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Synthesis and Antimicrobial Studies of Newly Synthesized 1-Substituted-3-Substituted Propane-1, 3-Diones

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ABSTRACT

I this study, a new series of 1-substituted-3-substitutedpropane-1, 3-diones i.e. β-diketones 4(a-e) have been synthesized from 4-Hydroxy-3-methoxybenzaldehyde i.e. Vanillin which is a phenol as well as aldehyde. The structures of newly synthesized compounds of the series have been established on the basis of usual chemical characteristics, elemental analysis and spectral studies of IR and NMR. They have also been studied for their antimicrobial effects against growth response of bacterial and fungal strains through agar diffusion method.

Keywords: *Vanillin*; *Spectral studies; Antimicrobial effects*

INTRODUCTION

Propane-1, 3-diones or commonly referred as β-diketones are one of the important classes of organic compounds frequently encountered in synthetic chemistry. They are important intermediates not only as key building blocks for the synthesis of core heterocycles such as pyrazolo, isoxazole, triazole, flavone, benzodiazepine and pyrimidine in medicinal chemistry, but also as an invaluable chelating ligand for various lanthanide and transition metals in material chemistry. Aside from their synthetic importance, β-diketones have showed wide assortment of pharmacological activities like antibacterial, antiviral, systematic insecticidal, antioxidant, prophylactic antitumor as well as an anti-sunscreen agent that filters harmful U.V. radiation to protect skin. In addition, β-diketones have examined as breast cancer chemo-preventive blocking agent, antiestrogenic and anticarcinogenic agent. Furthermore, β-diketones are well known to have a keto-enol tautomerism and recently it has been reported that β-keto-enols are the important pharmacophore for HIV-I Integrase (IN) inhibitor [1]. Presence of such varying pharmacological activities in β-diketones developed our interest to synthesize some new β-diketone molecules containing phenolic as well as aldehydic group. With this view here, we have synthesized a new series of 1-substituted-3-substituted derivatives of propane-1, 3-dione i.e. β-diketones containing moiety of vanillin, characterized them by usual chemical characteristics, elemental analysis and spectral techniques as well as investigated its antimicrobial activities through method of agar diffusion.

The chemicals and solvents used were of highest purity purchased commercially from Merck, S.D. Fine and Alfa Aesar Company Ltd. The melting points of all the synthesized compounds were recorded by Thiele's melting point apparatus as uncorrected values. The elemental analysis was carried out on Thermo Scientific CHNS elemental

analyser. IR spectra were recorded on a Shimadzu instrument using KBr pallet. 1H NMR spectra were scanned by Brucker at 400 MHz using DMSO-d6 as solvent and TMS as an internal reference. 13C NMR spectrum of one sample (4a) was recorded on same instrument at 100 MHz. Experimental procedure for synthesis of 1-substituted-3-substitutedpropane-1, 3-diones 4(a-e).

Preparation of 4-Formyl-2-methoxyphenyl acetate

Initially Vanillin (a) was refluxed along with acetic anhydride and sodium acetate for 1 hr. The reaction mixture was cooled and poured into cold water containing crushed ice. Two layers were formed out of which lower organic layer was separated by means of separating funnel, washed number of times by distilled water and then purified by distillation to get 4-Formyl-2-methoxyphenyl acetate. Mp. 78-80°C, Yield 86%.

Preparation of 5-Formyl-2-hydroxy-3-methoxyacetophenone

4-Formyl-2-methoxyphenyl acetate (1) was heated with anhydrous AlCl3 (1:3) at 120°C for 1 hr in an oil bath (Fries rearrangement). The reaction mixture was cooled and decomposed by 10% ice cold HCl to form crude ketone. It was then purified by dissolving it in glacial acetic acid and pouring the solution drop wise in ice cold distilled water with continuous stirring to get 5-Formyl-2-hydroxy-3-methoxyacetophenone. M.p. 102-104°C, Yield 78%.

