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Novel Synthesis and Antimicrobial Evaluation of Some New Cyclic Ketones

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Abstract A series of 5-oxohexannitrile derivatives IIa-d was prepared by reaction of acrylonitrile with ketones Ia-d. On the other hand, semicarbazone derivatives IVa-d were obtained upon reaction of IIa-d with semicarbazide. Hydrolysis and esterification in one step reaction of δ-ketonitrile IIa-d resulted in the formation of the corresponding δ-ketoesters Va-d. The δ-ketoesters Va-d is readily cyclized to the corresponding cyclohexan-1,3-diones VIa-d when heated with alcoholic sodium methoxide. Moreover, coupling of VIa, VIb and VId with aryl diazonium chloride afforded the corresponding 2-(aryl diazenyl) derivatives VIIa-f, respectively. Furthermore, bis-(2,6-diketo-3-phenylcyclohexyl)methane VIII was synthesized by condensing VIa with benzaldehyde. Bromination of VId in dilute acetic acid afforded the corresponding bromo derivative IX. Heating of cyclohexanone-2-methylpropionate in alcoholic sodium methoxide afforded bicycle[1,3,3]nonan-2,9-dione X. These compounds were characterized by analytical and spectral analyses and screened for their antibacterial activity against Gram-possitive bacteria and Gram-negative bacteria. The synthesized compounds (VIIa-f)-X showed significant antibacterial activity against P. Aeruginosa (MIC 0.30-0.45 μg/mL), S. Aureus (MIC 0.25-0.45 μg/mL) and B. Subtilis (MIC 0.20-0.45 μg/mL) and exhibited moderate antibacterial activity against E. Coli (MIC 0.30-0.45 μg/mL) compared with the standard drug Ciprofloxacin.

Keywords Cyclohexan-1,3-Dione, Semicarbazone, Cyclic Ketones, Antimicrobial Activity, Minimum Inhibitory Concentration (MIC)

1. Introduction

The use of cyano compounds in organic synthesis is now receiving considerable interest[1, 2]. Our group has been involved in the last years in a program aiming to develop efficient procedures for the synthesis of polyfunctionally substituted azoles[3, 4], azines[5, 6] and their condensed derivatives[7, 8] utilizing simple and readily obtainable polyfunctionally substituted nitriles.

2. Results and Discussion

2.1. Chemistry

The synthesis of cyclohexan-1,3-dione derivatives using acrylonitrile as starting material has now been achieved and reported herein. Thus, it has been found that when acrylonitrile was treated with ketones Ia-d in the presence of alkaline medium afforded the corresponding 5-oxohexannitrile derivatives IIa-d in good yield.

The IR spectra of IIa-d, in general, showed absorption bands at 1730-1710 cm-1 corresponding to CO function and 2220 cm-1 due to C≡N group. The 1H-NMR spectrum of IIa revealed a singlet signal at δ 2.11 ppm due to CH_3 protons, a triplet signal at δ 2.41 ppm attributable to $COCH_2$ protons, two multiplet signals at δ 1.94 and 1.87 ppm due to CH_2CH_2CN protons. The 1H-NMR spectra of IIb-d showed characteristic signals, so compound IIb showed two singlet signals at δ 1.11 and 1.99 ppm corresponding to $2CH_3$ groups, while IIc showed signals due to the n-propyl group (n-C_3H_7) at δ 0.9 (s, CH_3), 1.33 (m, CH_2) and 1.53 ppm (q, CH_2), finally, the 1H-NMR spectrum of IId showed the aromatic protons at δ 7.29-7.45 ppm as multiplet signals. Structure II was further confirmed by its conversion to the corresponding semicarbazone derivative IV. The IR spectra of the semicarbazone derivatives IVa-d, in general, showed absorption bands at 3420-3350 cm-1 due to NH2 and NH functions, while, their 1H-NMR spectra showed two singlet exchangeable signals at δ 6.06 and 7.09 ppm corresponding to NH2 and NH protons.

Hydrolysis and esterification in one step reaction of δ-ketonitriles IIa-d resulted in the formation of the corresponding δ-ketoesters Va-d. Structure V was established based on spectral analysis. So, the IR spectra of Va-d showed in general, well defined bands due to carbonyl functions (ester at 1720 cm-1 and ketonic at 1695 cm-1). The ^{1}H-NMR spectrum of Va revealed two singlet signals at δ

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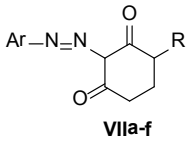
2.11 and 3.66 ppm due to protons of two methyl groups ($COCH_3$ and $COOCH_3$, respectively), two triplet signals at δ 2.14, 2.31 and multiplet at δ 2.4 ppm attributable to three CH_2 groups, its mass spectrum showed the molecular ion peak at m/z = 144 (M^+, 27%).

