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# Synthesis of condensed heteroaromatics: novel synthesis of aminoquinolizinone derivatives as anti-HIV agents

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**Abstract**—New routes for the synthesis of aminoquinolizinone derivatives with interesting biological activities are reported. Reactions enaminones **2** and **9** with malononitrile affords aminoquinolizinone derivatives **7a** and **7b**. Fusion of acetylcyclohexanone (**1**) with DMF DMA and ethyl cyanoacetate affords only product **11**. Treatment of the latter product with malononitrile affords the aminoquinolizinone derivative **15**. Reaction of chalcone **17** with malononitrile furnished the product **22**. Condensation of (**1**) with arylidenemalononitrile **23a**,**b** affords compounds **28a**,**b**, respectively. The structure of the newly synthesized compounds was elucidated by elemental analyses and $^1$H NMR spectra and in some cases by $^{13}$C NMR investigation. 

Quinolizine derivatives have attracted a great deal of interest due to their biological activities such as anti-HIV,[1] anti-tumor,[2] anti-hypertensive,[3] anti-allergic,[4] anti-ulcer,[5] anti-mycobacterial,[6] anti-bacterial,[7] anti-shock,[8] anti-inflammatory[9] and as potent, selective human steroid.[10] In conjunction with our interest in the synthesis of functionally substituted heteroaromatic compounds as potential pharmaceuticals,[11–14] we report here on the utility of enaminones as building blocks for the synthesis of aminoquinolizinone derivatives with potential biological activities.

Thus, treatment of 2-acetylcyclohexanone **1** with dimethylformamide dimethyl acetal (DMF DMA) in refluxing xylene yielded a product that could be formulated as **2** or its isomers **3**. However, the product **2** was assigned as the E-structure based on the $^1$H NMR which revealed the ethylene protons as two doublets at $\delta$ 4.94 and 7.65 ppm with $J$=13 Hz as required for such E-coupled protons.

The reactivity of the enaminone derivative toward active methylene nitriles was investigated. Thus, treatment of compound **2** with malononitrile **4a** in refluxing ethanol and in the presence of a catalytic amount of piperidine gave the aminoquinolizinone derivative, **7a**. The structure of the latter product was established on the basis of its elemental analysis and spectral data. Thus, the IR spectrum of the reaction product **7a** showed absorption band at 3465 and 3304 cm$^{-1}$ due to $NH_2$ group in addition to the two strong absorption bands at 2208 and 1649 cm$^{-1}$ assignable to nitrile and amide carbonyl absorption, respectively. Its mass spectrum revealed molecular ion peak at $m/z$ 264. The $^1$H NMR spectrum of **7a** revealed abroad signal ($D_2O$-exchangeable) at $\delta$ 12.30 ppm due to $NH_2$ protons. $^{13}$C NMR indicated the presence of two CN signals.

The formation of **7** is assumed to proceed via initial attack of the anion of first malononitrile molecule on the cyclic carbonyl carbon compound **2** to form the ylidene malononitrile derivative **5**, that then cyclizes into **6**.

Addition of a second malononitrile molecule to the enamino double bond of **6**, which loses a molecule of dimethylamine and cyclizes to afford the quinolizinone derivative **7a** (Scheme 1). In a similar manner, compound **2** reacted with cyanothioacetamide under the same experimental conditions gave a brown product in good yield. The structure of the obtained product was assigned as tetrahydroisoquinoline derivative **9b** (Scheme 1). The latter product was treated with one mole of malononitrile in ethanolic piperidine at reflux temperature, afforded a red crystalline product identified as 8-amino-6-thioxocyclohexa[*c*]quinolizine-5,9-dicarbonitrile **7b** (Scheme 1). The structure of the isolated product was confirmed on the basis of its elemental analysis and spectral data. A further evidence for the proposed structure **7** was obtained by an independent synthesis of compound **7** via treatment of 2-acetylcyclohexanone **1** with **4a** or **4b** in refluxing ethanol and in the presence of a catalytic amount of piperidine to afford the corresponding isoquinoline derivative **8a** whose structure was established on the basis of spectral data (IR and $^1$H NMR) similar to those reported in the literature.[15] On the other hand, compound **1** on reaction with cyanothioacetamide **4c** afforded the 1-methyl-3-thioxo-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile **8b**. The structure of **8b** was established on the basis of its elemental analysis and spectral data (see Section 2).

*Keywords*: condensed heteroaromatics; aminoquinolizinone; anti-HIV agents.

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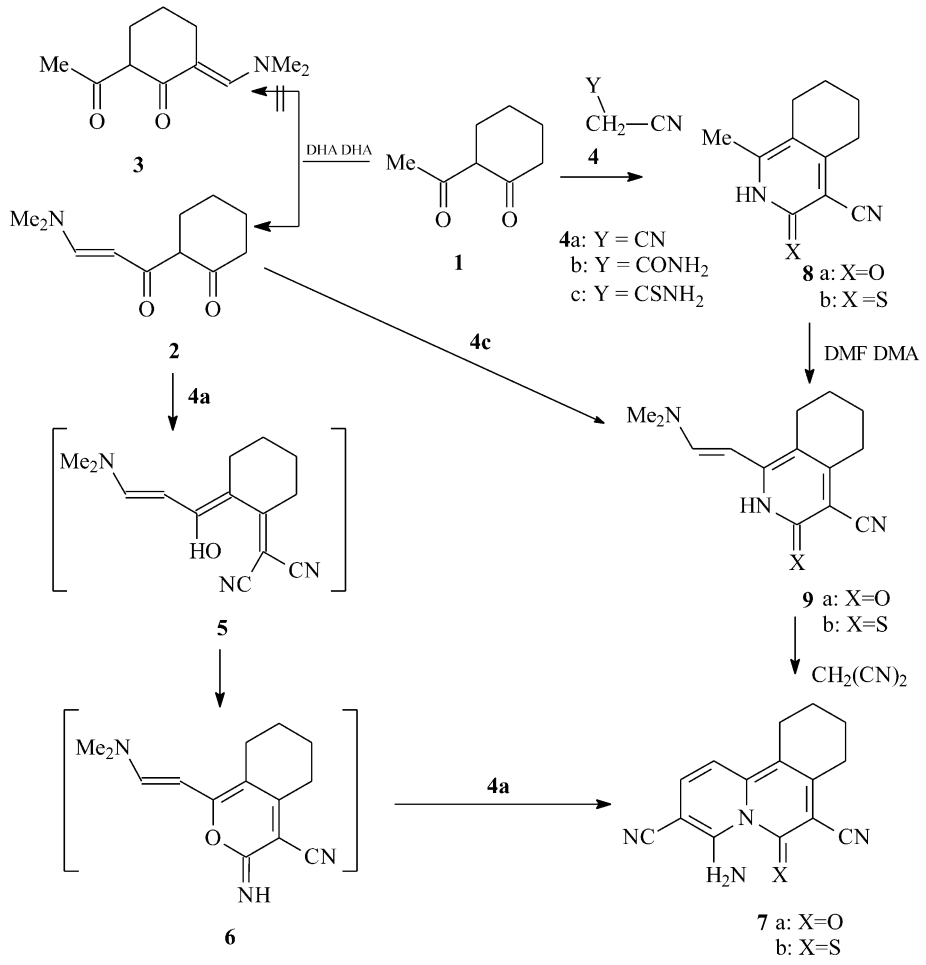


