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Further Biologically Active Derivatives of 1, 3-Diketones

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Abstract

This study presents the synthesis and characterisation of new compounds of antimicrobial activity by the coupling of aromatic aldehydes with 5,5-dimethylcyclohexan-1,3-dione (dimedone). The products were refluxed with N–benzyl-N-phenylhydrazine in acetic acid. With the help of micro- and IR-spectral analysis, the molecular structures of the synthesised products were determined. These were ascertained using ^{1}H NMR at 60MHz and TMS as internal standard. Biological activity of the derivatives against gram-positive Cocci and Bacilli as well as gram-negative Bacilli was tested and found to vary widely from inactive to highly active, which could prove to be of practical pharmaceutical application.

Key words: Aromatic aldehydes, dimedone, coupling derivatives, Antimicrobial activity.

Introduction

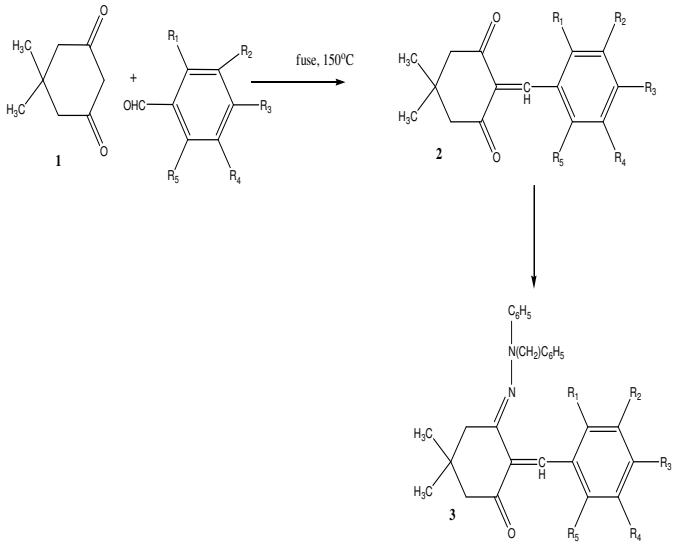
Pursuant upon an earlier communication[1] in which we reported some new biologically active compounds from 1,3-diketones using aromatic amines, the present paper reports on further derivatives with aromatic aldehydes. These compounds have been found to exhibit similar biological activity as their aromatic amine counterparts. The chemistry[2-6] and ready availability of cyclohexane-1,3-diones[7-11] render it a suitable starting material[12,13] for the synthesis of organic compounds such as oxozolidinones with known antibacterial activity[14-16], and phenylbutazone which is quite effective in the treatment of the pain associated with rheumatoid arthritis and Tietze's syndrome[18-20].

The aim of the present study was to create new derivatives of 1, 3-diketones using aromatic aldehydes and *N*-benzyl-*N*-phenylhydrazine, consequent upon which their biologically active properties would be investigated and established.

Material and Methods

The chemicals and solvents used in this study were obtained from Merck, Fluka and Sigma (Aldrich). They were of reagent grade and required little further purification. An open-tube capillary method was employed to determine melting points in ℃ which are quoted uncorrected. Thin layer chromatography (TLC) was of invaluable help in controlling the purity of the compounds. A Mattson 5000 FTIR spectrophotometer (USA) was used to record the IR spectra in KBr pellets. Also, a Perkin-Elmer Instrument (200B, USA) was used to estimate the C, H, N, Cl constitutional data of the derivatives. The ^{1}H NMR spectra of the compounds were measured in $CDCl_3$ and DMSO-d_6 solution on a DRX – 300MHz spectrometer (Bruker, UK) with TMS as internal standard.

Synthesis of 2-arylidene-1, 3-diones (2): Requisite amounts of aromatic aldehyde (0.002 mol) and 5, 5-dimethylcyclohexan-1, 3-dione, dimedone (0.28 g, 0.002 mol) were fused at 150°C for 30 minutes (see Scheme) in a dry pear-shaped 50 ml flask in an oil-bath. The residue was cooled and shaken with benzene. The resulting solid product was filtered off, re-crystallised and the melting point taken.



