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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Eco-friendly synthesis and antimicrobial activities of substituted-5-(1H-indol-3-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione derivatives

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Abstract L-Tyrosine is an efficient catalyst for the condensation of substituted indole-3-aldehydes **1**(**a–d**), *N*-methyl indole-3-aldehydes **4**(**a–d**), and *N*-ethyl indole-3-aldehydes **6**(**a–d**) with meldrum's acid (**2**) containing a cyclic active methylene group to produce **3**(**a–d**), **5**(**a–d**), and **7**(**a–d**), respectively, in water at room temperature for 30 min. The antimicrobial activities of **3**(**a–d**), **5**(**a–d**), and **7**(**a–d**) have been studied.

Keywords Anti-bacterial activities · Anti-fungal activities · Indole-3-aldehyde · Meldrum's acid · L-Tyrosine · Water

Introduction

The carbon–carbon bond formation reaction is the most important reaction in organic synthesis (Jones, 1967; Knoevenagel, 1898; Tietze and Beifuss, 1991; Freeman, 1980). The Knoevenagel condensation is one such reaction which facilitates C–C double bond formation and has been widely used in synthesis of alkenes of biological significance (Zidar *et al.*, 2010; Ibrahim *et al.*, 2011; Oguchi *et al.*, 2000; Malamas *et al.*, 2000; Murugan *et al.*, 2009). These reactions are usually catalyzed by bases (Desai *et al.*, 2004; Fildes *et al.*, 2001; Texier-Boullet and Foucod, 1982; Cabello *et al.*, 1984; Yadav *et al.*, 2004; Yang *et al.*, 2006; Narsaiah *et al.*, 2004; Rodriguez *et al.*, 1999) such as ethylenediamine, potassium fluroiodide, primary, and secondary amines, and their corresponding ammonium salts, Lewis acids (Prajapati *et al.*, 1996; Rao and Ratnam, 1991; Narsaiah and Nagaiah, 2003), zeolite (Martins *et al.*, 2008; Tran *et al.*, 2011; Reddy and Verma, 1997), and ionic liquids (Formentin *et al.*, 2004; Hu *et al.*, 2004; Santamarta *et al.*, 1978) 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 a variety of reactions (Mc Nab, 1978). They are used in cycloaddition reactions (Kraus and Krolski, 1986), 1,4-conjugate addition reactions, preparation of mono alkyl Meldrum's acid derivatives (Huang and Xie, 1986), and preparation of deuterated carboxylic acid derivatives (Kadam *et al.*, 1999). These derivatives are also used in the preparation of ketenes by α, β-pyrolysis (Brown *et al.*, 1974), which are then used for preparation of different compounds such as cyclobutadiene derivatives (Brown and McMullen, 1974), α, β-unsaturated esters (Nakamura *et al.*, 2004), and α, β-unsaturated amides (Thorat *et al.*, 1987; Rao and Venkataratnam, 1993) .

Earlier in 1986, Jones et al. reported (Miroslav *et al.*, 2009) the reaction of meldrum's acid with indole-3-carboxaldehyde under flash vacuum pyrolysis to yield the Knoevenagel derivative of 5-((1H-indol-3-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione with 61 % yield. This method is more time-consuming and not very good for the preparation of large amounts of these products; moreover, it is a very good intermediate for the preparation of anticancer drugs (Tara and Gordon, 2001). L-Tyrosine is known to be an efficient, bi-functional, zwitterionic, 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

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acid as well as a base catalyst in chemical condensation reactions.

Results and discussion

Treatment of substituted indole-3-carboxaldehydes **1**(**a**–**d**), its *N*-methyl derivatives 4(**a**–**d**), and *N*-ethyl derivatives **6**(**a**–**d**), each with meldrum's acid containing cyclic active methylene group (**2**), in water at room temperature for 30 min resulted in the corresponding Knoevenagel products **3**(**a–d**), **5**(**a–d**), and **7**(**a–d**) in excellent yields (94–97 %) (Scheme 1; Table 1). L-Tyrosine is used 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.

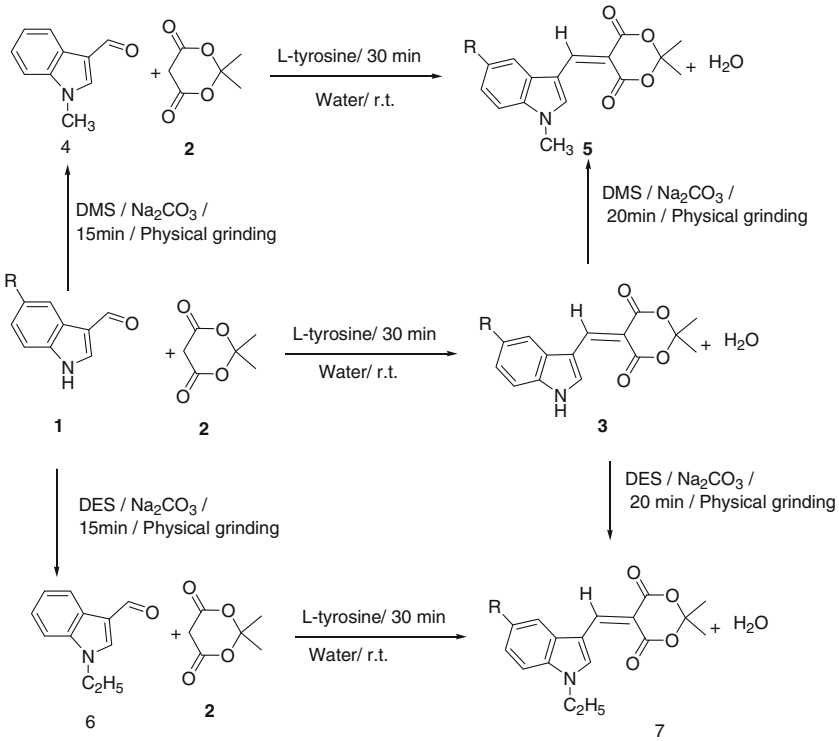
In the absence of L-tyrosine, the reaction did not proceed even after refluxing the reactants in water for 24 h. The use of L-tyrosine as a catalyst helps to complete the reaction in 30 min. Thus, L-tyrosine has been found to be an efficient and eco-friendly catalyst for the Knoevenagel condensation reaction of indole-3-carboxyaldehyde (**1**) and its *N*-methyl derivative **4**(**a–d**) and *N*-ethyl derivative **6**(**a–d**), each with meldrum's acid containing cyclic active methylene group (**2**).The use of L-tyrosine as a catalyst helps to avoid the use of environmentally unfavorable organic solvents as the reaction medium.

