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A novel trans-amination process in 3-arylamino-5,5-dimethylcyclohex-2-en-1-one with nucleophiles and antimicrobial activity of selected products

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Abstract: Reaction of dimedone with arylamines afforded the respective enaminones. Some N-acetyl derivatives were prepared. The reaction of enaminones with hydroxylamine was found to be dependent on the nature of the arylamine moiety and the molar ratio of hydroxylamine to give the mono-, di- or tri-oximes. Cyclization of the trioxime by acetic anhydride gave dihydrobenzo[*c*][1,2,5]oxadiazol-4(5H)-one-5-O-acetyloxime. Coupling of the synthesized enaminones with benzene diazonium chloride gave 2,4-bis-phenylhydrazones or a mixture of 2-mono hydrazones and bis-hydrazones depending on the nature of the arylamine moiety. Trans-amination of the arylamine of the bis hydrazones with hydroxylamine gave the same1,3-bis oxime derivative. The structures of the synthesized compounds were confirmed by IR, ^{1}HNMR, ^{13}C NMR spectra. The antimicrobial activity of some selected products showed promising results.

Keywords: Dimedone, enaminones, hydrazones, oxime, tautomerism, trans-amination.

Introduction

Enaminones are versatile reagents in organic synthesis due to their incorporation of electrophilic and nucleophilic centers as well as their tendency to form a dipolar structure capable of undergoing cyclocondensation reactions [1-10]. Moreover, they play a role in anionic and cationic interactions as well as charge-transfer complexes. Enaminones have been used as effective carriers for pharmacologically active groups and as synthetic intermediates in pharmaceutical developments [11,12]. Continuing our work on the utilization of dimedone as a precursor for heterocyclic compounds [13-18], we report here the reactivity of functionalized enaminones, namely 3-arylamino-5,5-dimethylcyclohex-2-en-1-ones, derived from dimedone, towards some nucleophiles and electrophiles. The anti-microbial activity of some of the synthesized compounds has been tested.

Results and Discussion

The *β*-enaminone derivatives are mostly obtained by reaction of a *ß*-diketone with an amine in benzene with azeotropic removal of water [19]. Approaches to the acceleration of the reaction and improvement of the yield were attempted using a variety of catalysts [20-29]. However, grinding induced catalyst-free and solvent synthesis of *β*-enaminones and *β*-enamino esters were achieved [30].

Herein, we report a mild and efficient method for the synthesis of 3-arylamino-5,5-dimethylcyclohex-2-en-1-one **8-13** (Scheme 1) in 88-96% yield, by boiling dimedone with the arylamines **1-6** in acetic acid for two hours. Under similar conditions, the antipyrinyl derivative 5,5-dimethyl-3-[*N*-(2,3-dimethyl-1-phenylpyrazolin-5-on-4-yl)]aminocyclo-hex-2-en-1-one **14** was obtained in low yield. A better yield (50%) of **14** was obtained when dimedone reacted with **7**in formic acid either under reflux for 30 minutes or at room temperature for 24 hours. The structure of **14** was deduced from its spectral data. Thus, the FAB mass spectrum showed a molecular ion peak at m/z 326 [$M^{+\cdot}$+1], and its elemental analysis agreed with the molecular formula $C_{19}H_{23}N_3O_2$. The ^{1}H-NMR spectrum of **14** showed the vinylic C-2 proton as a singlet atδ 5.04 ppm and the NH-proton as a broad singlet at δ 7.98 ppm. The other signals agreed with the assigned structure (experimental section).

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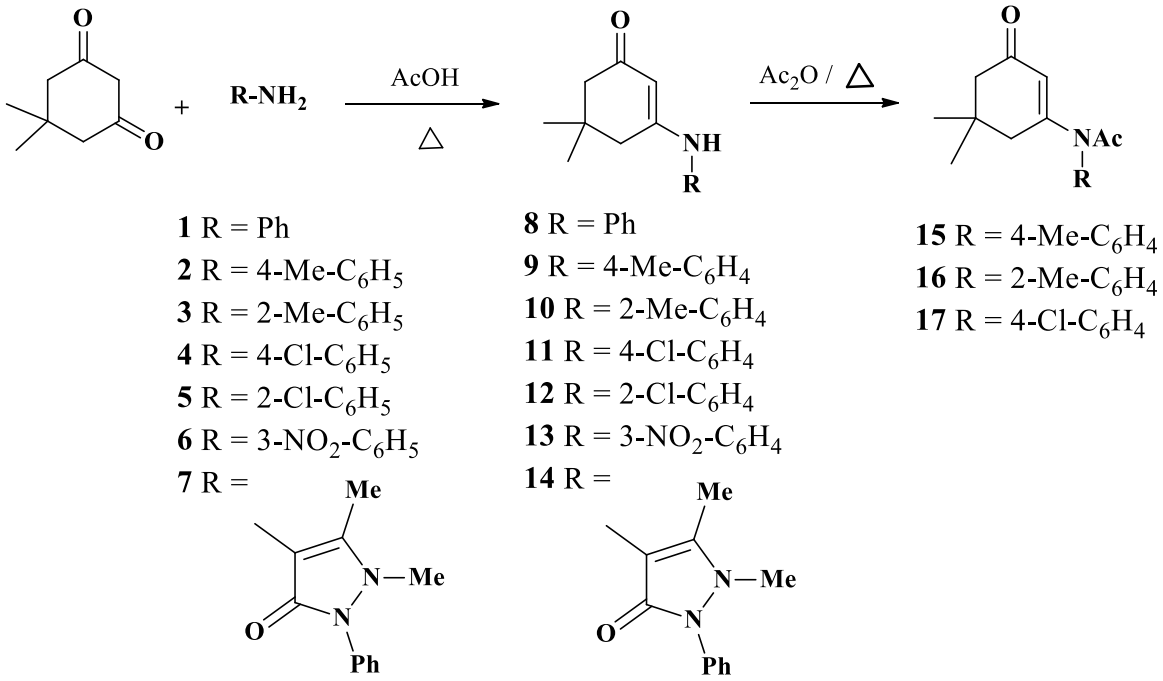