Scheme-1
An illustrated reaction pathway for the synthesis of antimicrobial products using dimedone (1), aromatic aldehydes and N-benzyl-N-phenyl hydrazine

		2	**3**
i)	R_1=R_2=R_4=R5=H, R_3=N $(CH_3)_2$	(2a)	(3a)
ii)	R_1=R_2=R_4=R_5=H, R_3=OH	(2b)	(3b)
iii)	R_1=R_2=R_4=R_5=H, R_3=Cl	(2c)	(3c)
iv)	R_3=R_4=R_5=H, R_1=NO_2, R_3=Cl	(2d)	(3d)
v)	R_2=R_4=R_5=H, R_1=Cl, R_3=NO_2	(2e)	(3e)

Synthesis of 2-arylidene-1, 3-diketone derivatives (3): An appropriate quantity of 2- arylidenecyclohexan-1, 3-

dione (see Scheme, 0.002 mol) was dissolved in a mixture of 50% acetic acid (25 ml) and *N*-benzyl-*N*-phenylhydrazine (0.002 mol, 0.396 g, 0.4 ml), refluxed for 3 to 4 hours, left to cool and the products re-crystallised. The melting points and percentage yields were determined.

Biological activity tests[21-22]: The required amounts of liquid agar media were poured into sterile petri-dishes to a depth of 3 to 4 mm. After solidifying, the liquid media test organism was spread over the solidified agar media and incubated in the petri-dish at 37°C for 24 hours to facilitate the growth of the micro-organisms. With the help of a sterile rod, a hole was made on the medium and poured on the known (1000 µg/ml concentration) test solution in that hole. The biological activity of the derivatives was evaluated by determining the average diameter of the inhibition zone (figure-1).

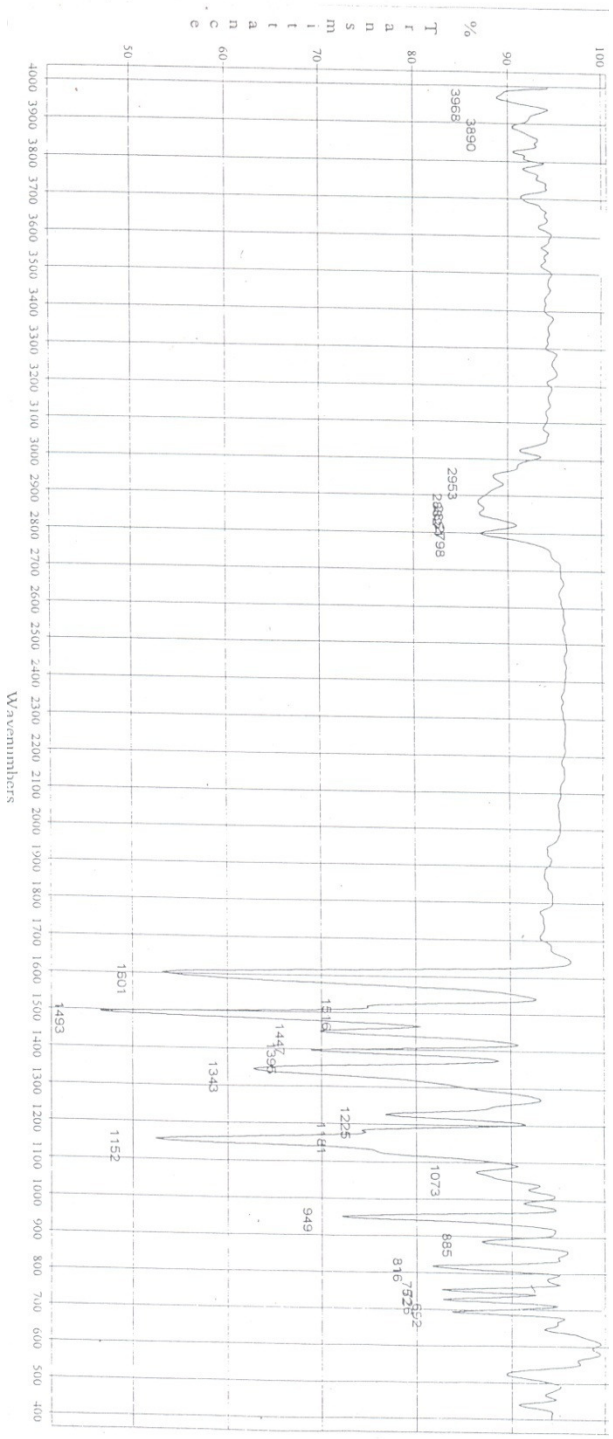


Figure-1
IR spectrum for Compound 3a (see Scheme)

