

## Facile Synthesis and Biological Evaluation of Substituted 5-(1*H*-Indol-3-ylmethylene)pyrimidine-2,4,6-trione Derivatives Using L-Tyrosine in Aqueous Medium

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L-Tyrosine as an efficient catalyst for the Knoevenagel condensation of substituted indole-3-aldehydes **1(a-d)**, N-methyl indole-3-aldehydes **4(a-d)**, N-ethyl indole-3-aldehydes **6(a-d)** with barbituric acid (**2**) containing cyclic active methylene group to produce **3(a-d)**, **5(a-d)** and **7(a-d)**, respectively in water at room temperature for 10 min. The antimicrobial activities of **3(a-d)**, **5(a-d)** and **7(a-d)** have been studied.

**Key Words:** Antibacterial activities, Antifungal activities, Indole-3-aldehyde, Barbituric acid, L-Tyrosine, Knoevenagel reaction.

### INTRODUCTION

Carbon-carbon bond formation reaction is the most important reaction in organic synthesis<sup>1-4</sup>. The Knoevenagel condensation is one such reactions which facilitates C-C double bond formation and has been widely used in synthesis of alkenes of biological significance<sup>5-9</sup>. These reactions are usually catalyzed by bases<sup>10-17</sup> such as ethylenediamine, potassium fluoroiodide, primary, secondary amines and their corresponding ammonium salts, Lewis acids<sup>18-20</sup>, zeolite<sup>21-23</sup> and ionic liquids<sup>24-27</sup> have also been added to the existing list of substances that assisted Knoevenagel condensation in organic synthesis.

Knoevenagel condensation of meldrum's acid and aldehydes gives rise to substrates for variety of reactions<sup>28</sup>. They are used in cycloaddition reactions<sup>29</sup>, 1,4-conjugate addition reactions and preparation of mono alkyl meldrum's acid derivatives, preparation of deuterated carboxylic acid derivatives. These derivatives are also used in the preparation of ketenes by  $\alpha,\beta$ -pyrolysis, which are then used for preparation of different compounds such as cyclobutadiene derivatives<sup>30</sup>,  $\alpha,\beta$ -unsaturated esters<sup>31</sup> and  $\alpha,\beta$ -unsaturated amides<sup>32-33</sup>.

Jones *et al.*<sup>34</sup> reported the reaction of meldrum's acid with indole-3-carboxaldehyde under flash-vacuum pyrolysis to yield the Knoevenagel derivative of 5-[(1*H*-indol-3-yl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione with 61 % yield. This method is more time-consuming and not so good for the preparation of large amounts of these products. Moreover, it is a very good intermediate for the preparation of anticancer drug<sup>38</sup>.

L-Tyrosine is known to be an efficient, bi-functional, zwitter ionic and eco-friendly catalyst. It is available in both the enantiomeric, (S)-tyrosine and (R)-tyrosine forms. The two functional groups of tyrosine enable it to act both as an acid as well as a base catalyst in chemical condensation reactions.

### EXPERIMENTAL

Melting points were measured in open capillary tubes and are uncorrected. TLC was done on plates coated with silica gel-G and spotting was done using iodine or UV lamp. IR spectra were recorded using FT-IR in KBr phase. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at 400 MHz, respectively.

**General procedure for the preparation of 3 from 1:** A mixture of **1** (10 mmol), barbituric acid **2** (10 mmol) and L-tyrosine (2 mmol) and water (25 mL) was stirred at room temperature for a specified period of time (Table-1). After completion of reaction (as shown by TLC checking), the mixture was poured into ice cold water (50 mL). The separated solid was filtered, washed with water (100 mL) and dried to obtain crude product **3**. The latter were then recrystallized from ethyl acetate to afford pure compound **3**. Compounds are known and products were identified by spectral and melting-point comparison with the authentic samples.

**General procedure for the preparation of 5 from 3:** A mixture of compound **3** (10 mmol), DMS (10 mmol) and Na<sub>2</sub>CO<sub>3</sub> was physically ground in solvent free condition under grindstone method at room temperature for a specified period of time (Table-1). After completion of reaction (as shown by TLC checking), the mixture was poured into ice-cold water

(50 mL). The separated solid was filtered, washed with water (100 mL) and dried to obtain crude **5**. The latter were then recrystallised from ethyl acetate to afford pure **5**. Compounds are known and products were identified by spectral and melting-point comparison with the authentic samples.

**General procedure for the preparation of 7 from 3:** A mixture of compound **3** (10 mmol), DES (10 mmol) and  $\text{Na}_2\text{CO}_3$  was physical grinded in solvent free condition under grindstone method at room temperature for a specified period of time (Table-1). After completion of reaction (as shown by TLC checking), the mixture was poured into ice-cold water (50 mL). The separated solid was filtered, washed with water (100 mL) and dried to obtain crude compound **7**. The latter were then recrystallised from ethyl acetate to afford pure compound **7**. Compounds are known and products were identified by spectral and melting-point comparison with the authentic samples.

**5-(1*H*-Indol-3-ylmethylene)-pyrimidine-2,4,6-trione (3a):** Yellow solid; yield = 2.448 g (96 %); m.p. 251-253 °C; IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3210 (NH-indole), 3040 (aromatic C-H), 1685 (C=O), 1674 (N-CO-N); 1620 (C=C).  $^1\text{H}$  NMR (DMSO- $d_6$ /TMS):  $\delta$  7.31-7.62 (m, 4H, aryl protons of the indole ring), 7.84 (s, 1H,  $\alpha$ -proton of the indole ring), 8.32-8.45 (s, 1H, vinylic proton of the indole ring), 9.85-9.96 (br, s, 1H, NH proton of indole ring); 11.15-11 (brs, s, 2H, NH barbituric).  $^{13}\text{C}$  spectrum (DMSO- $d_6$ /TMS):  $\delta$  113.01, 117.74, 122.6, 123.6, 131.5, 140.4, 141.5, 144.95, 163.6 (C=O), 171.31 (N-CO-N); MS:  $m/z$  = 256.23 ( $M + 1$ ).

**5-(5-Methoxy-1*H*-indol-3-ylmethylene)-pyrimidine-2,4,6-trione (3b):** Yellow solid; yield = 2.70 g (95 %); m.p. 243-245 °C; IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3210 (NH-indole), 3040 (aromatic C-H), 1685 (C=O), 1674 (N-CO-N); 1620 (C=C).  $^1\text{H}$  NMR (DMSO- $d_6$ /TMS):  $\delta$  3.83 (s, 3H,  $\text{OCH}_3$ ), 7.31-7.62 (m, 4H, aryl protons of the indole ring), 7.84 (s, 1H,  $\alpha$ -proton of the indole ring), 8.32-8.45 (s, 1H, vinylic proton of the indole ring), 9.85-9.96 (br, s, 1H, NH proton of indole ring); 11.15-11 (brs, s, 2H, NH-barbituric).  $^{13}\text{C}$  spectrum (DMSO- $d_6$ /TMS):  $\delta$  54.21, 113.01, 117.74, 122.6, 123.6, 131.5, 140.4, 141.5, 144.95, 163.6 (C=O), 171.31 (N-CO-N); MS:  $m/z$  = 286.25 ( $M + 1$ ).