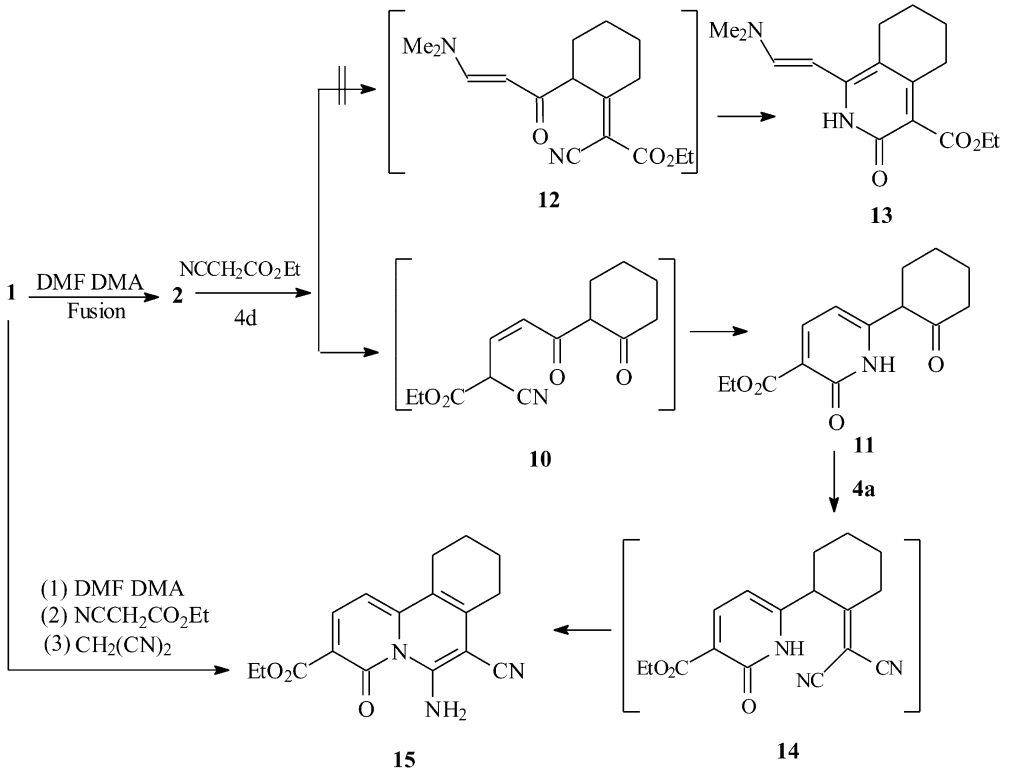

**Scheme 1.**

Treatment of compound **8** with DMF DMA in dimethylformamide at reflux to afforded (*E*)-dimethylaminoethylene isoquinolinone derivatives **9**. The structure of the isolated product was confirmed on the basis of its elemental analysis and spectral data. Compound **9a** reacted with malononitrile in a mixture of ethanol and dimethyl formamide in the presence of a catalytic amount of piperidine to afford a product identical in all respects (mp and spectra) with that obtained previously from the reaction of **2** with malononitrile.

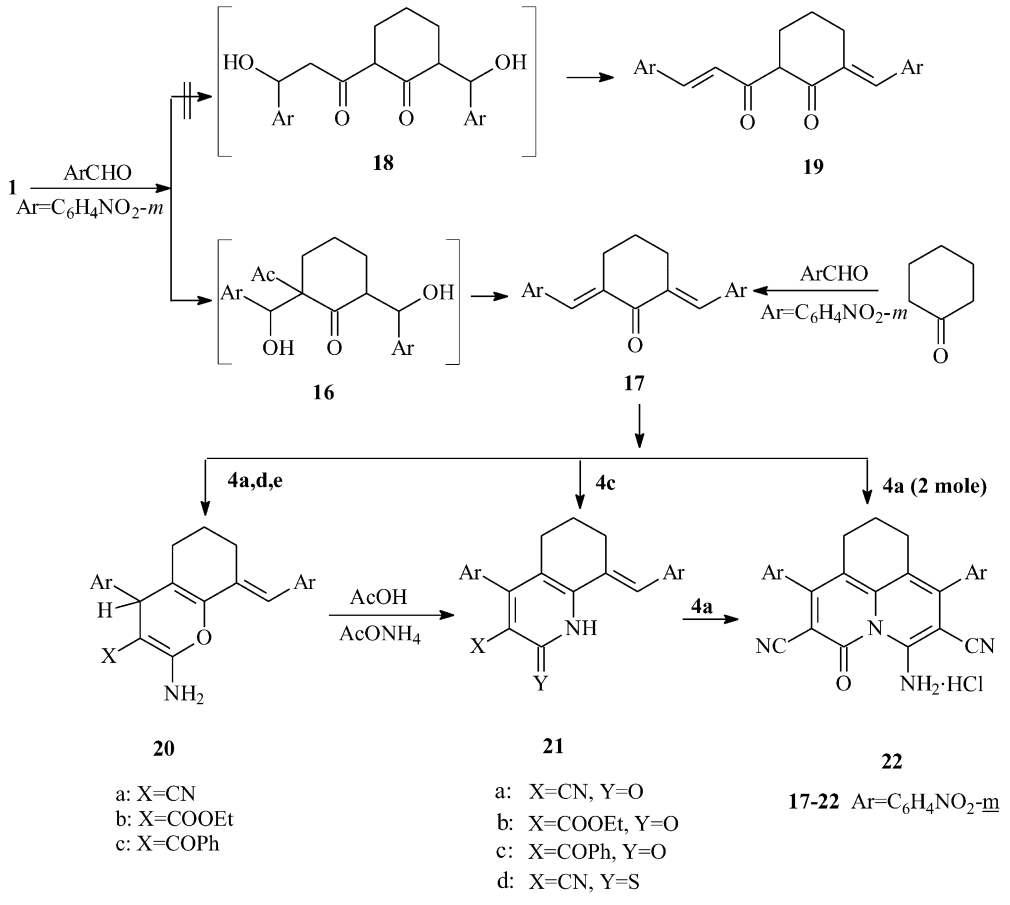
On the other hand, fusion of compound **1** with DMF DMA and then followed by addition of ethyl cyanoacetate **4d** afforded the corresponding pyridinone **11** or **13** through the non-isolated intermediates **10** and **12**, respectively. The structure **11** was established for the reaction product based of its elemental analysis and spectral data. Thus, $^{1}$H NMR spectrum of the product revealed an absence of any signals for dimethylamino group but showed the ethyl group as triplet and quartet at $\delta$ 1.24 and 4.16 ppm with $J$=6 Hz, respectively. The IR spectrum of the reaction product shows the NH, and carbonyl functions (ester, cyclic ketone and amide) at 3359, 1700, 1680 and 1644 cm$^{-1}$, respectively. Its mass spectrum revealed a molecular ion peak at *m*/*z* 263 ($M^{+}$). The formation of **11** is assumed to be proceed via addition of methylene function in ethyl cyanoacetate to the activated double bond in the enaminone **2** to form non-isolable intermediate **10** via loss of a molecule of dimethylamine which underwent an intramolecular cyclization to afford the pyridinone 3-carboxylate derivative **11** (Scheme 2).

