An Efficient One-Pot Three-Component Synthesis of Some New Polyhydroquinolines via Enaminone Intermediates

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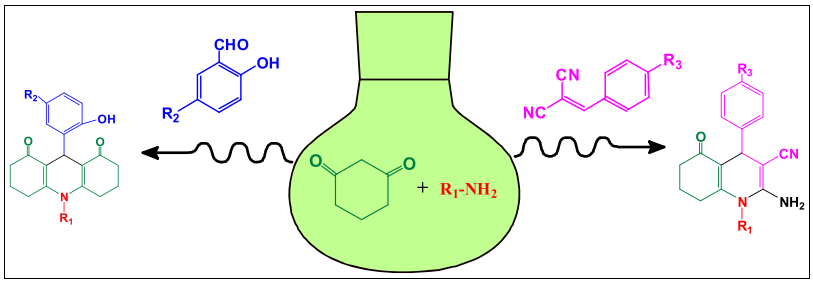

For a wide spectrum of pharmacological effects of polyhydroquinolines, this study introduces a developed safe, simple, higher yields and fast method for the synthesis of some new hexahydroquinoline derivatives using one-pot three-component cyclocondensation reaction, via the reaction of 1,3-cyclohexanedione with primary amine and arylidinemalononitrile or salicylaldehyde derivatives. The prepared compounds were reacted with different reagents as *N*,*N*-dimethylformamide dimethylacetal, acetic anhydride, sulphuric acid, and hydrazine hydrate forming several polycyclic hexahydroquinoline and acridine derivatives. All these new compounds have been characterized by spectral data and expected to be effective pharmaceutical drugs.

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INTRODUCTION

Quinoline and some of its derivatives are the most widespread *N*-heterocyclic compounds associated into the structures of most pharmaceutical and antimicrobial drugs [1]. Recently, much interest has been dedicated to the synthesis of polyhydroquinoline compounds because of their diverse therapeutic and pharmacological properties. Various quinoline derivatives characterize moderate toxicity and central nervous system stimulants [2,3]. Some fluoroquinolines, for example, 8-difluoro-methoxy-1-ethyl-6-fluoro-1,4-dihydro-7-[4-(2-methoxyphenyl)-1-pipernzinyl]-4-oxoquinoline-3-carboxylic acid] and 7-(3,4-dihydro-4-phe nyl-piperidnyl)-1,4-dihydro-6-fluoro-1-methyl-8-trifluorome thyl-4-oxo-quinolone-3-carboxylic acid have been reported as inhibitors for human immunodeficiency virus-1 replication through interference with the transcription process [4–6]. The known quinoline nucleus existed in different natural compounds like quinones, chloroquine, and papaverine [7,8]. The two former nuclei are antimalarial natural products, whereas the third one is a smooth muscle relaxant, a coronary vasodilator, an antispasmodic drug, and also primarily used in the treatment of visceral spasm and vasospasm (especially those involving the heart and the brain) [9,10]. Additionally, naturally occurring quinolone derivatives as 2-methyl-1,2,3,4-tetra-hydroquinoline exist in human brain. Dynemycin is acting as antitumor and antibiotic effectives [11]. Different 1,2,3,4-tetrahydroquinolines have been tested as potential drugs, for example, schistosomicide, nicainoprol [12], and oxamniquine [13] are antiarrhythmic drug, and virantmycin [14] is an antibiotic drug. Tetrahydroquinoline L-689,560 is one of the most useful NMDA antagonists yet found [15,16] (Fig. 1). In continuation to our previous work [17], this study has been undertaken to synthesize some new hexahydroquinolines via one-pot three-component cyclocondensation reaction of 1,3-cyclohexanedione, aryledenmalononitrile, and amine as reagents in aqueous medium expected to have an effective pharmaceutical activities (Scheme 1), the higher effective of the quinolone and acridine encouraged to synthesis of 16 new compounds of these nuclei.