Preparation of 2-(Substituted benzoyloxy)-5-formyl-3-methoxyacetophenones 3(a-e)

5-Formyl-2-hydroxy-3-methoxyacetophenone (0.04 mol) and appropriate substituted benzoic acid (0.05 mol) were dissolved in pyridine and POCl3 was added drop by drop with continuous stirring below the temperature of 10°C. The reaction mixture was kept overnight at room temperature and then decomposed by 10% ice cold HCl. The solid product thus separated was filtered, washed with water followed by 10% NaHCO3 washing and again number of times with distilled water. It was then recrystalized from hot ethanol to get 2-(Substituted benzoyloxy)-5-formyl-3-methoxy-acetophenones 3(a-e) as.

- 2-(4'-Nitrobenzoyloxy)-5-formyl-3-methoxyacetophenone (3a), M.p.126-130°C, Yield 80%.
- 2-(4'-Methoxybenzoyloxy)-5-formyl-3-methoxyacetophenone (3b), M.p.116-120°C, Yield 71%.
- 2-(2'-Chlorobenzoyloxy)-5-formyl-3-methoxyacetophenone (3c), M.p.110-114°C, Yield 75%.
- 2-(4'-Chlorobenzoyloxy)-5-formyl-3-methoxyacetophenone (3d), M.p.124-128°C, Yield 76%.
- 2-(2', 4'-Dichlorobenzoyloxy)-5-formyl-3-methoxyacetophenone (3e), M.p.134-136°C, Yield 84%.

2-(Substituted benzoyloxy)-5-formyl-3-methoxyacetophenones 3(a-e) (0.05 mol) were dissolved in pyridine (40 mL). The solution was warmed up to 60°C and pulverized KOH was added slowly with continuous stirring. After 6-8 hrs the reaction mixture was acidified by ice cold dil. HCl (1:1). The solid product thus separated was filtered, washed with 10% NaHCO3 and then number of times with distilled water. It was then recrystalized from ethanol-acetic acid mixture to get corresponding β-diketones namely 1-(5'-Formyl-2'-hydroxy-3'-methoxyphenyl)-3-(substituted phenyl) propane-1, 3-diones 4(a-e). The complete experimental scheme for synthesis of above titled compounds is depicted in (Figure1).

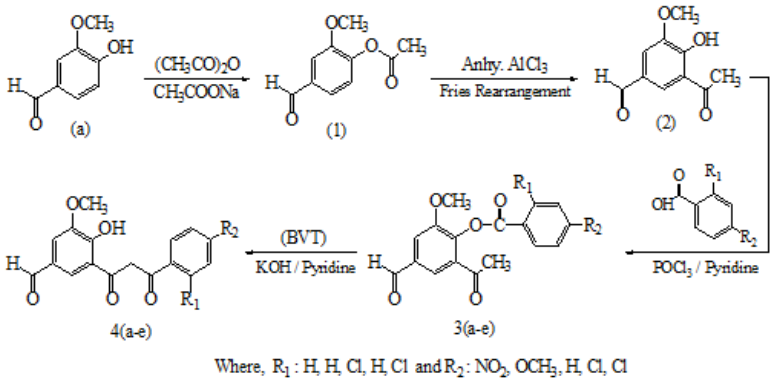

Figure 1: Experimental scheme for synthesis of 1-(5'-formyl-2'-hydroxy-3'-methoxyphenyl)-3-(substitutedphenyl) propane-1, 3-diones 4(a-e)

Antimicrobial Study

In this section, all newly synthesized 1-(5'-Formyl-2'-hydroxy-3'-methoxyphenyl)-3-(substitutedphenyl)propane-1, 3-diones 4(a-e) were screened for their antimicrobial activities by Agar diffusion method [23-24] in order to investigate their effects against growth response of two strains of bacteria viz. E. coli (Gram -ve), and S. aureus (Gram +ve) and one strain of fungi viz. A. flavus at six different concentrations ranging from 25 µg/mL to 1000 µg/mL. DMSO was used to prepare the solutions of above concentrations. The Nutrient-agar and Czapek-Dox media were used respectively for antibacterial and antifungal analysis as well as reference drugs Ciprofloxacin and Amphotericin were utilized for the purpose of comparison [2].