The target ring system, quinolizine could be obtained when the compound **11** reacted with malononitrile in refluxing ethanol and in the presence of piperidine afforded a yellow product identified as 6-aminoquinolizine-9-carboxylate derivative **15** (Scheme 2). The IR spectrum of compound **15** showed an amino and nitrile absorption bands at 3420, 3363 and 2214 cm$^{-1}$, respectively, in addition to the two strong carbonyl bands at 1720 and 1651 cm$^{-1}$. The mass spectrum revealed a molecular ion peak at *m*/*z* 311 ($M^{+}$). Moreover the $^{13}$C NMR of the reaction product revealed two signals at $\delta$ 164.73 and 160.77 ppm corresponding to ester and ring carbonyl carbons. The formation of compound **15** was assumed to take place via the condensation of the carbonyl cyclohexanone of **11** with malononitrile to yield the corresponding non-isolated ylidene **14** which readily undergoes cyclization into quinolizine derivative **15**.

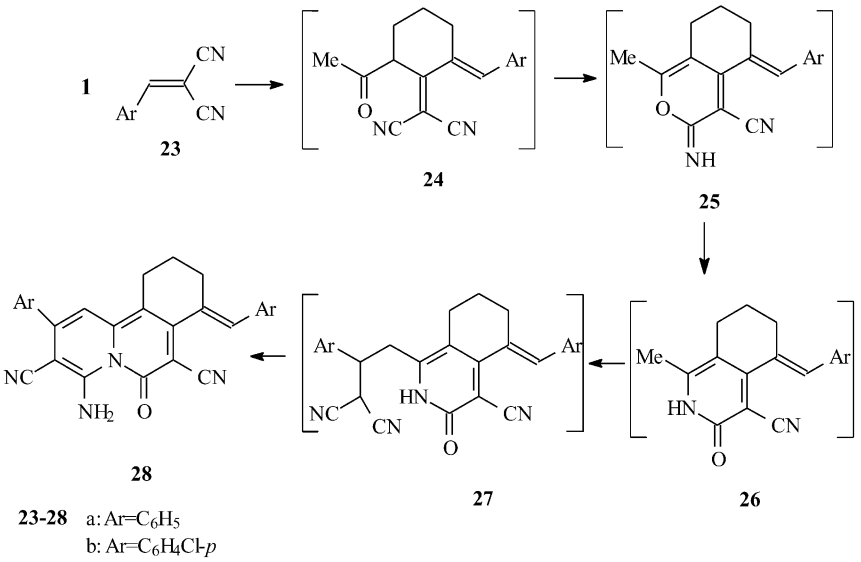
Compound **15** could be obtained in situ, via a one step process by fusion of 2-acetyl cyclohexanone **1** with DMF DMA followed by treatment of the reaction mixture with **4d** in refluxing ethanolic piperidine. After cooling, the mixture was treated with malononitrile at reflux for 4 h, to afford a product identical in all respects (mp, TLC and spectra) with




**Scheme 2.**




**Scheme 3.**




**Scheme 4.**

that obtained previously from the reactions of **11** with malononitrile.

Furthermore, treatment of 2-acetylcyclohexanone with *m*-nitrobenzaldehyde in ethanolic sodium hydroxide at room temperature afforded the corresponding chalcone **17** in excellent yield. The structure of **17** was established on the basis of its elemental analysis and spectral data. Further evidence for proposed structure **17** by an independent synthesis via treatment of cyclohexanone with *m*-nitrobenzaldehyde in ethanolic sodium hydroxide to afford a product identical in all respects (mp and spectra) with that obtained previously from the reaction of 2-acetylcyclohexanone with *m*-nitrobenzaldehyde.

The formation of compound **17** depends on the acidity of α-protons in which the addition of the two α-carbons in cyclohexanone to carbon oxygen double bond of aromatic aldehydes to form the non-isolable intermediate **16** which gives an aldol condensation **17** via loss of water and acetic acid molecules. The reactivity of chalcone **17** towards active methylene nitrile was investigated. Thus, compound **17** was treated with malononitrile **4a**, ethyl cyanoacetate **4d** and benzoylacetonitrile **4e** in basic medium to give 2-aminopyran derivatives **20a–c** in good yield (Scheme 3).

Both elemental analysis and spectral data were in complete agreement with assigned structures. The IR spectra of isolated products showed in each case the absence of carbonyl band and revealed the presence of two bands in the regions of 3440–3300 $cm^{-1}$ due to the $NH_2$ group. Their $^1H$ NMR spectra showed in each case, a broad signal ($D_2O$-exchangeable) at $\delta_H$ 8.08 ppm due to $NH_2$ protons in addition to a singlet signal at $\delta_H$ 4.31 ppm for pyran-4H. Moreover, the $^{13}C$ NMR of the reaction product revealed high field signals at $\delta_C$ 43.47 ppm corresponding to the $sp^3$ carbon coupled with a proton.