Scheme 1. Synthesis of enamine 8-14 and their N-acetyl derivatives

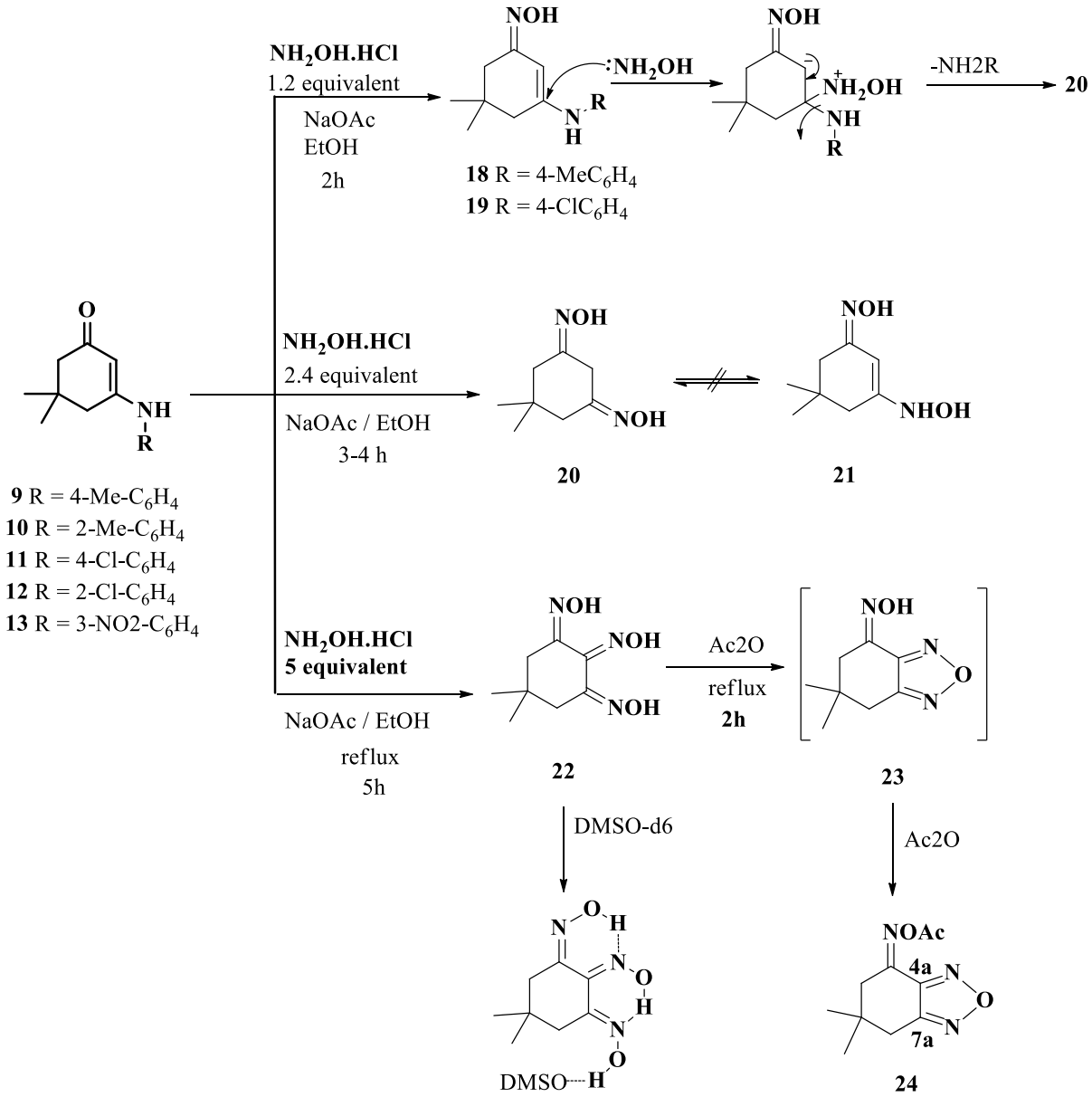
Acetylation of **9-11** with acetic anhydride under reflux afforded the *N*-acetyl derivatives **15-17,** respectively as that deduced from their spectral analyses. The mass spectrum of **16** showed a molecular ion peak at m/z 271 which in agreement with the introduction of only one acetyl group. The ^{1}H-NMR spectra of **15-17** showed the absence of the signal corresponding to the NH-proton and the appearance of a singlet at δ 1.82- 2.11 ppm corresponding to only one acetyl group. Their vinylic C-2 proton resonated at δ 5.12-5.51 ppm, and one of the two methylene protons were assigned to the two singlets at δ 2.12 - 2.30 and 2.46-2.73 ppm. Whereas, the second methylene of **16** appeared as ABq at δ 2.95 ppm with J_{ABq} 17.2 Hz. The ^{13}CNMR spectra of **16** agreed with the assigned structure.

The reaction of **9** and **11** with 1.2 equivalent of hydroxylamine hydrochloride in the presence of sodium acetate for two hours afforded the mono oxime derivatives **18** and **19,** respectively. Their ^{1}H-NMR spectra showed a signal for the N-OH proton at the downfield region (δ 10.58 ppm) in addition to the NH-proton assigned at δ 11.07-11.20 ppm. When compounds **10, 12** and **13** were similarly treated, only slight conversion to their mono oximes was detected by using TLC. On the other hand, increasing the molar equivalents of hydroxylamine hydrochloride to 2.4 was required to yield the dioxime **20** within 3-4 hours [31]. Thus, the mass spectrum of **20** showed a molecular ion peak at m/z 170 which indicated a trans-amination process of the aryl amine moiety had taken place with an oxime group. Also, the ^{1}H-NMR spectrum of **20** showed the disappearance of the aryl protons and the presence of D_2O exchangeable singlet of two protons intensity at δ 10.42 ppm due to the two N-OH protons. The possible existence of the enol form **21** was excluded since C-4, and C-6 methylene protons were assigned for a singlet at δ 2.13 ppm of four protons intensity whereas those of C-2 were assigned at a higher frequency (δ 3.40 ppm) in addition to the absence of the vinyl H-2 proton. The ^{13}C-NMR of **20** showed signals corresponding to C-1 and C-3 at higher frequency region at δ 153.04 ppm. The two methylene carbons C-4 and C-6 were assigned at δ_c 32.18 ppm where the flanked C-2 was assigned to the higher frequency signal at δ_c 44.35 ppm because of the two oxime groups at C-1 and C-3.

When the hydroxylamine hydrochloride was increased to five equivalents in its reaction with enaminones **9-13**, an unexpected product was obtained within two hours from each, in 50-76 % yield which could be assigned the trioxime structure **22** [32]. The ^{1}H-NMR spectrum of **22** showed the presence of two singlet signals at δ 2.42 and 2.45 ppm which were assigned to the two methylene protons. The spectrum showed the absence of signals corresponding to the aryl moiety and the presence of three D_2O exchangeable signals at the downfield region at δ 11.33, 11.89 and 12.77 ppm corresponding to the three N-OH protons. The presence of last three signals at a low magnetic field indicated their involvement in hydrogen bonding; two within the chelated structure and the third one can be hydrogen bonded with DMSO-$d_6$that was used as a solvent (Scheme 2). The mass spectrum of **22** confirmed the assigned structure which showed a molecular ion peak at m/z 198 [$M^{+\cdot}$+1]. Loss of NOH fragment gave a bis-oxime **20** as the base peak at m/z 170. The ^{13}C-NMR spectrum of **22** showed a signal for C-1, C-2 and C-3 at δ_c 153.79 ppm whereas C-4, C-5 and C-6 were