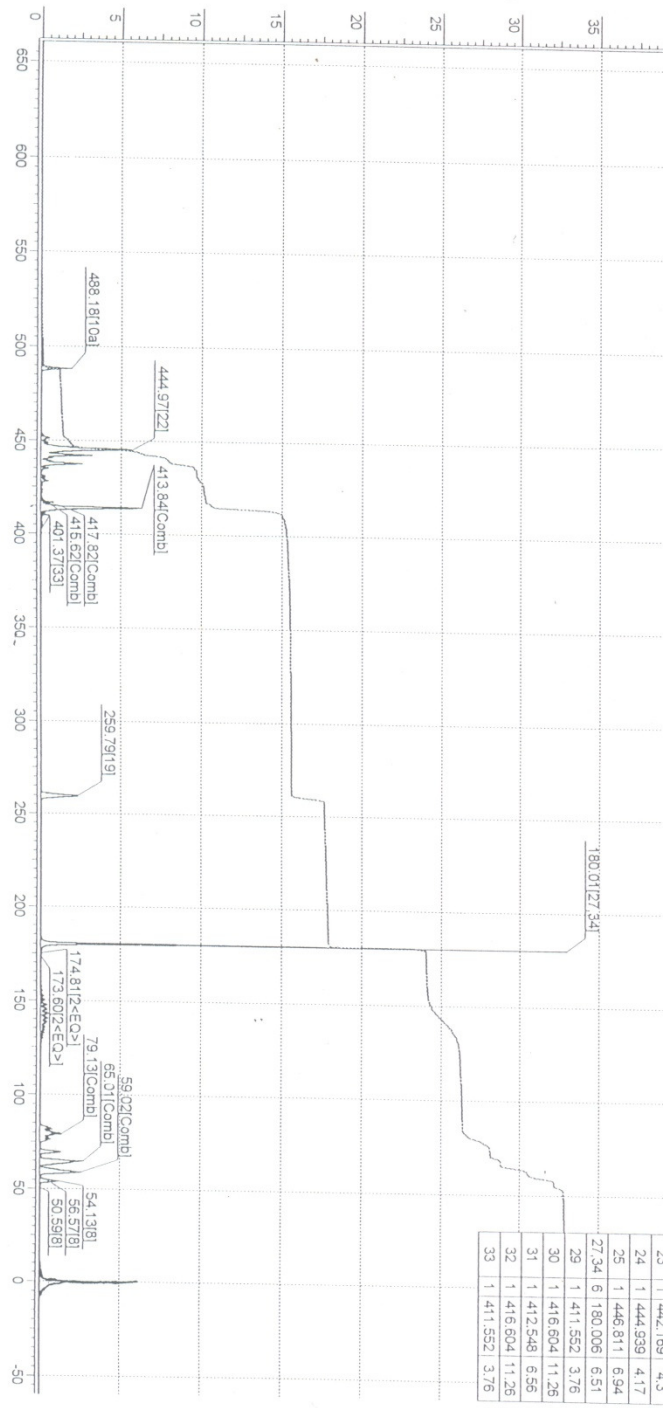


Figure-2
Confirmatory ^{1}H nmr spectrum for Compound 3a

Results and Discussion

Compound (**2a**) was obtained as orange crystals in 70% yield, m.p. 197°C, $C_{17}H_{21}NO_2$ (RMM, 267.35); IR, υ_{max} in cm^{-1}: 3039, 1520 (CH-aromatic), 2960-2633, 1448, 1369 (CH_3, -N(CH_3)), 811(=CH). Compound (**2b**) was obtained as yellow crystals in 62% yield, m.p. 246.0°C, $C_{15}H_{16}O_3$ (RMM, 244.28). Compound (**2c**) was obtained as yellow crystals in 52.3% yield, m.p. 185.0°C, $C_{15}H_{15}N_3O_4$ (RMM, 257.27). Compound (**2d**) was obtained as yellow crystals in 66.0% yield, m.p. 218.0°C, $C_{15}H_{16}O_3$ (RMM, 273.28). Compound (**2e**) was obtained as light yellow crystals in 64.0% yield, m.p. 207.0°C, $C_{15}H_{16}O_2$ (RMM, 228.28); IR, υ_{max} in cm^{-1}: 3058 (=CH, aromatic), 2961-2568, 1449, 1372 (CH_3), 776, 693 (=CH). Derivatives of 2-arylidene-1,3-diketones were obtained in fairly quantitative yields. The products (**3a – 3e**) were isolated, re-crystallised (from mixtures of methanol and water) and afforded in 40-60% yields. Compound (**3a**), figure 1, was obtained as yellow crystals in 40.0% yield, m.p. 170.0°C; IR, υ_{max} in cm^{-1}: 3050, 1601, 1493 (aromatic), 2953, 2851, 1447, 1343 (CH_3), 692, 816 (=CH). Anal. calcd for $C_{30}H_{33}N_3O$ (RMM, 451.58): C, 79.73; H, 7.37; N, 9.31; Found: C, 79.65; H, 7.45; N, 9.11%. ^{1}H NMR spectra, figure 2, at 60 MHz (δ units ppm) showed: 1.083 and 0.984 (s, 3H, CH_3), 8.14 (s, 5H, $=CH_{ar}$), 7.236 (s, 4H, $=CH_{ar}$), 7.414 (s, 2H, $=CH_{ar}$), 4.33 (s, 2H, CH), 7.447 (s,2H, $=CH_{ar}$), 7.416 (s, 2H, =CH), 3.0 (s, 3H, CH_3), 6.859 (s, 2H, $=CH_{ar}$), 6.934 (s, 2H, $=CH_{ar}$), 6.876 (s, H, $=CH_{ar}$). Compound (**3b**) was obtained as red crystals in 