The above reactions of **1**(**a**–**d**), **4**(**a**–**d**), and **6**(**a**–**d**) with meldrum's 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 20 h.

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

Treatment of substituted indole-3-carboxaldehydes **1**(**a**–**d**), its *N*-methyl derivative **4**(**a**–**d**), and *N*-ethyl derivative **6**(**a**–**d**), each with meldrum's acid containing cyclic active methylene group (**2**), was attempted in the presence of various bases like NaOH and KOH, which were too strong to result in more by-products. Low yield was obtained and a 12-h reaction time is needed using K_2CO_3, ammonium acetate, piperidine, and triethylamine as the catalyst for condensation of substituted indole-3-aldehydes **1**(**a**–**d**), **4**(**a**–**d**), and **6**(**a**–**d**) with meldrum's acids containing cyclic active methylene group (**2**) in water at room temperature.

From Table 1, it is shown that the condensation of substituted indole-3-aldehydes **1**(**a**–**d**), **4**(**a**–**d**), and **6**(**a**–**d**) with electron-withdrawing groups such as $–NO_2$ and –Br at the 5th position with meldrum's acid containing cyclic



Scheme 1 Condensation of indole-3-aldehyde with meldrum's acid in the presence of L-Tyrosine in aqueous medium and alkylation under solvent-free condition using alkylating agents

Table 1 Synthesis substituted-5-(1H-indol-3-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione derivatives using L-Tyrosine as eco-friendly catalyst in water at room temperature and alkylation under solvent-free condition using alkylating agents

S. no.	Reactants		Product	Time (min)	Yield (%)	M.P. °C
1	**1a** (R=H)	2	**3a** (R=H)	10	95	241–243
2	**1b** (R=OMe)	2	**3b** (R=OMe)	12	94	255
3	**1c** (R=Br)	2	**3c** (R=Br)	9	96	251–253
4	**1d** (R=NO_2)	2	**3d** (R=NO_2)	9	97	241
5	**4a** (R=H)	2	**5a** (R=H)	11	93	218–221
6	**4b** (R=OMe)	2	**5b** (R=OMe)	14	91	198–200
7	**4c** (R=Br)	2	**5c** (R=Br)	13	92	265
8	**4d** (R=NO_2)	2	**5d** (R=NO_2)	13	94	215
9	**6a** (R=H)	2	**7a** (R=H)	11	93	203–205
10	**6b** (R=OMe)	2	**7b** (R=OMe)	14	91	140–142
11	**6c** (R=Br)	2	**7c** (R=Br)	13	92	198–200
12	**6d** (R=NO_2)	2	**7d** (R=NO_2)	13	94	151–153
13	**3a** (R=H)	DMS	**5a** (R=H)	20	93	218–221
14	**3b** (R=OMe)	DMS	**5b** (R=OMe)	23	91	198–200
15	**3c** (R=Br)	DMS	**5c** (R=Br)	21	92	265
16	**3d** (R=NO_2)	DMS	**5d** (R=NO_2)	20	94	215
17	**3a** (R=H)	DES	**7a** (R=H)	20	93	203–205
18	**3b** (R=OMe)	DES	**7b** (R=OMe)	23	91	140–142
19	**3c** (R=Br)	DES	**7c** (R=Br)	21	92	198–200
20	**3d** (R=)	DES	**7d** (R=NO_2)	20	94	151–153

active methylene compounds can be carried out in relatively shorter time and higher yield than with electron-donating group such as $-OCH_3$ 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 the 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_6H_6, DMSO, $CHCl_3$, CH_3CN, 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_6H_6, 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-carboxy aldehyde, *N*-ethyl-5-methoxyindole-3-carboxaldehyde,5-bromoindole-3-carboxaldehyde, *N*-methyl-5-bromo indole-3-carboxy aldehyde, and *N*-ethyl-5-bromoindole-3-carboxaldehyde underwent condensation very easily with meldrum's acid in the presence of L-tyrosine in water at room temperature.