RESULTS AND DISCUSSION

Firstly, the protocol for the previously mentioned reaction has been established without any catalyst in refluxing aqueous condition, the desired product not prepared. The same reaction was employed incorporating a small amount of triethylamine as catalytic amount under the same reflux condition, so an excellent yield (about 80%) of the desired hexahydroquinolines has been obtained. The target compounds 2-amino-3-cyano-hexahydroquinoline derivatives **2a–e** were prepared in a very good yield, via a one-pot three-component

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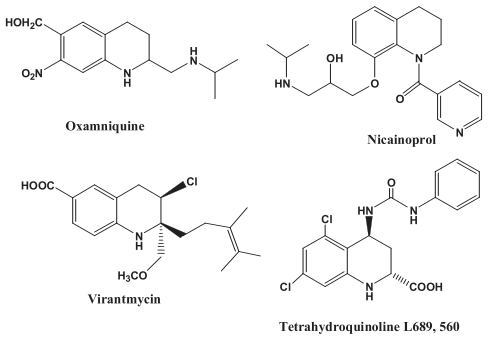
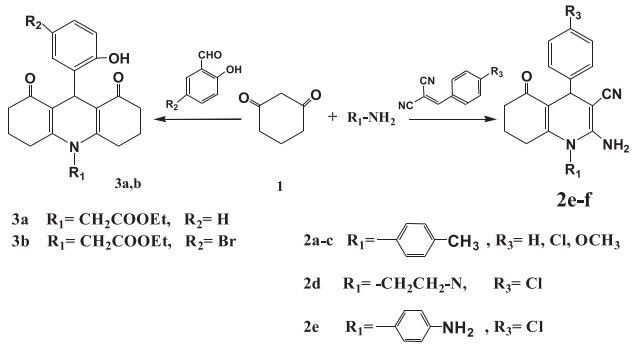


Figure 1. The oxamniquine, nicainoprol, virantmycin, and tetrahydroquinoline L-689,560.

Scheme 1. Synthesis of hexahydroquinoline **3a**,**b** and octahydroacridine derivatives **2e**–**f**.



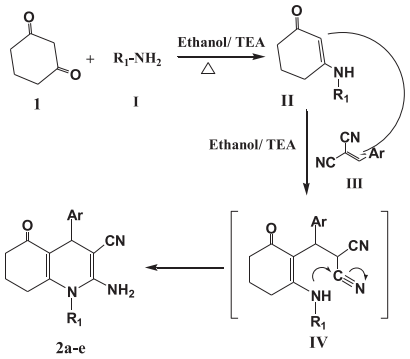
cyclocondensation reaction of 1,3-cyclohexanedione **1** with *p*-toluidine and a series of substituted arylidinemalononitrile (benzylidinemalononitrile, *p*-chloro benzylidinemalononitrile [17], and *p*-methoxybenzylidine malono-nitrile) forming **2a**–**c** derivatives, in addition to the reaction of 1,3-cyclohexanedione **1** with diamens examply (1,2-diaminoethane or 1,4-diaminobenzene) and *p*-chlorobenzylidinemalono-nitrile in refluxing ethanol containing a catalytic amount of triethylamine. The condensation reaction of 1,2-diaminoethane took place via the two amino groups but of 1,4-di-aminobenzene took place via one amino group only forming ethane-1,2-bis-[2-amino-1-(4-methylphenyl)-5-oxo-4-(4-chlorophenyl)(1,4,5,6,7,8-hexahydroquinolone-3-carbonitrile] and 2-amino-4-(4-chloro phenyl)-1-(4-aminophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile derivatives **2d**,**e**, respectively (Scheme 1). The spectral analyses of compound **2e** pointed to the presence of an ethanol molecule joined with octahydroacridine moiety during the crystal lattice building. The molecular structures of the products **2a**–**e** were illustrated from their IR, ^{1}H-NMR, and ^{13}C-NMR spectral analyses. The empirical mechanism for this transformation can be rationalized through two different steps [18]. Step 1 involves the formation of the required cyclohex-2-enaminones from the reaction of 1,3-cyclohexanedione with the amines under aqueous conditions. The formed enaminone contains a nucleophilic character of both of enamine and enone [19]. Step 2 comprises Michael addition reaction with intramolecular cyclization between enaminone and different arylidenemalononitriles affording the final product hexahydroquinoline derivatives **2a**–**e** (Scheme 2).