Antibacterial Analysis

First of all, the stock cultures of bacteria were revived by inoculating in broth media and grown at the temperature 37ºC for 18 hrs. The agar plates of above media were prepared and wells were made in the plates. Each plate was inoculated with 18 hrs old cultures (100 µL, 104 CFU) and spread evenly on the plate. After 20 minutes, the wells were filled with different concentration of compounds and antibiotic. All the plates were incubated at temperature 37ºC for 24 hrs and diameter of inhibition zones were measured in mm [3].

Antifungal Analysis

First of all, the stock culture of fungus was revived by inoculating in broth media and grown at temperature 27ºC for 48 hrs. The agar plates of the above media were prepared and wells were made in the plates. Each plate was inoculated with 48 hrs old cultures (100 µL, 104 CFU) and spread evenly on the plate. After 20 minutes, the wells were filled with different concentrations of compounds and antibiotic. All the plates were incubated at temperature 27ºC for 96 hrs and diameter of inhibition zones were measured in mm.

RESULTS AND DISCUSSION

Spectroscopic Data

The IR, 1H NMR and 13C NMR spectral data showed expected signals or peaks which correspond to various groups present in each compound. Also, elemental analysis was found in full agreement with the proposed structures. The elemental analysis, IR, 1H NMR and 13C NMR spectral data of compounds 4(a-e) are shown below.

1-(5'-Formyl-2'-hydroxy-3'-methoxyphenyl)-3-(4'-nitrophenyl) propane-1, 3-dione (4a)

Brown solid; Yield 76%; M.p. 180-184oC; Elemental Anal. Calcd. for C17H13NO7: C, 59.48; H, 3.82; O, 32.62. Found: C, 59.41, H, 3.75, O, 32.56. IR (KBr) cm-1: 3120 (Phenolic OH stretch), 2980 (Aromatic C-H stretch), 2850 (Aliphatic C-H stretch), 1695 (C=O stretch), 1520 (Aromatic C=C stretch), 1285 (C-N stretch).1H NMR (400 MHz, DMSO-d6) δ (ppm): 2.51 (s, 3H, -OCH3), 3.43 (s, 2H, -CH2), 3.80 (s, 1H, -OH), 8.15-8.32 (m, 6H, Ar-H), 13.54 (s, 1H, -CHO). 13C NMR (100MHz, DMSO-d6) δ (ppm): 40 (-CH2), 190 (-CHO), 195 (C=O), 123-136 (Ar-C), 149-165 (C=C).

1-(5'-Formyl-2'-hydroxy-3'-methoxyphenyl)-3-(4'-methoxyphenyl) propane-1, 3-dione (4b)

Dark brown solid; Yield 68%; M.p. 140-144oC; Elemental Anal. Calcd. for C18H16O6: C, 65.85; H, 4.91; O, 29.24. Found: C, 65.72; H, 4.87; O, 29.03. IR (KBr) cm-1: 3340 (Phenolic OH stretch), 2980 (Aromatic C-H stretch), 2910 (Aliphatic C-H stretch), 1615 (C=O stretch), 1515 (Aromatic C=C stretch), 1260 (C-O stretch).1H NMR (400MHz, DMSO-d6) δ (ppm): 2.51 (s, 3H, -OCH3), 3.81 (s, 2H, -CH2), 5.13 (s, 1H, -OH), 6.99-7.90 (m, 6H, Ar-H), 10.10 (s, 1H, -CHO).

1-(5'-Formyl-2'-hydroxy-3'-methoxyphenyl)-3-(2'-chlorophenyl) propane-1, 3-dione (4c)

Dark brown solid; Yield 72%; M.p. 133-136oC; Elemental Anal. Calcd. for C17H13ClO5: C, 61.36; H, 3.94; O, 24.04. Found: C, 61.28; H, 3.87; O, 24.0. 1H NMR (400MHz, DMSO-d6) δ (ppm): 2.50 (s, 3H, -OCH3), 3.38 (s, 2H, -CH2), 4.10 (s, 1H, -OH), 6.77-7.65 (m, 6H, Ar-H), 9.88 (s, 1H, -CHO).

