Revised: December 23, 2023 Accepted: January 02, 2024 DOI: 10.2174/0113852728285959240108060645

Keywords: Synthesis methods, heterocycles, pyrazoloquinoline, pyrazole, quinolines, pharmacological activities. 1.

INTRODUCTION Nitrogen-heterocycles are commonly found in natural products, agrochemicals, dyes, and pharmaceutical intermediates, and they have potential biological activities [1-4]. Among of them, quinoline and pyrazole, are essential components of numerous FDA□approved, commercially available medications (Fig. 1). Additional□ly, Pyrazoloquinoline motifs are represent important fused nitrogen□heterocycles in synthetic and medicinal chemistry owing to their valuable pharmacological activities [5], for instance, antimicrobial [6], benzodiazepine antagonist [7, 8], anti-cancer [9], selective cy□clooxygenase-2 (COX-2) inhibitors [10], anti-inflammatory [11, 12], and antioxidant agents [13]. In addition, they have highly fluo□rescent properties [14] and are promising material for electrolumi□nescence applications [15, 16]. As shown in (Fig. 2), pyrazoloquin□oline has seven types of isomers. In this review, the synthetic methods of pyrazoloquinolines are categorized into three types: i) from pyrazole derivatives; ii) from quinoline derivatives; and iii) miscellaneous methods. Fig. (3) de□picted the retrosynthetic analysis used to construct the pyrazolo□quinoline derivatives. Although the useful import of pyrazoloquino□lines, and in line with our preceding work [17-23], the synthetic methods of those compounds have not been reviewed since 2012. 2. SYNTHETIC METHODS 2.1. From Pyrazole Derivatives In addition to being a valuable building block [24], alkyl ethers are also used as an alluring cross-dehydrogenative coupling (CDC) reaction partner in the synthesis of numerous intriguing molecules [25]. For example, the activation of sp3 C-H bonds in ethers has been widely used to build several C-C [26], C-N [27], C-S [28], and C-O [29] structures. Mu and coworker [30] was reported the *Address correspondence to this author at the Chemical Industry Research Institute, National Research Centre, Dokki, Giza, P.O. Box 12622, Egypt; E-mail: rizkkhidre@yahoo.com cyclization reaction of pyrazolyl anilines 1 with tetrahydrofuran 2to afford 3-(1H-pyrazolo[4,3-c]quinolin-4-yl)propan-1-ol derivatives 3, via the cleavage of C-O bond (Scheme 1). On the same fashion, β-diketones had shown to be effective C1 synthons for cylization processes through C-C bond cleavage. For

instance, Xie et al. reported the synthesis of pyrrolo[1,2- a]quinoxalines using β-keto esters or β-diketones [31-35]. Further more, Bao's group introduced the synthesis of benzoxazoles, benzo thiazoles, and benzimidazoles using β-diketones as a catalyst and Brønsted acid [32, 34]. Moreover, Nan and Xie have documented the cyclization of β-diketones and 2-alkenylaniline derivatives to produce 2-substituted quinoline framework [36]. Pyrazoloquino lines 5 was synthesized by the combination of compound 1 and ethyl benzoyl acetate 4 in hexafluoroisopropanol (HFIP) containing p-toluenesulfonic acid (TsOH) via cleavage of C-C bonds [37] (Scheme 2). In a similar manner, pyrazolo[4,3-c]quinolines 5 were prepared from reaction between compound 1 and (bromomethyl)benzene in DMSO containing potassium iodide [38] (Scheme 3). Additionally, pyrazoloquinolines 5 were synthesized from the reaction of compound 1 with either aryl methanol or aryl methyla mine [39] (Scheme 4). The proposed mechanism for preparation of pyrazoloquinolines 13 was shown in Scheme 5. Aldehyde A was produced via oxida tion of alcohol. Two molecules of amine eliminate NH3 to give intermediate B. Next, coupling of 1 and A/B produces intermediate C, which undergoes protonation to give the intermediate D. Then, the intramolecular cyclization of D produces intermediate E, fol lowed by oxidation to give product 5 [39]. One-pot intermolecular cyclization reaction of 6-bromo-1-