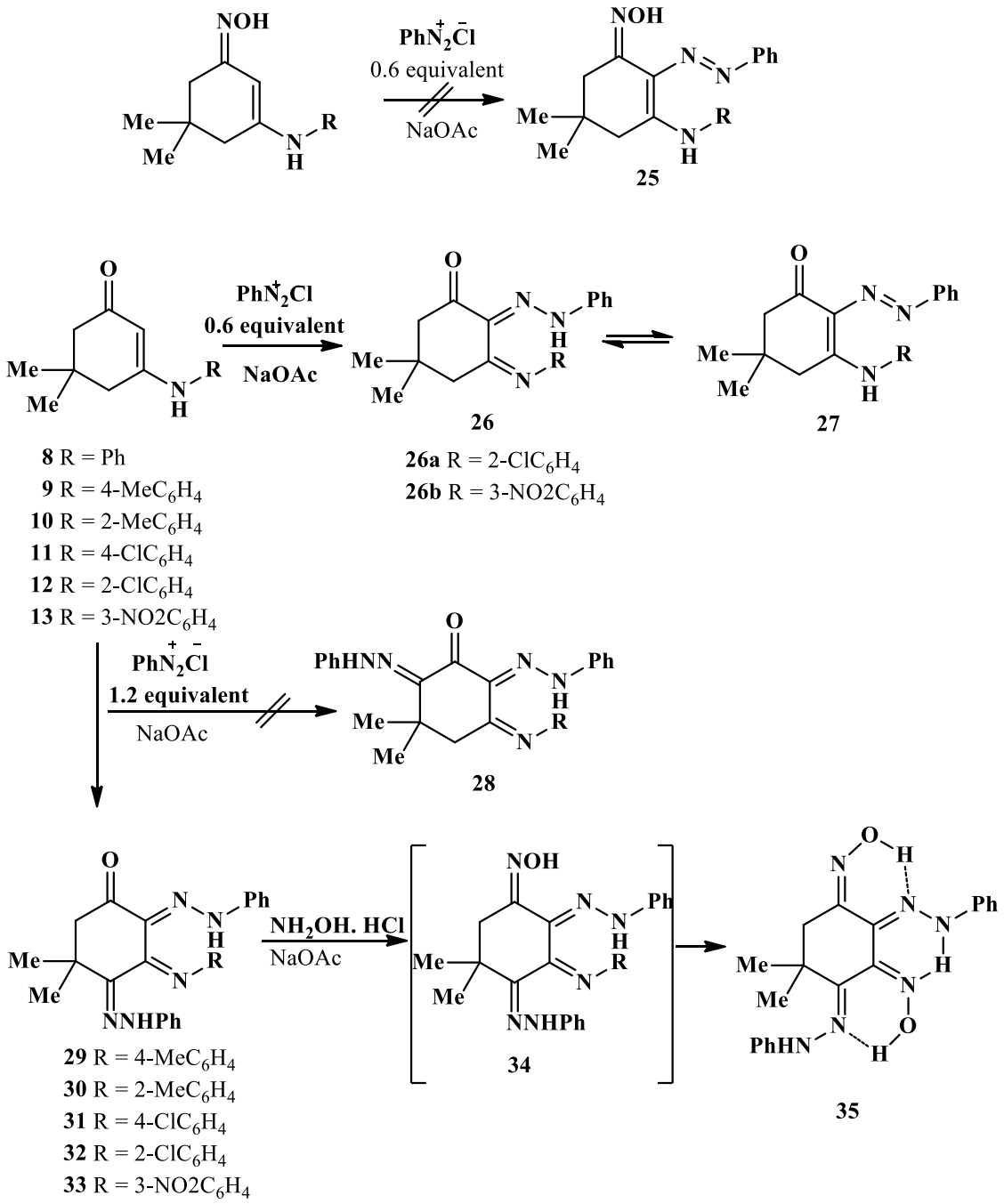
assigned at lower frequency region at δc 37.45, 32.18 and 44.32 ppm.

1,2,5-Oxadiazole and benzo-1,2,5-oxadiazole, as well as their *N*-oxide derivatives, have potent biological activities.[33-36] The synthesis of 1,2,5-oxadiazole can be readily achieved by the dehydration of vicinal dioximes in basic or acidic media [37-40]. Thus, dehydrative cyclization of **22** with acetic anhydride under reflux for two hours gave the respective 1,2,5-oxadiazole **24**. The ^{1}H-NMR spectrum of **24** showed the absence of N-OH protons at the downfield region of its precursor **22** and the appearance of a new signal at δ2.27 attributed to an *N*-*O*-acetyl proton that confirmed the cyclization of the vicinal dioxime to form the 1,2,5-oxadiazole **23** which subsequently acetylated under the reaction conditions to give **24** (Scheme 2). The cyclization process and *O*-acetylation of the oxime group were confirmed from its ^{13}C-NMR ($CDCl_3$) spectrum that showed three signals at δc134.2, 144.51 and 161.3 ppm corresponding to C-7a, C-4a, and C-4, respectively. The *O*-acetyl group carbons were confirmed by the presence of signals at δ 19.85 (Me) and 171.93 ppm (CO).



Scheme 2. Reaction of hydroxylamine with enaminones 9-13

Attempted azo coupling of benzene diazonium chloride with the oxime derivatives **18** and **19** did not afford the respective azo derivative **25**, and the oximes were recovered unchanged. However, coupling the enaminones**9**-**11**with benzene diazonium chloride (1.2 molar equivalent) for four hours to give crystalline products, but they could not be assigned the expected structure 3-(*N*-aryl)imino-5,5-dimethylcyclohex-2-en-1-one-2-phenylhydrazone **26** or their azo tautomers**27** (Scheme 3**)**.



Scheme 3. Reaction of phenyl diazonium chloride with enaminones **8-13**.

On the other hand, coupling the enaminones **9-11** with benzene diazonium chloride (5 molar equivalent) give compounds **29-31,** their structures were deduced from their ^{1}H NMR spectral data which showed the absence of signals corresponding to both vinylic H-2 and the presence of only one of the methylene singlets of dimedone moiety. The disappearance of one of the methylene groups indicated its involvement in the reaction. Moreover, extra ten protons at δ 6.61-7.38 ppm were assigned to the aromatic protons, attributed to two phenyl groups in addition to those of the pre-existing aryl group. Furthermore, the mass spectrum of **30** showed a molecular ion peak at m/z 437.0 [M^{+-}-1] which in agreement with the bis-hydrazone **30** rather than their monohydrazone **26**. Accordingly, a double azo coupling reaction took place by successive electrophilic attacks of two diazonium ions on C-2 to give **26** which subsequently attacked one of the methylene group at C-6 to give **28** or on the methylene group at C-4to give **29-31**. The formation of **29-31** rather than **28** was confirmed from ^{13}C-NMR spectrum of **30** which showed three signals at the lower frequency region at δ_c 28.41, 37.61 and 52.67 ppm characteristic for two methyl groups and methylene group at C-5 and C-6, respectively whereas signals corresponding to C-4, C-2 and C-3 were shifted to the downfield to resonate at δ 144.54, 150.31 and 154.47 ppm, respectively. The

introduction of the second phenylhydrazone group at C-4 rather than C-6 could be as a result of activation of this methylene group by the neighboring enamine group. The formation of the hydrazones **29-31** rather than azo tautomer was established from the assignment of only two exchangeable N-H protons δ 14.00–14.59 ppm whereas the second N-H was overlapped with the aromatic protons for compounds **29** and **31** whereas compound **30** showed two NH signals at δ at 14.60 ppm and 14.88 ppm. The presence of N-H proton at the higher frequency region (14.00-14.60 and 14.54-14.88) suggested its involvement in a strong intramolecular hydrogen bonding [41]. Moreover, the assignment of the location of the second molecule from diazonium salt at C-4 as hydrazone rather than at C-6 as in **28** has been based on spectral studies of related compounds reported by Simunek et al. [42-43].