The δ-ketoesters Va-d is readily cyclized to the corresponding cyclohexan-1,3-dione derivatives VIa-d when heated with alcoholic sodium methoxide (Scheme 1). Structures VIa-d were elucidated by correct analytical and spectral data. The IR spectra showed in general well defined absorption bands at 1735 cm-1 due to cyclic C=O group. The 1H-NMR spectrum of VIb showed two signals, one of them is doublet at δ 1.11 ppm and the other is multiplet at δ 2.52 ppm attributable to CH3 and CH protons at C_4, respectively. The $COCH_2CO$ protons appeared as doublet of doublet at δ 3.56: 3.66 ppm and two multiplet signals at δ 1.94: 1.64 and 2.4: 2.5 ppm for other two CH_2 groups, while its mass spectrum showed the molecular ion peak at m/z = 126 (M+). The 1H-NMR spectra of VIc, d showed characteristic signals corresponding to the alkyl and aryl groups at position-4. So, the n-propyl group at position-4 in VIc appeared as triplet signal for CH_3 protons at δ 0.9 ppm, quartet signal at δ 1.53 ppm for CH_2 protons and at δ 1.33 ppm as multiplet for the other CH_2 protons, while the benzene ring protons in VId appeared at δ 7.29-7.51 ppm as multiplet signals.

< Scheme 1 >



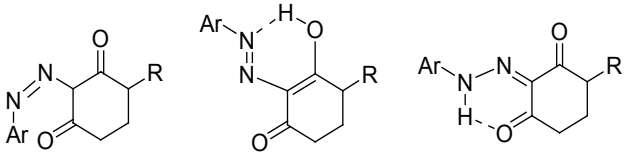
VIIa-f

VIIa, R = H; Ar = C_6H_5
VIIb, R = H; Ar = C_6H_4-CH_3-*p*
VIIc, R = CH_3; Ar = C_6H_5
VIId, R = CH_3; Ar = C_6H_4-NO_2-*p*
VIIe, R = C_6H_5; Ar = C_6H_5
VIIf, R = C_6H_5; Ar = C_6H_4-OCH_3-*p*

Figure 1. Structures of 2-arylazo of cyclohexane-1,3-dione derivatives **VIIa-f**

The structures of VI were further confirmed by preparing its 2-arylazo derivatives VIIa-f in three cases (from VIa, VIb and VId, respectively). Therefore, it has been found that coupling of VIa, VIb and VId with aryl diazonium chloride afforded the corresponding 2-(aryl diazenyl) derivatives VIIa-f, respectively (Figure 1). Structures VII were assigned on the basis of their correct analytical and spectral data.

The possible tautomeric forms of arylazo derivatives VII could be set out as follows (Figure 2):



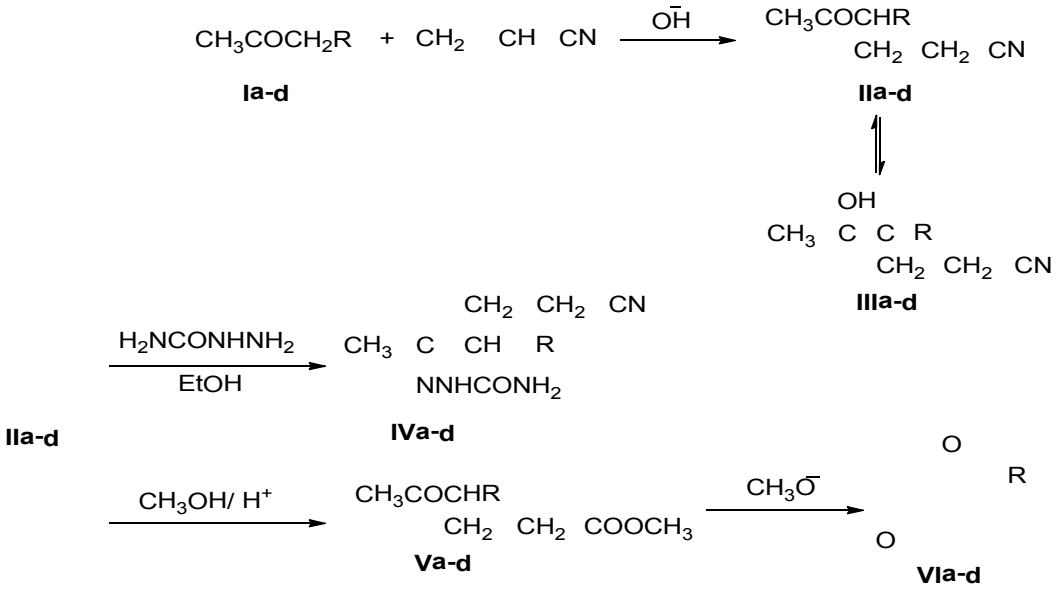
(**A**) (**B**) (**C**)

Figure 2. The tautomeric structures of compounds **VIIa-f**

These are referred as the CH azo form (A), the OH azo form (B) and the ketohydrazone form (C). The presently available data indicate that the tautomeric structure VII is the chelated hydrazone form (C).

