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Synthesis and Antimicrobial Activity of Some Furfural Substituted Bisdimedone Derivatives

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Abstract: Bisdimedone derivatives were synthesized by the method adopted by Horning and Honing. All the newly synthesized compounds showed antimicrobial activities against certain bacterial and fungal strains. The compounds 2-(2-chloro-phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)-methylfura**n** and 2-(4-flor-phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)methylfuran showed good activity against Proteus mirabilis and Klebsiella pneumonia and 2-(4-chloro-phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)-methylfuran and 2-(2-chloro-phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)-methylfuran showed prominant activity against Staphylococcus aureus. Bisdimedone derivatives shows fungicide activity as well.

Keywords: bisdimedone, antimicrobial activity, fungicide xanthenes.

1 Introduction

A thorough basic concept and knowledge of drug synthesis may ultimately help a medicinal chemist to produce lifesaving drugs [1] such as: penicillin, quinine, prostaglandins, steroids, antineoplastic agents. Synthetic medicinal chemistry, with the skill, wisdom and effort has proved to be a major endeavor not only confined to the laboratories of universities in general, but also to the bulk-drug industry in particular. Biological activities of a compound is a function of the structure. Minor changes may cause prominent implication over activity. Replacement of one group by the other in a specific location in the molecule may sometimes completely reverse the action of the compound. Chemicals that are used to diagnose, treat or prevent a disease are called pharmaceutical agents [2].Some pharmacological agents [3] synthesized from organic compounds may have chemical structures closely resembling those of active natural products. Some pharmaceutical agents are discovered accidentally, other are intentionally designed for use against certain disorders. Antibiotics are one of the most important therapeutic discoveries in medicine [4]. Antibiotics are chemical substance produced by metabolism of living organisms and that in high dilution antagonizes the growth and/or the survival of one or more species of microorganism[5] and some other animal cells e.g.,tumour cells and viruses. The probable points of differences amongst the antibiotics may be physical, chemical and pharmacological properties, antibacterial spectra and mechanism of action. Depending upon clinical effectiveness, spectrum of activity and degree of selectivity, those inhibiting only one group of microorganism are called as narrow spectrum antibiotics e.g.nystatin and bacitracin. These antibiotics exhibit a high degree of selectivity. A few antibiotics inhibit both Gram-positive and Gramnegative bacteria and/or other intracellular organism may be termed as broad spectrum antibiotics e.g., chloramphenicol and tetracyclins. The emergence of microbial strains that are resistant to the antibacterial agents obviously limits therapeutic value of these agents. This rapidly developing problem of antimicrobial agent resistance is global and is related to pattern of antibiotic use [6][7]. The pharmaceutical industries have provided alternative antibiotics or developed new ones. The result has been a steady supply of new agents to keep ahead of the problem. Different groups of antimicrobials [8] are recommended for different types of pathogens. Each compound has a specific mode of action. Human toxicity is low when the mode of action is specific for the target pathogen and spares human tissues. Toxicity is higher when the agent is relatively non-specific. The antiseptics and disinfectants [9] differ fundamentally from systemically active chemotherapeutic agents in the latter posses little or no selective toxicity. The antibacterial action of antiseptics and disinfectants are depended on concentration, temperature and time. For certain organism, higher concentrations may be inhibitory and still higher concentrations may be bactericidal. Bisdimedone derivatives,acridines [12],acridinediones [13], xanthene derivatives show antimicrobial activities against certain bacterial and fungal strains. Xanthene, the parent

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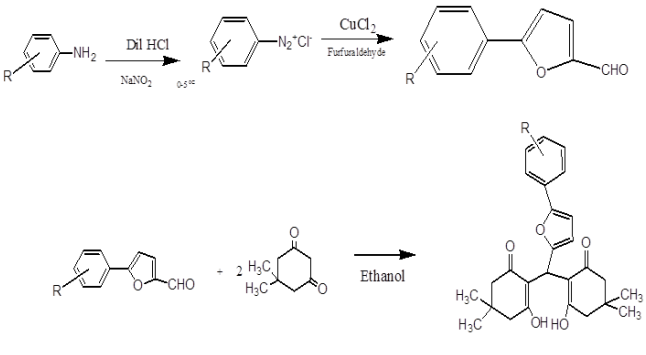
compound of a number of naturally occurring substances. Xanthylium and the carbonyl compound xanthone are derived from xanthene. Xanthenes are important because of their use in medicine and they possess biological activities [14]. Xanthene dyes were reported to possess antifungal activity [15] suppressing oriental fruit fly populations [16] [17].