On the other hand, the enaminones**12** and **13** under the same reaction conditions afforded a mixture of the monohydrazone (**26a, 26b)** and the bishydrazones (**32** and **33)**, respectively which were fractionally separated by crystallization from ethanol. Consequently, decreasing the equivalent of benzene diazonium chloride to 0.6 molar equivalent on coupling reaction with **12** and **13** for two hours resulted in the formation of the monohydrazones **26a** and **26b** with a minor amount of **32** and **33**, respectively. The ^{1}H-NMR and ^{13}C-NMR spectra of **32** and **33** showed a similar pattern to those of compounds **29-31**. On the other hand, the ^{1}H-NMR spectra of **26a** and **26b** showed only one exchangeable N-H proton at δ 14.55-14.59 ppm. Moreover, two methylene protons of C-4 and C-6 were assigned to the two singlets at δ 1.56-1.58 ppm and 2.73-2.75 ppm, respectively which confirmed the formation of the monohydrazone derivatives. Furthermore, only nine protons were assigned in the aromatic region which agrees with the assigned structure. The ^{13}C-NMR spectra of **26a** and **26b** also confirmed the introduction of the monohydrazone moiety since three signals corresponding to C-5, C-4 and C-6 were assigned at δ_c 37.72–37.91, 37.92–37.99 and 52.52-52.64 ppm, respectively whereas the other three carbons C-2, C-3 and C-1 were resonated at higher frequency region at δ_c 145.41–152.54, 155.49-155.51 and 196.59- 197.15 ppm, respectively.

Treatment of compounds **29-33** with excess hydroxylamine hydrochloride in the presence of sodium acetate in ethanol under reflux did not afford the respective oxime derivative **34**, but the same crystalline product **35** resulted from each of them. Its elemental analysis as well as its mass spectrum which showed a molecular ion peak at m/z 378, were inconsistent with **34,** but in agreement with the molecular formula $C_{20}H_{22}N_6O_2$ indicating the displacement of the arylamine residue by an oxime group. The ^{1}HNMR spectrum of the isolated product, measured in deuterated chloroform, showed the absence of signals corresponding to the aryl moiety, and the presence of signals corresponding to ten protons of two phenyl groups. Moreover, four exchangeable singlets at δ 8.22, 12.35, 12.93 and 15.06 ppm can be assigned to the 2 OH, and 2 NH and at least two of them are involved in hydrogen bonding**.**

Antimicrobial study for some selected compounds

Compounds **11**, **14**, **17**, **18**, **19**, **29**, **31** and **35** were screened for their antimicrobial activity against *S. aureus* and *C. albicans* using agar diffusion method [44] and ampicillin and clotrimazole as references. The results (Table 1) showed that compounds **14**, **17**, **18,** and **19** have moderate inhibition against *S. aureus* (IZ 21-28 mm). On the other hand, the presence of the phenylhydrazone moieties in compounds **29** and **31** resulted in the loss of activity against S. aureus. However, the chloro compound **19** showed a higher antimicrobial activity (IZ 30-31 mm) against *C. albicans* and *p*-tolyl analogue **18** showed the same activity (IZ 23 mm) compared to that of clotrimazole. The other tested compounds showed lower inhibition activity (IZ 14-20).

Table 1. Antimicrobial activity of some selected compounds.

Compd. No.	Inhibition zone (IZ)			
	S. aureus	*C. albicans*		
11 **14**	24 21	20 18		
17	24	20		
18	24	23		
19	28	30-31		
29	-	15		
31	-	14-15		
35	13	19		
Ampicillin	35	-		
Chlotrimazole	-	23		

Conclusion

The enaminones derived from dimedone have proved its utility as reactive intermediates upon reaction with nucleophilic and electrophilic reagents. The formation of the oxime derivatives can be rationalized by nucleophilic attack of hydroxylamine at C-1 carbonyl group to give the respective C-1 mono oximes that underwent a trans-amination process of the arylamine moiety with hydroxylamine to form the bis-oxime**s**. Further reaction of the bis oxime with NH_2OH, probably at the more reactive methylene carbon C-2 rather than C-6 gave the tri-oxime. The preference for the first attack of hydroxylamine at C-1 rather than C-3 can be deduced from the formation of the mon-oximes without affecting the arylamine residue. The trans-amination process has supported by a displacement of such type, but with hydrazine, of 3-benzylamino group in 3-benzylamino-2-carboxamido derivative of dimedone with hydrazine [45], and reactions of enamines with nitrogen nucleophiles [3]. Moreover, good antimicrobial activity against *S. aureus* and *C. albican* was shown.

Experimental

Melting points were determined with a Mel-Temp apparatus and are uncorrected. TLC was performed on Baker-Flex silica gel 1B-F (1.5-5.0 cm) plates, and the spots were detected by UV light absorption. IR spectra were recorded in a matrix of KBr with Perkin-Elmer 1430 spectrometer. ^{1}H NMR spectra were recorded on Jeol spectrometer (500 MHz) and Bruker AC (300 MHz) spectrometer. Chemical shifts (δ) are given in ppm relative to the signal for TMS as an internal standard. ^{13}CNMR were recorded on the Bruker Avance AV spectrometer at 75 MHzChemical shifts (δ) are given in ppm. Mass spectra were recorded using electron ionization (EI) on a Finnigan MAT 312 spectrometer orJeol (JMS.600H) instrument and fast-atom-bombardment (FAB) on a Kratos MS50 spectrometer.

3-N-(Aryl)amino-5,5-dimethylcyclohex-2-en-1-ones (8-14).

Method a. A mixture of dimedone (0.01mol) and arylamines**1-6** or 4-aminoantipyrine**7** (0.01mol) in acetic acid (5 mL) was heated under reflux for 2 hours. The reaction mixture was left to cool, then poured onto cold water (50 mL). The product was filtered off and crystallized from ethanol.

Method b. A mixture of dimedone(0.01 mol) and 4-aminoantipyrine (0.01 mol) was heated under reflux in formic acid (98 %, 20 mL) for 30 min, or left at room temperature for 24 hours then evaporated under reduced pressure. The residue was washed with warm water and then re-crystallized from ethanol to give **14** (50 % yield) identical with that obtained from method a.