**5-(5-Bromo-1*H*-indol-3-ylmethylene)-pyrimidine-2,4,6-trione (3c):** Yellow solid; yield = 3.06 g (96 %); m.p. 281-282 °C; IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3210 (NH-indole), 3040 (aromatic C-H), 1685 (C=O), 1674 (N-CO-N); 1620 (C=C).  $^1\text{H}$  NMR (DMSO- $d_6$ /TMS):  $\delta$  7.31-7.62 (m, 4H, aryl protons of the indole ring), 7.84 (s, 1H,  $\alpha$ -proton of the indole ring), 8.32-8.45 (s, 1H, vinylic proton of the indole ring), 9.85-9.96 (br, s, 1H, NH proton of indole ring); 11.15-11 (brs, s, 2H, NH-barbituric).  $^{13}\text{C}$  spectrum (DMSO- $d_6$ /TMS):  $\delta$  113.01, 117.74, 122.6, 123.6, 131.5, 140.4, 141.5, 144.95, 163.6 (C=O), 171.31 (N-CO-N); MS:  $m/z$  = 320.11 ( $M + 1$ ).

**5-(5-Nitro-1*H*-indol-3-ylmethylene)-pyrimidine-2,4,6-trione (3d):** Yellow solid; yield = 2.88 g (96 %); m.p. 262-263 °C; IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3210 (NH-indole), 3040 (aromatic C-H), 1685 (C=O), 1674 (N-CO-N); 1620 (C=C).  $^1\text{H}$  NMR (DMSO- $d_6$ /TMS):  $\delta$  7.31-7.62 (m, 4H, aryl protons of the indole ring), 7.84 (s, 1H,  $\alpha$ -proton of the indole ring), 8.32-8.45 (s, 1H, vinylic proton of the indole ring), 9.85-9.96 (br,

s, 1H, NH proton of indole ring); 11.15-11 (brs, s, 2H, NH-barbituric).  $^{13}\text{C}$  spectrum (DMSO- $d_6$ /TMS):  $\delta$  113.01, 117.74, 122.6, 123.6, 131.5, 140.4, 141.5, 144.95, 163.6 (C=O), 171.31 (N-CO-N); MS:  $m/z$  = 301.23 ( $M + 1$ ).

**5-(1-Methyl-1*H*-indol-3-ylmethylene)-pyrimidine-2,4,6-trione (5a):** Yellow solid; yield = 2.52 g (94 %); m.p. 247-249 °C; IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3210 (NH-indole), 3040 (aromatic C-H), 1685 (C=O), 1674 (N-CO-N); 1620 (C=C).  $^1\text{H}$  NMR (DMSO- $d_6$ /TMS):  $\delta$  4.01 (s, 3H, N  $\text{CH}_3$ ), 7.31-7.62 (m, 4H, aryl protons of the indole ring), 7.84 (s, 1H,  $\alpha$ -proton of the indole ring), 8.32-8.45 (s, 1H, vinylic proton of the indole ring), 9.85-9.96 (br, s, 1H, NH proton of indole ring); 11.15-11 (brs, s, 2H, NH-barbituric).  $^{13}\text{C}$  spectrum (DMSO- $d_6$ /TMS):  $\delta$  34.02 (N- $\text{CH}_3$ ), 113.01, 117.74, 122.6, 123.6, 131.5, 140.4, 141.5, 144.95, 163.6 (C=O), 171.31 (N-CO-N); MS:  $m/z$  = 270.26 ( $M + 1$ ).

**5-(5-Methoxy-1-methyl-1*H*-indol-3-ylmethylene)-pyrimidine-2,4,6-trione (5b):** Yellow solid; yield = 2.78 g (93 %); m.p. 241-243 °C; IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3210 (NH-indole), 3040 (aromatic C-H), 1685 (C=O), 1674 (N-CO-N); 1620 (C=C).  $^1\text{H}$  NMR (DMSO- $d_6$ /TMS):  $\delta$  4.01 (s, 3H, N  $\text{CH}_3$ ), 3.45 (s, 3H,  $-\text{OCH}_3$ ), 7.31-7.62 (m, 4H, aryl protons of the indole ring), 7.84 (s, 1H,  $\alpha$ -proton of the indole ring), 8.32-8.45 (s, 1H, vinylic proton of the indole ring), 9.85-9.96 (br, s, 1H, NH proton of indole ring); 11.15-11 (brs, s, 2H, NH-barbituric).  $^{13}\text{C}$  spectrum (DMSO- $d_6$ /TMS):  $\delta$  34.02 (N- $\text{CH}_3$ ), 53.11, 113.01, 117.74, 122.6, 123.6, 131.5, 140.4, 141.5, 144.95, 163.6 (C=O), 171.31 (N-CO-N); MS:  $m/z$  = 300.28 ( $M + 1$ ).

**5-(5-Bromo-1-methyl-1*H*-indol-3-ylmethylene)-pyrimidine-2,4,6-trione (5c):** Yellow solid; yield = 3.27 g (94 %); m.p. 265-266 °C; IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3210 (NH-indole), 3040 (aromatic C-H), 1685 (C=O), 1674 (N-CO-N); 1620 (C=C).  $^1\text{H}$  NMR (DMSO- $d_6$ /TMS):  $\delta$  4.01 (s, 3H, N  $\text{CH}_3$ ), 7.31-7.62 (m, 4H, aryl protons of the indole ring), 7.84 (s, 1H,  $\alpha$ -proton of the indole ring), 8.32-8.45 (s, 1H, vinylic proton of the indole ring), 9.85-9.96 (br, s, 1H, NH proton of indole ring); 11.15-11 (brs, s, 2H, NH-barbituric).  $^{13}\text{C}$  spectrum (DMSO- $d_6$ /TMS):  $\delta$  34.02 (N- $\text{CH}_3$ ), 113.01, 117.74, 122.6, 123.6, 131.5, 140.4, 141.5, 144.95, 163.6 (C=O), 171.31 (N-CO-N); MS:  $m/z$  = 349.15 ( $M + 1$ ).