2 Results and Discussion



	R
I.	[(2-chloro-phenyl)]
II.	[(4-chloro-phenyl)]
III.	[(2-nitro-phenyl)]
IV.	[(4-nitro-phenyl)]
V.	[(2-floro-phenyl)]
VI.	[(4-floro-phenyl)]
VII.	[(2-methyl-phenyl)]
VIII.	[(4-methyl-phenyl)]

Scheme 1: Synthesis

5-[(substituted-phenyl)]-furan-2-carbaldehyde was prepared by reported method [24] A mixture of substituted aromatic aniline (8.0 g, 0.1 M) dil HCl (15%, 30 ml) and water (40 ml) was heated on water bath to get a clear solution. The solution was cooled to 0°C to 5°C and diazotized with NaNO2 solution (15%, 12 ml). After diazotization, a freshly distilled furfural aldehyde (6.0 ml, 0.1 M) and aqueous cupric chloride (1.2 g in 5 ml of water) were added with stirring. The stirring was continued for 8 h and kept overnight. After completing the reaction, the solid was filtration and washed with water and crystallized from ethyl acetate (step1st). Dimedone was treated with 5-[(substituted-phenyl)]-furan-2-carbaldehyde in ethanol (50%, 20 ml). The reaction mixture was heated for 25 minutes. After cooling the reaction mixture, the product (bisdimedone1) was collected by filtration and dried. The crude product was purified by crystallization from methanol (step2nd).

Antimicrobial activity of synthesized bisdimedone derivatives

Method: Well diffusion method, Medium: The nutrient agar medium, Solvent: Chloroform. Concentrations: 50µM and 100 µM. Condition: 24 hours at 24-28°C, Standard: The antibiotic Streptomycin and Amphotericin. The nutrient agar medium, 20 mL was poured into the sterile petri dishes. To the solidified plates, wells were made using a sterile cork borer 10 mm in diameter. The 24 hour subcultured bacterial and fungal strains was inoculated in the petri-plates, with a sterile cotton swab dipped in the nutrient broth medium. After inoculating, the compounds were dissolved separately with the chloroform solvent and poured into the wells with varying concentrations ranging from 50 & 100 µM using a micropipette. The plates were left over for 24 hours at 24-28 °C. The antibiotic Streptomycin and Amphotericin was used as a standard for comparative study. Zone of inhibition is measured in mm (given in table 1).

Table 1 zone of inhibition in mm

Testing compd.	Zone of Inhibition								
	Bacterial strains					Fungal strains			
	S. aureus	*E. coli*	*P. mirabilis*	*P. aeruginosa*	*K. pneumonia*	*A. flavus*	*A. fumigatus*	*A. niger*	*C. albicans*
1	17	10	12	18	13	11	10	12	13
2	16	11	13	8	14	16	12	14	12
3	14	9	13	10	16	13	10	10	11
4	12	13	14	12	14	9	8	12	10
5	9	12	12	13	13	11	12	13	9
6	8	64	14	11	12	10	11	10	12
7	13	10	14	10	12	12	10	13	14
8	12	12	61	9	11	13	12	14	12

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3 Material and Methods

All the chemicals were purchased from Sigma-Aldrich and used without further purification. Thin layer chromatography was performed using silica gel 60 F 254 pre coated almunium sheets from Merck. The progress of the reaction was monitored by TLC.

1 Synthesis of compound 2-(4-chloro-phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)-methylfuran :5-(4-chloro-phenyl)-furan-2-carbaldehyde (0.030mol) is treated with dimedone (2g,0.015mol) in ethanol (50% 30 ml) The reaction mixture was heated for 15 minutes. The compound was collected by filtration and purified by repeated recrystallization from 95% ethanol.

Characterization of 1st compound: - Yield: 83%, m.p. 166 - 167°C; IR (KBr) 3423, 2959, 1641, 1366, 1147 cm-1. 1H NMR (300 MHz, CDCl3): 1.07 (s, 6H, 2-CH3), 1.38 (s, 6H, 2-CH3), 2.32 (s, 8H, 4-CH2), 4.11(s, 1H, CH), 6.79-6.95 (m, 2H, furan ring), 7.00-7.32 (m, 4H, Ar-H)C13 NMR : 24.64 (C-C), 34.64 (C-CH3), 40.05 (CH2), 46.28 (CH2), 56.75 (CH2), 114.81-151.64 (C-Ar), 194.81 (C=O) EM-MS: m/z 469.0 (M+1) .