5,5-Dimethyl-3-N-(Phenyl)amino-cyclohex-2-en-1-one (8).
Yellow crystals (70 %yield); m. p. 167-168 ºC, lit.[19] m.p. 165-167ºC.

5,5-Dimethyl-3-N-(4-methylphenyl)amino-cyclo-hex-2-en-1-one (9).
Pale yellow crystals (79% yield); m. p. 202-203 ºC; lit.[19] m. p. 203-204 ºC,
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H ppm: 1.10 (s, 6H, 2Me), 2.18 (s, 2H, CH_2), 2.30 (s, 3H, Me), 2.31 (s, 2H, CH_2), 5.49 (s,1H, H-2), 6.63 (bs, 1H, D_2O exchangeable, NH), 7.02 (d, 2H, *J* 8.4 Hz, Ar-H), 7.11 (d, 2H,*J* 8.4 Hz, Ar-H).

5,5-Dimethyl-3-N-(2-methylphenyl)amino-cyclo-hex-2-en-1-one(10).
Pale yellow crystals (88 % yield); m. p. 138-140 ºC, lit.[19] m.p. 136 ºC.
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H ppm:1.05 (s, 6H, 2Me), 2.19 (s, 2H, CH_2), 2.22 (s, 3H, Me), 2.35 (s, 2H, CH_2), 4.95 (s,1H, H-2), 7.06-7.20 (m, 5H, ArH+NH).

3-N-(4-Chlorophenyl)amino-5,5-dimethylcyclo-hex-2-en-1-one (11).
Pale yellow crystals (60 %yield); m. p. 205-206 ºC, lit.[19] m. p. 209-210 ºC.

3-N-(2-Chlorophenyl)amino-5,5-dimethylcyclo-hex-2-en-1-one (12).
Pale yellow crystals (96 % yield); m. p. 144-145 ºC, lit.[19] m.p. 141-142 ºC.
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H ppm:1.09 (s, 6H, 2Me), 2.20 (s, 2H, CH_2), 2.35 (s, 2H, CH_2), 5.43 (s, 1H, H-2), 6.68 (s, 1H, D_2O exchangeable, NH), 7.16 (t, 1H, *J* 7.65 Hz, Ar-H), 7.22 (t, 1H,*J*7.65 Hz, Ar-H), 7.35, 7.40 (2d, 2H, *J* 7.65 Hz, Ar-H).

5,5-Dimethyl-3-N-(3-nitrophenyl)amino-cyclohex-2-en-1-one(13).
Pale yellow crystals (96 % yield); m.p. 173-174 ºC, lit.[19] m. p. 174-175 ºC,
^{1}H NMR ($CDCl_3$, 500 MHz) $\delta_H$ppm:1.08 (s, 6H, 2Me), 2.30 (s, 2H, CH_2), 2.53 (s, 2H, CH_2), 5.77 (s, 1H, D_2O exchangeable, N-H), 7.25 (s, 1H, H-2), 7.51-7.60 (m, 2H, Ar-H), 8.03 (d, 2H, *J* 8.6 Hz, Ar-H).

5,5-Dimethyl-3-N-[(2,3-dimethyl-1-phenylpyrazolin-5-one-4-yl)]aminocyclohex-2-en-1-one (14).
Pale yellow crystals (22 % yield) from ethanol; m.p. 218 ºC
IR (solid, KBr, vmax, cm^{-1}): 3234 (NH), 1649 and 1612 (CO, C=C);
^{1}H NMR ($CDCl_3$, 300 MHz) δ_H ppm: 1.08 (s, 6H, 2Me), 2.08 (s, 3H, Me), 2.13 (s, 2H, CH_2), 2.28 (s, 2H, CH_2), 3.06 (s, 3H, N-Me), 5.04 (s, 1H, H-2), 7.31-7.49 (m, 5H, Ar-H), 7.98 (bs, 1H, D_2O exchangeable, NH). FABMS: m/z 326 ($M^{+\cdot}$+1, 100 %).
Analysis Calcd. for $C_{19}H_{23}N_3O_2$ (325.39):C, 70.12; H, 7.12; N, 12.60. Found: C, 70.32; H, 7.00; N, 12.74.

3-*(*N-Acetyl-N-Aryl)amino-5,5-dimethylcyclohex-2-en-1-ones (15-17).

General method. A suspension of **9 - 11** (5 mmol) in acetic anhydride (15 mL) was heated under reflux for 1hour. The reaction mixture was cooled then poured onto crushed ice. The separated syrup was dissolved in chloroform, and the solution was washed with a dilute solution of $NaHCO_3$in water. The chloroform layer was dried over anhydrous sodium sulfate, then evaporated and the residue was recrystallized from ethanol to give **15-17**, respectively.

3-(N-Acetyl-N-4-methylphenyl)-5,5-dimethyl-cyclohex-2-en-1-one(15).

Pale yellow crystals (23 % yield); m.p. 78-80 ºC;
IR (solid, KBr, vmax,cm^{-1}): 1689, 1653 (CO);
^{1}H-NMR ($CDCl_3$, 500 MHz)δ_H ppm: 1.06 (s, 6H, 2Me), 1.94 (s, 3H, Ac), 2.30 (s, 2H, CH_2), 2.35 (s, 3H, Me), 2.73 (s, 2H, CH_2), 5.34 (s, 1H, H-2), 7.00 (d, 2H, *J* 8.4 Hz, Ar-H), 7.24 (d, 2H, J 8.4 Hz, Ar-H).
Analysis Calcd. for $C_{17}H_{21}NO_2$ (271.35): C, 75.52; H, 7.80; N, 5.16. Found: C, 75.23; H, 7.33; N, 5.26.

3-(N-Acetyl-N-2-methylphenyl)-5,5-dimethyl-cyclohex-2-en-1-one(16).

Pale yellow crystals (22 % yield); m.p. 103-105 ºC;
^{1}H-NMR ($CDCl_3$, 500 MHz) δ_H ppm:1.04, 1.06 (2s, 6H, 2Me), 1.82 (s, 3H, Ac), 2.17 (s, 3H, Me),2.23 (s, 2H, CH_2), 2.95 (ABq, 2H, *J*17.2 Hz, CH_2), 5.12 (s, 1H, H-2), 7.05 (d, 1H, *J* 7.65 Hz,Ar-H), 7.26–7.33 (m, 3H, Ar-H),
^{13}C NMR ($CDCl_3$) δ_c ppm: 21.4 ($CO\underline{CH_3}$), 25.3 (2-Me), 27.9, 28.4 (2Me), 34.1 (C-5), 43.4 (C-4), 50.5 (C-6), 115.6, 127.9, 129.0,129.4, 132.0, 135.5 (Ar-C), 139.7 (C-2), 160.4 (C-3), 171.2 NCO and 199.7 (C-1).
MS (EI) m/z (%): 271 (20, $M^{+\cdot}$), 228 (85, $M^{+\cdot}$-$COCH_3$), 214 (base peak $M^{+\cdot}$ –$^{\cdot}$N-CO-CH_3).
Analysis Calcd. for $C_{17}H_{21}NO_2$ (271.35): C, 75.52; H, 7.80; N, 5.16. Found: C, 75.33; H, 7.60; N, 5.26.