Moreover, under the same previous condition, two molar ratio 1,3-cyclohexandione **1** was reacted with equimolar ratio of the aldehyde, namely, salicylaldehyde or *p*-bro mosalicylaldehyde and ethyl glycinate hydrochloride in presence of two molar ratio of triethylamine in refluxing ethanol to afford ethyl-2-[9-(2-hydroxyphenyl)-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridin-10-yl]acetate and ethyl-2-[9-(3-bromo-2-hydroxyphenyl)-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-deca-hydroacridin-10-yl]-acetate [20] **3a**,**b**, respectively, in good yields 80% (Scheme 1). In our previous work, compound **3b** was obtained with another synthetic route [20] that leads to relatively lower yield. The structures of these compounds were established using IR, ^{1}H-NMR, ^{13}C-NMR, and MS spectral analyses.

When an equimolar ratio of compound **2b** was subjected to react with *N*,*N*-dimethylformamide dimethylacetal in boiling dimethylformamide (DMF) resulting in the formation of [9-(2-hydroxyphenyl)-*N*′-[3-cyano-1-(4-methylphenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinolin-2-yl]-*N*,*N*-dimethylimidoformamide (**4**). ^{1}H-NMR spectrum (DMSO-d_6) revealed a singlet signal at δ 7.67 due to the olefinic proton CH═N and two singlet signals due to the dimethylamino group at δ 2.90 and 2.34 ppm (cf. experimental).

However, the reaction of the target compound **2b** with refluxing acetic anhydride leads to the formation of pyrimidohexahydroquinoline derivative **5** in 68% yield. During an attempt to recrystallize compound **5** from DMF, a DMF molecule was joined with pyrimidohexahydroquinoline moiety during the crystal lattice building. The presence of the DMF molecule was proven in the basis of ^{1}H-NMR and ^{13}C-NMR spectral analyses. ^{1}H-NMR (DMSO-d_6) spectrum pointed to a

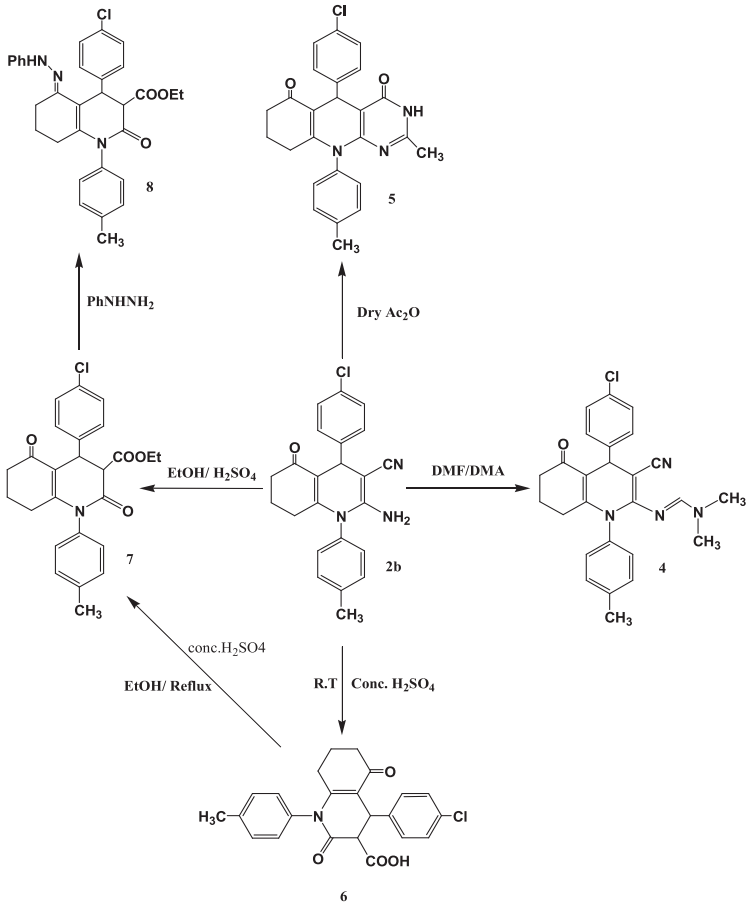
Scheme 2. The reaction mechanism of formation of a hexahydroquinoline derivatives (**2a**–**e**).