**5-(1-Methyl-5-nitro-1*H*-indol-3-ylmethylene)-pyrimidine-2,4,6-trione (5d):** Yellow solid; yield = 2.95 g (94 %); m.p. 254-257 °C; IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3210 (NH-indole), 3040 (aromatic C-H), 1685 (C=O), 1674 (N-CO-N); 1620 (C=C).  $^1\text{H}$  NMR (DMSO- $d_6$ /TMS):  $\delta$  4.01 (s, 3H, N  $\text{CH}_3$ ), 7.31-7.62 (m, 4H, aryl protons of the indole ring), 7.84 (s, 1H,  $\alpha$ -proton of the indole ring), 8.32-8.45 (s, 1H, vinylic proton of the indole ring), 9.85-9.96 (br, s, 1H, NH proton of indole ring); 11.15-11 (brs, s, 2H, NH-barbituric).  $^{13}\text{C}$  spectrum (DMSO- $d_6$ /TMS):  $\delta$  34.02 (N- $\text{CH}_3$ ), 113.01, 117.74, 122.6, 123.6, 131.5, 140.4, 141.5, 144.95, 163.6 (C=O), 171.31 (N-CO-N); MS:  $m/z$  = 315.25 ( $M + 1$ ).

**5-(1-Ethyl-1*H*-indol-3-ylmethylene)-pyrimidine-2,4,6-trione (7a):** Yellow solid; yield = 2.66 g (94 %); m.p. 243-245 °C; IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3210 (NH-indole), 3040 (aromatic C-H), 1685 (C=O), 1674 (N-CO-N); 1620 (C=C).  $^1\text{H}$  NMR (DMSO- $d_6$ /TMS):  $\delta$  1.53 (t, 3H,  $\text{CH}_3$ ), 4.03 (q, 2H,

CH<sub>2</sub>), 7.31-7.62 (m, 4H, aryl protons of the indole ring), 7.84 (s, 1H,  $\alpha$ -proton of the indole ring), 8.32-8.45 (s, 1H, vinylic proton of the indole ring), 9.85-9.96 (br, s, 1H, NH proton of indole ring); 11.15-11 (brs, s, 2H, NH-barbituric). <sup>13</sup>C spectrum (DMSO-*d*<sub>6</sub>/TMS):  $\delta$  36.5, 47.9, 113.01, 117.74, 122.6, 123.6, 131.5, 140.4, 141.5, 144.95, 163.6 (C=O), 171.31 (N-CO-N); MS: *m/z* = 284.28 (M + 1).

**5-(1-Ethyl-5-methoxy-1*H*-indol-3-ylmethylene)-pyrimidine-2,4,6-trione (7b):** Yellow solid; yield = 2.91 g (93 %); m.p. 240-241 °C; IR (KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3210 (NH-indole), 3040 (aromatic C-H), 1685 (C=O), 1674 (N-CO-N); 1620 (C=C). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>/TMS):  $\delta$  1.54 (t, 3H, CH<sub>3</sub>), 3.62 (s, 3H, OCH<sub>3</sub>), 4.15 (q, 2H, CH<sub>2</sub>), 7.31-7.62 (m, 4H, aryl protons of the indole ring), 7.84 (s, 1H,  $\alpha$ -proton of the indole ring), 8.32-8.45 (s, 1H, vinylic proton of the indole ring), 9.85-9.96 (br, s, 1H, NH proton of indole ring); 11.15-11 (brs, s, 2H, NH-barbituric). <sup>13</sup>C spectrum (DMSO-*d*<sub>6</sub>/TMS):  $\delta$  36.5, 47.9, 56.5, 113.01, 117.74, 122.6, 123.6, 131.5, 140.4, 141.5, 144.95, 163.6 (C=O), 171.31 (N-CO-N); MS: *m/z* = 314.31 (M + 1).

**5-(5-Bromo-1-ethyl-1*H*-indol-3-ylmethylene)-pyrimidine-2,4,6-trione (7c):** Yellow solid; yield = 3.40 g (94 %); m.p. 261-262 °C; IR (KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3210 (NH-indole), 3040 (aromatic C-H), 1685 (C=O), 1674 (N-CO-N); 1620 (C=C). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>/TMS):  $\delta$  1.51 (t, 3H, CH<sub>3</sub>), 4.23 (q, 2H, CH<sub>2</sub>), 7.31-7.62 (m, 4H, aryl protons of the indole ring), 7.84 (s, 1H,  $\alpha$ -proton of the indole ring), 8.32-8.45 (s, 1H, vinylic proton of the indole ring), 9.85-9.96 (br, s, 1H, NH proton of indole ring); 11.15-11 (brs, s, 2H, NH-barbituric). <sup>13</sup>C spectrum (DMSO-*d*<sub>6</sub>/TMS):  $\delta$  36.5, 47.9, 113.01, 117.74, 122.6, 123.6, 131.5, 140.4, 141.5, 144.95, 163.6 (C=O), 171.31 (N-CO-N); MS: *m/z* = 363.18 (M + 1).

**5-(1-Ethyl-5-nitro-1*H*-indol-3-ylmethylene)-pyrimidine-2,4,6-trione (7d):** Yellow solid; yield = 3.08 g (94 %); m.p. 252-253 °C; IR (KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3210 (NH-indole), 3040 (aromatic C-H), 1685 (C=O), 1674 (N-CO-N); 1620 (C=C). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>/TMS):  $\delta$  1.56 (t, 3H, CH<sub>3</sub>), 4.65 (q, 2H, N CH<sub>2</sub>), 7.31-7.62 (m, 4H, aryl protons of the indole ring), 7.84 (s, 1H,  $\alpha$ -proton of the indole ring), 8.32-8.45 (s, 1H, vinylic proton of the indole ring), 9.85-9.96 (br, s, 1H, NH proton of indole ring); 11.15-11 (brs, s, 2H, NH-barbituric). <sup>13</sup>C spectrum (DMSO-*d*<sub>6</sub>/TMS):  $\delta$  36.5, 47.9, 113.01, 117.74, 122.6, 123.6, 131.5, 140.4, 141.5, 144.95, 163.6 (C=O), 171.31 (N-CO-N); MS: *m/z* = 329.28 (M + 1).

## RESULTS AND DISCUSSION

Treatment of substituted indole-3-carboxaldehydes **1(a-d)** and its N-methyl derivative **4(a-d)**, N-ethyl derivative **6(a-d)**, each with barbituric acid containing cyclic active methylene group (**2**) in water at room temperature for 10 min resulted corresponding Knoevenagel products **3(a-d)**, **5(a-d)** and **7(a-d)** in excellent yields (**93-96 %**) (**Scheme-I**) (Table-1). L-Tyrosine as an eco-friendly and efficient catalyst to induce the reaction. Structures of all the products have been assigned based on spectral and analytical data.

In the absence of L-tyrosine, the reaction did not proceed even after refluxing the reactants in water for 20 h. The use of L-tyrosine as a catalyst helps to complete the reaction in 10

min. Thus, L-tyrosine has been found to be efficient and eco-friendly catalyst for the Knoevenagel condensation reaction of indole-3-carboxaldehyde (**1**) and its N-methyl derivative **4(a-d)**, N-ethyl derivative **6(a-d)**, each with barbituric acid containing cyclic active methylene group (**2**). The use of L-tyrosine as a catalyst helps to avoid the use of environmentally unfavourable organic solvents as reaction medium.