1-(5'-Formyl-2'-hydroxy-3'-methoxyphenyl)-3-(4'-chlorophenyl) propane-1, 3-dione (4d)

Brown solid; Yield 77%; P.m. 145-148oC; Elemental Anal. Calcd. for C17H13ClO5: C, 61.36; H, 3.94; O, 24.04. Found: C, 61.30; H, 3.83; O, 24.0. IR (KBr) cm-1: 3340 (Phenolic OH stretch), 2970 (Aromatic C-H stretch), 2885 (Aliphatic C-H stretch), 1590 (C=O stretch), 1385 (C-O stretch), 875 (C-Cl stretch).1H NMR (400MHz, DMSO-d6) δ (ppm): 2.52 (s, 3H, -OCH3), 3.36 (s, 2H, -CH2), 4.30 (s, 1H, -OH), 7.23-7.74 (m, 6H, Ar-H), 10.9 (s, 1H, -CHO).

1-(5'-Formyl-2'-hydroxy-3'-methoxyphenyl)-3-(2',4'-dichlorophenyl) propane-1, 3-dione (4e)

Yellow-brown solid; Yield 80%; M.p. 168-170oC; Elemental Anal. Calcd. for C17H12Cl2O5: C, 55.61; H, 3.29; O, 21.79. Found: C, 55.58; H, 3.21; O, 21.67. 1H NMR (400MHz, DMSO-d6) δ (ppm): 2.51 (s, 3H, -OCH3), 3.36 (s, 2H, -CH2), 4.15 (s, 1H, -OH), 7.48-7.83 (m, 6H, Ar-H), 13.54 (s, 1H, -CHO).

Antimicrobial Activity

In the present work, total five 1-substituted-3-substituted derivatives of propane-1, 3-dione 4(a-e) were synthesized, purified by recrystallization and used individually to investigate their antimicrobial effects against pathogenic microorganisms *viz*. E. coli, S. aureus and A flavus. The resulting data on antimicrobial activity of newly synthesized compounds 4(a-e) and antibiotics against E. coli, S. aureus and A. flavus with zone of inhibition in mm are tabulated in (Table1 and 4) and their photographs are shown under respectively [4]. From the results on antimicrobial activities, it was observed that, out of all these compounds 4(a-e), compound (4b) and (4c) has not showed any inhibition zone against E. coli at all the concentrations tested, while the compounds (4a), (4d) and (4e) showed (3,5,8), (3,3,5) and (3,6,8) mm of inhibition zones at 250, 500 and 1000 µg/mL concentrations respectively. The minimum inhibitory concentration at which these compounds (4a), (4d) and (4e) showed inhibition against the growth of E. coli was at 250 µg/mL but in case of compounds (4b) and (4c) for E. coli, MICs was not found [5]. In case of S. aureus, compound (4a) showed (3, 5, 10, 11) mm of zones at 100, 250, 500 and 1000 µg/mL

concentrations respectively with a MICs at 100 µg/mL. Compound (4b) and (4d) showed 4 and 3 mm of inhibition zones at 1000 µg/mL concentrations only while compound (4e) showed (3, 5, 7) mm of zones at 250, 500 and 1000 µg/mL respectively with MICs at 250 µg. The compound (4c) not showed any inhibition zones for S. aureus at all the tested concentrations. The results on antifungal activity was shocked us because all these newly synthesized compounds 4(a-e) not gave any zones of inhibitions and showed negligible activity against fungi Aflavus.

Table 1: Antibacterial activity of synthesized compounds 4(a-e) against *E. coli*

Compound	25 µg	50 µg	100 µg	250 µg	500 µg	1000 µg	MIC µg
4a	NI	NI	NI	3	5	8	250
4b	NI	NI	NI	NI	NI	NI	NF
4c	NI	NI	NI	NI	NI	NI	NF
4d	NI	NI	NI	3	3	5	250
4e	NI	NI	NI	3	6	8	250

Table 2: Antibacterial activity of synthesized compounds 4(a-e) against *S. aureus*