On the basis of the IR spectrum, each of the compounds investigated possessed a weak and broad band in the region 3100-3300 cm-1. This was assigned to NH stretching of the hydrazone moiety. The large shift and broadening of this band, as reported by Ramirez and Kerby[9] for simple hydrazones, can result only from intramolecular hydrogen bonding as in (C). The fact that the compound VII shows evidence for intramolecular hydrogen bonding is in favor of the hydrazone structure.

Solid 2,3-dioxobutyranilide-2-phenyl hydrazone and ethyl 2,3-dioxobutyrate-2-phenyl hydrazone exhibited their CO stretching near 1623 and 1620 cm^{-1}, respectively[10].



For I-VI **a**, R = H; **b**, R = CH_3; **c**, R = *n*-C_3H_7; **d**, R = C_6H_5

Scheme 1. Synthetic routes for 4-substituted-cyclohexane-1,3-dione **VIa-d**

As the diazonium coupling products in this study, each exhibited, in general, two medium bands in the region 1610-1680 cm^{-1}. Some compounds, however, showed only one band near 1660 cm^{-1}, Fadda suggested in previous work[11], these bands are due to the stretching vibrations of carbonyl group. Among the structural factors that lead to the lowering of the stretching vibration of CO group are conjugation and hydrogen bonding. However, even if allowance is made for conjugation, the CO frequencies of the compounds studied are still much lower than those encountered in other α,β-unsaturated ketones. This significant difference suggested that CO group of these compounds should be involved in hydrogen bonding in the solid state, as shown in the proposed structure (C).

Hence, conjugation of the CO group and possible intramolecular hydrogen bonding in compounds VII as required by structure (C) probably result in the shifting of the CO frequencies to a lower weave length. The IR spectra of almost all compounds showed absorption bands in the region 1400-1450 cm-1. These bands, however, can not be assigned to N=N vibrations according to Le Fevre[12], since the corresponding β-ketoanilide and 3-oxo-2-(2-phenyl hydrazono)-N-(pyridine-2-yl)butanamide exhibited similar absorption bands. Thus, the absence of bands characteristic for the N=N group might be taken as an indication that structure (A) is not present in the series studied. Since, it has deduced that compounds VII exist as phenylhydrazones (C), a band due to C=N would be expected in the double bond region. Bellamy[13] quoted a range of 1690-1640 cm-1 for the C=N stretching vibration falling slightly to 1680-1630 cm^{-1} for α,β-unsaturated compounds. The IR spectral data revealed that none of the compounds under investigation exhibited absorption bands above 1600 cm^{-1} other than those of CO stretching vibration. However, each compound showed strong absorption between the aromatic 1500 cm^{-1} band and NH deformation band near 1550 cm^{-1} this band is relatively strong and in some cases it could not be resolved from the 1500 cm^{-1} band. Such a band was not observed in the spectra of the corresponding starting ketone. This new band may be due to the C=N vibration. The downward shift of the C=N band of the compounds in Table 1 may be attributed to its conjugation with the carbonyl group.

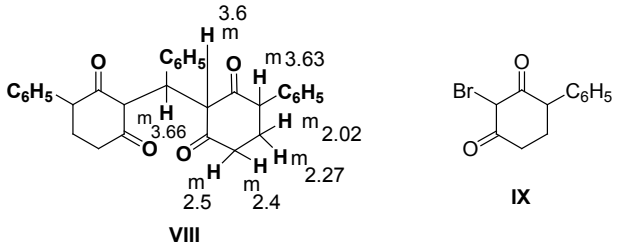
The UV spectra of the diazonium coupling products of VII provide additional evidence that such compounds have the hydrazone structure (C) rather than (A) or (B). Most of the dyes show three main absorption bands in the region 240-390 nm. These bands are referred to as A, B and C, stretching from the long wavelength side. The data indicate that absorption maxima in the solvent examined almost coincide. This suggests that such a compound is not a tautomeric equilibrium, but exists in one form. The relatively small differences in λ_{max} may be due to the polarity change of the absorbing system caused by solvent interactions due to the general solvent effect[14].