65.0% yield, m.p. 217.0°C; IR, υ_{max} in cm^{-1}: 3400-3208 (OH), 3068, 1599, 1490 (aromatic), 2959, 2876, 1456, 1366 (CH_3), 1635 (>C=O). Anal. calcd. for $C_{28}H_{28}N_2O$ (RMM, 408.52): C, 82.17; H, 6.91; N, 6.86; Found: C, 82.41; H, 6.77; N, 6.67%. ^{1}H NMR spectra at 60MHz (δ units ppm) showed: 1.103 and 1.024 (s, 3H, CH_3), 7.984 (s, 5H, $=CH_{ar}$), 7.152 (s, 4H, $=CH_{ar}$), 7.295 (s, 2H, $=CH_{ar}$), 4.329 (s, 2H, CH), 7.507 (s,2H, $=CH_{ar}$), 7.392 (s, 2H, =CH), 3.214 (s, H, OH), 6.901 (s, 2H, $=CH_{ar}$), 6.788 (s, 2H, $=CH_{ar}$), 6.674 (s, H, $=CH_{ar}$). Compound (**3c**) was obtained as orange crystals in 66.5% yield, m.p. 238.0°C; IR, υ_{max} in cm^{-1}: 2960, 2874, 1460, 1354 (CH_3), 1667 (>C=O), 1660, 1495 (aromatic). Anal. calcd. for $C_{28}H_{27}N_3O_3$ (RMM, 453.52): C, 74.15; H, 6.00; N, 9.26; Found: C, 74.44; H, 6.12; N, 9.35%. Compound (**3d**) was obtained as light orange crystals in 40.0% yield, m.p. 172.0°C; IR, υ_{max} in cm^{-1}: 2955, 2872, 1452, 1373 (CH_3), 1643 (>C=O), 753, 697 (=CH). Anal. calcd. for $C_{28}H_{27}N_3O_3$ (RMM, 453.52): C, 74.15; H, 6.00; N, 9.27; Found: C, 73.81; H, 5.97; N, 9.10%. Compound (**3e**) was obtained as orange crystals in 60.0% yield, m.p. 202.0°C; IR, υ_{max} in cm^{-1}: 3456-3247 (NH), 3063, 3030, 1626, 1495 (aromatic), 1662 (>C=O), 2957, 2872, 1465, 1362 (CH_3), 745, 697 (=CH). Anal. calcd. for $C_{28}H_{28}N_2O$ (RMM, 394.508): C, 85.24; H, 7.15; N, 3.55; Found: C, 85.03; H, 6.94; N, 3.41%. ^{1}H NMR spectra at 60MHz (δ units ppm) showed: 1.066 and 0.974 (s, 3H, CH_3), 8.027 (s, 5H, $=CH_{ar}$), 7.035 (s, 4H, $=CH_{ar}$), 7.398 (s, 2H, $=CH_{ar}$), 4.242 (s, 2H, CH), 7.357 (s,2H, $=CH_{ar}$), 7.219 (s, 2H, =CH), 7.149 (s, 2H, $=CH_{ar}$), 7.240 (s, 2H, $=CH_{ar}$), 6.689 (s, H, $=CH_{ar}$).