The above reactions of **1(a-d)**, **4(a-d)** and **6(a-d)** with barbituric acid were attempted in the presence of various amino acids like valine, glycine, alanine and Lysine but, there was not much progress in the reactions as seen by TLC examination of crude reaction mixtures. In the presence of phenyl alanine in water at room temperature, there was a little bit of progress, but the reaction was not completed for 16 h.

The above reactions of substituted indole-3-aldehydes **1(a-d)**, **4(a-d)** and **6(a-d)** with barbituric acid containing cyclic active methylene group were attempted in the presence of L-proline and L-tryptophan low yields were obtained for 1 h in water at room temperature.

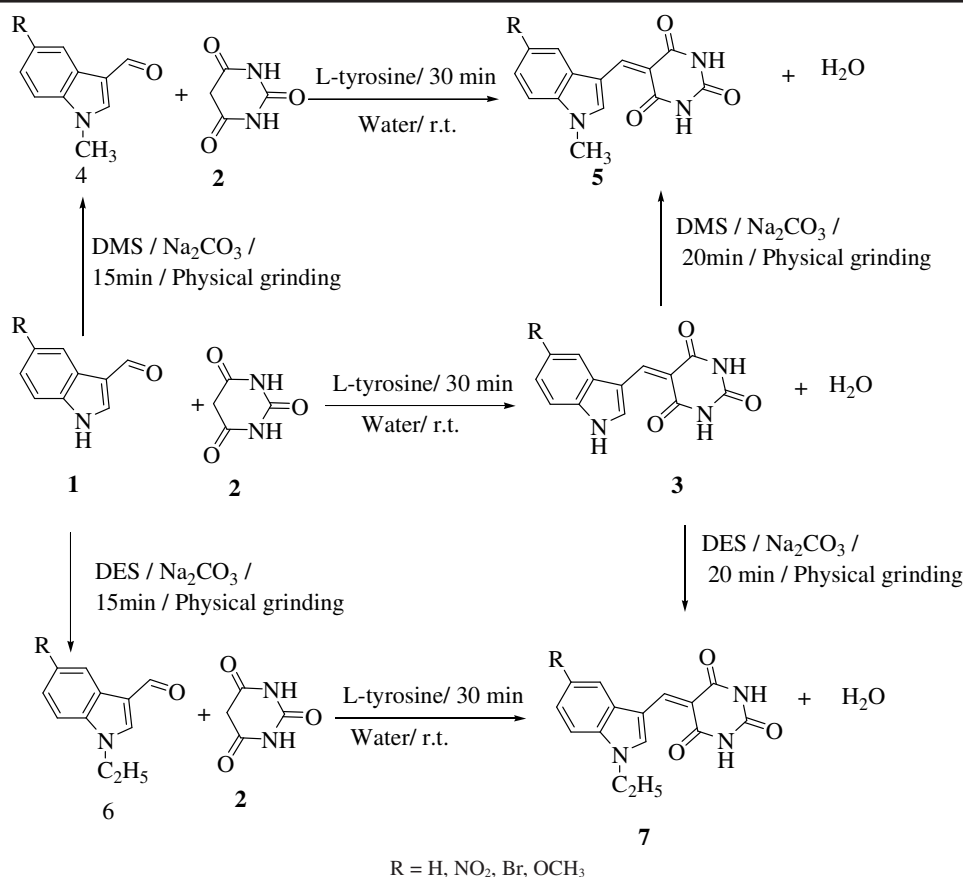
Treatment of substituted indole-3-carboxaldehydes **1(a-d)** and its N-methyl derivative **4(a-d)**, N-ethyl derivative **6(a-d)**, each with barbituric acid containing cyclic active methylene group (**2**) were attempted in the presence of various bases like NaOH, KOH were too strong bases to result in more by-products. Low yield was obtained and 5 h reaction time is needed using K<sub>2</sub>CO<sub>3</sub>, ammonium acetate, piperidine and triethylamine as catalyst for condensation of substituted indole-3-aldehydes **1(a-d)**, **4(a-d)** and **6(a-d)** with barbituric acids containing cyclic active methylene group (**2**) in water at room temperature.

**Table-1** showed that the condensation of substituted indole-3-aldehydes **1(a-d)**, **4(a-d)** and **6(a-d)** with electron withdrawing group such as -NO<sub>2</sub> and -Br at 5th position with barbituric acid containing cyclic active methylene compounds can be carried out in relatively shorter time and higher yield than with electron donating group such as -OCH<sub>3</sub> in water at room temperature.

This method was very facile and convenient for the preparation of large amounts of Knoevenagel adducts with high yields in less time. L-Tyrosine acted as base to induce the reaction. The use of L-tyrosine as a catalyst helps to avoid the use of environmentally unfavorable organic solvents (DMF, C<sub>6</sub>H<sub>6</sub>, DMSO, CHCl<sub>3</sub>, CH<sub>3</sub>CN, *etc.*) as the reaction medium. The L-tyrosine was readily reactive in water at room temperature compared to solvents such as methanol, ethanol, DMF, C<sub>6</sub>H<sub>6</sub>, *etc.*; that is why the yield was also very high when the reaction was carried out in water at room temperature.

In some cases, yields were very high when the nucleophile was very active such as 5-nitroindole-3-carboxaldehyde, N-methyl-5-nitroindole-3-carboxaldehyde and N-ethyl-5-nitroindole-3-carboxaldehyde.

However, 5-methoxy indole-3-carboxaldehyde, N-methyl-5-methoxyindole-3-carboxaldehyde, N-ethyl-5-methoxyindole-3-carboxaldehyde, 5-bromoindole-3-carboxaldehyde, N-methyl-5-bromo indole-3-carboxaldehyde, N-ethyl-5-bromoindole-3-carboxaldehyde under went condensation very easily with barbituric acid in the presence of L-tyrosine in water at room temperature.