Treatment of **3**(**a**–**d**) independently with DMS and DES each, in the presence of Na_2CO_3 as the base in solvent-free condition, under the grindstone method at room temperature for 20 min resulted in **5**(**a**–**d**) and **7**(**a**–**d**), respectively, in excellent yields 91–94 % (Scheme 1). 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_2CO_3 as the base in solvent-free condition under the grindstone method at room temperature.

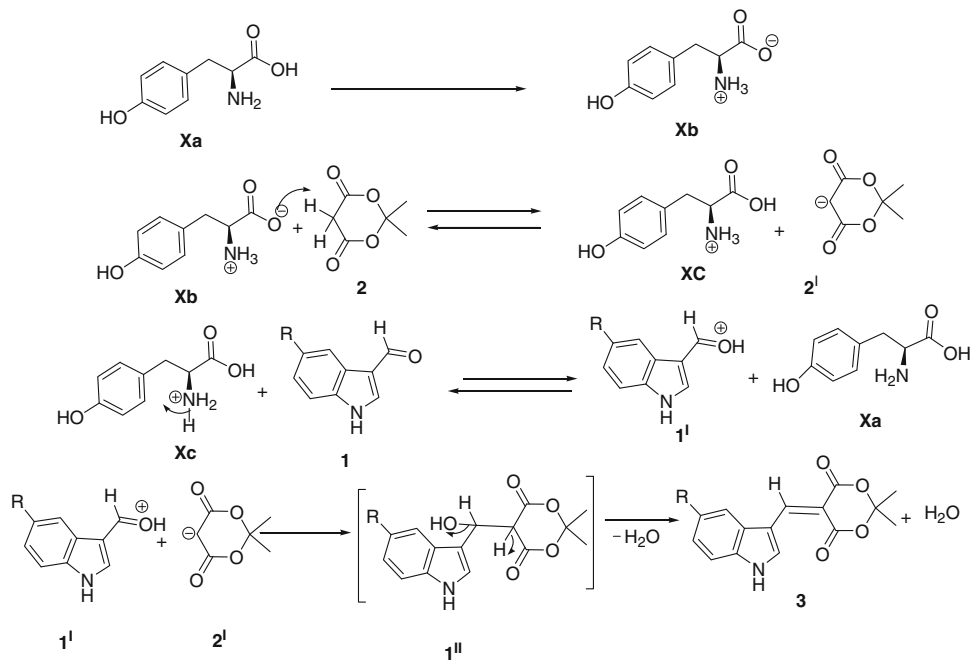
A comparative study of the progress of condensation reactions **1**(**a**–**d**), **4**(**a**–**d**), and **6**(**a**–**d**) with **2** was carried out in different solvents containing L-tyrosine as the catalyst and the result is summarized in Table 2.

A plausible mechanism for the formation of **3** from **1** and **2** in the presence of L-tyrosine as the catalyst is shown

Table 2 Progress of reaction in different solvent media

Entry	Solvent	Time (h)	Temp (°C)	Yield
1.	L-Tyrosine/water	1	r.t.	94–97
2.	L-Tyrosine/EtOH	2-5	r.t.	74–76
3.	L-Tyrosine/Benzene	8	r.t.	42–46
4.	L-Tyrosine/DMSO	10	r.t.	36–40
5.	Without catalyst in water	24	r.t./reflux at 100 °C	NIL
6.	L-Tyrosine/DMF	7	r.t.	26–28
7.	L-Tyrosine/CH_3CN	12	r.t.	18–20
8.	L-Tyrosine/$CHCl_3$	18	r.t.	NIL

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



in Scheme 2. The reaction mechanism is supported by the literature reference (Darvatkar *et al.*, 2006; Thirupathi *et al.*, 2012a, b, c; Venkatanarayana and Dubey, 2012) .

In the mechanism shown in Scheme 2, L-tyrosine, in its zwitterionic form (**Xb**), abstracts a proton from meldrum's acid containing cyclic active methylene group (**2**) forming the carbanion of meldrum's acid ($\mathbf{2^I}$), which then attacks the protonated indole-3-aldehydes ($\mathbf{1^I}$) forming the corresponding intermediate ($\mathbf{1^{II}}$) that loses water to form the end product **3**, which on alkylation results in the title compounds **5** and **7.**

Conclusions

In summary, L-tyrosine has been employed as an efficient, eco-friendly catalyst for the preparation of substituted-5-(1H-indol-3-yl methylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione derivatives by the knoevenagel reaction in water at room temperature. This method is applicable to a wide range of indole-3-carboxyldehydes, 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-(1H-indol-3-yl methylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione derivatives in water at room temperature. **3**(**a**–**d**), **5**(**a**–**d**), and **7**(**a**–**d**) compounds tested were found to have excellent anti-bacterial activity against *Klebsiella pneumoniae* and *Escherichia coli* and also had very good activity against *Staphylococcus aureus* and *Bacillus subtilis*. **3**(**a**–**d**) compounds tested were found to have more anti-bacterial activities compared with **5**(**a**–**d**) and **7**(**a**–**d**) against *K. pneumoniae*, *E. coli, S. aureus*, and *B. subtilis.*

3(**a**–**d**) compounds have NH functional groups due to having more anti-bacterial activities compared with **5**(**a**–**d**) and **7**(**a**–**d**). **5**(**a**-**d**) and **7**(**a**–**d**) compounds have *N*-alkylated functional groups due to having less anti-bacterial activities compared with **3**(**a**–**d**).