2 Synthesis of compound 2-(2-chloro-phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)-methylfuran :5-(2-chloro-phenyl)-furan-2-carbaldehyde (0.030mol) is treated with dimedone (2g,0.015mol) in ethanol (50% 30 ml) The reaction mixture was heated for 15 minutes. The compound was collected by filtration and purified by repeated recrystallization from 95% ethanol.

Characterization of 2nd compound: - Yield: 90%, m.p. 180 - 182°C; IR (KBr) 3466, 2945, 1632, 1355, 1127 cm-1. 1H NMR (300 MHz, CDCl3): 1.07 (s, 6H, 2-CH3), 1.38 (s, 6H, 2-CH3), 2.32 (s, 8H, 4-CH2), 4.11(s, 1H, CH), 6.79-6.95 (m, 2H, furan ring), 7.00-7.32 (m, 4H, Ar-H) C13NMR : 24.61 (C-C), 34.60 (C-CH3), 40.05 (CH2), 46.28 (CH2), 56.75 (CH2), 114.06-151.50 (C-Ar), 194.85 (C=O). EM-MS: m/z 469.0 (M+1)

3 Synthesis of compound 2-(2-nitro-phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)-methylfuran :5-(2-chloro-phenyl)-furan-2-carbaldehyde (0.030mol) is treated with dimedone (2g,0.015mol) in ethanol (50% 30 ml) The reaction mixture was heated for 25 minutes. The compound was collected by filtration and purified by repeated recrystallization from 95% ethanol.

Characterization of 3rd compound: - Yield: 75%, m.p. 210 - 212°C; IR (KBr) 3426, 2926, 1634, 1369, 1139 cm-1. 1H NMR (300 MHz, CDCl3): 1.58 (s, 12H, 4-CH3), 2.32 (s, 8H, 4-CH2), 4.32(s, 1H, CH), 6.80 (s, 2H, furan ring),7.34-7.42 (m, 4H, Ar-H) C13NMR : C 25.61 (C-C), 36.62 (C-CH3), 40.05 (CH2), 47.28 (CH2), 56.75 (CH2), 104.81-151.61 (C-Ar), 195.85 (C=O).. EM-MS: m/z 477.0 (M+1)

4 Synthesis of compound 2-(4-nirto-phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)-methylfuran :5-(4-nitro-phenyl)-furan-2-carbaldehyde (0.030mol) is treated with dimedone (2g,0.015mol) in ethanol (50% 30 ml) The reaction mixture was heated for 25 minutes. The compound was collected by filtration and purified by repeated recrystallization from 95% ethanol.

Characterization of 4th compound: - Yield: 85%, m.p. 188-190°C; IR (KBr) 3447, 2943, 1654, 1356, 1137 cm-1. 1H NMR (300 MHz, CDCl3): 1.58 (s, 12H, 4-CH3), 2.32 (s, 8H, 4-CH2), 4.32(s, 1H, CH), 6.80 (s, 2H, furan ring),7.34-7.42 (m, 4H, Ar-H) C13NMR : C 25.61 (C-C), 36.62 (C-CH3), 40.05 (CH2), 47.28 (CH2), 56.75 (CH2), 104.81-151.61 (C-Ar), 195.85 (C=O).. EM-MS: m/z 477.0 (M+1)

5 Synthesis of compound 2-(4-floro-phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)-methylfuran :5-(4-floro-phenyl)-furan-2-carbaldehyde (0.030mol) is treated with dimedone (2g,0.015mol) in ethanol (50% 30 ml) The reaction mixture was heated for 15 minutes. The compound was collected by filtration and purified by repeated recrystallization from 95% ethanol.

Characterization of 5th compound: - Yield: 80%, m.p. 174 - 176°C; IR (KBr) 3473, 2959, 1624, 1366, 1145 cm-1. 1H NMR (300 MHz, CDCl3): 1.05 (s, 6H, 2-CH3), 1.32 (s, 6H, 2CH3), 2.30 (s, 8H, 4-CH2), 4.09 (s, 1H, CH), 6.72-6.93 (m, 2H, furan ring), 7.00-7.32 (m, 4H, Ar-H)C13 NMR : 24.54 (C-C), 34.54 (C-CH3), 39.85 (CH2), 46.34 (CH2), 56.62 (CH2), 114.64-151.74 (C-Ar), 195.22 (C=O) EM-MS: m/z 452.0 (M+1) .