It has been reported that the UV spectra of monophenylazo compounds differ from those of monophenylhydrazones. The azo compounds generally show two absorption bands at 410-400 and 290-300 nm corresponding to n-π* and π-π* transitions, respectively[15]. The monophenylhydrazones, on the other hand, show three intense bands in the 220-228, 250-280 and 330-390 nm regions[14]. The UV spectra of compounds VII investigated can not be interpreted in terms of the azo structure of the type A or B, but evidently they appear compatible with the indicated hydrazone structure (C). the presence of the diazonium coupling products of VII, apparently exclusively, in the hydrazone form can be explained by a smaller degree of resonance stabilization of the azo forms (A and B). The six-membered hydrogen – bonded ring structure in the hydrazone form, as in (C), would also undoubtedly enhance its relative stability[16], since the color of an azo dye depends on the structure of the diazotized amines. It is clear that these dyes exhibits three absorption bands, of these, the medium and high wavelength bands seem to be affected by the nature of the polar substituent in the aryl azo group, and the low wavelength band is unaffected. Table 1 also shows that both electron withdrawing and electron donating groups cause the absorption to occur at higher wavelength. Table 1 also shows that the presence of electron donating or electron withdrawing groups has not brought about any marked increase or decrease in λ_{max} in the visible region and log ε has nearly remained constant. This does point towards the hydrazone structure (C) where the resonance interactions with the substituents in the diazo component are minimal, owing to steric factors.

Table 1. UV absorption bands of arylhydrazones **VIIa-f**

Dye	λ_{max} (nm*)		
VIIa	395 (4.5)	275 (4.1)	248 (4.3)
VIIb	385 (4.5)	280 (4.1)	248 (4.3)
VIIc	390 (4.6)	275 (4.2)	248 (4.2)
VIId	390 (4.6)	285 (4.0)	245 (4.1)
VIIe	395 (4.7)	275 (4.2)	248 (4.2)
VIIf	390 (4.7)	280 (4.1)	248 (4.1)

* Values in parentheses show log ε



VIII **IX**

Figure 3. Structures of phenylbis-(2,6-diketo-3-phenyl cycloh yl)methane (**VIII**) and 2-bromo-4-phenyl cyclohexan-1,3-dione (**IX**)

Moreover, bis-(2,6-diketo-3-phenylcyclohexyl)methane VIII was synthesized by condensing VIa with benzaldehyde. Structure VIII was proved by both analytical and spectral data. The IR spectrum showed stretching vibration at 1730 cm-1 due to the carbonyl function. The mass spectrum showed the molecular ion peak at m/z = 464 (M^+, 20%). The ^{1}H-NMR spectrum showed the following pattern (Figure 3), in addition to the aromatic protons at δ 7.1-7.5 ppm.

Bromination of VId in dilute acetic acid afforded the

corresponding bromo derivative IX. The 1H-NMR spectrum of IX showed singlet signal at δ 5.15 ppm due to CH proton at C_2, triplet signal at δ 3.63 ppm for C_4-H, multiplet signals at δ 2.01-2.5 for two CH_2 groups, besides aromatic protons at δ 7.2-7.4 ppm. The mass spectrum showed the molecular ion peak at m/z = 265 (M+, 100%).

The cyanoethylation reaction of the ketone I with acrylonitrile can be considered as a novel rout for the synthesis of not only cyclic ketones but also for the synthesis of bicyclic ketones. Thus, it was found that heating of cyclohexanone-2-methyl propionate in alcoholic sodium methoxide afforded bicycle[1,3,3]nonan-2,9-dione (X). Structure X was established on the basis of analytical and spectral data. The IR spectrum showed absorption band at 1740 cm^{-1} for carbonyl group. The mass spectrum showed the molecular ion peak at *m/z* = 152 (M^+, 66%). The ^{1}H-NMR spectrum can be shown as follow (Figure 4):

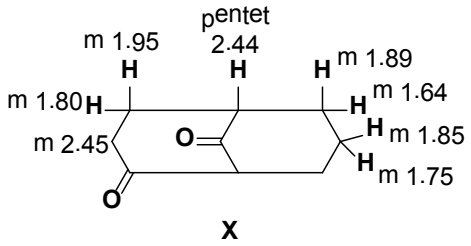


Figure 4. Structure of (5*R*)bicyclo-[1.3.3]nonan-2,9-dione (**X**)

2.2. Pharmacology

2.2.1. Antimicrobial Evaluation

The reference standard Ciprofloxacin inhibited Gram negative bacteria *E. Coli* and *P. Aeruginosa* at a MIC of 0.01 μg/mL and 0.25 μg/mL, respectively, whereas, against Gram positive bacteria *S. Aureus* and *Bacillus Subtilis* MIC was found to be 0.15 μg/mL and 0.12 μg/mL, respectively.