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

3(**a**–**d**) compounds tested were found to have more anti-fungal activities compared with **5**(**a**–**d**) and **7**(**a**–**d**) against *R. solani*, *F. oxysporum, A. niger*, and *A. flavus.*

3(**a**–**d**) compounds have NH functional groups due to having more anti-fungal activities compared with **5**(**a**–**d**) and **7**(**a**–**d**).

5(**a**–**d**) and **7**(**a**–**d**) compounds have *N*-alkylated functional groups due to having less anti-fungal activities compared with **3**(**a**–**d**).

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 a UV lamp.

IR spectra were recorded using FT-IR in KBr phase. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded at 400 MHz. The compounds are known and products were identified by spectral and melting-point comparisons with the authentic samples.

Biological evaluation

Anti-bacterial activity

All the compounds, substituted-5-(1H-indol-3-yl methylene)-2,2-dimethyl-[1,3]di oxane-4,6-dione derivatives **3**(**a**–**d**), **5**(**a**–**d**), and **7**(**a**–**d**), were screened for their anti-bacterial activities (Ravichandran *et al.*, 2011) against gram-positive bacteria such as *B. subtilis* and *S. aureus* (ATCC6538) and also against gram-negative bacteria such as *K. pneumonia*, and *E. coli* (ATCC8739) bacterial strains (Kaspady *et al.*, 2010) 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 a hot air oven at 190 °C for 45 min. The mueller hinton agar and saline (0.82 % Nacl) media were sterilized in an 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 (Frankel *et al.*, 1970). The mueller hinton agar plates were prepared by the pour plate method. The activity of the compounds was tested by the 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*-dimethylformamide (DMF), 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 disk was measured and results are recorded in Table 3. **3**(**a**–**d**), **5**(**a**–**d**), and **7**(**a**–**d**) compounds tested were found to have excellent anti-bacterial activity against *K. pneumoniae* and *E. coli*. However, they were found to have very good activity against *S. aureus* and *B. subtilis.* **3**(**a**–**d**) compounds tested were found to have more anti-bacterial activities compared with **5**(**a–d**) and **7**(**a–d**) against *K. pneumoniae*, *E. coli, S. aureus*, and *B. subtilis.*

Anti-fungal activity

All the compounds synthesized **3**(**a**–**d**), **5**(**a**–**d**), and **7**(**a**–**d**) were screened for anti-fungal activity (Kaspady *et al.*, 2010; Navneet *et al.*, 2012) against *R. solani, F. oxysporum, A. niger*, and *A. 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 the basal medium for test fungi. The glass petri dishes used were sterilized. Sterilized melted PDA medium (~45 °C) was poured at the rate of 15 ml into each petri dish (90 mm). After solidification of the medium, small portions of the mycelium of each fungus were spread carefully over the center of each PDA plate with the help of sterilized needles. Thus, each fungus was transferred to a number of PDA plates, which were then incubated at (25 ± 2) °C and ready for use after 5 days of incubation. PDA plates were prepared by the pour plate method. The activity of the compounds, freshly seeded with the test organisms with sterile forceps, was tested by the agar well diffusion method. A control ager well was also prepared on the test plates to compare the effect of the test samples and to nullify the effect of the solvent. 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 (DMF) was used as solvent to prepare the desired solutions of the compounds and also to maintain proper control. The diameter (mm) of the zone of inhibition around each agar well was measured and results are recorded in Tables 4, 5, and 6.

3(**a–d**), **5**(**a–d**), and **7**(**a–d**) compounds tested were found to have very good anti-fungal activity against *R. solani* and *F. oxysporum.* However, they were found to have good activity against *A. niger* and *A. flavus.*

3(**a**–**d**) compounds tested were found to have more anti-fungal activities compared with **5**(**a**–**d**) and **7**(**a**–**d**) against *R. solani*, *F. oxysporum, A. niger*, and *A. flavus.*

General procedure for the preparation of 3 from 1

A mixture of **1** (10 mmol), meldrum's acid **2** (10 mmol), L-tyrosine (2 mmol) ,and water (25 ml) was stirred at room temperature for a specified period of time (Table 1). After completion of the reaction (as shown by TLC checking), the mixture was poured onto ice-cold water (50 ml). The separated solid was filtered, washed with water (100 ml), and dried to obtain crude product **3.** The product was then recrystallized from ethyl acetate to afford pure **3.**

General procedure for the preparation of 5 from 3

A mixture of **3** (10 mmol), DES (10 mmol), and Na_2CO_3 was physically ground in solvent-free condition under the grindstone method at room temperature for a specified period of time (Table 1). After completion of the reaction (as shown by TLC checking), the mixture was poured onto ice-cold water (50 ml).The separated solid was filtered, washed with water (100 ml), and dried to obtain crude **5.** The product was then recrystallized from ethyl acetate to afford pure **5.**