**Scheme-I:** Knoevenagel condensation of indole-3-aldehyde with barbituric acid in the presence of L-tyrosine in water at room temperature

TABLE-1  
SYNTHESIS OF NOVEL KNOEVENAGEL PRODUCTS BY USING L-TYROSINE  
AS ECO-FRIENDLY CATALYST IN WATER AT ROOM TEMPERATURE

| S. No. | Reactants                      |     | Product                        | Time (min) | Yield (%) | m.p. (°C) |
|--------|--------------------------------|-----|--------------------------------|------------|-----------|-----------|
| 1      | <b>1a</b> (R=H)                | 2   | <b>3a</b> (R=H)                | 10         | 96        | 251-253   |
| 2      | <b>1b</b> (R=OMe)              | 2   | <b>3b</b> (R=OMe)              | 12         | 95        | 243-245   |
| 3      | <b>1c</b> (R=Br)               | 2   | <b>3c</b> (R=Br)               | 9          | 96        | 281-282   |
| 4      | <b>1d</b> (R=NO <sub>2</sub> ) | 2   | <b>3d</b> (R=NO <sub>2</sub> ) | 9          | 96        | 262-264   |
| 5      | <b>4a</b> (R=H)                | 2   | <b>5a</b> (R=H)                | 11         | 94        | 247-249   |
| 6      | <b>4b</b> (R=OMe)              | 2   | <b>5b</b> (R=OMe)              | 14         | 93        | 240-243   |
| 7      | <b>4c</b> (R=Br)               | 2   | <b>5c</b> (R=Br)               | 13         | 94        | 265-266   |
| 8      | <b>4d</b> (R=NO <sub>2</sub> ) | 2   | <b>5d</b> (R=NO <sub>2</sub> ) | 13         | 94        | 254-257   |
| 9      | <b>6a</b> (R=H)                | 2   | <b>7a</b> (R=H)                | 11         | 94        | 243-245   |
| 10     | <b>6b</b> (R=OMe)              | 2   | <b>7b</b> (R=OMe)              | 14         | 93        | 240-242   |
| 11     | <b>6c</b> (R=Br)               | 2   | <b>7c</b> (R=Br)               | 13         | 94        | 261-262   |
| 12     | <b>6d</b> (R=NO <sub>2</sub> ) | 2   | <b>7d</b> (R=NO <sub>2</sub> ) | 13         | 94        | 252-253   |
| 13     | <b>3a</b> (R=H)                | DMS | <b>5a</b> (R=H)                | 20         | 94        | 247-249   |
| 14     | <b>3b</b> (R=OMe)              | DMS | <b>5b</b> (R=OMe)              | 23         | 93        | 240-243   |
| 15     | <b>3c</b> (R=Br)               | DMS | <b>5c</b> (R=Br)               | 21         | 94        | 265-266   |
| 16     | <b>3d</b> (R=NO <sub>2</sub> ) | DMS | <b>5d</b> (R=NO <sub>2</sub> ) | 20         | 94        | 254-257   |
| 17     | <b>3a</b> (R=H)                | DES | <b>7a</b> (R=H)                | 20         | 94        | 243-245   |
| 18     | <b>3b</b> (R=OMe)              | DES | <b>7b</b> (R=OMe)              | 23         | 93        | 240-242   |
| 19     | <b>3c</b> (R=Br)               | DES | <b>7c</b> (R=Br)               | 21         | 94        | 261-262   |
| 20     | <b>3d</b> (R=NO <sub>2</sub> ) | DES | <b>7d</b> (R=NO <sub>2</sub> ) | 20         | 94        | 252-253   |

Treatment of **3(a-d)** independently with DMS and DES each, in the presence of Na<sub>2</sub>CO<sub>3</sub> as base in solvent free condition under grindstone method at room temperature for 1 h resulted corresponding **5(a-d)** and **7(a-d)**, respectively in excellent yields 93-94 % (**Scheme-I**). The compounds **5(a-d)** and **7(a-d)** could also be synthesized in an alternative manner. The compounds **4(a-d)** and **6(a-d)** were obtained from **1(a-d)**

by alkylation with DMS and DES each, in the presence of Na<sub>2</sub>CO<sub>3</sub> as base in solvent free condition under grindstone method at room temperature.

A comparative study of the progress of condensation reactions **1(a-d)**, **4(a-d)** and **6(a-d)** with **2** were carried out in different solvents containing along with L-tyrosine as catalyst and is summarized in Table-2.



TABLE-2  
PROGRESS OF REACTION IN DIFFERENT SOLVENT MEDIA

| Entry | Solvent                       | Time (h) | Temp. (°C)         | Yield (%) |
|-------|-------------------------------|----------|--------------------|-----------|
| 1     | L-Tyrosine/water              | 1        | r.t.               | 93-96     |
| 2     | L-Tyrosine/EtOH               | 2-5      | r.t.               | 72-76     |
| 3     | L-Tyrosine/benzene            | 8        | r.t.               | 44-46     |
| 4     | L-Tyrosine/DMSO               | 10       | r.t.               | 38-40     |
| 5     | Without catalyst in water     | 24       | r.t./reflux at 100 | Nil       |
| 6     | L-Tyrosine/DMF                | 7        | r.t.               | 28-30     |
| 7     | L-Tyrosine/CH <sub>3</sub> CN | 12       | r.t.               | 19-21     |
| 8     | L-Tyrosine/CHCl <sub>3</sub>  | 18       | r.t.               | Nil       |

A plausible mechanism for the formation of **3** from **1** and **2** in the presence of L-tyrosine as catalyst is shown in the **Scheme-II**. The reaction mechanism is supported by literature reference.

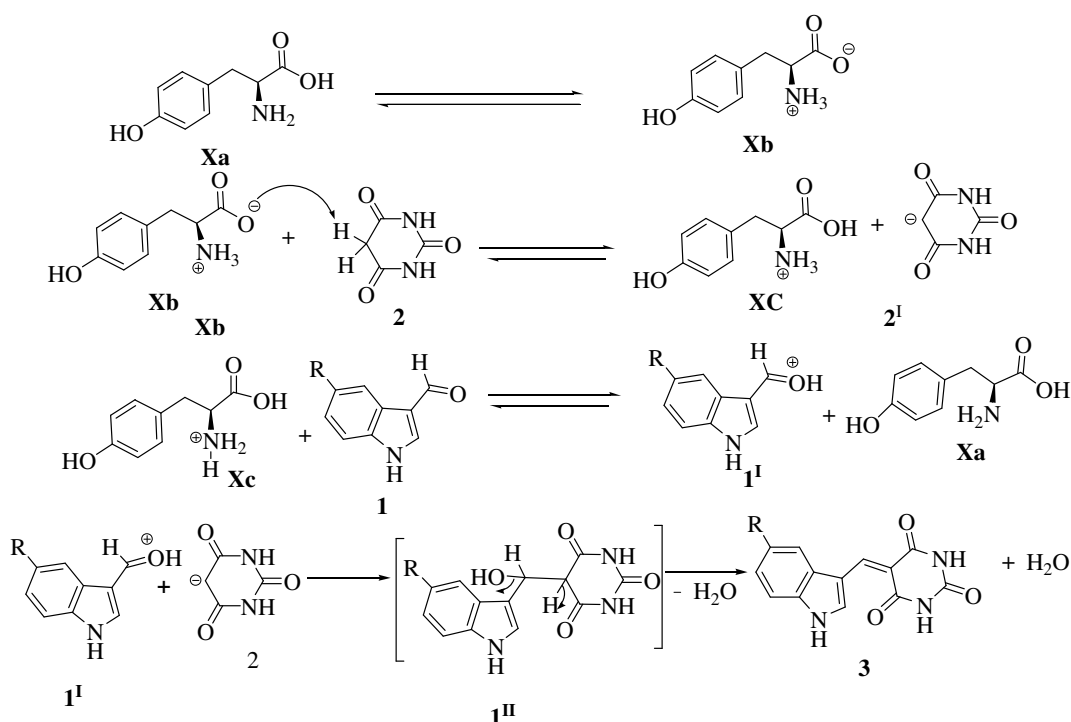
In the mechanism shown in **Scheme-II**, L-tyrosine, in its zwitter ionic form (**Xb**), abstracts a proton from barbituric acid containing cyclic active methylene group (**2**) forming the carbanion of barbituric acid (**2<sup>I</sup>**) which then attacks the protonated indole-3-aldehydes (**1<sup>I</sup>**) forming the corresponding intermediate (**1<sup>II</sup>**) that loses water to form the end product **3**.