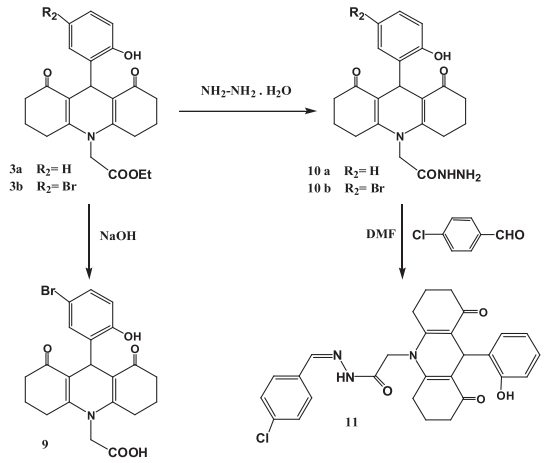
singlet signal at δ 7.97 due to CH group and two singlet signals at δ 2.90 and 2.75 due to two CH_3 groups of DMF molecule. Also, ^{13}C-NMR (DMSO-d_6) spectrum showed three signals of C═O carbon at 196.09 of DMF, in addition to another two carbonyl carbons at 172.70 and 162.13 ppm of pyrimidohexahydroquinoline moiety and two CH_3 carbons at 21.45 and 21.27 of DMF in addition to another CH_3 carbon at 28.36 ppm of pyrimidohexahydroquinoline moiety. The reaction of compound **2b** with concd sulphuric acid took place at 25°C via the acid hydrolysis of the cyano group and the oxidation reaction of the amino group to form the keto carboxylic acid derivative **6.** The structural elucidation of the synthesized compounds **5** and **6** was carried out by IR, ^{1}H-NMR, and ^{13}C-NMR spectral analyses, where IR spectrum of compound **6** revealed the existence of the three strong stretching vibrations at ν 1705, 1671, and 1631 cm^{-1} due to three carbonyl groups functions of 2,5-dioxo-octahydroquinoline-3-carboxylic acid. The keto acid derivative **6** was allowed to react with absolute ethanol in the presence of concd sulphuric acid under reflux for 4 h to form the expected corresponding ethyl ester derivative **7**. The structure of this compound has been further confirmed by refluxing the parent compound 2-amino-3-cyano-hexahydroquinoline derivative **2b** with sulphuric acid in absolute ethanol for 4 h. The spectral data of the product were typical with those of compound **7** (Scheme 3). The condensation reaction of compound **7** with equimolar amounts of phenyl hydrazine and catalytic amount of trifloroacetic acid was studied. This reaction took place only at the carbonyl group of cyclohexenone moiety resulting in phenylhydrazone derivative **8** in a good yield (Scheme 3). The structures of these new products **7** and **8** have been unambiguously confirmed by IR, ^{1}H-NMR, and ^{13}C-NMR spectral analyses.

Basic hydrolysis of compound **3b** affording the corresponding carboxylic acid derivative [9-(3-bromo-2-hydroxyphenyl)-2, 3, 4, 5, 6, 7, 8, 9-octahydroacridin-10(1*H*)-yl] acetic acid (**9**), during its recrystallization from ethanol, an ethanol molecule was joined with octahydroacridine moiety during the crystal lattice building. IR, ^{1}H-NMR, and ^{13}C-NMR analyses gave a good evidence for its structure. The hydrazide derivatives

Scheme 3. The reaction take place on 2-amino-4-(4-chlorophenyl)-1-(4-methylphenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**2b**).



Scheme 4. The reaction take place on ethyl-2-[9-(3-subsituted-2-hydroxyphenyl)-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-acridin-10-yl] acetate (**3a**,**b**).



10a,**b** were prepared via the reaction of the acridine derivatives **3a**,**b** with hydrazine hydrate in boiling ethanol. When compound **10a** was reacted with *p*-chlorobenzaldehyde in DMF via a nucleophilic condensation reaction, [9-(2-hydroxyphenyl)]-*N*′-[(1*E*)-ethylidene]-2-[2,3,4,5, 6, 7,8,9-octahydroacridin-10(1*H*)-yl]acetohydrazide (**11**) has been formed in 50% yield (Scheme 4). All the new compounds were investigated with spectral analyses as shown in the experimental section.

