RSC Advances

PAPER

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Cite this: *RSC Adv.*, 2016, **6**, 91420

Ferrocenyl based pyrazoline derivatives with vanillic core: synthesis and investigation of their biological properties†

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Vanillin *O*-alkylated derivatives and acetylferrocene reacted under Claisen–Schmidt conditions yielding the corresponding ferrocene containing chalcones in good-to-high yields. Under similar conditions, *O*-alkylated derivatives of acetovanillone were reacted with ferrocenylcarbaldehyde. Two series of novel *N*-acetyl and *N*-formyl pyrazoline derivatives were prepared by cyclocondensation of previously described chalcones (containing ferrocene framework and vanillic fragment) with hydrazine hydrate in acidic solvent (formic acid or acetic acid). All synthesized compounds were fully characterized by spectral and physical data and were tested for their biological activity. The antimicrobial activity was estimated by determination of the minimal inhibitory concentration using the broth microdilution method. The activity of the synthesized compounds was compared with standard antibiotics. The most active antibacterial compounds were 1-[5-(3,4-dimethoxyphenyl)-3-ferrocenyl-4,5-dihydro-1*H*-pyrazol-1-yl]ethanone (**4a**) and 1-[5-(4-benzyloxy-3-methoxyphenyl)-3-ferrocenyl-4,5-dihydro-1*H*-pyrazol-1-yl]ethanone (**4f**); the best antifungal activity was shown by compounds of type **4**. The interaction of **4a**, **4f**, **5a** and **5e** with DNA and bovine serum albumin (BSA) were investigated by fluorescence spectroscopic method. The results achieved in competitive experiments with ethidium bromide (EB) indicated that **4a** and **5e** have larger affinity to displace EB from the EB–DNA complex than **4f** and **5a**, probably through intercalation. Fluorescence spectroscopy data show that the fluorescence quenching of BSA is a result of the formation of the **4a**, **4f**, **5a** and **5e**–BSA complex species. Measured values of K_a showed that compounds which contain the acetovanillone-formyl core (**5a** and **5e**) formed more stable complexes with BSA than compounds with the vanillin-acetyl core (**4a** and **4f**), suggesting that **4a**– and **4f**–BSA are less suitable for drug–cell interactions.

Received 26th July 2016
Accepted 16th September 2016

DOI: 10.1039/c6ra18977f

www.rsc.org/advances

Introduction

Chalcones are an important class of organic compounds, since they often represent core structures of various natural products and pharmaceuticals. Chalcones are easily accessible compounds and can be prepared by Claisen–Schmidt condensation. Two aromatic rings (rings A and B) enables great variability of products, due to the nature of various substituents and their positions in the ring(s) which have effects on the stereochemistry and the electronic structure.[1]

This unique chalcone structure, containing a planar enone system and aromatic rings offers a bifunctional site for 1,3-dinucleophiles.[2] For this reason, chalcones exhibit a broad spectrum of various biological activities such as antifungal,[3–5] antimicrobial,[6,7] antiprotozoal,[8] anti-inflammatory,[9,10] anticonvulsant[11] or anti-cancer.[12–16]

It is well known that substitution of an aromatic nucleus of tested organic compounds with a ferrocene unit can lead to products possessing unexpected therapeutic properties,[17–19] which are absent or less manifested in the parent molecule. This fact was the main driving force in the synthesis of most known ferrocene derivatives that were designed to be derivatives of known compounds that already possess desired properties.[20,21] Ferrocenyl derivatives are among the most promising compounds which can be used in microbiological research. Water-soluble ferrocenyl derivatives are more potent as drugs than water-insoluble ones. In our previous work we reported on the synthesis of different ferrocene derivatives with expressed biological activities.[15,22–24] Ferrocene derivatives containing

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† Electronic supplementary information (ESI) available: Characterization of compounds **3–6(a–f)**, copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/c6ra18977f