Similar to the reported[14,16–18] rearrangement of 2-aminopyrans into pyridines on refluxing in a mixture of acetic acid and ammonium acetate, compounds **20a–c** were converted into tetrahydroisoquinoline **21a–c** by similar treatment. Similarly, compound **17** reacted with cyanothioacetamide **4c** in ethanol and in the presence of a catalytic amount of piperidine at reflux afforded a yellow product which was identified as 5,6,7,8-tetrahydro-2-thioxoquinoline derivative **21d** (Scheme 3).

Chalcone **17** reacts also with 2 mol of malononitrile in ethanolic piperidine at reflux in a one step reaction to give a high yield of a crystalline 1,8-propanoquinolizone derivative for which structure **22** as assigned. To the best of our knowledge, this is the first report for such ring system. Thus, the IR spectrum of the reaction product, showed an amino, nitrile and carbonyl absorption bands at 3452, 3344, 2190 and 1654 $cm^{-1}$, respectively, which are compatible with assigned structure. Moreover, treatment of compound **21a** with malononitrile in a basic medium afforded a product identical in all respects (mp and spectra) with that obtained previously from the reaction of **17** with malononitrile.

Condensation of 2-acetylcyclohexanone **1** with arylidenemalononitrile **23a**,**b** in pyridine at reflux temperature afforded aminoquinolizinone derivatives **28a**,**b** (Scheme 4). The structures **28a**,**b** of the isolated product were confirmed on the basis of their elemental analyses and spectral data. For example, the IR spectra of **28a** and **28b** shows in each case two strong absorption bands in the region at 3420–3356 $cm^{-1}$ assignable to amino group in addition to strong absorption bands at 2211 and 1634 $cm^{-1}$ due to nitrile and carbonyl functions, respectively. The mass spectra of **28a** and **28b** revealed molecular ion peak at *m*/*z* 428 ($M^+$) and 497 ($M^+$), respectively. The $^1H$ NMR spectra displayed in each case, a broad signal ($D_2O$-exchangeable) near 12.2 ppm due to $NH_2$ protons and singlets at $\delta_H$ 7.95 and 8.59 ppm for both ylidene-CH and quinolizine-H; in addition to multiplets at $\delta$ 7.25–7.66 and 1.60–2.50 ppm, corresponding to aromatic and methylene protons, respectively.

The formation of compound **28a** and **28b** is assumed to take place via ylidene exchange[19] with one molecule of

**Table 1.** In vitro bactericidal and fungicidal activity of some newly synthesized compounds (slight effect=+; moderate effect=++; severe effect=+++, ++++)

| Compound | *E. coli* | *B. subtilis* | *S. aureus* | *A. niger* |
|---|---|---|---|---|
| **7a** | + | +++ | ++ | – |
| **7b** | +++ | +++ | +++ | – |
| **9a** | – | – | ++++ | – |
| **9b** | – | – | +++ | – |
| **11** | – | – | +++ | – |
| **22** | +++ | ++++ | ++ | – |

arylidenemalononitrile to give **24** followed by cyclization to pyrans **25** and then rearrange into the non-isolated isoquinoline intermediate **26** which underwent reaction with another molecule of **23** to afford the final isolated product **28** through the Michael adduct **27**.

## 1. Biological activity

The diverse biological activities of *N,N*-dimethylamino derivatives of pyran, pyridine and quinazoline promoted our attention to test the biological activities of some newly synthesized compounds. Most of the tested samples showed a bacterial activity while all of them did not show any activity toward fungi. Table 1 shows in vitro bactericidal and fungicidal activities of some newly synthesized compounds.

## 2. Experimental

### 2.1. General

Melting points are uncorrected, IR spectra recorded on a Shimadzu 2000 FT/IR spectrometer. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Brucker 400 MHz with dimethyl-$d_6$-sulfoxide as solvent and tetramethylsilane as an internal standard, chemical shifts are reported as $\delta$ units (ppm). Mass spectra were measured on formed on a LECO-CHNS 932 analyzer. Compound **8a** was prepared by method reported in the literature.[15]

**2.1.1. 3-(*N,N*-Dimethylamino)-1-(oxocyclohexa-2-yl)-2-propenone 2.** A suspension of **1** (1.40 g, 0.01 mol) in xylene (20 mL) was treated with DMF DMA (1.33 g, 0.01 mol). The reaction mixture was refluxed for 6 h and then allowed to cool to room temperature. The solid product so formed, was collected by filtration and recrystallized from ethanol as yellow crystals (1.48 g, 76%); mp 88–90°C (Found: C, 67.39; H, 8.69; N, 7.21; $C_{11}H_{17}NO_2$ requires: C, 67.66; H, 8.77; N, 7.17%); $\nu_{max}$: 1630 $cm^{-1}$ (CO). $\delta_H$: 1.58–1.68 (6H, m, $3CH_2$), 2.17–2.21 (3H, m, H-2 and $CH_2$), 2.96 (6H, s, $NMe_2$), 4.94 (1H, d, $J$=13 Hz, vinylic-H) and 7.65 (1H, d, $J$=13 Hz, vinylic-H).

**2.1.2. 8-Amino-6-oxocyclohexa[*c*]quinolizine-5,9-dicarbonitrile 7a.** *Method A*: a mixture of the enaminone **2** (1.95 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) in ethanol (30 mL) and few drops of piperidine was refluxed for 3 h and then allowed to cool to room temperature. The solid product so formed, was collected by filtration and recrystallized from ethanol as yellow crystals (1.80 g, 68%).

