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Synthesis, structure characterization and preliminary biological evaluation of novel 5-alkyl-2-ferrocenyl-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one derivatives

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Abstract

A series of novel 5-alkyl-2-ferrocenyl-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one derivatives were synthesized by the reaction of ethyl 1-(2-bromoethyl)-3-ferrocenyl-1*H*-pyrazole-5-carboxylate with non-aromatic primary amines in one-pot procedure and characterized by ^{1}H NMR, ^{13}C NMR, IR, HRMS and X-ray diffraction analysis. The effects of all the compounds on A549 cell growth were investigated. The results showed that all compounds had almost inhibitory effects on the growth of A549 cells.

Keywords: Ferrocene; Pyrazole-fused pyrazinone; Synthesis; X-ray structure; Bioactivity; A549 cell

1. Introduction

Since the discovery of ferrocene in 1951 [1], its fascinating sandwich structure has captured the imagination of chemists, to the point of being nowadays among the most important structural motifs in organometallic chemistry, materials science, and, especially, catalysis. Recently, ferrocene and its derivatives have been attracted much more attention in the biological activities [2,3]. Incorporation of a ferrocene fragment into a molecule of an organic compound often obtained unexpected biological activity, which is rationalized as being due to their different membrane permeation properties and anomalous metabolism [4]. Furthermore, the stability and non-toxicity of the ferrocenyl moiety is of particular interest rendering such drugs compatible with other treatment [5–7]. In this sense, the integration of one or more ferrocene units into a heterocyclic ring molecule has been recognized as an attractive way to endow a novel molecule functionally [8–12].

The pyrazole unit is one of the core structures in a number of natural products. Many pyrazole derivatives are known to exhibit a wide range of biological properties such as anti-hyperglycemic, analgesic, anti-inflammatory, antipyretic, anti-bacterial, antifungal hypoglycemic, sedative-hypnotic activity, antitumor and anticoagulant activity [13–15]. The incorporation of heterocyclic rings into prospective pharmaceutical candidates is a major tactic to gain activity and safety advantages. Although much work has been directed toward the design and synthesis of fused-pyrazole derivatives [16–21], a search of the literatures revealed very few reports concerning pyrazolo-pyrazinones [22]. In the previous papers, we synthesized a series of novel pyrazole derivatives including ethyl 1-(2′-hydroxy-3′-aroxypropyl)-3-aryl-1*H*-pyrazole-5-carboxylate derivatives [23], 6-(aroxymethyl)-2-aryl-6,7-dihydropyrazolo[5,1-

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c][1,4]oxazin-4-one derivatives [24], ethyl 1-arylmethyl-3-aryl-1*H*-pyrazole-5-carboxylate derivatives [25], 1-arylmethyl-3-aryl-1*H*-pyrazole-5-carbohydrazide derivatives [26] and 1-arylmethyl-3-aryl-1*H*-pyrazole-5-carbohydrazide hydrazone derivatives [27]. The evaluation of biological activity showed that these compounds can inhibit A549 lung cancer cell growth.

One would expect that the introduction of additional ferrocenilic fragments into molecules of pyrazoles of this class will afford products possessing a broader spectrum of useful biological characteristics. In our ongoing interest in the preparation of novel pyrazole derivatives, herein, we would like to report the synthesis, structure characterization and preliminary biological evaluation of a series of novel 5-alkyl-2-ferrocenyl-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one derivatives.