Table 2. *In vitro* antibacterial activity of compounds (**VIIa-f)-X**

Compound No.	Minimal inhibitory concentration (MIC, μg/mL)			
	E. Coli	P. Aeruginosa	S. Aureus	B. Subtilis
VIIa	0.40	0.45	0.40	0.40
VIIb	0.40	0.40	0.40	0.45
VIIc	0.40	0.45	0.40	0.40
VIId	0.30	0.35	0.30	0.30
VIIe	0.45	0.45	0.40	0.45
VIIf	0.45	0.40	0.45	0.40
VIII	0.35	0.30	0.30	0.35
IX	0.30	0.35	0.40	0.40
X	0.30	0.30	0.25	0.20
Ciprofloxacin	0.01	0.25	0.15	0.12

All the synthesized compounds (VIIa-f)-X showed significant antibacterial activity against P. Aeruginosa (MIC 0.30-0.45 μg/mL), S. Aureus (MIC 0.25-0.45 μg/mL) and B. Subtilis (MIC 0.20-0.45 μg/mL) whereas, moderate antibacterial activity was found against E. Coli (MIC 0.30-0.45 μg/mL) as compared to the standard drug Ciprofloxacin (Table 2). Compounds VIId contain nitro group, compound VII contain bromine atom and bicycle X were found to be most active. The results of the MIC for the standard drug, Ciprofloxacin, against the bacterial strains used were found to be within the range as reported in the literature[17, 18].

In conclusion, we have described a straight forward synthesis of new 2-arylazocyclohexan-1,3-dione derivatives VIIa-f and some cyclohexan-1,3-dione derivatives VIII-X and studied their in vitro antibacterial activity. Compounds VIId, VIII and X exhibited significant activity against all the bacterial strains used in this study.

3. Experimental

3.1. Instruments

All melting points are recorded on Gallenkamp electrothermal melting point apparatus. The IR spectra were recorded for KBr disc on a Mattson 5000 FTIR spectrophotometer. The ^{1}H-NMR spectra were measured on a Bruker AC 300 (300 MHz) in DMSO-d_6 as solvent, using TMS as an internal standard, and chemical shifts are expressed as δ_{ppm}. The mass spectra were determined on Finnigan Incos 500 (70 ev). Elemental analyses were carried out at the Microanalytical Unit of the Faculty of Science, Cairo University, Giza, Egypt.

Synthesis of nitrile derivatives IIa-d

General procedure: Sodium metal (0.46 g, 0.02 mol) is dissolved in the appropriate ketone **Ia-d** (0.7 mol) at 90℃. Then the solution was cooled to 0℃ and acrylonitrile (28 g, 0.52 mol) is added dropwise within 20 min at 50-60℃. The reaction mixture was stirred for 15 min, then cooled and neutralized with glacial acetic acid (3 mL), and extracted with ether; the ethereal extract was dried and the solvent evaporated under vacuo to give compounds **IIa-d** in good yields.

5-Oxohexanenitrile (IIa):[19, 20]

Yield (60%); b.p. 110-115 ℃ / 16 torr (Lit.[20], b.p. 112 ℃ / 14 torr); IR (Nojel): ν/cm-1= 2220 (C≡N), 1725 (CO); 1H-NMR(DMSO-d6) δ (ppm): 2.11 (s, 3H, CH_3), 2.41 (t, 2H, CH_2), 1.94 (m, 2H, CH_2CN), 1.87 (m, 2H, CH_2).

4-Methyl-5-oxohexanenitrile (IIb):[21]

Yield (53%); b.p. 110 ℃ / 12 torr (Lit.[21], b.p. 115 ℃ / 15 torr); IR (Nojel): ν/cm^{-1}= 2220 (C≡N), 1730 (CO); ^{1}H-NMR(DMSO-d_6) δ (ppm): 1.11 (s, 3H, CH_3), 1.99 (t, 2H, CH_3CO), 2.0 (q, 2H, CH_2), 2.41 (t, 2H, CH_2), 2.52 (m, 2H, CH_2).

4-Acetylheptanenitrile (IIc):[22]

Yield (35%); b.p. 125 ℃ / 14 torr; IR (Nojel): ν/cm^{-1}= 2225 (C≡N), 1730 (CO); ^{1}H-NMR(DMSO-d_6) δ (ppm): 0.9 (t, 3H, CH_3), 1.31 (m, 2H, CH_2), 1.5 (q, 2H, CH_2), 1.9 (s, 3H, CH_3), 2.1 (q, 2H, CH_2), 2.31 (q, 1H, CH), 2.40 (t, 2H, CH_2).

5-Oxo-4-phenylhexanenitrile (IId): B.p. 160℃/ 10 torr (Lit.[23] b.p. 170-172℃/ 12 torr).

Semicarbazone (IVa):[24] Yield (52%); m.p. 128℃; IR

(KBr): ν/cm^{-1}= 3420-3315 (NH_2), 3150 (NH), 1675 (CO); ^{1}H-NMR(DMSO-d_6) δ (ppm): 2.0 (m, 2H, CH_2), 1.91 (m, 2H, CH_2), 2.10 (s, 3H, CH_3), 2.4 (t, 2H, CH_2), 6.06 (s, 2H, NH_2), 7.09 (s, 1H, NH).