*Method B*: to a suspension of compound **9** (2.78 g, 0.01 mol) in a mixture of ethanol and dimethylformamide (2:1) (30 mL), malononitrile (0.66 g, 0.01 mol) and few drops of piperidine were added. A mixture was heated under refluxed for 6 h and then allowed to cool to room temperature. The solid product so formed, was collected by filtration and recrystallized from a mixture of ethanol and DMF (2:1) as yellow crystals (1.91 g, 72%); mp 365–367°C; (Found: C, 67.98; H, 4.74; N, 20.90; $C_{15}H_{12}N_4O$ requires: C, 68.17; H, 4.58; N, 21.10%); $\nu_{max}$: 3430, 3304 ($NH_2$), 2208 (2CN) and 1649 $cm^{-1}$ (ring CO); $\delta_H$: 1.53–1.67 (4H, m, $2CH_2$), 2.04–2.26 (2H, m, $CH_2$), 2.31–2.71 (2H, m, $CH_2$); 6.75 (1H, d, $J$=7 Hz, H-11); 7.68 (1H, d, $J$=7 Hz, H-10) and 12.30 ppm (2H, br, $NH_2$); $\delta_C$: 163.44 (C-6), 160.74 (C-8), 157.190, 153.33, 150.74, 145.98, 138.46, 117.45, 116.98, 113.79, 111.67, (aromatic and other carbon atoms); 25.34, 24.17, 22.65 and 21.56 ppm ($4CH_2$). MS (EI); $m/z$=264.1 ($M^+$).

**2.1.3. 8-Amino-6-thioxocyclohexa[*c*]quinolizine-5,9-dicarbonitrile 7b.** A mixture of **1** (1.4 g, 0.01 mol) and DMF DMA (1.33 g, 0.01 mol) was fused at 180°C for 15 min. The reaction mixture was dissolved in 20 mL ethanol and cyanothioacetamide with a few drops of piperidine were added. The reaction mixture was refluxed for 3 h. To the reaction mixture malononitrile (0.66 g, 0.01 mol) was added, then refluxed for 3 h. The solvent was evaporated under reduced pressure. The solid product so formed, was collected by filtration and recrystallized from ethanol as red crystals (2.40 g, 86%); mp 195–197°C. (Found: C, 64.27; H, 4.32; N, 19.99; $C_{15}H_{12}N_4S$ requires: C, 64.21; H, 4.50; N, 19.76%); $\nu_{max}$: 3430, 3313 ($NH_2$) and 2214 $cm^{-1}$ (2CN); $\delta_H$: 1.69–1.82 (4H, m, $2CH_2$); 2.34–2.50 (2H, m, $CH_2$); 2.67–2.70 (2H, m, $CH_2$); 7.26 (1H, d, $J$=7 Hz, H-11), 7.86 (1H, d, $J$=7 Hz, H-10) and 9.45 (2H, br, $NH_2$); $\delta_C$: 170.00(C-6); 156.83 (C-8); 153.26, 147.36, 136.64, 125.02, 120.51, 117.05, 116.16, 113.59, 112.19 (aromatic and other carbon atoms), 25.34, 24.49, 22.35 and 21.43 ppm ($4CH_2$).

**2.1.4. 1-Methyl-5,6,7,8-tetrahydro-3-thioxoisoquinoline-4-carbonitrile 8b.** A solution of **1** (1.40 g, 0.01 mol) in ethanol (30 mL) was treated with cyanothioacetamide (1.0 g, 0.01 mol) and few drops of piperidine was added. The reaction mixture was refluxed for 4 h. The solvent was then evaporated under reduced pressure. The solid product was collected by filtration and recrystallized from ethanol as yellow crystals. (1.60 g, 78%), mp 328–330°C, (Found: C, 64.98; H, 5.91; N, 13.86. $C_{11}H_{12}N_2S$ requires: C, 64.70; H, 5.88; N, 13.72%), $\nu_{max}$: 3429 (NH), 2218 $cm^{-1}$, (CN); $\delta_H$: 1.53–1.85 (4H, m, $2CH_2$), 2.09–2.17 (2H, m, $CH_2$), 2.33 (3H, s, Me); 2.41–2.67 (2H, m, $CH_2$) and 13.95 (1H, br, NH).

**2.1.5. 1-[2′-(*N,N*-Dimethylaminoethenyl)]-3-oxo-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile 9a.** A suspension of **8a** (1.88 g, 0.01 mol) in dimethyl formamide (20 mL) was treated with DMF DMA (1.33 g, 0.01 mol). The reaction mixture was refluxed for 20 min, then allowed to cool to room temperature. The solid product, so formed, was

collected by filtration and recrystallized from ethanol as yellow crystals (2.01 g, 83%); mp 322–324°C. (Found: C, 69.00; H, 6.95; N, 17.26. $C_{14}H_{17}N_3O$ requires: C, 69.11; H, 7.04; N, 17.27%); $\nu_{max}$: 3446 (NH), 2202 (CN) and 1625 (ring CO); $\delta_H$: 1.66–1.68 (4H, m, $2CH_2$); 2.21–2.37 (2H, m, $CH_2$); 2.50 (6H, s, $NMe_2$), 2.50–2.60 (2H, m, $CH_2$); 4.77 (1H, d, $J$=14 Hz, vinylic-H), 7.87 (1H, d, $J$=14 Hz, vinylic-H), 12.20 (1H, br, NH); $\delta_C$: 160.73 (C-3), 150.75 (C-1), 149.50 (C-2′), 122.75 (C-1′), 117.02 (CN), 113.78 (C-4), 112.45, 98.75, (aromatic), 29.80 ($NMe_2$), 24.17, 22.15, 21.82, 19.27 ppm ($4CH_2$) carbons; MS (EI); $m/z$=243.1 ($M^+$).

**2.1.6. 1-[2′-(*N*,*N*-Dimethylaminoethenyl)]-5,6,7,8-tetrahydro-3-thioxoisoquinoline-4-carbonitrile 9b.** *Method A*: in a similar manner to that described earlier for compound **9a**, compound **8b** (2.04 g, 0.01 mol) in DMF (20 mL) and DMF DMA (1.33 g, 0.01 mol) gave compound **9b** (1.99 g, 77%).

*Method B*: a mixture of 2-acetylcyclohexanone **1** (1.40 g, 0.01 mol) and DMF DMA (1.33 g, 0.01 mol) was fused at 180°C for 15 min. The reaction mixture was dissolved in ethanol (20 mL) and cyanothioacetamide (1.0 g, 0.01 mol) with a few drops of piperidine were added and the mixture was refluxed for 3 h. The solvent was evaporated under reduced pressure. The solid product was collected by filtration and recrystallized from ethanol as brown crystals (1.83 g, 71%); mp 322–324°C, (Found: C, 64.75; H, 6.82; N, 16.11. $C_{14}H_{17}N_3S$ requires: C, 64.84; H, 6.61; N, 16.21%); $\nu_{max}$: 3429 (NH) and 2218 $cm^{-1}$ (CN); $\delta_H$: 1.53–1.85 (4H, m, $2CH_2$); 2.17–2.41 (2H, m, $CH_2$); 2.50 (6H, s, $NMe_2$), 2.51–2.62 (2H, m, $CH_2$); 5.96 (1H, d, $J$= 12 Hz, vinylic-H), 7.21 (1H, d, $J$=12 Hz, vinylic-H), and 13.76 (1H, br, NH). $\delta_C$: 174 (C-3), 156.96 (C-1), 152.81 (C-2′), 122.30, 121.13, 117.43, 114.78, 113.60, (aromatic and other carbon atoms), 29.65 ($NMe_2$), 27.88, 24.60, 22.04 and 19.41 ppm ($4CH_2$).