CONCLUSION

Regarding to the importance of the polyhydroquinolines effects, a developed safe method for the synthesis of some new hexahydroquinoline derivatives using one-pot three-component cyclocondensation reaction, via the combination of 1,3-cyclohexanedione with primary amine and arylidinemalononitrile or the combination of 1,3-cyclohexanedione with primary amine and salicylaldehyde derivatives was carried out.

EXPERIMENTAL

All chemical reagents and instruments were bought from Aldrich, Merck, and used directly without further purification. Our products were investigated by IR spectra measured on a Nicolet 710 Fourier transform infrared spectroscopy spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in deuterated dimethyl sulfoxide at 400 and 100 MHz on a BRUKER spectrometer and DELTA 2-NMR spectrometer using tetramethylsilane as an internal reference. The purity of the substances and the progress of the reactions were screened on thin-layer chromatography, and all melting points are uncorrected and were recorded on Melt-Tem II melting point apparatus.

Synthesis of 2-amino-1-(4-methylphenyl)-5-oxo-4-(aryl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (2a–c) (general procedure). To a solution of 1,3-cyclohexanedione (3.36 g, 0.03 mol) and *p*-toludine (3.21 g, 0.03 mol) in ethanol (40 mL), a catalytic amount of triethylamine was added. The reaction mixture was heated under reflux for 3 h. Arylidinemalononitrile, namely, benzylidenemalono trile, 4-chlorobenzylidenemalononitrile, and 4-methoxy benzylidenemalononitrile (0.03 mol) was added to the reaction mixture while reflux for another 3 h. The separated solid was filtered on hot washed with ethanol and crystallized from the suitable solvent.

2-Amino-4-phenyl-1-(4-methylphenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (2a). Crystalized as brown crystal from ethanol; yield 70%; mp 290–292°C; IR (λ_{max}, cm^{-1}): 3470 m, 3312 m (NH_2), 3062–3030 w ($CH_{arom.}$), 2946–2888 m ($CH_{aliph.}$), 2178 m (C≡N), 1632 s (C═O), 1610 s (C═C); ^{1}H-NMR (400 MHz, DMSO-d_6), δppm: 7.31–7.16 (m, 9H, $CH_{arom.}$), 5.26 (s, 2H, NH_2, disappeared by D_2O), 4.51 (s, 1H, CH–Ar), 2.40 (s, 3H, CH_3–Ar), 2.29–2.19 (t, 2H, CH_2–C═O), 1.94–1.81 (t, 2H, CH_2–C═C), 1.66–1.61 (m, 2H, CH_2–$\underline{CH_2}$–CH_2); ^{13}C-NMR (100 MHz, DMSO-d_6), δppm: 195.47 (C═O), 152.91, 151.59, 147.08, 139.84, 134.11 (5–C), 131.04, 130.02, 128.82, 127.19, 126.66 (9–CH), 121.88 (C), 113.18 (C≡N), 61.03 (C), 56.53 ($\underline{CH_2}$–C═O), 36.53 (CH), 28.20, 21.19 (2–CH_2), 21.10 (CH_3); analysis: calculated for $C_{23}H_{21}N_3O$ (355.43): C, 77.71; H, 5.96; N, 11.82%. Found: C, 77.65; H, 5.81; N, 11.97%.

