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An Efficient Synthesis of Novel Pyrazole-Based Heterocycles as Potential Antitumor Agents

Magda A. Abdallah [1], Sobhi M. Gomha [1,*], Ikhlass M. Abbas [1], Mariam S. H. Kazem [2], Seham S. Alterary [3] and Yahia N. Mabkhot [3,*]

1 Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt; mkamalh2009@yahoo.com (M.A.A.); son2karim@gmail.com (I.M.A.)
2 Department of Chemistry, Faculty of Dentistry, October University for Modern Science & Arts, Giza 12613, Egypt; mariamkazem@hotmail.com
3 Department of Chemistry, College of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia; salterary@ksu.edu.sa
* Correspondence: s.m.gomha@gmail.com (S.M.G.); yahia@ksu.edu.sa (Y.N.M.); Tel.: +20-237-400-304 (S.M.G.); +966-11-467-5898 (Y.N.M.); Fax: +20-025-685-799 (S.M.G.); +966-11-467-5992 (Y.N.M.)

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Abstract: A new series of pyrazolylpyridines was prepared by reaction of ethyl-3-acetyl-1,5-diphenyl-1*H*-pyrazole-4-carboxylate with the appropriate aldehyde, malononitrile, or ethyl acetoacetate and an excess of ammonium acetate under reflux in acetic acid. Similarly, two novel bipyridine derivatives were prepared by the above reaction using terephthaldehyde in lieu of benzaldehyde derivatives. In addition, a series of 1,2,4-triazolo[4,3-*a*]pyrimidines was synthesized by a reaction of 6-(pyrazol-3-yl)pyrimidine-2-thione with a number of hydrazonoyl chlorides in dioxane and in the presence of triethylamine. The structure of the produced compounds was established by elemental analyses and spectral methods, and the mechanisms of their formation was discussed. Furthermore, the pyrazolyl-pyridine derivatives were tested as anticancer agents and the results obtained showed that some of them revealed high activity against human hepatocellular carcinoma (HEPG2) cell lines.

Keywords: pyrazoles; pyridines; multicomponent reactions; pyrazolyl-pyridines; antitumor activity

1. Introduction

A literature survey revealed that compounds, including the pyrazole nucleus, are extensively used as a precursor for the synthesis of compounds presenting many applications, such as electrolyte additives in batteries [1], catalysis [2], photographic materials [3], agrochemicals [4], and dyes [5]. The chemical versatility of the pyrazole and its analogues has attracted interest because it allows a range of applications in the pharmaceutical industry. Many pyrazole-derived compounds are known to exhibit anticancer [6–10], antimicrobial [11,12], antiviral [13], antiparasitic [14], anti-inflammatory [15,16], antipyretic [17], analgesic [18], anticoagulant [19], and anti-obesity [20] biological activities. The pyridine nucleus is a key constituent, present in a range of bioactive compounds, occurring both synthetically and naturally with wide range of biological applications [21,22]. Among the successful examples as drug candidates possessing pyridine nuclei are streptonigrin, streptonigrone, and lavendamycin, which are described in the literature as anticancer drugs. Some pyridine derivatives were studied for their topoisomerase inhibitory activity and cytotoxicity against several human cancer cell lines for the development of novel anticancer agents. As a result, it has been reported that various pyridine derivatives, as bioisosteres of α-terthiophene (potent protein kinase C inhibitor) [23], have significant topoisomerase I and/or II inhibitory activity, and cytotoxicity against several human cancer cell lines [24–28]. Early reports on the ability of α-terpyridine to form metal complexes [29] and to