Table 1
Collective data showing the spectra of antimicrobial activity of the compounds (3a – 3e) at 100µg/ml concentration level against micro-organisms used

Test strains of micro-organisms	Test Compounds				
	3a	**3b**	**3c**	**3d**	**3e**
A) Gram-Positive *Cocci*					
1. Staphylococcus aureus	-	-	+	±	+
2. Staphylococcus epidermis	-	-	+	±	+
3. Sarcina lutea	-	-	+	+	+
B) Gram- Positive *Bacilli*					
1. Bacillus permal	-	-	+	+	+
2. Bacillus subtilis	-	-	+	±	+
C) Gram-Negative *Bacilli*					
1. Aerobacterium klebsiella	-	-	+	±	+
2. Bacillus Arizona	-	-	+	+	+
3. Bacillus proteus	-	-	+	+	+
4. Bacillus pseudomonas	-	-	+	+	+
5. Escherichia coli	-	-	+	+	+
6. *Salmonella paratyphi* A	-	-	+	±	+
7. *Salmonella paratyphi* B	-	-	+	+	+
8. *Salmonella paratyphi* C	-	-	+	+	+
9. Shigella flexneri	-	-	+	±	+
10. Shigella sonnei	-	-	+	±	+

N.B. (+) no growth (High activity), (±) Moderate growth (moderate activity), (-) High growth (inactive)

Biological Screening: The 2-arylidene-1,3-diketone derivatives (**3**) were examined *in vitro* against bacterial species which included gram-positive *Cocci*, gram-positive *Bacilli* and gram-negative *Bacilli*. The photographs provided (figure 3) are representative of the major observations made. Tables 1 and 2 show the spectral data of the synthesised biologically active compounds (**3a – 3e**) at 100 and 1000 µg/ml concentrations, respectively, against the micro-organisms.

Table 2
Collective data showing the spectra of antimicrobial activity of the compounds (3a – 3e) at 1000µg/ml concentration level against micro-organisms used

Test strains of micro-organisms	Test Compounds				
	3a	3b	3c	3d	3e
D) Gram-Positive *Cocci*					
4. Staphylococcus aureus	-	-	+	±	+
5. Staphylococcus epidermis	-	-	+	±	+
6. Sarcina lutea	-	-	+	+	+
E) Gram- Positive *Bacilli*					
3. Bacillus permal	-	-	+	+	+
4. Bacillus subtilis	-	-	+	±	+
F) Gram-Negative *Bacilli*					
11. Aerobacterium klebsiella	-	-	+	±	+
12. Bacillus Arizona	-	-	+	±	+
13. Bacillus proteus	-	-	+	±	+
14. Bacillus pseudomonas	-	-	+	+	+
15. Escherichia coli	-	-	+	+	+
16. *Salmonella paratyphi* A	-	-	+	+	+
17. *Salmonella paratyphi* B	-	-	+	+	+
18. *Salmonella paratyphi* C	-	-	+	±	+
19. Shigella flexneri	-	-	+	±	+
20. Shigella sonnei	-	-	+	±	+