6 Synthesis of compound 2-(2-floro-phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)-methylfuran :5-(2-floro-phenyl)-furan-2-carbaldehyde (0.030mol) is treated with dimedone (2g,0.015mol) in ethanol (50% 30 ml) The reaction mixture was heated for 15 minutes. The compound was collected by filtration and purified by repeated recrystallization from 95% ethanol.

characterization of 6th compound :- Yield: 82%, m.p. 204 - 206°C; IR (KBr) 3426, 2962, 1647, 1364, 1143 cm-11H NMR (300 MHz, CDCl3): 1.05 (s, 6H, 2-CH3), 1.32 (s, 6H, 2-CH3), 2.30 (s, 8H, 4-CH2), 4.09 (s, 1H, CH), 6.72-6.93 (m, 2H, furan ring), 7.00-7.32 (m, 4H, Ar-H) C13NMR : 24.32 (C-C), 34.60 (C-CH3), 40.05 (CH2), 46.28 (CH2), 56.75 (CH2), 114.06-151.50 (C-Ar), 194.85 (C=O). EM-MS: m/z 452.0 (M+1)

7 Synthesis of compound 2-(4-methyl-phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)-methylfuran :5-(4-methyl-phenyl)-furan-2-carbaldehyde (0.030mol) is treated with dimedone (2g,0.015mol) in ethanol (50% 30 ml) The reaction mixture was heated for 20 minutes. The compound was collected by filtration and purified by repeated recrystallization from 95% ethanol.

characterization of 7th compound :- Yield: 83%, m.p. 166 - 167°C; IR (KBr) 3450, 2960, 1615, 1376, 1160 cm-11H NMR (300 MHz, CDCl3):1.40 (s,-CH3) 1.58 (s, 12H, 4-CH3), 2.19 (s, 8H, CH2), 2.32 (s, 3H, CH3), 4.77 (s, 1H, CH), 6.79-6.95 (m, 2H, furan ring), 7.00-7.36 (m, 4H, Ar-H): 24.64 (C-C), 34.64 (C-CH3), 40.05 (CH2), 46.28

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Table 2 MIC

Testing compd.	Minimum inhibition concentration (µg/ml)								
	Bacterial strains					Fungal strains			
	S. aureus	*E. coli*	*P. mirabilis*	*P. aeruginosa*	*K. pneumoniae*	*A. flavus*	*A. fumigatus*	*A. niger*	*C. albicans*
1	100	15	50.	15.	150	100	50	100	25
2	200	25.50	20	25.	200	25	20	25	15
3	200	30	50.	25	100	50	50	100	100
4	100	20	25	50	100	50	50	50	25
5	150	50	25	20	125	75	40	100	125
6	200	25	40	25	150	75	20	125	135
7	100	40	25	25	125	100	50	150	100
8	125	30	50	40	150	150	50	200	50

(CH2), 56.75 (CH2), 114.81-151.64 (C-Ar), 145 (C=C), 194.81 (C=O) EM-MS: m/z 449.0 (M+1).

8 Synthesis of compound 2-(2-methyl-phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)-methylfuran :5-(2-methyl-phenyl)-furan-2-carbaldehyde (0.030mol) is treated with dimedone (2g,0.015mol) in ethanol (50% 30 ml) The reaction mixture was heated for 20 minutes. The compound was collected by filtration and purified by repeated recrystallization from 95% ethanol.

characterization of 8th compound :- Yield: 88%, m.p. 201 - 203°C; IR (KBr) 3490, 2959, 1640, 1380, 1161 cm-11H NMR (300 MHz, CDCl3): 1.40 (s,-CH3) 1.58 (s, 12H, 4-CH3), 2.19 (s, 8H, CH2), 2.32 (s, 3H, CH3), 4.77 (s, 1H, CH), 6.79-6.95 (m, 2H, furan ring), 7.00-7.36 (m, 4H, Ar-H)C13NMR : 24.61 (C-C), 34.60 (C-CH3), 40.05 (CH2), 46.28 (CH2), 56.75 (CH2), 114.06-151.50 (C-Ar), 194.85 (C=O). EM-MS: m/z 449.0 (M+1) Minimum inhibitory concentration (MIC) studies : The preliminary antibacterial and antifungal screening of the compounds 1-8 were conducted by using two fold serial dilution method.The bacterial strains, Staphylococcus aureus, Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa, Klebsiella pneumoniae and the fungal strains Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, Candida albicans species are used for the study. The MIC of compound 1-8 against tested bacterial and fungal strains are furnished in Table 2

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