2-Amino-4-(4-chlorophenyl)-1-(4-methylphenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (2b). Crystalized as pale yellow crystal from DMF; yield: 79%; mp 300°C; IR (λ_{max}, cm^{-1}): 3472 s, 3325 s (NH_2), 3032 w ($CH_{arom.}$), 2972–2879 w ($CH_{aliph.}$), 2177 m (C≡N), 1631 s (C═O); ^{1}H-NMR (400 MHz, DMSO-d_6), δppm: 7.39–7.29 (m, 8H, $CH_{arom.}$), 5.32 (s, 2H, NH_2, disappeared by D_2O), 4.51 (s, 1H, CH–Ar), 2.4 (s, 3H, CH_3), 2.23–2.19 (t, J = 8 Hz, 2H, CH_2–C═O), 1.93–1.81 (t, 2H, CH_2–C═C), 1.65–1.61 (m, 2H, CH_2–$\underline{CH_2}$–CH_2); ^{13}C-NMR (100 MHz, DMSO-d_6), δ ppm: 195.45 (C═O), 153.14, 151.70, 146.07, 139.86, 133.96, 131.26 (6–C), 131.03, 130.10, 129.13, 128.79 (8–CH), 121.78 (C), 112.72 (C≡N), 60.26 (C), 36.45 (CH), 36.21, 28.23, 21.22 (3–CH_2), 21.06 (CH_3); analysis: calculated for $C_{23}H_{20}N_3OCl$ (389.87): C, 70.85; H, 5.18; N, 10.78%. Found: C, 70.76; H, 5.27; N, 10.71%.

2-Amino-4-(4-methoxyphenyl)-1-(4-methylphenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (2c). Crystalized as brown crystal ethanol; yield 72%; mp 252°C; IR (λ_{max}, cm^{-1}): 3468 m, 3318 m (NH_2), 3039 w ($CH_{arom.}$), 2941–2838 w ($CH_{aliph.}$), 2180 m (C≡N), 1634 s (C═O); ^{1}H-NMR (400 MHz, DMSO-d_6), δppm: 7.38–6.88 (m, 8H,

$CH_{arom.}$), 5.12 (s, 2H, NH_2, disappeared by D_2O), 4.48 (s, 1H, CH–Ar), 3.75 (s, 3H, –O–CH_3), 2.41 (s, 3H, CH_3–Ar), 2.21–2.19 (t, J = 4 Hz, 2H, –CH_2–C═O), 1.94–1.81 (t, 2H, CH_2–C═C), 1.66–1.61 (m, 2H, CH_2–$\underline{CH_2}$–CH_2); ^{13}C-NMR (100 MHz, DMSO-d_6), δ ppm: 195.36 (C═O), 158.39, 152.43, 151.47, 139.81, 139.41, 134.25 (6–C), 131.02, 130.02,128.23, 114.37 (8–CH), 121.82 (C), 113.67 (C≡N), 61.59 (C), 55.59 (O–CH_3), 36.59 ($\underline{CH_2}$–C═O), 35.72 (CH), 28.17, 21.21 (2–CH_2), 21.15 (CH_3); analysis: calculated for $C_{24}H_{23}N_3O_2$ (385.45): C, 74.78; H, 6.02; N, 10.90%. Found: C, 74.69; H, 6.15; N, 10.83%.

Synthesis of ethane-1,1′-1,2-diyl-bis-[2-amino-5-oxo-4-(4-chlorophenyl)-1,4,5,6,7,8–hexahydroquinolone-3-carbonitrile] and 2-amino-1-(4-aminophenyl)-4-(4-chlorophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (2d,e). To a solution of 1,3-cyclohexanedione (0.896 g, 0.008 mol) and 1,2-diaminoethane or 1,4-diaminobenzene (0.004 mol) in ethanol (20 mL), a catalytic amount of triethylamine was added, and the reaction mixture was heated under reflux for 3 h. 4-Chlorobenzylidene- malononitrile (1.52 g, 0.008 mol) was added to the reaction mixture while reflux for additionally 5 h. The reaction mixture was concentrated and cooled; the formed precipitate was filtered off and crystallized from the proper solvent.