#### Biological evaluation

**Antibacterial activity:** All the compounds substituted-5-(1*H*-Indol-3-ylmethylene)-pyrimidine-2,4,6-trione, *N*-alkyl derivatives **3(a-d)**, **5(a-d)** and **7(a-d)** were screened for their antibacterial activities<sup>35</sup> against gram positive bacteria such as *Bacillus subtilis*, *Staphylococcus aureus* (ATCC6538) and also against gram-negative bacteria such as *Klebsiella pneumonia*, *Escherichia coli* (ATCC8739) bacterial strains<sup>36</sup> at concentrations of 50, 100, 200, 300 and 500 µg/mL. Streptomycin was used as a reference standard. Petri plates and

necessary glassware were sterilized in hot air oven at 190 °C for 45 min. The Mueller Hinton Agar and saline (0.82 % NaCl) media were sterilized in autoclave (121 °C, 15 psi, 20 min). Inoculum was prepared in sterile saline (0.82 % NaCl) and the optical density of all pathogens was adjusted to 0.10 at 625 nm on a chemito spectra scan UV 2600 spectrophotometer that is equivalent to 0.5 Mc Farland standards. The Mueller Hinton Agar plates were prepared by the pour plate method. The activity of the compounds was tested by agar well diffusion method. All the bacterial cells were cultured in Mueller Hinton Agar plates and the compounds to be tested were dissolved in *N,N*-dimethyl formamide and were soaked in agar well and the Petri plates incubated at 37 °C for 24 h. The diameter (mm) of the zone of inhibition around each agar disc was measured and results were recorded in Table-3. **3(a-d)**, **5(a-d)** and **7(a-d)** compounds tested were found to have excellent antibacterial activity against *Klebsiella pneumoniae* and *Escherichia coli*. However, they were found to have very good activity against *Staphylococcus aureus* and *Bacillus subtilis*. **3(a-d)** compounds tested were found to have more antibacterial activities compare with **5(a-d)** and **7(a-d)** against *Klebsiella pneumoniae*, *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis*.

**Antifungal activity:** All the compounds **3(a-d)**, **5(a-d)** and **7(a-d)** were screened for antifungal activity against<sup>37,38</sup> *Rhizoctonia solani*, *Fusarium oxysporum*, *Aspergillus niger* and *Aspergillus flavus* at concentrations of 50, 100, 200, 300 and 500 µg/mL. Mycostatin was used as a reference standard. Potato dextrose agar (PDA) was used as basal medium for test fungi. Glass petridishes used were sterilized. Sterilized melted PDA medium (*ca.* 45 °C) was poured at the rate of 15 mL into each petridish (90 mm). After solidification of the medium, small portions of the mycelium of each fungus were spread carefully over the centre of each PDA plate with the help of



**Scheme-II:** Plausible mechanism for the formation of **3** from **1** and **2** in the presence of L-tyrosine in water at room temperature

TABLE-3  
ANTIBACTERIAL ACTIVITY OF **3(a-d)**, **5(a-d)** AND **7(a-d)** AGAINST  
*Klebsiella pneumonia*, *Escherichia Coli*, *Staphylococcus aureus* AND *Bacillus subtilis*