**2.1.7. Ethyl 1,2-dihydro-6-(cyclohexan-1-on-2-yl)-2-oxopyridine-3-carboxylate 11.** A mixture of **1** (1.40 g, 0.01 mol) and DMF DMA (1.33 g, 0.01 mol) was fused at 180°C for 15 min then allowed to cool at room temperature. The reaction mixture was treated with ethyl cyanoacetate (1.13 g, 0.01 mol) and refluxed for 3 h. The solvent was evaporated under reduced pressure. The solid product, so formed was collected by filtration and recrystallized from ethanol as yellow crystals (2.15 g, 82%); mp 138–140°C; (Found: C, 63.89; H, 6.73; N, 5.57. $C_{14}H_{17}NO_4$ requires: C, 63.86; H, 6.51; N, 5.32%); $\nu_{max}$: 1700 (ester CO), 1680 (ring CO) and 1644 $cm^{-1}$ (amide CO); $\delta_H$ 1.24 (3H, t, $J$=6 Hz, Me); 1.51–1.56 (4H, m, $2CH_2$); 2.09–2.32 (2H, m, $CH_2$); 2.39–2.50 (3H, m, cyclohexanone-H and $CH_2$); 4.16 (2H, q, $J$=6 Hz, $OCH_2$); 6.72 (1H, s, H-5); 7.99 (1H, s, H-4) and 8.32 ppm (1H, br, NH); MS: (EI), $m/z$=263.2.

**2.1.8. Ethyl 6-amino-5-cyano-8-oxocyclohexa[*c*]quinolizine-9-carboxylate 15.** *Method A*: a mixture of **1** (1.40 g, 0.01 mol) and DMF DMA was fused at 180°C for 15 min, and then allowed to cool at room temperature. The reaction mixture was dissolved in ethanol (20 mL) and ethyl cyanoacetate (1.13 g, 0.01 mol) with few drops of piperidine were added. The reaction mixture was refluxed for 4 h. To the reaction mixture, malononitrile (0.66 g, 0.01 mol) was added and refluxed for 3 h. The solvent was evaporated under reduced pressure. The solid product so formed, was collected by filtration and recrystallized from ethanol as brown red crystals (2.13 g, 68%).

*Method B*: a mixture of compound **11** (2.63 g, 0.01 mol) and (0.66 g, 0.01 mol) malononitrile in ethanol (30 mL), and 0.5 mL of piperidine was refluxed for 4 h and then allowed to cool at room temperature. The solid product so formed, was collected by filtration and recrystallized from ethanol as brown red crystals (2.21 g, 71%); mp >350°C; (Found: C, 65.35; H, 5.72; N, 13.80; $C_{17}H_{17}N_3O_3$ requires: C, 65.59; H, 5.46; N, 13.50%); $\nu_{max}$: 3420, 3363 ($NH_2$), 2214 (CN), 1720 (ester CO) and 1651 $cm^{-1}$ (ring CO). $\delta_H$: 1.24 (3H, t, $J$= 6 Hz, Me), 1.66–1.67 (4H, m, $2CH_2$), 2.16–2.20 (2H, m, $CH_2$); 2.22–2.56 (2H, m, $CH_2$); 4.17 (2H, q, $J$=6 Hz, $OCH_2$); 7.14 (1H, d, $J$=10 Hz, H-11); 7.89 (1H, d, $J$= 10 Hz, H-10) and 12.33 ppm (2H, br, $NH_2$). $\delta_C$: 164.73 (ester CO), 160.77 (C-8), 149.83, 148.61, 120.25, 118.03, 117.01, 116.31, 113.83, 110.93, (aromatic and other carbon atoms), 61.39 ($OCH_2$), 24.17, 23.28, 22.55 and 21.82 ($4CH_2$) and 17.69 ppm (Me); MS (EI): $m/z$=311.1 ($M^+$).

**2.1.9. 2,6-Di-(*m*-nitrophenylmethylene)cyclohexanone 17.** A mixture of **1** (1.39 g, 0.01 mol) and *m*-nitrobenzaldehyde (1.51 g, 0.01 mol) and sodium hydroxide (0.20 g in 5 mL $H_2O$) in ethanol (30 mL) was stirred at room temperature for 2 h. The solid product was collected by filtration and recrystallized from ethanol as yellow crystals (2.83 g, 78%), mp 140–142°C; (Found: C, 65.90; H, 4.57; N, 7.75. $C_{20}H_{16}N_2O_5$ requires: C, 65.93; H, 4.34; N, 7.69%). $\nu_{max}$: 1664 $cm^{-1}$ (ring CO), $\delta_H$: 1.66–1.67 (2H, m, $CH_2$), 2.56–2.58 (4H, m, $2CH_2$), 7.66–8.27 (10H, m, Ar-H and ylidene CH); $\delta_C$: 189.43 (CO), 148.70, 139.18; 137.40, 135.77, 134.56, 130.95, 129.41 and 124.91 (aromatic and other carbon atoms), 27.31 ($2CH_2$) and 22.93 ppm ($CH_2$), MS (EI): $m/z$=364.1 ($M^+$).

## 2.2. General procedure for the synthesis of 20a–c

A mixture of **17** (3.64 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) or benzoylacetonitrile (1.45 g, 0.01 mol) in ethanol (20 mL) and piperidine (0.5 mL) was refluxed for 4 h. Then solvent was evaporated under reduced pressure. The solid products were collected by filtration and recrystallized from a mixture of ethanol and DMF (3:1) to afford **20a**, **20b**, and **20c**, respectively.