3-(N-Acetyl-N-4-chlorophenyl)-5,5-dimethylcyclo-hex-2-en-1-one(17).

Colorless crystals (90% yield); m.p. 118 ºC;
IR (solid, KBr, vmax, cm^{-1}): 1690, 1653 (CO),
^{1}H-NMR (DMSO-d_6, 500 MHz) δ_H ppm:0.97 (s, 6H, 2Me), 2.11 (s, 3H, Ac), 2.12 (s, 2H, CH_2), 2.46 (s, 2H, CH_2), 5.51 (s, 1H, H-2), 7.39 (d, 2H, *J* 8.6 Hz, Ar-H), 7.58 (d, 2H, *J*8.6 Hz, Ar-H).
Analysis Calc for $C_{16}H_{18}NO_2Cl$ (291.765): C, 65.68; H, 6.21; N, 4.80. Found: C, 65.79; H, 6.27; N, 4.93.

3-N-(Aryl)amino-5,5-dimethylcyclohex-2-en-1-oximes(18-19).

General method. A solution of **9** or **11** (10mmol) in ethanol (30 mL) was treated with hydroxylamine hydrochloride (12 mmol) and sodium acetate (12 mmol). The mixture was boiled under reflux for 2 hours. The solution was then concentrated under reduced pressure. The product was filtered, washed with water, dried then crystallized from ethanol.

5,5-Dimethyl-3-N-(4-methylphenyl)aminocyclo-hex-2-en-1-oxime (18).

Colorless needles (82% yield); m.p. 177-179 ºC;
IR (solid, KBr, vmax, cm^{-1}): 3237(NH), 1615 (C=N).
^{1}H-NMR (DMSO-d_6, 300 MHz)δ_H ppm: 1.03 (s, 6H, 2Me), 2.32 (s, 3H, Me), 2.38 (s, 2H, CH_2), 2.55 (s, 2H, CH_2), 5.68 (s, 1H, H-2), 7.18 (d, 2H, *J* 8.0 Hz, Ar-H), 7.29 (d, 2H, *J* 8.0 Hz, Ar-H), 10.58, 11.07, (2s, 2H, D_2O exchangeable OH, NH).
FABMS: m/z 245 ($M^{+\cdot}$ +1, 100 %).
Analysis Calc for $C_{15}H_{20}N_2O$ (244.33): C, 73.73; H, 8.25; N, 11.46. Found: C, 73.59; H, 8.34; N, 11.37.

3-N-(4-Chlorophenyl)amino-5,5-dimethylcyclo-hex-2-en-1-oxime(19).

Colorless crystals (76% yield); m.p. 210-211 ºC;
IR (solid, KBr, vmax, cm^{-1}):3228 (NH), 1616 (C=N);
^{1}H-NMR (DMSO-d_6, 500 MHz)δ_H ppm:1.05 (s, 6H, 2Me), 2.39 (s, 2H, CH_2), 2.55 (s, 2H, CH_2), 5.75 (s, 1H, H-2), 7.33 (d, 2H, *J* 8.3 Hz, Ar-H), 7.55 (d, 2H, *J* 8.3 Hz, Ar-H), 10.58, 11.2 (2s, 2H, D_2O exchangeable OH, NH).
Anal. Calc for $C_{14}H_{17}N_2OCl$ (264.757): C, 63.50; H, 6.47; N, 10.58. Found: C, 63.35; H, 6.64; N, 10.39.

5,5-Dimethylcyclohexane-1,3-dioxime (20).

General method. A solution of **10**, **12** and**13** (5 mmol) in ethanol (30 mL) was treated with hydroxylamine hydrochloride (12.20 mmol) and sodium acetate (12.20mmol). The mixture was boiled under reflux for 3-4hours. The solution was then concentrated under reduced pressure. The residue was filtered, washed with water and dried. It was crystallized from ethanol to give **20** as colorless crystals in (70.4 % yield) from **10**, (70% yield) from **12** and (45 % yield) from **13**;
m.p.220-222 ºC lit.[31] m. p. 221-223ºC;
^{1}H-NMR (DMSO-d_6, 500 MHz) δ_H ppm: 0.86 (s, 6H, 2Me), 2.13 (s, 4H, $2CH_2$), 3.40 (s, 2H, CH_2), 10.42 (s, 2H, D_2O exchangeable 2NOH).
^{13}C NMR ((DMSO-d_6) δ_c ppm: 23.6 (2Me), 27.8 (C-5), 32.1 (C-4, C-6), 44.3 (C-2), 153.0 (C-1, C-3);
MS (EI) m/z (%): 170 $M^{+\cdot}$.
Analysis Calcd. for $C_8H_{14}N_2O_2$(170.21): C,56.45; H,8.29; N, 16.46; O, 18.80. Found: C, 56.30; H,8.10; N, 16.20;

5,5-Dimethylcyclohexan-1,2,3-trioxime (22).

General method. A solution of **9-13** (5 mmol) in ethanol (30 mL) was treated with hydroxylamine hydrochloride (25 mmol) and sodium acetate (25 mmol). The mixture was boiled under reflux for 2hoursThe mixture was then concentrated under reduced pressure. The residue was filtered, washed with water and dried, then crystallized from ethanol to give **22** as colorless crystals in 70 % yield from **9**, 76 % yield from **10**, 68 % yield from **11**, 60 % yield from **12** and 50% yield from **13**;
m.p.,200 ºC lit.[32] m.p. 200-201 ºC,

^{1}H-NMR DMSO-d_6, 500 MHz)δ_H ppm: 0.91 (s, 6H, 2Me), 2.42 (s, 2H, CH_2), 2.45 (s, 2 H, CH_2), 11.33, 11.89, 12.77 (3s, 3H, D_2O exchangeable, 3NOH),
^{13}C NMR (DMSO-d_6) δ_c ppm: 27.8 (2Me), 32.1 (C-5), 37.4 (C-4), 44.3 (C-6), 153.7 (C-1, C-2, C-3)
MS (EI) m/z (%): 198.1 (18, ($M^{+\cdot}$ -1), 170 (100, M^+ - NH_2OH).
Analysis Calc for $C_8H_{13}N_3O_3$(199.2): C, 48.23; H, 6.58; N, 21.09. Found: C, 48.20. H, 6.30; N, 20.80**.**

6,6-Dimethyl-6,7-dihydrobenzo[*c*][1,2,5]oxa-diazol-4(5H)-one-*O*-acetyloxime (24).
A solution of **22** (0.9 mmol) in acetic anhydride (5 mL) was boiled under reflux for 2 hours. The reaction mixture was then left to cool and poured onto cold water (30 mL). The product was filtered off purified by column chromatography using hexane-ethylacetate (4:1), then crystallized from ethanol to give **24** as colorless crystal (37% yield); m.p. 130-132 ºC, ^{1}H-NMR ($CDCl_3$) 500 MHz)δ_H ppm: 1.00 (s, 6H, 2Me), 1.59 (s, 2H,CH_2), 2.27 (s, 3H, $CO\underline{C}H_3$), 3.63 (s, 2H, CH_2), ^{13}C-NMR ($CDCl_3$) δ_c ppm: 19.8 ($CO\underline{C}H_3$), 28.6 (2Me), 29.1 (C-6), 42.4, 47.2 (C-7, C-5), 134.2 (C-7a), 144. (C-4a), 161. (C-4), 171.9 ($\underline{C}OCH_3$).
Analysis.Calc for $C_{10}H_{13}N_3O_3$(223.22): C, 53.80; H, 5.87; N, 18.82; O, 21.50. Found: C, 53.62. H, 5.53; N, 18.78; O, 21.48.