| S. No. | Compound No. | Types of bacteria            | Zone of inhibition in mm for concentration of |             |             |             |             |
|--------|--------------|------------------------------|-----------------------------------------------|-------------|-------------|-------------|-------------|
|        |              |                              | 50 (µg/mL)                                    | 100 (µg/mL) | 200 (µg/mL) | 300 (µg/mL) | 500 (µg/mL) |
| 1      | <b>3a</b>    | <i>Klebsiella pneumonia</i>  | 9                                             | 14          | 18          | 23          | 31          |
|        |              | <i>Escherichia coli</i>      | 8                                             | 13          | 16          | 20          | 30          |
|        |              | <i>Staphylococcus aureus</i> | 6                                             | 10          | 14          | 18          | 25          |
|        |              | <i>Bacillus subtilis</i>     | 4                                             | 9           | 12          | 15          | 23          |
| 2      | <b>3b</b>    | <i>Klebsiella pneumonia</i>  | 9                                             | 14          | 18          | 23          | 32          |
|        |              | <i>Escherichia coli</i>      | 8                                             | 13          | 15          | 20          | 31          |
|        |              | <i>Staphylococcus aureus</i> | 6                                             | 10          | 13          | 16          | 26          |
|        |              | <i>Bacillus subtilis</i>     | 4                                             | 9           | 11          | 14          | 22          |
| 3      | <b>3c</b>    | <i>Klebsiella pneumonia</i>  | 9                                             | 14          | 18          | 23          | 32          |
|        |              | <i>Escherichia coli</i>      | 8.4                                           | 13.5        | 14          | 21          | 30          |
|        |              | <i>Staphylococcus aureus</i> | 6                                             | 10          | 13          | 17          | 25          |
|        |              | <i>Bacillus subtilis</i>     | 5                                             | 9.5         | 11          | 15          | 23          |
| 4      | <b>3d</b>    | <i>Klebsiella pneumonia</i>  | 9                                             | 14          | 18          | 23          | 32          |
|        |              | <i>Escherichia coli</i>      | 8                                             | 13          | 15          | 20          | 31          |
|        |              | <i>Staphylococcus aureus</i> | 6                                             | 10          | 13          | 16          | 26          |
|        |              | <i>Bacillus subtilis</i>     | 4                                             | 9           | 11          | 14          | 22          |
| 5      | <b>5a</b>    | <i>Klebsiella pneumonia</i>  | 9                                             | 14          | 18          | 23          | 31          |
|        |              | <i>Escherichia coli</i>      | 8                                             | 13          | 16          | 20          | 30          |
|        |              | <i>Staphylococcus aureus</i> | 6                                             | 10          | 14          | 18          | 25          |
|        |              | <i>Bacillus subtilis</i>     | 4                                             | 9           | 12          | 15          | 23          |
| 6      | <b>5b</b>    | <i>Klebsiella pneumonia</i>  | 9                                             | 14          | 18          | 23          | 32          |
|        |              | <i>Escherichia coli</i>      | 8                                             | 13          | 15          | 20          | 31          |
|        |              | <i>Staphylococcus aureus</i> | 6                                             | 10          | 13          | 16          | 26          |
|        |              | <i>Bacillus subtilis</i>     | 4                                             | 9           | 11          | 14          | 22          |
| 7      | <b>5c</b>    | <i>Klebsiella pneumonia</i>  | 9                                             | 14          | 18          | 23          | 32          |
|        |              | <i>Escherichia coli</i>      | 8.4                                           | 13.5        | 14          | 21          | 30          |
|        |              | <i>Staphylococcus aureus</i> | 6                                             | 10          | 13          | 17          | 25          |
|        |              | <i>Bacillus subtilis</i>     | 5                                             | 9.5         | 11          | 15          | 23          |
| 8      | <b>5d</b>    | <i>Klebsiella pneumonia</i>  | 9                                             | 14          | 18          | 23          | 31          |
|        |              | <i>Escherichia coli</i>      | 8                                             | 13          | 16          | 20          | 30          |
|        |              | <i>Staphylococcus aureus</i> | 6                                             | 10          | 14          | 18          | 25          |
|        |              | <i>Bacillus subtilis</i>     | 4                                             | 9           | 12          | 15          | 23          |
| 9      | <b>7a</b>    | <i>Klebsiella pneumonia</i>  | 9                                             | 14          | 18          | 23          | 31          |
|        |              | <i>Escherichia coli</i>      | 8                                             | 13          | 16          | 20          | 30          |
|        |              | <i>Staphylococcus aureus</i> | 6                                             | 10          | 14          | 18          | 25          |
|        |              | <i>Bacillus subtilis</i>     | 4                                             | 9           | 11          | 14          | 22          |
| 10     | <b>7b</b>    | <i>Klebsiella pneumonia</i>  | 8                                             | 13          | 15          | 20          | 31          |
|        |              | <i>Escherichia coli</i>      | 6                                             | 10          | 13          | 16          | 26          |
|        |              | <i>Staphylococcus aureus</i> | 4                                             | 9           | 11          | 14          | 22          |
|        |              | <i>Bacillus subtilis</i>     | 4                                             | 8           | 10          | 13          | 21          |
| 11     | <b>7c</b>    | <i>Klebsiella pneumonia</i>  | 8.4                                           | 13.4        | 14          | 21          | 30          |
|        |              | <i>Escherichia coli</i>      | 6                                             | 10          | 13          | 17          | 25          |
|        |              | <i>Staphylococcus aureus</i> | 5                                             | 9.5         | 11          | 15          | 23          |
|        |              | <i>Bacillus subtilis</i>     | 5                                             | 9.5         | 11          | 15          | 23          |
| 12     | <b>7d</b>    | <i>Klebsiella pneumonia</i>  | 9                                             | 14          | 18          | 23          | 32          |
|        |              | <i>Escherichia coli</i>      | 8                                             | 13          | 15          | 20          | 31          |
|        |              | <i>Staphylococcus aureus</i> | 6                                             | 10          | 13          | 16          | 26          |
|        |              | <i>Bacillus subtilis</i>     | 4                                             | 9           | 11          | 14          | 22          |
| 13     | Streptomycin | <i>Klebsiella pneumonia</i>  | 11                                            | 16          | 22          | 26          | 35          |
|        |              | <i>Escherichia coli</i>      | 10                                            | 15          | 21          | 24          | 34          |
|        |              | <i>Staphylococcus aureus</i> | 8                                             | 13          | 17          | 20          | 29          |
|        |              | <i>Bacillus subtilis</i>     | 7                                             | 12          | 15          | 18          | 26          |

sterilized needles. Thus, each fungus was transferred to a number of PDA plates, which were then incubated at  $(25 \pm 2)$  °C and ready for use after 5 days of incubation agar plates were prepared by the pour plate method. The activity of the compounds was tested by agar well diffusion method, freshly seeded with the test organisms with sterile forceps. A control agar well was also prepared on the test plates to compare the

effect of the test samples and to nullify the effect of solvent, respectively. The plates were then kept in a refrigerator at 4 °C for 24 h so that the materials had sufficient time to diffuse over a considerable area of the plates. After this, the plates were incubated at 37 °C for 72 h. N,N-Dimethyl formamide was used as solvent to prepare desired solutions of the compounds and also to maintain proper control. The diameter

TABLE-4  
ANTIFUNGAL ACTIVITY OF **3(a-d)**, **5(a-d)** AND **7(a-d)** AGAINST  
*Rhizoctonia solani*, *Fusarium oxysporum*, *Aspergillus niger* AND *Aspergillus flavus*