**2.2.1. 2-Amino-4*H*-4-(*m*-nitrophenyl)-8-(*m*-nitrophenylmethylene)-cyclohexa[*b*]-pyran-3-carbonitrile 20a.** This compound was obtained as yellow crystals (3.26 g, 76%), mp 233–235°C; (Found: C, 63.93; H, 4.23; N, 12.98. $C_{23}H_{18}N_4O_5$ requires: C, 64.18; H, 4.18; N, 13.00%). $\nu_{max}$: 3440, 3330 ($NH_2$) and 2191 $cm^{-1}$ (CN); $\delta_H$: 1.66–1.67 (2H, m, $CH_2$); 2.16–2.20 (2H, m, $CH_2$), 2.22–2.56 (2H, m, $CH_2$), 4.31 (1H, s, H-4), 6.93 (1H, s, ylidene-H), 7.09–7.74 (8H, m, Ar-H) and 8.08 ppm (2H, br, $NH_2$); $\delta_C$: 160.85 (C-2), 148.89, 148.59, 146.97, 141.62, 139.11, 136.13, 135.34, 133.24, 132.56, 131.27, 130.76, 124.22, 123.13, 122.34, 121.29, 121.08, 116.91, 117.18 (aromatic and other carbon

atoms), 43.47 (C-4), 27.39, 27.08 and 22.36 ($3CH_2$), MS (EI): $m/z$=430 ($M^+$).

**2.2.2. Ethyl 2-amino-4*H*-(*m*-nitrophenyl)-8-(*m*-nitrophenylmethylene)-cyclohexa[*b*]pyran-3-carboxylate 20b.** This compound was obtained as yellow crystals (3.29 g, 69%), mp 168–170°C. (Found: C, 62.67; H, 5.01; N, 8.86. $C_{25}H_{23}N_3O_7$ requires: C, 62.89; 4.82; N, 8.80%). $\nu_{max}$: 3408, 3300 ($NH_2$) and 1680 $cm^{-1}$ (CO); $\delta_H$: 1.08 (3H, t, $J$=7 Hz, Me); 1.66–1.67 (2H, m, $CH_2$), 2.16–2.20 (2H, m, $CH_2$), 2.22–2.56 (2H, m, $CH_2$), 3.90 (2H, q, $J$=7 Hz, $OCH_2$), 4.43 (1H, s, H-4), 7.17 (1H, s, ylidene-H), 7.59–8.05 (8H, m, Ar-H) and 8.14 ppm (2H, br, $NH_2$), MS (EI): $m/z$=477.1 ($M^+$).

**2.2.3. 2-Amino-3-benzoyl-4*H*-4(*m*-nitrophenyl)-8-(*m*-nitrophenylmethylene)-cyclohexa[*b*]pyran 20c.** This compound was obtained as yellow crystals (3.70 g, 73%), mp 130–132°C. (Found: C, 68.07; H, 4.50; N, 8.46. $C_{29}H_{23}N_3O_6$ requires: C, 68.36; 4.55; N, 8.24%). $\nu_{max}$: 3424, 3332 ($NH_2$) and 1625 $cm^{-1}$ (CO); $\delta_H$: 1.70–1.77 (2H, m, $CH_2$); 1.84–1.91 (2H, m, $CH_2$), 2.43–2.59 (2H, m, $CH_2$); 4.04 (1H, s, H-4), 6.92 (1H, s, ylidene-H), 7.52–8.69 (13H, m, Ar-H) and 9.40 ppm (2H, br, $NH_2$); $\delta_C$: 189.53 (CO), 160.23 (C-2), 148.77, 148.17, 139.27, 139.20, 137.76, 137.41, 136.15, 134.98, 134.50, 132.53, 130.97, 130.81, 130.68, 129.39, 128.99, 128.80, 126.51, 125.24, 124.17, 122.18, 120.27 (aromatic and other carbon atoms), 44.55 (C-4), 28.45, 27.06 and 22.95 ppm ($3CH_2$).

### 2.3. General procedure for the synthesis of 21a–c

A solution of each of **20a–c** (0.01 mol) in acetic acid (20 mL) and ammonium acetate (2 g) was heated under reflux for 2 h. The mixture allowed to cool to room temperature, then poured into ice-cold water. The solid products were collected by filtration and recrystallized from a mixture of ethanol and DMF (2:1).

**2.3.1. 4-(*m*-Nitrophenyl)-8-(*m*-nitrophenylmethylene)-2-oxo-5,6,7-trihydroquinoline-3-carbonitrile 21a.** This compound was obtained as yellow crystals (3.59 g, 84%) mp 130–132°C; (Found: C, 64.67, H, 3.56, N, 13.28. $C_{23}H_{16}N_4O_5$ requires C, 64.48, H, 3.76, N, 13.08%); $\nu_{max}$: 3382 (NH), 2212 (CN) and 1625 $cm^{-1}$ (CO). $\delta_H$: 1.63–1.75 (2H, m, $CH_2$), 2.05–2.21 (2H, m, CH), 2.35–2.79 (2H, m, $CH_2$), 6.81 (1H, s, ylidene-H), 7.00–8.35 (8H, m, Ar-H) and 9.54 ppm (1H, br, NH).

**2.3.2. Ethyl-4-(*m*-nitrophenyl)-8-(*m*-nitrophenylmethylene)-2-oxo-5,6,7-trihydroquinoline-3-carboxylate 21b.** This compound was obtained as yellow crystals (3.84 g, 81%) mp 125–127°C; (Found: C, 63.01, H, 4.72, N, 8.54. $C_{25}H_{21}N_3O_7$ requires C, 63.15, H, 4.45, N, 8.84%); $\nu_{max}$: 3382 (NH), 1678 (CO) and 1625 $cm^{-1}$ (ring CO); $\delta_H$: 1.76–1.81 (2H, m, $CH_2$), 2.04–2.26 (2H, m, $CH_2$), 2.71–2.75 (2H, m, $CH_2$), 1.08 (3H, t, $J$=7 Hz, Me), 3.91 (2H, q, $J$=7 Hz, $OCH_2$), 7.28 (1H, s, ylidene-H), 7.57–8.17 (9H, m, Ar-H and NH).

**2.3.3. 3-Benzoyl-4-(*m*-nitrophenyl)-8-(*m*-nitrophenylmethylene)-2-oxo-5,6,7-trihydroquinoline 21c.** This compound was obtained as yellow crystals (4.20 g, 83%) mp 110–112°C. (Found: C, 68.68, H, 4.32, N, 8.32. $C_{29}H_{21}N_3O_6$ requires C, 68.63, H, 4.17, N, 8.28%). $\nu_{max}$: 3389 (NH), 1673 (CO) and 1625 $cm^{-1}$ (ring CO). $\delta_H$: 1.70–1.76 (2H, m, $CH_2$), 1.91–2.20 (2H, m, $CH_2$), 2.22–2.50 (2H, m, $CH_2$),6.92 (1H, s, ylidene-H), 7.52–8.40 (13H, m, Ar-H), and 9.50 ppm (1H, br, NH).

