

Cite this: *RSC Adv.*, 2016, 6, 39452

# Solvent-free synthesis of novel vanillidene derivatives of Meldrum's acid: biological evaluation, DNA and BSA binding study†

Nenad Janković,<sup>\*a</sup> Jovana Muškinja,<sup>a</sup> Zoran Ratković,<sup>a</sup> Zorica Bugarčić,<sup>a</sup> Branislav Ranković,<sup>b</sup> Marijana Kosanić<sup>b</sup> and Srđan Stefanović<sup>c</sup>

A series of novel *O*-alkyl vanillidene derivatives containing Meldrum's acid scaffold under solvent-free conditions were synthesized. The antimicrobial activity was estimated by determination of the minimal inhibitory concentration (MIC) using the broth microdilution. The most active compounds were 5-(4'-hydroxy-2'-iodo-3'-methoxybenzylidenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3a**), 5-(4'-acetoxy-3'-methoxybenzylidenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3f**), and 5-(4'-bromopropoxy-3'-methoxybenzylidenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3h**) with the MIC values ranging from 0.039 to 10 mg mL<sup>-1</sup>. Antioxidant activity was evaluated by DPPH free radical scavenging activity. **3h** showed the largest scavenging activity with an IC<sub>50</sub> value of 55.61 µg mL<sup>-1</sup> (0.14 mmol L<sup>-1</sup>). The interaction of **3a** and **3h** with DNA and bovine serum albumin (BSA) were investigated by the fluorescence spectroscopic method. The results achieved in competitive experiments with ethidium bromide (EB) indicated that **3a** and **3h** have an affinity to displace EB from the EB–DNA complex through intercalation. Fluorescence spectroscopy data show that the fluorescence quenching of BSA is a result of the formation of the **3a**- and **3h**-BSA complex species, and indicate that **3a**-BSA is more stable, suggesting that **3h**-BSA is less suitable for drug–cell interactions.

Received 24th March 2016  
Accepted 12th April 2016

DOI: 10.1039/c6ra07711k

[www.rsc.org/advances](http://www.rsc.org/advances)

## Introduction

Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione; isopropylidene-malonate) was prepared by A. N. Meldrum in 1908, in a reaction between acetone, malonic acid and acetic anhydride.<sup>1</sup> This acid is distinguished from other 1,3-dicarbonyl compounds in two main ways: first, it is extremely acidic, and second, it is highly electrophilic.<sup>2</sup> In light of this, reactions with Meldrum's acid provide easy and rapid access to various libraries of organic compounds with diverse substitution patterns, which allows for the formation of several new carbon–carbon and carbon–heteroatom bonds.<sup>3</sup>

One of the most important carbon–carbon bond formations in organic synthesis is the Knoevenagel condensation, which has been widely used in synthesis of alkenes of biological significance.<sup>4–8</sup> The Knoevenagel condensation of Meldrum's acid and aldehydes has been used for preparation of arylidene

analogues of Meldrum's acid. These compounds exhibit different biopotentials, such as antimalarial and antioxidant activities.<sup>9</sup> Also, arylidene analogues of Meldrum's acid have been reported as the key precursors in cycloaddition reactions,<sup>10</sup> for synthesis of mono alkyl Meldrum's acid derivatives,<sup>11</sup> epoxides,<sup>12</sup> deuterium labelled carboxylic acids,<sup>13</sup> oxopyridines,<sup>14</sup> pyridines,<sup>15</sup> lactones,<sup>16</sup>  $\beta$ -aryl aldehydes,<sup>17</sup> and for the synthesis of heterocyclic compounds of biological importance such as cardiotonic<sup>18</sup> and HIV integrase inhibitory activities.<sup>19</sup>

Bearing in mind the mentioned facts, there is a reasonable tendency to synthesize a novel Meldrum's acid derivatives.

Various catalysts have been used for synthesis of arylidene analogues of Meldrum's acid, such as *L*-tyrosine,<sup>20</sup> SbCl<sub>3</sub>,<sup>21</sup> gel-entrapped KOH,<sup>22</sup> ionic liquids,<sup>23</sup> K<sub>3</sub>PO<sub>4</sub>,<sup>24</sup> pyrrolidinium acetate,<sup>25</sup> morpholine/acetic acid,<sup>26</sup> (*R*)-methyl 3-phenyl-2-(3-(pyridin-2-yl)ureido)propanoate,<sup>27</sup> Zr(O<sub>3</sub>POK)<sub>2</sub>,<sup>28</sup> and NAP (3-aminopropylated silica gel).<sup>29</sup> However, the usage of these catalysts is characterized with different undesirable effects, such as complicated procedures for catalysts preparation, difficulty to isolate, the application of harmful solvents and special apparatus<sup>30</sup> (e.g., microwave irradiation), etc.

Development of green chemical methods is one of the very important purposes of organic synthesis. Reactions in the absence of solvents (solvent-free) present very powerful and green methodology for the construction of structurally different

<sup>a</sup>Faculty of Science, University of Kragujevac, Department of Chemistry, Radoja Domanovića 12, 34000 Kragujevac, Serbia. E-mail: nenad.jankovic@kg.ac.rs

<sup>b</sup>Faculty of Science, University of Kragujevac, Department of Biology and Ecology, Radoja Domanovića 12, 34000 Kragujevac, Serbia

<sup>c</sup>Institute of Meat Hygiene and Technology, Kačanskog 13, 11000 Belgrade, Serbia

† Electronic supplementary information (ESI) available: Characterization of compounds **3a–j**, copies of <sup>1</sup>H and <sup>13</sup>C NMR spectrums. See DOI: 10.1039/c6ra07711k