2. Results and discussion

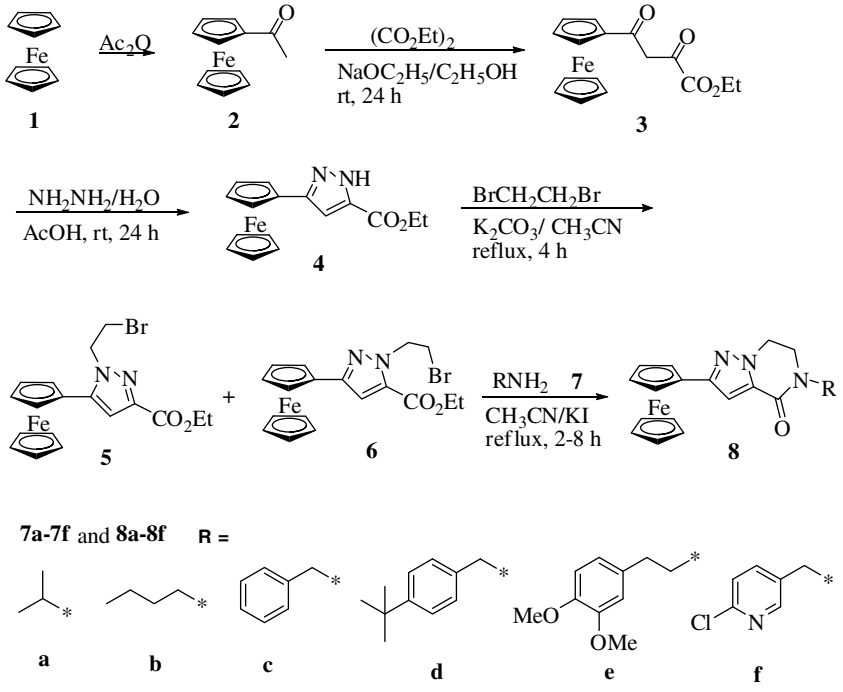
The synthetic strategies adopted to obtain the target compounds are depicted in Scheme 1. The key intermediate in the present study is the ethyl 1-(2-bromoethyl)-3-ferrocenyl-1*H*-pyrazole-5-carboxylate (**6**).

*2.1. Synthesis of ethyl 3-ferrocenyl-1H-pyrazole-5-carboxylate (**4**)*

Firstly, acetylferrocene (**2**) was prepared from ferrocene (**1**) and acetic anhydride with the catalytic phosphoric acid in 80% yield according to the known method [28]. It has proven to be successful that synthesis of ethyl 3-aryl-1*H*-pyrazole-5-carboxylate from ethyl 2,4-dioxo-4-arylbutanoate and hydrazine hydrate in the presence of acetic acid at room temperature [23]. Thus, ethyl 3-ferrocenyl-1*H*-pyrazole-5-carboxylate (**4**) was readily synthesized in 76% yield by the reaction of ethyl 2,4-dioxo-4-ferrocenylbutanoate (**3**), which can be obtained from acetylferrocene (**2**) and diethyl oxalate, with hydrazine hydrate in the presence of acetic acid at room temperature as shown in Scheme 1.

*2.2. Synthesis of ethyl 1-(2-bromoethyl)-3-ferrocenyl-1H-pyrazole-5-carboxylate (**6**)*

It is known that nitrogen atom in 1st position of a pyrazole moiety possesses nucleophilic ability to react with alkyl halide under a suitable condition [25]. The *N*-alkylation reaction between ethyl 3-ferrocenyl-1*H*-pyrazole-5-carboxylate (**4**) and excess 1,2-dibromoethane was achieved in the presence of potassium carbonate as the base in acetonitrile. After flash chromatography on silica gel, the ethyl 1-(2-bromoethyl)-3-ferrocenyl-1*H*-pyrazole-5-carboxylate (**6**) and the isomer, ethyl 1-(2-bromoethyl)-5- ferrocenyl-1*H*-pyrazole-3-carboxylate (**5**) were obtained in 57% and 25% yields, respectively (Scheme 1). It should be easily understood that owing to annular tautomerism, pyrazoles can exist in two tautomeric forms such as ethyl 3-ferrocenyl-1*H*-pyrazole-5-carboxylate (**4**) and ethyl 5-ferrocenyl-1*H*-pyrazole-3-carboxylate (**4′**) to lead two isomers of product. It should be noted that it was difficult to distinguish two isomers in general because there is a lack of specific spectroscopic data in the literature [12]. In present work, we differentiated successfully two isomers on X-ray diffraction analysis. The general view of the molecule **6** is given in Fig. 1 [29]. Thus, we can compare the chemical



Scheme 1.