Table 3 Anti-bacterial 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	**3a**	*Klebsiella pneumonia*	11	16	20	25	33
		Escherichia coli	10	15	18	22	32
		Staphylococcus aureus	8	12	16	20	27
		Bacillus subtilis	6	11	14	17	25
2	**3b**	*Klebsiella pneumonia*	11	16	20	25	34
		Escherichia coli	10	15	17	22	33
		Staphylococcus aureus	8	12	15	18	28
		Bacillus subtilis	4	9	11	14	22
3	**3c**	*Klebsiella pneumonia*	11	16	20	25	34
		Escherichia coli	10.4	15.5	16	23	32
		Staphylococcus aureus	8	12	15	19	27
		Bacillus subtilis	7	11.5	13	17	25
4	**3d**	*Klebsiella pneumonia*	11	16	20	25	34
		Escherichia coli	10	15	17	22	33
		Staphylococcus aureus	8	12	15	18	28
		Bacillus subtilis	6	11	13	16	24
5	**5a**	*Klebsiella pneumonia*	9	14	18	23	31
		Escherichia coli	8	13	16	20	30
		Staphylococcus aureus	6	10	14	18	25
		Bacillus subtilis	4	9	12	15	23
6	**5b**	*Klebsiella pneumonia*	9	14	18	23	32
		Escherichia coli	8	13	15	20	31
		Staphylococcus aureus	6	10	13	16	26
		Bacillus subtilis	4	9	11	14	22
7	**5c**	*Klebsiella pneumonia*	9	14	18	23	32
		Escherichia coli	8.4	13.5	14	21	30
		Staphylococcus aureus	6	10	13	17	25
		Bacillus subtilis	5	9.5	11	15	23
8	**5d**	*Klebsiella pneumonia*	9	14	18	23	31
		Escherichia coli	8	13	16	20	30
		Staphylococcus aureus	6	10	14	18	25
		Bacillus subtilis	4	9	12	15	23
9	**7a**	*Klebsiella pneumonia*	9	14	18	23	31
		Escherichia coli	8	13	16	20	30
		Staphylococcus aureus	6	10	14	18	25
		Bacillus subtilis	4	9	11	14	22
10	**7b**	*Klebsiella pneumonia*	8	13	15	20	31
		Escherichia coli	6	10	13	16	26
		Staphylococcus aureus	4	9	11	14	22
		Bacillus subtilis	4	8	10	13	21
11	**7c**	*Klebsiella pneumonia*	8.4	13.4	14	21	30
		Escherichia coli	6	10	13	17	25
		Staphylococcus aureus	5	9.5	11	15	23
		Bacillus subtilis	5	9.5	11	15	23

Table 3 continued

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
12	**7d**	*Klebsiella pneumonia*	9	14	18	23	32
		Escherichia coli	8	13	15	20	31
		Staphylococcus aureus	6	10	13	16	26
		Bacillus subtilis	4	9	11	14	22
13	Streptomycin	*Klebsiella pneumonia*	13	18	24	28	37
		Escherichia coli	12	17	23	26	36
		Staphylococcus aureus	10	15	19	22	31
		Bacillus subtilis	9	14	17	20	28

General procedure for the preparation of 7 **from** 3

A mixture of **3** (10 mmol), DES (10 mmol), and Na_2CO_3 was physically ground in solvent-free condition under the grindstone method at room temperature for a specified period of time (Table 1). After completion of the reaction (as shown by TLC checking), the mixture was poured onto ice-cold water (50 ml). The separated solid was filtered, washed with water (100 ml), and dried to obtain crude **7.** The product was then recrystallized from ethyl acetate to afford pure **7.**

5-((1H-indol-3-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3a**)

Yellow solid; Yield = 2.57 g (95 %); m.p.: 241–243 °C; IR (KBr): 3,191 cm^{-1} (very broad, NH), 1,733 cm^{-1} (very strong, CO) and 1,684 cm^{-1} (very strong, CO); ^{1}H NMR (DMSO-d_6/TMS): δ 1.7 (s, 6H, $2CH_3$), 7.3–7.9 (m, 4H, aryl protons of the indole ring), 8.8 (s, 1H, α-proton of the indole ring), 9.3–9.4 (s, 1H, vinylic proton of the indole ring), 12.8–12.9 (br, s, 1H, NH proton); ^{13}C spectrum (DMSO-d_6/TMS): δ 27.2, 103.44, 103.86, 111.74, 113.78, 118, 123.46, 124.44, 129.30, 134, 140, 146.58, 159.4; MS: m/z = 272 (M+1).

5-((5-methoxy-1H-indol-3-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3b**)

Yellow solid; Yield = 2.82 g (94 %); m.p.: 255 °C; IR(KBr): 3,171 cm^{-1} (very broad, NH), 1,727 cm^{-1}(very strong, CO–) and 1,676 cm^{-1}(very strong, CO); ^{1}H NMR (DMSO-d_6/TMS): δ 1.72 (s, 6H, $2CH_3$), 3.83 (s, 3H, OCH_3), 6.9–7.49 (m, 3H, aryl protons of the indole ring), 8.7 (s, 1H, α-proton of the indole ring), 9.24 (s, 1H, vinylic proton of the indole ring), 12.77 (br, s, 1H, NH proton); ^{13}C spectrum (DMSO-d_6/TMS): δ 27.81, 54.21, 102.98, 104.23, 112.40, 117.28, 119.1, 120.71, 124.12, 128.48, 132.10, 147, 151, 159.8; MS : m/z = 302 (M+1).