Compound	25 µg	50 µg	100 µg	250 µg	500 µg	1000 µg	MIC µg
4a	NI	NI	3	5	10	11	100
4b	NI	NI	NI	NI	NI	4	1000
4c	NI	NI	NI	NI	NI	NI	NF
4d	NI	NI	NI	NI	NI	3	1000
4e	NI	NI	NI	3	5	7	250

Table 3: Antibacterial activity of std. Ciprofloxacin against human pathogens

Organism	25 µg	50 µg	100 µg	200 µg	400 µg	800 µg	MIC µg
E. coli	18	20	23	26	28	31	25
S. aureus	13	18	21	25	27	34	25

Table 4: Antifungal activity of std. Amphotericin against fungi *A. flavus*

Organism	25 µg	50 µg	100 µg	200 µg	400 µg	800 µg	MIC µg
A. flavus	NI	NI	NI	NI	7	10	400

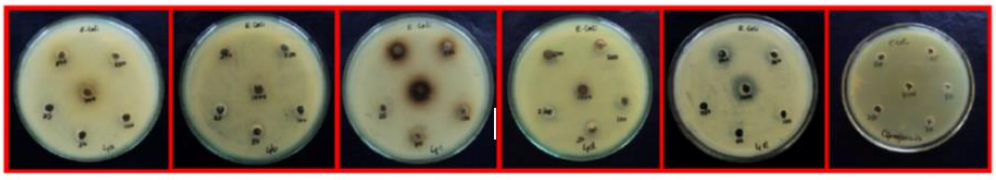

Figure 2: Effects of synthesized compounds 4(a-e) and std. Ciprofloxacin on the growth response of *E. coli*

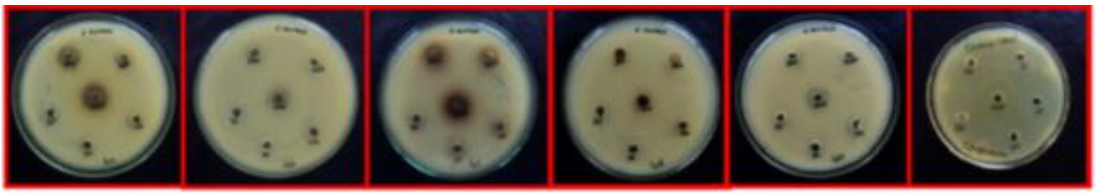

Figure 3: Effects of synthesized compounds 4(a-e) and std. Ciprofloxacin on the growth response of *S. aureus*

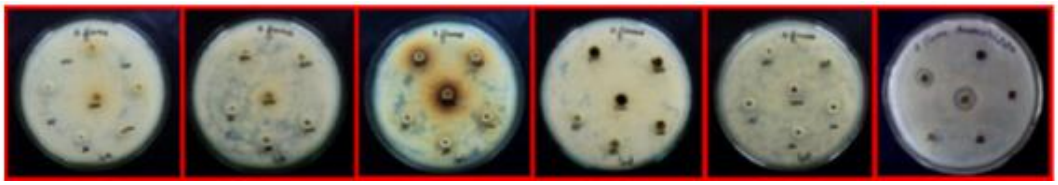

Figure 4: Effects of synthesized compounds 4(a-e) and std. Amphotericin on the growth response of *A. flavus*

CONCLUSION

In conclusion, a new series of 1-substituted-3-substituted derivatives of propane-1, 3-dione 4(a-e) bearing 4-Hydroxy-3-methoxybenzaldehyde i.e. Vanillin moiety were successfully synthesized in satisfactory yield by employing Baker-Venkataraman rearrangement of corresponding substituted 2-benzoyloxyacetophenones 3(a-e) and their structures were elucidated by chemical characteristics, elemental analysis and IR, 1H NMR and 13C NMR spectroscopic techniques. The results on antimicrobial studies reveals that all the five compounds 4(a-e) were found to have low to moderate antibacterial effects against the growth response of pathogens E. coli and S. aureus as compared to std. Ciprofloxacin drug but in case of antifungal activity against a pathogen A. flavus, they were found to have negligible effects or said to be inactive at all the analysed range of concentrations.

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