Semicarbazone (IVb): Yield (45%); m.p. 130℃ (Lit.[21] m.p. 132℃).

Semicarbazone (IVc): Yield (50%); m.p. 141℃ (Lit.[23] m.p. 163-165℃); IR (KBr): ν/cm^{-1}= 3400-3310 (NH_2), 3300 (NH), 1680 (CO); ^{1}H-NMR(DMSO-d_6) δ (ppm): 0.9 (t, 3H, CH_3), 1.30 (m, 2H, CH_2), 1.31 (m, 2H, CH_2), 1.4 (m, 1H, CH), 1.41 (q, 2H, CH_2), 1.71 (q, 2H, CH_2), 1.95 (s, 3H, CH_3), 6.1 (s, 2H, NH_2), 7.2 (s, 1H, NH).

Semicarbazone (IVd): m.p. 160 ℃ (Lit.[21] m.p. 163-165℃).

Methyl-4-phenyl-4-acetylbutirate (Vd)

A mixture of **IId** (0.4 mol) and 200 mL anhydrous methanol saturated with dry HCl gas was stirred, left to stand overnight, then cooled to 0℃, diluted with water and extracted with benzene. The organic layer washed with water and then with 5% sodium bicarbonate solution and finally with water. The solvent evaporated under vacuum to give **Vd**. Yield (60%); b.p. 142-144 / 4 mm (Lit.[23] b.p. 112-114 / 0.1 mm); IR (Nojel): ν/cm^{-1}= 1720 (CO ester), 1695 (CO); ^{1}H-NMR(DMSO-d_6) δ (ppm): 2.13 (s, 3H, CH_3), 2.25 (m, 2H, CH_2), 2.35 (m, 2H, CH_2COO), 3.65 (t, H, COC<u>H</u>), 3.70 (s, 3H, $COOCH_3$), 7.29-7.40 (m, 5H, Ar-H). η_D^{20} 1.5078; d_4^{29} 1.0814.

Methyl 5-oxohexanoate (Va)

It was prepared by the above method. b.p. 85-89 / 7 mm (Lit.[24] b.p. 85-89 / 7 mm); ^{1}H-NMR(DMSO-d_6) δ (ppm): 2.11 (s, 3H, CH_3), 2.14 (t, 2H, CH_2), 2.31 (t, 2H, CH_2COO), 2.40 (m, 2H, $COCH_2$), 3.66 (s, 3H, $COOCH_3$). η_D^{20} 1.4269; d_4^{29} 1.0267. MS (*m/z*, %) = 144 (M^+, 10).

Methyl 4-methyl-5-oxo-hexanoate (Vb)

It was prepared by the above method. b.p. 90-91 / 6 mm (Lit.[25] b.p. 90-91 / 6 mm); ^{1}H-NMR(DMSO-d_6) δ (ppm): 1.11 (s, 3H, CH_3), 1.90 (s, 3H, CH_3CO), 1.98 (m, 2H, CH_2), 2.35 (t, 2H, CH_2COO), 2.52 (t, 1H, COCH), 3.65 (s, 3H, $COOCH_3$). η_D^{20} 1.4325; d_4^{29} 1.0096. MS (*m/z*, %) = 158 (M^+, 15).

Methyl 4-acetylheptanoate (Vc)

It was prepared by the above method. b.p. 95-100 / 6 mm (Lit.[26] b.p. 95-100 /6 mm); ^{1}H-NMR(DMSO-d_6) δ (ppm): 0.9 (t, 3H, CH_3), 1.33 (m, 2H, CH_2), 1.53 (m, 2H, CH_2), 1.91 (s, 3H, CH_3CO), 1.97 (m, 2H, CH_2), 2.31 (m, 1H, COCH), 2.40 (m, 2H, CH_2COO), 3.66 (s, 3H, $COOCH_3$). η_D^{20} 1.4380; d_4^{29} 0.9773. MS (*m/z*, %) = 186 (M^+, 28).

4-Phenylcyclohexan-1,3-dione (VId)

To a solution of sodium methoxide (0.05 mol, 20 mL methanol) in methanol was added **Vd** (0.05 mol) and refluxed with continuous stirring. The reaction mixture was cooled, neutralized with H_2SO_4 (30 mL, 2N), excess methanol removed under vacuum. To the residue 10 mL water was added and extracted with ether (30 mL). The extract was worked up with 20% cold sodium hydroxide and then acidified with 20% H_2SO_4 to give the diketone as oily material. The oily product extracted with ether again, dried (sodium sulfate) and the solvent was removed under vacuum. The resulting oily residue was triturated with acetone to give **VId** as a solid. Yield (60%); m.p. 112℃; IR (KBr): ν/cm^{-1}= 1735 (CO); ^{1}H-NMR(DMSO-d_6) δ (ppm): 1.69: 1.94 (m, 2H, CH_2), 2.4: 2.5 (m, 2H, CH_2), 3.52 (m, 1H, CH), 3.56:3.66 (d.d., $COCH_2CO$), 7.29-7.51 (m, 5H, Ar-H). MS (*m/z*, %) = 188 (M^+, 70).