N.B. (+) no growth (High activity), (±) Moderate growth (moderate activity), (-) High growth (inactive

The results presented in table 1 suggested that compounds **3a** and **3b** were inactive (at 100 µg /ml) against all the tested micro-organisms. This is attributed to the presence of the methylsubstituted amino (-N $(CH_3)_2$) and hydroxyl (-OH) groups. The reactivity of the amino group might be severely hampered by the steric hindrance arising as a result of the bulkiness of the substituent at that position of the aromatic ring[4,5]. Compounds **3c** and **3e** exhibited high antimicrobial activity against all the test micro-organisms most probably due to the presence of the nitro (-NO_2) group that is dependent of the electronic richness of the nitrogen atoms[4,5]. Compound (**3d**) showed high antimicrobial activity against *Sarcina lutea*, *Bacillus permal*, *Bacillus arizona*, *Bacillus proteus*, *Bacillus pseudomonas*, *Escherichia coli*, *Salmonella paratypi* B and *Salmonella paratypi* C. It however exhibited moderate biological activity towards *Staphylococcus aureus*, *Staphylococcus epidermis*, *Bacillus subtilis*, *Aerobacterium klebsiella*, *Salmonella paratypi* A, *Shigella flexneri* and *Shigella sonnei*.

When concentrations were increased to 1000 µg/ml, there was little change in the antimicrobial activity of the compounds **3a, 3b, 3c** and **3e** (table 2) against all the micro-organisms under investigation. The antimicrobial activity of compound 3d was obstructed on a few micro-organisms such as *Bacillus Permal*, *Bacillus arizona*, *Bacillus proteus* and *Salmonella paratypi* C.

Conclusion

Dimedone has been shown to be an adaptable source of a number of biologically active compounds that might be of use in pharmaceutical research.

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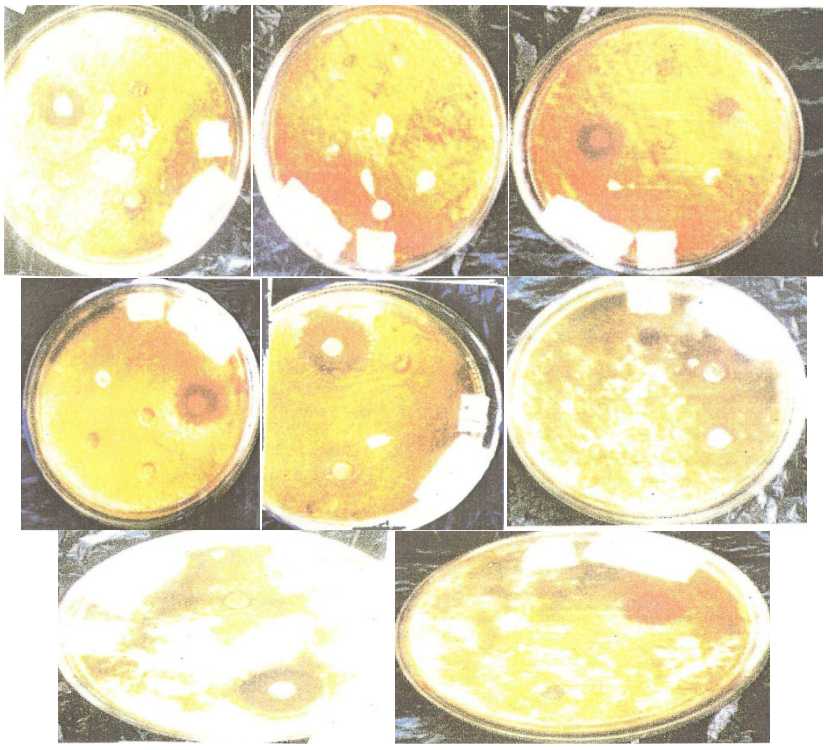

Figure-3