| S. No. | Compound No. | Types of bacteria         | Zone of inhibition in mm for concentration of |             |             |             |             |
|--------|--------------|---------------------------|-----------------------------------------------|-------------|-------------|-------------|-------------|
|        |              |                           | 50 (µg/mL)                                    | 100 (µg/mL) | 200 (µg/mL) | 300 (µg/mL) | 500 (µg/mL) |
| 1      | <b>3a</b>    | <i>Rhizoctonia solani</i> | 9                                             | 14          | 18          | 23          | 31          |
|        |              | <i>Fusarium oxysporum</i> | 9                                             | 13.8        | 17          | 22.6        | 30          |
|        |              | <i>Aspergillus niger</i>  | 6                                             | 10          | 14          | 18          | 25          |
|        |              | <i>Aspergillus flavus</i> | 6.5                                           | 11          | 13.6        | 18.3        | 25.2        |
| 2      | <b>3b</b>    | <i>Rhizoctonia solani</i> | 8                                             | 13          | 15          | 20          | 31          |
|        |              | <i>Fusarium oxysporum</i> | 8                                             | 13          | 14          | 19          | 30          |
|        |              | <i>Aspergillus niger</i>  | 4                                             | 9           | 11          | 14          | 22          |
|        |              | <i>Aspergillus flavus</i> | 4.3                                           | 8.9         | 11.1        | 13.9        | 22.1        |
| 3      | <b>3c</b>    | <i>Rhizoctonia solani</i> | 8.4                                           | 13.5        | 14          | 21          | 30          |
|        |              | <i>Fusarium oxysporum</i> | 8                                             | 13          | 13          | 20          | 29          |
|        |              | <i>Aspergillus niger</i>  | 5                                             | 9.5         | 11          | 15          | 23          |
|        |              | <i>Aspergillus flavus</i> | 5                                             | 9           | 10.8        | 14.8        | 23          |
| 4      | <b>3d</b>    | <i>Rhizoctonia solani</i> | 9                                             | 14          | 18          | 23          | 32          |
|        |              | <i>Fusarium oxysporum</i> | 8                                             | 13          | 15          | 20          | 31          |
|        |              | <i>Aspergillus niger</i>  | 6                                             | 10          | 12          | 15          | 23          |
|        |              | <i>Aspergillus flavus</i> | 4                                             | 9           | 11          | 14          | 22          |
| 5      | <b>5a</b>    | <i>Rhizoctonia solani</i> | 9                                             | 14          | 18          | 23          | 31          |
|        |              | <i>Fusarium oxysporum</i> | 8                                             | 13          | 16          | 20          | 30          |
|        |              | <i>Aspergillus niger</i>  | 6                                             | 10          | 14          | 18          | 25          |
|        |              | <i>Aspergillus flavus</i> | 4                                             | 9           | 12          | 15          | 23          |
| 6      | <b>5b</b>    | <i>Rhizoctonia solani</i> | 9                                             | 14          | 18          | 23          | 32          |
|        |              | <i>Fusarium oxysporum</i> | 8                                             | 13          | 15          | 20          | 31          |
|        |              | <i>Aspergillus niger</i>  | 6                                             | 10          | 13          | 16          | 26          |
|        |              | <i>Aspergillus flavus</i> | 4                                             | 9           | 11          | 14          | 22          |
| 7      | <b>5c</b>    | <i>Rhizoctonia solani</i> | 9                                             | 14          | 18          | 23          | 32          |
|        |              | <i>Fusarium oxysporum</i> | 8.4                                           | 13.5        | 14          | 21          | 30          |
|        |              | <i>Aspergillus niger</i>  | 6                                             | 10          | 13          | 17          | 25          |
|        |              | <i>Aspergillus flavus</i> | 5                                             | 9.5         | 11          | 15          | 23          |
| 8      | <b>5d</b>    | <i>Rhizoctonia solani</i> | 9                                             | 14          | 18          | 23          | 32          |
|        |              | <i>Fusarium oxysporum</i> | 8                                             | 13          | 15          | 20          | 31          |
|        |              | <i>Aspergillus niger</i>  | 6                                             | 10          | 13          | 16          | 26          |
|        |              | <i>Aspergillus flavus</i> | 4                                             | 9           | 11          | 14          | 22          |
| 9      | <b>7a</b>    | <i>Rhizoctonia solani</i> | 9                                             | 14          | 18          | 23          | 31          |
|        |              | <i>Fusarium oxysporum</i> | 9                                             | 14          | 17          | 22          | 30          |
|        |              | <i>Aspergillus niger</i>  | 5                                             | 9           | 12          | 15          | 23          |
|        |              | <i>Aspergillus flavus</i> | 4.8                                           | 8.7         | 11.8        | 14.6        | 23          |
| 10     | <b>7b</b>    | <i>Rhizoctonia solani</i> | 9                                             | 14          | 18          | 23          | 32          |
|        |              | <i>Fusarium oxysporum</i> | 9                                             | 13.9        | 18          | 22.7        | 31.8        |
|        |              | <i>Aspergillus niger</i>  | 6                                             | 10          | 12          | 15          | 23          |
|        |              | <i>Aspergillus flavus</i> | 5.4                                           | 9.7         | 11          | 14.6        | 22          |
| 11     | <b>7c</b>    | <i>Rhizoctonia solani</i> | 9                                             | 14          | 18          | 23          | 32          |
|        |              | <i>Fusarium oxysporum</i> | 8.4                                           | 13.5        | 17          | 22          | 31          |
|        |              | <i>Aspergillus niger</i>  | 5.3                                           | 10          | 11          | 15          | 24          |
|        |              | <i>Aspergillus flavus</i> | 5                                             | 9.5         | 11          | 14.7        | 23          |
| 12     | <b>7d</b>    | <i>Rhizoctonia solani</i> | 8                                             | 13          | 17          | 22          | 30          |
|        |              | <i>Fusarium oxysporum</i> | 8                                             | 12          | 16          | 21          | 29          |
|        |              | <i>Aspergillus niger</i>  | 4                                             | 8           | 11.2        | 14.3        | 22          |
|        |              | <i>Aspergillus flavus</i> | 4                                             | 8           | 11          | 14          | 22          |
| 13     | Mycostanin   | <i>Rhizoctonia solani</i> | 13                                            | 16          | 20          | 28          | 35          |
|        |              | <i>Fusarium oxysporum</i> | 13                                            | 16          | 19          | 27          | 35          |
|        |              | <i>Aspergillus niger</i>  | 9.2                                           | 11          | 14.6        | 21          | 30          |
|        |              | <i>Aspergillus flavus</i> | 9                                             | 11          | 14          | 20          | 29          |

(mm) of the zone of inhibition around each agar well was measured and results were recorded in Table-4.

**3(a-d)**, **5(a-d)** and **7(a-d)** compounds tested were found to have very good antifungal activity against *Rhizoctonia solani* and *Fusarium oxysporum*. However, they were found to good activity against *Aspergillus niger* and *Aspergillus flavus*.

**3(a-d)** compounds tested were found to have more anti-fungal activities compare with **5(a-d)** and **7(a-d)** against

*Rhizoctonia solani*, *Fusarium oxysporum*, *Aspergillus niger* and *Aspergillus flavus*.

## Conclusion

In summary, L-tyrosine has been employed as efficient, eco-friendly catalyst for the preparation of substituted-5-(1*H*-Indol-3-ylmethylene)-pyrimidine-2,4,6 trione derivatives by Knoevenagel reaction in water at room temperature. This

method is applicable to a wide range of indole-3-carboxylaldehydes, including N-substituted indole-3-carboxyaldehydes. The attractive features of this procedure are the mild reaction conditions, high conversions, operational simplicity and inexpensive and ready availability of the catalyst, all of which make it a useful and attractive strategy for the preparation of substituted-5-(1*H*-indol-3-ylmethylene)-pyrimidine-2,4,6-trione derivatives in water at room temperature. The antibacterial and antifungal activities of **3(a-d)**, **5(a-d)** and **7(a-d)** have been studied. **3(a-d)**, **5(a-d)** and **7(a-d)** compounds tested were found to have excellent antibacterial activities against *Klebsiella pneumoniae* and *Escherichia coli*. **3(a-d)** compounds tested were found to have excellent antibacterial activities compare with **5(a-d)** and **7(a-d)** against *Klebsiella pneumoniae* and *Escherichia coli*. However, they were found to very good activities against *Rhizoctonia solani* and *Fusarium oxysporum*. **3(a-d)** compounds tested were found to have very good antifungal activities compare with **5(a-d)** and **7(a-d)** against *Rhizoctonia solani* and *Fusarium oxysporum*.

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