**2.3.4. 4-(*m*-Nitrophenyl)-8-(*m*-nitrophenylmethylene)-5,6,7-trihydro-2-thioxo-quinoline-3-carbonitrile 21d.** A mixture of **17** (3.64 g, 0.01 mol) and cyanothioacetamide (1.0 g, 0.01 mol) in ethanol (20 mL) and piperidine (0.5 mL) was refluxed for 3 h. The excess of solvent was evaporated under reduced pressure. The solid product was collected by filtration and crystallized from a mixture of ethanol and DMF to afford yellow crystals (3.08 g, 88%); mp 88–90°C; (Found: C, 61.98, H, 3.82, N, 12.41. $C_{23}H_{16}N_4SO_4$ requires C, 62.16, H, 3.63, N, 12.61%); $\nu_{max}$: 3388 (NH) and 2212 $cm^{-1}$ (CN); $\delta_H$: 1.02–1.06 (2H, m, $CH_2$), 1.67–1.70 (2H, m, $CH_2$), 2.46–2.78 (2H, m, $CH_2$), 7.28 (1H, s, ylidene-H), 7.68–8.28 (9H, m, Ar-H and NH).

**2.3.5. 6-Amino-4,10-di-*m*-dinitrophenyl-8-oxo-1,9-propanoquinolizine-5,9-dicarbonitrile hydrochloride 22.** *Method A*: a mixture of compound **17** (3.64 g, 0.01 mol), malononitrile (1.32 g, 0.02 mol) in ethanol (30 mL) and few drops of piperidine were refluxed for 3 h. The reaction mixture was allowed to cool to room temperature, then poured into ice-cold water and neutralized with HCl. The solid product, so formed, was collected by filtration and recrystallized from DMF/EtOH (2:1) as yellow crystals (3.9 g, 75%).

*Method B*: to a mixture of compound **21a** (0.01 mol) and malononitrile (0.66 g, 0.01 mol) in DMF (30 mL), few drops of piperidine were added. The mixture was refluxed for 5 h, then allowed to cool, poured into ice-cold water and neutralized with HCl. The solid product, so formed, was collected by filtration and recrystallized from DMF/EtOH (2:1) as yellow crystals (4.2 g, 80%); mp 118–120°C (Found: C, 59.23; H, 3.38; N, 16.05; $C_{26}H_{16}N_6O_5Cl$ requires: C, 59.03; H, 3.23; N, 15.88%), $\nu_{max}$: 3452, 3344 ($NH_2$), 2190 (CN) and 1654 $cm^{-1}$ (CO); $\delta_H$: 1.56–1.70 (2H, m, $CH_2$), 2.50–2.73 (4H, m, $2CH_2$), 7.09–8.16 (10H, m, 8Ar-H and $NH_2$).

### 2.4. General procedure for the synthesis of 28a,b

To a solution of **1** (1.39 g, 0.01 mol) in pyridine (20 mL) either benzylidinemalononitrile **23a** or *p*-chlorobenzylidinemalononitrile **23b** (0.1 mol) was added. The reaction mixture was heated under refluxed for 15 h, then left to cool, poured into ice-cold water and neutralized with hydrochloric acid. The solid products were collected by filtration and recrystallized from the proper solvent.

**2.4.1. 8-Amino-4-(benzylidenyl)-10-phenyl-6-oxocyclohexa[*c*]quinolizine-5,9-dicarbonitrile 28a.** This compound was crystallized from ethanol as brown crystals (3.48 g, 82%), mp 160–162°C; (Found: C, 78.45; H, 4.90; N, 13.26. $C_{28}H_{20}N_4O$ requires: C, 78.48; 4.71; N, 13.08%). $\nu_{max}$: 3449, 3363 ($NH_2$), 2211 (2CN) and 1634 $cm^{-1}$ (ring CO); $\delta_H$: 1.66–1.70 (2H, m, $CH_2$), 2.16–2.20 (2H, m, $CH_2$),

2.22–2.51 (2H, m, $CH_2$), 7.41–7.65 (10H, m, Ar-H), 7.95 (1H, s, ylidene-CH), 8.59 (1H, s, H-11) and 12.20 ppm (2H, br, $NH_2$), MS (EI): $m/z$=428.1 ($M^+$).

**2.4.2. 8-Amino-4-(*p*-chlorobenzylidenyl)-10-*p*-chlorophenyl-6-oxocyclohexa[*c*]quinolizine-5,9-dicarbonitrile 28b.** This compound was crystallized from a mixture of ethanol and dimethyl formamide (2:1) as brown crystals (4.21 g, 85%), mp 230–232°C; (Found: C, 67.52; H, 3.37; N, 11.12. $C_{28}H_{18}N_4OCl_2$ requires: C, 67.74, 3.65; N, 11.28%); $\nu_{max}$: 3450, 3356 ($NH_2$), 2193 (CN) and 1633 $cm^{-1}$ (ring CO); $\delta_H$: 1.60–1.70 (2H, m, $CH_2$), 2.10–2.23 (2H, m, $CH_2$), 2.28–2.50 (2H, m, $CH_2$), 7.25–7.66 (8H, m, Ar-H), 7.95 (1H, s, ylidene-H), 8.59 (1H, s, H-11) and 12.20 ppm (2H, bs, $NH_2$), MS (EI): $m/z$=497.1 ($M^+$).

### 2.5. Biological test

Some of the newly synthesized compounds were tested against the specified microorganism as 400 μg $mL^{-1}$ (w/v) solution in sterile DMSO. A solution of the tested compound (0.01 mol) was poured aseptically in a well of 6 mm diameter made by a borer in the seeded agar medium. After pipetting the same volume in wheels of all tested microorganisms, plates were incubated at 37°C for 24 h. The activities were expressed as inhibition zones (mm, diameter, clear areas) as antibacterial and antifungal effect. The least concentration which showed inhibitory effect on any specific micoorganism was considered as the minimum inhibitory concentration (MIC) which was determined using streptomycin and mycostatin as the references.

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