5-((5-Bromo-1H-indol-3-yl)methylene)-2, 2-di-methyl-1,3-dioxane-4,6-dione (**3c**)

Yellow solid; Yield = 3.36 g (96 %); m.p.: 251–253 °C; IR(KBr) : 3,142 cm^{-1}(very NH), 1,731 cm^{-1}(broad very strong CO) and 1,679 cm^{-1} (very strong CO).^{1}H NMR (DMSO-d_6/TMS): δ 1.69 (s, 6H, $2CH_3$) 7.44–7.57 (m, 3H, aryl proton of the indole ring), 8.66 (s, 1H, α-proton of the indole ring), 9.27 (s, 1H vinylic proton of the indole ring); 12.93 (br, s, 1H, D_2O-exchangeble NH proton); ^{13}C spectrum (DMSO-d_6/TMS): δ 27.12, 103.12, 103.93, 112.12, 116.12, 117.14, 123.12, 124.91, 130.8, 138.12, 146.12, 153.12, 159.12; MS : m/z = 351 (M+1).

5-((5-Nitro-1H-indol-3-yl)methylene)-2,2-dimeth-yl-1,3-dioxane-4,6-dione (**3d**)

Yellow solid; Yield = 3.065 g (97 %); m.p.: 241 °C; IR(KBr): 3,144 cm^{-1} (very broad, NH) 1,732 cm^{-1} (sharp, strong, CO), 1,678 cm^{-1} (very strong, CO); ^{1}H NMR (DMSO-d_6/TMS): δ 1.61 (s, 6H, $2CH_3$), 7.7–8.1 (m, 3H aryl protons of the indole ring), 8.84 (s, 1H, α-proton of the indole ring), 9.38 (s, 1H, vinylic proton of the indole ring), 12.8 (br, s, 1H, NH proton); ^{13}C spectrum (DMSO-d_6/TMS): δ 27.38, 103.12, 104.1, 111.12, 113.6, 119, 122.3, 124.1, 128.12, 134.14, 142, 148.12, 160.4; MS : m/z = 317 (M+1).

2,2-Dimethyl-5-((1-methyl-1H-indol-3-yl)methyl-ene)-1,3-dioxane-4,6-dione (**5a**)

Yellow solid; Yield = 2.65 g (93 %); m.p.: 218–221 °C; IR (KBr): 1,700 cm^{-1} (very strong, CO) and 1,679 cm^{-1} (very strong, CO); 1H NMR (DMSO-d6/TMS): δ 1.69 (s, 6H, $2CH_3$), 4.01 (s, 3H, N CH_3), 7.36–7.91 (m, 4H aryl protons of the indole ring), 8.68 (s, 1H, α-proton of the indole ring), 9.30 (s, 1H, vinylic proton of the indole ring); 13C spectrum (DMSO-d6/TMS): δ 27.41,44.3, 103.51,

Table 4 Anti-fungal 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 fungi	Zone of inhibition in mm for concentration of				
			50 μg/ml	100 μg/ml	200 μg/ml	300 μg/ml	500 μg/ml
1	**3a**	*Rhizoctonia solani*	10	15	19	24	32
		Fusarium oxysporum	10	14	17	21	31
		Aspergillus niger	7	11	15	19	26
		Aspergillus flavus	5	10	13	17	24
2	**3b**	*Rhizoctonia solani*	10	15	19	24	31
		Fusarium oxysporum	10	15	18	24	30
		Aspergillus niger	7	12	15	14	24
		Aspergillus flavus	5	9	12	13	22
3	**3c**	*Rhizoctonia solani*	10	15	19	24	32
		Fusarium oxysporum	10	14	17	21	31
		Aspergillus niger	7	11	15	19	26
		Aspergillus flavus	5	10	13	17	24
4	**3d**	*Rhizoctonia solani*	10	15	19	24	32
		Fusarium oxysporum	10	14	17	21	31
		Aspergillus niger	7	11	15	19	26
		Aspergillus flavus	5	10	13	17	24
5	**5a**	*Rhizoctonia solani*	7	12	16	21	29
		Fusarium oxysporum	7	12	16	21	29
		Aspergillus niger	6	10	14	18	25
		Aspergillus flavus	4	9	12	15	23
6	**5b**	*Rhizoctonia solani*	7	12	16	21	29
		Fusarium oxysporum	7	12	16	21	29
		Aspergillus niger	6	10	14	18	25
		Aspergillus flavus	4	9	12	15	23
7	**5c**	*Rhizoctonia solani*	7	12	16	21	29
		Fusarium oxysporum	7	12	16	21	29
		Aspergillus niger	6	10	14	18	25
		Aspergillus flavus	4	9	12	15	23
8	**5d**	*Rhizoctonia solani*	7	12	16	21	29
		Fusarium oxysporum	7	12	16	21	29
		Aspergillus niger	6	10	14	18	25
		Aspergillus flavus	4	9	12	15	23
9	**7a**	*Rhizoctonia solani*	7	12	16	21	29
		Fusarium oxysporum	7	12	16	21	29
		Aspergillus niger	6	10	14	18	25
		Aspergillus flavus	4	9	12	15	23
10	**7b**	*Rhizoctonia solani*	7	12	16	21	29
		Fusarium oxysporum	7	12	16	21	29
		Aspergillus niger	6	10	14	18	25
		Aspergillus flavus	4	9	12	15	23
11	**7c**	*Rhizoctonia solani*	7	12	16	21	29
		Fusarium oxysporum	7	12	16	21	29
		Aspergillus niger	6	10	14	18	25
		Aspergillus flavus	4	9	12	15	23