Cyclohexan-1,3-dione (VIa). It was prepared by the above method from **Va** as yellow oil which solidified on cooling for long time, m.p. 102^{o}C; yield 75%.

4-Methyl cyclohexan-1,3-dione (VIb)

It was prepared by the above method from **Va** as yellow oil. b.p. 140-145 / 9 mm (Lit.[27] b.p. 111 /0.025 mm); ^{1}H-NMR(DMSO-d_6) δ (ppm): 1.11 (d, 3H, CH_3), 1.69: 1.94 (m, 2H, CH_2), 2.40: 2.51 (m, 2H, CH_2), 2.53 (m, 1H, CH), 3.56: 3.66 (d.d., 2H, $COCH_2CO$). MS (*m/z*, %) = 126 (M^+, 35).

4-Propyl cyclohexan-1,3-dione (VIc)

It was prepared by the above method from **Vc**; m.p. 75-76℃ (from ether); yield (60%); ^{1}H-NMR(DMSO-d_6) δ (ppm): 0.9 (t, 3H, CH_3), 1.33 (m, 2H, CH_2), 1.53 (q, 2H, CH_2), 1.69: 1.94 (m, 2H, CH_2), 2.34 (m, 1H, CH), 2.41: 2.50 (m, 2H, CH_2), 3.56: 3.66 (d.d., 2H, $COCH_2CO$). MS (*m/z*, %) = 154 (M^+, 63).

2-Phenylazocyclohexan-1,3-dione (VIIa)

To a solution of cyclohexan-1,3-dione (**VIa**) (0.05 mol) in 10% sodium hydroxide (10 mL) was added dropwise with continuous stirring a cold solution of benzene diazonium chloride (0.15 g, 7 mL HCl, 0.1 g sodium nitrite). After cooling for 2 h, the reaction mixture was left to stand at room temperature overnight, when a yellow solid was obtained, m.p. 130℃ (from ethanol); UV λ_{max} (methanol) 395, 275, 248 nm; log ε 4.5, 4.1, 4.3, respectively (Lit.[27] m.p. 135℃).

2-(p-Methyl phenyl)azocyclohexan-1,3-dione (VIIb)

It was prepared by the above method from *p*-tolyl diazonium chloride and **VIa**; m.p. 172℃; yield (80%); IR (KBr): ν/cm^{-1}= 3150 (NH), 1610-1680 (CO), 1500 (C=N); UV λ_{max}: 385, 280, 248 nm; log ε 4.5, 4.1, 4.3, respectively. Analysis for $C_{13}H_{14}N_2O_2$: Calc. C, 67.81; H, 6.13; N, 12.17%. Found: C, 67.77; H, 6.10; N, 12.09%. MS (*m/z*, %) = 230 (M^+, 100).

4-Methyl-2-phenylazocyclohexan-1,3-dione (VIIc)

It was prepared by the above method from benzene diazonium chloride and **VIb**; m.p. 116℃; yield (50%); IR (KBr): ν/cm^{-1}= 3155 (NH), 1675 (CO), 1550 (C=N); UV λ_{max}: 390, 275, 248 nm; log ε 4.6, 4.2, 4.2, respectively. Analysis for $C_{13}H_{14}N_2O_2$: Calc. C, 67.81; H, 6.13; N, 12.17%. Found: C, 67.79; H, 6.09; N, 12.10%. MS (*m/z*, %) = 230 (M^+, 100).

4-Methyl-2-(p-nitrophenylazo)cyclohexan-1,3-dione derivatives (VIId)

It was prepared by the above method from *p*-nitrophenyl diazonium chloride and **VIb**; m.p. 157℃; yield (62%); IR (KBr): ν/cm^{-1}= 3250 (NH), 1680 (CO), 1530 (NO_2), 1500 (C=N), 1350 (NO_2); UV λ_{max}: 390, 285, 245 nm; log ε 4.6, 4.0, 4.1, respectively. Analysis for $C_{13}H_{13}N_3O_4$: Calc. C, 56.72; H, 4.76; N, 15.27%. Found: C, 56.66; H, 4.71; N,

15.19%. MS (*m/z*, %) = 275 (M^+, 100).

4-Phenyl-2-phenylazocyclohexan-1,3-dione (VIIe)

It was prepared by the above method from benzene diazonium chloride and **VId**; m.p. 130℃; yield (80%); IR (KBr): ν/cm^{-1} = 3150 (NH), 1675 (CO), 1510 (C=N); UV λ_{max}: 395, 275, 248 nm; log ε 4.7, 4.2, 4.2, respectively. Analysis for $C_{18}H_{16}N_2O_2$: Calc. C, 73.95; H, 5.52; N, 9.58%. Found: C, 73.89; H, 5.48; N, 9.49%. MS (*m/z*, %) = 292 (M^+, 100).