3-*N*-(Aryl)imino-5,5-dimethyl-2-(phenylhydrazone)cyclohexanone (26a-b) Method a. A solution of aniline (5 mmol) in conc. hydrochloric acid (1.5 mL) and water (2.5 mL) was cooled to 0 ºC and treated with a chilled solution of sodium nitrite (6 mmol) in water (2.5 mL). The resulting solution of benzenediazonium chloride was added with stirring to a solution of **12-13** (8.0mmol) and sodium acetate (4.75 mmol) in methanol (30 mL). The reaction mixture was maintained at 0 ºC for 2 hours. The product was filtered off, washed with methanol and then re-crystallized from ethanol.

3-*N*-(2-Chlorophenyl)imino-5,5-dimethyl-2-(phenylhydrazone)cyclohexanone (26a). Red plates (75 % yield); m.p.162-164 ºC;
IR (solid, KBr, vmax,cm^{-1}): 3441 (NH), 1642 (CO);
^{1}H-NMR ($CDCl_3$, 500 MHz) δ_H ppm: 1.45 (s, 6H, 2Me), 1.58 (s, 2H, CH_2), 2.75 (s, 2H, CH_2), 6.60-7.10 (m, 4H, Ar-H),, 7.18-7.25 (m, 2H, Ar-H), 7.29-7.38 (m, 2H, Ar-H), 7.45 (dd, 1H, *J* 10 Hz, Ar-H), 14.59 (s, 1H, D_2O exchangeable, NH).
^{13}CNMR($CDCl_3$) δ_c ppm: 28.5(2Me), 37.7, 37.9 (C-5, C-4), 52.6 (C-6),114.1, 115.9, 120.7, 121.7, 129.1,129.2, 129.9, 136.7, 144.4 (Ar-C), 148.4 (C-2), 155.5(C-3),196.5 (C-1).
Anal.Calc for $C_{20}H_{20}N_3OCl$ (353.837): C,67.88; H 5.69; N,11.87.Found: C,67.99; H 5.49; N,11.88.

5,5-Dimethyl-3-*N*-(3-nitrophenyl)imino-2-(phenylhydrazone)cyclohexanone(26b).
It was obtained as red plates (70 % yield); m.p.160-161 ºC;
IR (solid, KBr, vmax, cm^{-1}): 3445 (NH), 1640 (CO);
^{1}H-NMR ($CDCl_3$, 500 MHz) δ_H ppm: 1.42 (s, 6H, 2Me), 1.56 (s, 2H, CH_2), 2.73 (s, 2H, CH_2), 6.58 (t, 1H, *J*10 Hz, 5 Hz, Ar-H), 7.00 (t, 1H, Ar-H), 7.08 (t, 1H, Ar-H), 7.19 (t, 3H, Ar-H), 7.48 (t, 1H, Ar-H), 7.85 (s, 1H, Ar-H), 7.94 (d, 1H, Ar-H), 14.55 (s, 1H, D_2O exchangeable, N-H).
^{13}C-NMR ($CDCl_3$) δ_c ppm:28.4 (2Me),37.9, 37.9 (C-5, C-4), 52.5 (C-6), 114.3, 115.7, 117.1, 125.34, 126.1, 129.3, 136.5, 144.0, 149.2 (Ar-C), 152.5 (C-2), 155.4 (C-3), 197.1 (C-1).
Anal.Calc for $C_{20}H_{20}N_4O_3$(364.39):C, 65.92; H 5.53; N, 15.37. Found: C, 65.80; H 5.57; N, 15.19.

3-*N*-(Aryl)imino-5,5-dimethyl-2,4-bis-(phenylhydrazone)cyclohexanones(29-33).
General method. A solution of aniline (10 mmol) in conc. hydrochloric acid (3.0 mL) and water (5 mL) was cooled to 0 ºC and treated with a chilled solution of sodium nitrite (12 mmol) in water (5 mL). The resulting solution of benzene diazonium chloride was added with stirring to a solution of **9-13**(8.0mmol) and sodium acetate (9.5 mmol) in methanol (30 mL). The reaction mixture was maintained at 0 ºC for 4 hours. The product was filtered off, washed with methanol and then re-crystallized from ethanol.

5,5-Dimethyl-3-*N*-(4-methylphenyl)imino-2,4-bis-(phenylhydrazone)cyclohexanone (29).
Red plates (29% yield); m.p 194-196 ºC;
IR (solid, KBr, vmax, cm^{-1}): 3441 (NH), 1642 (CO);
^{1}H-NMR ($CDCl_3$, 500 MHz) δ_H ppm: 1.39 (s, 6H, 2 Me), 2.32 (s, 3H, Me), 2.71 (s, 2H, CH_2), 6.51 (d, 2H, J 8.4 Hz, Ar-H), 6.78 (d, 2H, J 7 Hz, Ar-H), 6.93 (t, 1H, *J*7.6Hz, Ar-H), 7.06 (t, 1H, *J* 6.9 Hz, Ar-H), 7.15 (d, 4H, *J* 7.7 Hz, Ar-H), 7.22–7.29 (m, 5 H, Ar-H+NH), 14.5 (s, 1H, D_2O exchangeable NH).
Anal. Calc for $C_{27}H_{27}N_5O$ (437.53): C, 74.11; H 6.22; N, 16.00.Found:C, 74.20; H 6.39; N, 16.19.