Table 4 continued

S. no.	Compound no.	Types of fungi	Zone of inhibition in mm for concentration of				
			50 μg/ml	100 μg/ml	200 μg/ml	300 μg/ml	500 μg/ml
12	**7d**	*Rhizoctonia solani*	7	12	16	21	29
		Fusarium oxysporum	7	12	16	21	29
		Aspergillus niger	6	10	14	18	25
		Aspergillus flavus	4	9	12	15	23
13	Mycostanin	*Rhizoctonia solani*	16	20	22	30	38
		Fusarium oxysporum	15	18	21	29	37
		Aspergillus niger	11.2	14	16.6	23	34
		Aspergillus flavus	11	13	16	22	32

Table 5 Anti-bacterial activity of **3(a–d)**, **5(a–d)**, and **7(a–d)** against *Klebsiella pneumonia, Escherichia coli, Staphylococcus aureus*, and *Bacillus subtilis* in minimum inhibitory concentration (MIC) in μg/ml

S. no.	Compound no.	Types of bacteria and minimum inhibitory concentration (MIC) in μg/ml			
		Klebsiella pneumonia (MIC)	*Escherichia coli* (MIC)	*Staphylococcus aureus* (MIC)	*Bacillus subtilis* (MIC)
1	**3a** (R=H)	10	10	20	20
2	**3b** (R=OMe)	10	10	20	20
3	**3c** (R=Br)	10	10	20	20
4	**3d** (R=NO_2)	10	10	20	20
5	**5a** (R=H)	15	15	25	30
6	**5b** (R=OMe)	15	15	25	30
7	**5c** (R=Br)	15	15	25	30
8	**5d** (R=NO_2)	15	15	25	30
9	**7a** (R=H)	15	15	25	30
10	**7b** (R=OMe)	15	15	25	30
11	**7c** (R=Br)	15	15	25	30
12	**7d** (R=NO_2)	15	15	25	30
13	**5a** (R=H)	15	15	25	30
14	**5b** (R=OMe)	15	15	25	30
15	**5c** (R=Br)	15	15	25	30
16	**5d** (R=NO_2)	15	15	25	30
17	**7a** (R=H)	15	15	25	30
18	**7b** (R=OMe)	15	15	25	30
19	**7c** (R=Br)	15	15	25	30
20	**7d** (R=NO_2)	15	15	25	30
21	Streptomycin	5	5	10	20

104.61, 111.12, 119.12, 122.9, 123.14, 126.39, 134.12, 136.12, 142.1, 150.21, 160.2; MS : $m/z = 286$ (M+1).

5-((5-Methoxy-1-methyl-1H-indol-3-yl)methyle-ne)-2,2-dimethyl-1,3dioxane-4,6-dione (**5b**)

Light orange color solid; Yield = 2.866 g (91 %); m.p.: 198–200 °C; IR (KBr): 1,743 cm^{-1} (very strong, CO) and 1,664 cm^{-1} (very strong, CO). ^{1}H NMR (DMSO-d_6/TMS): δ 1.68 (s, 6H, $2CH_3$), 3.45 (s, 3H, $-OCH_3$), 3.96 (s, 3H, N CH_3), 6.9–7.58 (m, 3H aryl protons of the indole ring), 8.65 (s, 1H, α-proton of the indole ring), 9.23 (s, 1H, vinylic proton of the indole ring); ^{13}C spectrum (DMSO-d_6/TMS): δ 27.36, 45.2, 53.11, 103.18, 104.23, 111.60, 118.18, 121.8, 123.9, 127.48, 132.4, 146.4, 150, 159.7; MS : $m/z = 316$ (M+1).

Table 6 Anti-fungal activity of **3(a–d)**, **5(a–d)**, and **7(a–d)** against *Rhizoctonia solani, Fusarium oxysporum, Aspergillus niger*, and *Aspergillus flavus in* minimum inhibitory concentration (MIC) in μg/ml

S. no.	Compound no.	Types of fungi and minimum inhibitory concentration (MIC) in μg/ml			
		Rhizoctonia solani (MIC)	*Fusarium oxysporum* (MIC)	*Aspergillus niger* (MIC)	*Aspergillus flavus* (MIC)
1	**3a** (R=H)	25	25	30	35
2	**3b** (R=OMe)	25	25	30	35
3	**3c** (R=Br)	25	25	30	35
4	**3d** ($R=NO_2$)	25	25	30	35
5	**5a** (R=H)	35	35	40	40
6	**5b** (R=OMe)	35	35	40	40
7	**5c** (R=Br)	35	35	40	40
8	**5d** ($R=NO_2$)	35	35	40	40
9	**7a** (R=H)	35	35	40	40
10	**7b** (R=OMe)	35	35	40	40
11	**7c** (R=Br)	35	35	40	40
12	**7d** ($R=NO_2$)	35	35	40	40
13	**5a** (R=H)	35	35	40	40
14	**5b** (R=OMe)	35	35	40	40
15	**5c** (R=Br)	35	35	40	40
16	**5d** ($R=NO_2$)	35	35	40	40
17	**7a** (R=H)	35	35	40	40
18	**7b** (R=OMe)	35	35	40	40
19	**7c** (R=Br)	35	35	40	40
20	**7d** ($R=NO_2$)	35	35	40	40
21	Mycostanin	15	15	20	20

5-((5-Bromo-1-methyl-1H-indol-3-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**5c**)

Yellow solid; Yield = 3.34 g (92 %); m.p.: 265 °C; IR (KBr): 1,708 cm^{-1} (very strong CO) and 1,622 cm^{-1} (very strong, CO); 1H NMR (DMSO-*d*6./TMS): δ1.67 (s, 6H, $2CH_3$), 4.21 (s, 3H, N CH_3), 6.9–7.5 (m, 3H aryl protons of the indole ring), 8.47 (s, 1H, α-proton of the indole ring), 8.54 (s, 1H, vinylic proton of the indole ring); ^{13}C spectrum (DMSO-*d*6/TMS): δ 27.4, 45.4, 103.55, 104.13, 111.12, 117.1, 119.4, 122.34, 124.32, 130.8, 136.12, 144.1, 151.12,160; MS : $m/z = 365$ (M+1).