4-Phenyl-2-(p-methoxyphenylazo)cyclohexan-1,3-dione (VIIf)

It was prepared by the above method from *p*-methoxyphenyl diazonium chloride and **VId**; m.p. 177℃; yield (65%); IR (KBr): ν/cm^{-1} = 3150 (NH), 1680 (CO), 1500 (C=N); UV λ_{max}: 390, 280, 248 nm; log ε 4.7, 4.1, 4.1, respectively. Analysis for $C_{19}H_{18}N_2O_3$: Calc. C, 70.79; H, 5.63; N, 8.69%. Found: C, 70.71; H, 5.59; N, 8.78%. MS (*m/z*, %) = 322 (M^+, 100).

Phenylbis-(2,6-diketo-3-phenylcyclohexyl)methane (VIII). To a solution 25 mL, 4% of **VId** in ethanol (50 mL, 50%) was added 5 drops benzaldehyde. The reaction mixture was refluxed for 0.5 h then left to stand at room temperature for three days to give a solid product **VIII**; m.p. 160℃; yield (55%); IR (KBr): ν/cm^{-1} = 1730 (CO); ^{1}H-NMR(DMSO-d_6) δ (ppm): 2.02: 2.27 (m, 4H, 2CH_2), 2.40: 2.5 (m, 4H, 2CH_2), 3.6 (m, 2H, 2CH), 3.63 (m, 2H, 2CH-Ph), 7.2-7.45 (m, 15H, Ar-H). MS (*m/z*, %) = 464 (M^+, 100). Analysis for $C_{31}H_{28}O_4$: Calc. C, 80.15; H, 6.08%. Found: C, 80.0; H, 5.95%.

2-Bromo-4-phenylcyclohexan-1,3-dione (IX)

To **VId** (0.05 mol) in 200 mL cold water was added dropwise bromine (0.06 mol) and heated to obtain homogenous solution. The reaction mixture was cooled and the solid product was filtered and recrystallized from ethanol to give the bromo derivative **IX**; m.p. 151 ℃ ; ^{1}H-NMR(DMSO-d_6) δ (ppm): 2.01-2.50 (m, 4H, 2CH_2), 3.63 (t, 1H, C_4-H), 5.15 (s, 1H, C_2-H), 7.2-7.4 (m, 5H, Ar-H). MS (*m/z*, %) = 265 (M^+, 100). Analysis for $C_{12}H_{11}BrO_2$: Calc. C, 53.96; H, 4.15%. Found: C, 53.81; H, 3.95%.

(5R)Bicyclo-[1.3.3]nonan-2,9-dione (X)

It was obtained by the general previous method for preparing compound V from 2-(2'-methoxycarbonyl ethyl) cyclohexanone (**V**); m.p. 141^{o}C; IR (KBr): ν/cm^{-1} = 1725 (CO); ^{1}H-NMR(DMSO-d_6) δ (ppm): 1.76-1.81 (m, 5H, CH + 2CH_2), 2.04 (m, 2H, CH_2), 2.21 (m, 2H, CH_2), 2.45 (t, 2H, CH_2), 3.08 (t, 2H, CH_2). MS (*m/z*, %) = 152 (M^+, 81). Analysis for $C_9H_{12}O_2$: Calc. C, 71.03; H, 7.95%. Found: C, 71.0; H, 7.90%.

3.2. Antibacterial Activity

All the compounds were screened for their in vitro antibacterial activity against two Gram negative strains, *i.e. Escherichia Coli* (MTCC 40) and *Pseeudomonas Aeruginosa* (MTCC 2453) and two Gram positive strains, *i.e. Bacillus Subtilis* (MTCC 121) and *Staphylococcus Aureus*(MTCC 96).

Antibacterial activity was assessed by serial two fold dilution technique[28]. Ciprofloxacin was used as a standard drug. All the compounds were dissolved in dimethyl sulfoxide to give a concentration of 10 μg mL^{-1}. Double strength nutrient broth was used as a growth media. The stock solution was serially diluted to give concentration of 5.0-0.01 μg/mL in nutrient broth. The inoculums size was approximately 10^6 colony forming units (CFU/ mL). The inoculated tubes were incubated for 24 h, the inoculated culture tubes were macroscopically examined for turbidity. The culture tube showing turbidity (lower concentration) and the culture tube showing no turbidity (higher concentration) gave the minimum inhibitory concentration (MIC) for the compound. The MIC for the (**VIIa-f**)-**X** and the standard drug, *i.e.* Ciprofloxacin are given in Table 2.

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