5,5-Dimethyl-3-*N*-(2-methylphenyl)imino-2,4-bis-(phenylhydrazone)cyclohexanone (30).
It was obtained as brown plates (35 % yield);m.p. 150-152 ºC.
IR (solid, KBr, vmax, cm^{-1}): 3730 (NH), 1646 (CO);
^{1}H-NMR ($CDCl_3$, 500 MHz)δ_H ppm: 1.40 (s, 6H, 2Me), 2.22 (s, 3H, Me), 2.75 (s, 2H, CH_2, 6.56 (dd, 2H, *J* 5Hz, Ar-H), 6.70 (dd, 1H, *J*10Hz, Ar-H), 6.94-7.02 (m, 2H, Ar-H), 7.06-7.09 (m,1H, Ar-H), 7.14-7.21 (m, 3H, Ar-H), 7.26-7.27 (m, 2H, Ar-H), 7.29-7.32 (m, 3H, Ar-H), 14.60, 14.88 (2s, 2H, D_2O exchangeable, 2NH),
^{13}C-NMR ($CDCl_3$) δ_c ppm:19.9 (O-Me), 28.4 (2Me), 37.8 (C-5), 52.6 (C-6), 113.9, 116.1, 117.7, 121.4, 122.7, 125.5, 126.4, 126.5, 126.7,129.1, 129.2, 130.4, 136.9, 141.3 (Ar-C), 144.5 (C-4), 150.3 (C-2), 154.4 (C-3), 196.5 (C-1).
Anal. Calc for $C_{27}H_{27}N_5O$ (437.53): C, 75.65; H, 6.95; N, 12.60. Found: C, 75.29; H, 6.93; N, 12.97**.**

3-*N*-(4-Chlorophenyl)imino-5,5-dimethyl-2,4-bis-(phenylhydrazon)cyclohexanone(31).
Red plates (52 %yield); m.p. 198-200 ºC;
IR (solid, KBr, vmax, cm^{-1}): 1638 cm^{-1} (CO);
^{1}H-NMR (DMSO-d_6, 500 MHz) δ_H ppm: 1.31 (s, 6H, 2Me), 2.82 (s, 2H, CH_2), 6.70 (d, 2H, *J* 8.6 Hz, Ar-H), 6.96 (t, 2H, *J* 7.4 Hz, Ar-H), 7.07,7.10 (2d, 2H, *J* 8.6 Hz, *J* 7.5 Hz, Ar-H), 7.19 (t, 1H, *J* 8.0 Hz, Ar-H), 7.24 (d, 4H, *J* 8.6 Hz, Ar-H), 7.38 (t, 4H, *J* 8.0 Hz, *J* 8.6Hz, Ar-H+NH) 14.00 (s, 1H, D_2O exchangeable, NH).
Anal. Calc for $C_{26}H_{24}N_5OCl$ (457.947): C, 68.18; H, 5.28; N,15.29. Found: C, 68.39; H, 5.43; N, 15.46.

3-*N*-(2-Chlorophenyl)imino-5,5-dimethyl-2,4-bis-(phenylhydrazone) cyclohexanon(32).
By fractional crystallization compound **32** was obtained as browen plates (75%yield); m.p. 164-166 ºC;
IR (solid, KBr, vmax, cm^{-1}): 3730 (NH), 1646 (CO);
^{1}H-NMR (500 MHz, CDCl3) δ_H ppm: 1.44 (s, 6H, 2Me), 2.75 (s, 2H, CH_2); 6.62 (d, 2H, *J*10 Hz Ar-H), 6.93-7.01 (m, 3H, Ar-H), 7.10(t,1H, *J* 10 Hz, Ar-H), 7.18-7.26 (m, 4H, Ar-H), 7.28-7.33 (m, 3H, Ar-H), 7.45 (dd, 1H, *J*10 Hz Ar-H), 14.59, 14,64 (2s, 2H, D_2O exchangeable, 2NH).
^{13}C-NMR ($CDCl_3$)δ_c ppm: 28.5 (2Me), 37.7 (C-5), 52.6 (C-6), 114.1, 115.9, 120.7, 121.7, 123.51, 125.6, 127.4, 129.1, 129.2, 129.9, 136.7, 141.2 (Ar-C), 141.4(C-4), 148.4 (C-2), 155.5 (C-3), 196.7 (C-1).
Anal. Calc for $C_{26}H_{24}N_5OCl$ (457.947): C, 68.18; H, 5.28; N, 15.28. Found: C, 68.27; H, 5.03; N, 15.00.
Compound **26a** was separated from mother liquor in (40% yield) and was idental to that obtained from method a.

5,5-Dimethyl-3-*N*-(3-nitrophenyl)imino-2,4-bis-(phenylhydrazono)cyclohexanone (33).
By fractional crystallization **33** was obtained as red plates (30 % yield); m.p. 163-165 ºC;
^{1}H-NMR (500 MHz, CDCl3) δ_H ppm:1.45 (s, 6H, 2Me), 2.73 (s, 2H, CH_2), 6.59 (d, 2H, *J*5 Hz Ar-H), 7.00 (t,1H, *J* 10 Hz, Ar-H), 7.09 (t, 2H, *J* 10 Hz, Ar-H) 7.17-7.20 (m, 2H, Ar-H), 7.28-7.35 (m, 4H, Ar-H), 7.47 (t, 1H, Ar-H), 7.82 (d,1H,*J* 5 Hz, Ar-H), 7.89(dd, 1H, *J*10 Hz, 5 Hz, Ar-H), 14.55, 14.65 (2s, 2H,D_2O exchangeable**,** 2NH),
^{13}C-NMR ($CDCl_3$) δ_c ppm: 28.4 (2Me),37.9 (C-5), 52.5 (C-6), 114.3, 114.5, 115.7, 117.1. 122.2, 125.3, 125.7, 126.1, 129.3, 129.3, 129.8, 136.5, 140.9, 144.0 (Ar-C), 149.1 (C-4), 152.5 (C-2), 155.4 (C-3), 196.7 (C-1).
Anal. Calc for $C_{26}H_{24}N_6O_3$(468.5): C, 66.65; H, 5.16; N, 17.94. Found: C, 66.40; H, 5.0; N, 17.80.
Compound **26b** was separated from mother liquor in 15 % yield, and it was identical to that obtained from method a.

5,5-Dimethyl-2,4-bis-(phenylhydrazone)cyclo-hexan-1,3-dioxime(35).
General method. A solution of compounds **29-33** (0.3 mmol) in ethanol (15 mL) was treated with hydroxylamine hydrochloride (0.7 mmol) and sodium acetate (0.7 mmol). The reaction mixture was boiled under reflux for 4-5 hours. It was left to cool, and the product was filtered off, repeatedly washed with water and dried. It was re-crystallized from ethanol to give **35** as yellow crystals in 86, 85, 56, and 58 % yield from **29-33**, respectively, m.p. 179-181 ºC;
IR (solid, KBr, vmax, cm^{-1}): 3217 cm^{-1} (NH),
^{1}H-NMR ($CDCl_3$, 300 MHz)δ_H ppm: 1.31(s, 6H, 2Me), 2.81(s, 2H, CH_2),6.86-7.40(m, 10H, Ar-H), 8.22, 12.35, 12.93, 15.06 (4s, 4H, D_2O exchangeable, 2OH, 2NH);
MS (m/z %): 378 (8, $M^{+\cdot}$), 360 (18, $M^{+\cdot}$-H_2O), 342 (17 $M^{+\cdot}$-$2H_2O$).
Anal. Calc for $C_{20}H_{22}N_6O_2$ (378.43): C 63.47; H 5.86; N 22.21. Found: C 63.58; H, 5.82; N, 22.37.

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