5-((5-Nitro-1-methyl-1H-indol-3-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**5d**)

Yellow solid; Yield = 3.10 g (94 %); m.p.: 215 °C; IR (KBr): 1,722 cm^{-1} (very strong, CO) and 1,672 cm^{-1} (very strong, CO); 1H NMR (DMSO-*d*6/TMS): δ 1.71 (s, 6H, $2CH_3$), 4.20 (s, 3H, N CH_3), 7.6–8.0 (m, 3H aryl protons of the indole ring), 8.74 (s, 1H, α-proton of the indole ring), 9.28 (s, 1H, vinylic proton of the indole ring); ^{13}C spectrum (DMSO-*d*6/TMS): δ 27.38, 47.2, 103.12, 104.1, 111.12, 113.6, 119, 122.3, 124.1, 128.12, 134.14, 142, 148.12, 159.9; MS : $m/z = 331$ (M+1).

2,2-Dimethyl-5-((1-ethyl-1H-indol-3-yl)methylene)1,3-dioxane-4,6-dione (**7a**)

Yellow solid; Yield = 2.78 g (93 %); m.p.: 203–205 °C; IR (KBr):1,711 cm^{-1} (Very strong, CO), 1,689 cm^{-1}(Very strong, CO);^1H NMR (DMSO-d_6/TMS): δ 1.53 (t, 3H, CH_3), 1.66 (s, 6H, $2CH_3$), 4.03 (q, 2H, CH_2), 7.33–7.82 (m, 4H aryl protons of the indole ring), 8.61 (s, 1H, α-proton of the indole ring), 9.34 (s, 1H, vinylic proton of the indole ring); ^{13}C spectrum (DMSO-d_6/TMS): δ 14.7, 27.2, 44.5, 103, 110, 111, 113, 120.1, 121, 122, 127, 136.6, 138.2, 148.2, 161. MS : $m/z = 300$ (M+1).

5-((5-Methoxy-1-ethyl-1H-indol-3-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**7b**)

Yellow solid; Yield = 2.99 g (91 %); m.p: 140–142 °C; IR(KBr): 1,718 cm^{-1} (very strong, CO) and 1,661 cm^{-1} (very strong, CO); ^1H NMR (DMSO-d_6/TMS): δ 1.54 (t, 3H, CH_3), 1.67 (s, 6H, $2CH_3$), 3.62 (s, 3H, O CH_3), 4.15 (q,

2H, CH_2), 7.21–7.98 (m, 3H aryl protons of the indole ring), 8.61 (s, 1H, α-proton of the indole ring), 9.28 (s, 1H, vinylic proton of the indole ring); ^{13}C spectrum (DMSO-d_6/TMS): δ 14.6, 27.3, 43.4, 56.5, 102, 103.5, 110.1, 111, 113, 120.8, 126.3, 128.4, 152, 153.3, 161.1; MS : m/z = 330 (M+1).

5-((5-Bromo-1-ethyl-1H-indol-3-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**7c**)

Yellow solid; Yield = 3.477 g (92 %); m.p: 198–200 °C; IR(KBr): 1,703 cm^{-1} (very strong, CO) and 1,691 cm^{-1} (very strong, CO); ^{1}H NMR (DMSO-d_6/TMS): δ 1.51 (t, 3H, CH_3), 1.68 (s, 6H, $2CH_3$), 4.23 (q, 2H, CH_2), 7.32–8.03 (m, 3H aryl protons of the indole ring), 8.12 (s, 1H, α-proton of the indole ring), 8.87 (s, 1H, vinylic proton of the indole ring); ^{13}C spectrum (DMSO-d_6/TMS): δ 14.21, 27.8, 44.1, 104.5, 109.5, 113.2, 117.0, 120.5, 121, 121.8, 128.5, 134.5, 135.5, 150, 160.2; MS : m/z = 379 (M+1).

5-((5-Nitro-1-ethyl-1H-indol-3-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**7d**)

Yellow solid; Yield = 3.233 g (94 %); m.p.: 151–153 °C; IR(KBr): 1,709 cm^{-1} (very strong, CO) and 1,691 cm^{-1}(very strong, CO); ^{1}H NMR (DMSO-d_6/TMS): δ 1.56 (t, 3H, CH_3), 1.71 (s, 6H, $2CH_3$), 4.65 (q, 2H, N CH_2), 7.87–8.34 (m, 3H aryl protons of the indole ring), 8.23 (s, 1H, α-proton of the indole ring), 8.54 (s, 1H, vinylic proton of the indole ring); ^{13}C spectrum (DMSO-d_6/TMS): δ 14.5, 27.38, 47.2, 103.12, 104.1, 111.12, 113.6, 119, 122.3, 124.1, 128.12, 134.14, 142, 150.9, 160; MS : m/z = 345 (M+1).

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