

Vanillic Mannich bases: synthesis and screening of biological activity. Mechanistic insight into the reaction with 4-chloroaniline†

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One-step multi-component Mannich reaction of vanillin, aromatic amines (aniline and 4-chloroaniline), and cyclohexanone was successfully catalyzed by three chloroacetate ethanolamine based ionic liquids: diethanolammonium chloroacetate, and newly synthesized ethanolammoniumchloroacetate and *N,N*-diethylethanolammoniumchloroacetate. These reactions were performed in ethanol at room temperature. Mechanistic aspects of the reaction with 4-chloroaniline were considered by using density functional theory. The yield of obtained Mannich bases (**MB-Cl** and newly synthesized **MB-H**) was very good, while diastereoselectivity was excellent. These compounds were evaluated for their *in vitro* antioxidative activity by DPPH free radical scavenging assay. It was shown that both bases exhibit high activity against DPPH. *In vitro* cytotoxic and antioxidative effects of **MB-Cl** and **MB-H** against human breast carcinoma MDA-MB-231 and human colon carcinoma HCT-116 cell lines were also determined. The investigated Mannich bases show moderate or very weak cytotoxic effect on HCT-116 cells, while no cytotoxic effect was observed in the case of MDA-MB-231 cells. On the other hand, the tested substances induced oxidative stress in the treated cancer cell lines.

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Introduction

The Mannich-type reaction is one of the very important strategies in the production of chiral compounds. The final product of this reaction is a β -amino-carbonyl compound, also known as a Mannich base. The traditional catalysts for classical Mannich reaction of aldehydes, ketones and amines involve mainly Lewis acids,¹ Lewis bases,² Brønsted acids,³ rare metal salts,⁴ and organocatalysts.⁵ However, the usage of these catalysts has a number of serious disadvantages, such as harsh reaction conditions, toxicity and difficulty in separation of products. All these problems limit their usage, especially when it comes to the synthesis of the complex molecules. Ionic liquids proved to be a promising alternative to the conventional catalysts.⁶ They were initially introduced as alternative green reaction media, but today they play numerous roles. Ionic liquids, based on the Brønsted and Lewis acids, exhibit a great potential in replacement of conventional homogeneous and heterogeneous acidic catalysts. These substances have been successfully applied to a

variety of reactions including the Diels–Alder reaction,⁷ Mannich reaction,^{6,8} Friedel–Crafts reaction,⁹ aldol condensation,¹⁰ and esterification.¹¹

Mannich bases are structural fragments of many biologically active compounds and pharmaceutical products, such as nucleotides, peptides, alkaloids, steroid hormones, antibiotics, and vitamins.¹² These compounds show a wide range of bioactivities, such as antitubercular,¹³ antimalarial,¹⁴ vasorelaxing,¹⁵ anticancer,¹⁶ analgesic,¹⁷ anti-inflammatory,¹⁸ antifungal,¹⁹ antioxidative,²⁰ etc.

In this paper, one-pot multi-component Mannich reaction, which leads to the highly functionalized vanillin derivatives, is presented. The reaction was catalysed with chloroacetate ethanolamine based salts. As these substances are liquid at room temperature, they belong to the class of ionic liquids (ILs). To our best knowledge, there are no literature data on the mechanism of Mannich reaction catalysed with this type of ILs. In addition, cytotoxic effects of Mannich bases on cancer cells have been only little investigated. Thus, our investigation had two additional goals: to provide a mechanistic insight *via* the model reaction of vanillin, 4-chloroaniline and cyclohexanone, and to test the obtained Mannich bases for possible cytotoxic and antioxidative activities.

Results and discussion

The one-pot Mannich reactions of vanillin, aromatic amine (aniline or 4-chloroaniline), and cyclohexanone were carried out

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† Electronic supplementary information (ESI) available: Characterization of **MB-H** and **MB-Cl** (¹H, ¹³C NMR and ESI-MS spectra). See DOI: 10.1039/c4ra03909b