Ethane-1,1′-1,2-diyl-bis-[2-amino-1-(4-methylphenyl)-5-oxo-4-(4-chlorophenyl)(1,4,5,6,7,8-hexahydroquinolone-3-carbonitrile] (2d). Brown crystal from ethanol; yield 73%; mp 210–212° C; IR (λ_{max}, cm^{-1}): 3313 m, 3201 m (NH_2), 3051 w ($CH_{arom.}$), 2950–2872 w ($CH_{aliph.}$), 2176 m (C≡N), 1650 s (C═O), 1613 s (C═C); ^{1}H-NMR (400 MHz, DMSO-d_6), δppm: 7.33–7.18 (m, 8H, $CH_{arom.}$), 6.13 (s, 4H, $2NH_2$, disappeared by D_2O), 4.44 (s, 2H, 2CH–Ar), 3.97–3.94 (t, J = 8 Hz, 2H, N–CH_2), 3.74–3.71 (t, J = 8 Hz, 2H, CH_2–N), 2.86–2.82, 2.56–2.51 (t, 4H, $2CH_2CH_2\underline{CH_2}$–C═O), 2.27–2.24 (t, J = 4 Hz, 4H, $2\underline{CH_2}CH_2CH_2$–C═O), 2.08–1.89 (m, 4H, $2CH_2\underline{CH_2}CH_2$–C═O);^{13}C-NMR (100 MHz, DMSO-d_6), δ ppm: 195.43 (2–C═O), 153.48, 152.17, 145.19, 131.28 (8–C), 128.92, 128.79 (8–CH), 121.70 (2–C), 114.60 (2–C≡N), 62.99 (2–C), 42.47 (2–CH_2–N), 36.22 (2–CH), 35.95, 26.42, 21.29 (6–CH_2); analysis: calculated for $C_{34}H_{30}N_6O_2Cl_2$ (625.54): C, 65.27; H, 4.84; N, 13.43%. Found: C, 65.17; H, 4.76; N, 13.51%.

2-Amino-1-(4-aminophenyl)-4-(4-chlorophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (2e). White crystal from ethanol; yield 64%, mp 264°C.; IR (λ_{max}, cm^{-1}): 3453 m, 3334 m (NH_2), 3034 w ($CH_{arom.}$), 2944–2819 w ($CH_{aliph.}$), 2172 m (C≡N), 1641 s (C═O), 1608 s (C═C); ^{1}H-NMR (400 MHz, DMSO-d_6), δppm: 7.37–6.67 (m, 8H, $CH_{arom.}$), 5.48, 5.19 (s, 4H, $2NH_2$, disappeared by D_2O), 4.50 (s, 1H, CH–Ar), 4.21 (s, 1H,OH ethanol molecule in the crystal lattice), 3.48–3.45 (q, 2H,CH_2 ethanol molecule in the crystal lattice), 2.23–2.18 (t, 2H, CH_2–C═O), 2.04–2.00 (t, J = 8 Hz, 2H, CH_2–C═C), 1.86–1.62 (m, 2H, CH_2–$\underline{CH_2}$–CH_2), 1.09 (t, 3H, CH_3 ethanol molecule in the crystal lattice); ^{13}C-NMR (100 MHz, DMSO-d_6), δppm: 195.35 (C═O), 154.04, 152.24, 150.27, 146.25, 131.19 (5–C), 130.52, 129.08, 128.72, 114.82 (8–CH), 123.69, 121.85 (2–C),112.51 (C≡N), 59.83, 56.52 (2–C), 36.49 (CH), 36.16, 28.15, 21.12, 18.97 (3–CH_2); analysis: calculated for $C_{22}H_{19}N_4OCl$ (390.86): C, 67.59; H, 4.90; N, 14.33%. Found: C, 67.43; H, 4.86; N, 14.37%.

Synthesis of ethyl-2-[9-(2-hydroxyphenyl)-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridin-10-yl]acetate and ethyl-2-[9-(3-bromo-2-hydroxyphenyl)-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-de cahydroacridin-10-yl]acetate (3a,b) (general procedure). To a mixture of 1,3-cyclohexanedione (3.36 g, 0.03 mol), ethyl glycinate hydrochloride (2.09 g, 0.015 mol), and the appropriate aldehyde; salicaldehyde (1.58 mL, 0.015 mol) or 5-bromo-2-hydroxy benzaldehyde (3.015 g, 0.015 mol) in ethanol (30 mL), triethylamine (2.09 g, 0.015 mol) was added. The reaction mixture was heated under reflux for 5 h at 80–85°C left to cool, and the separated solid was filtered off, dried, and recrystallized from ethanol.

9-(2-hydroxyphenyl)-1,8-dioxo-2,3,4,5,6,7,8,9-octahydroacridine-10(1*H*)-yl)ethylacetate (3a). Yellow crystal from methanol; yield 77%; mp 230–232°C; IR (λ_{max}, cm^{-1}): 3111 br (OH), 3061 w ($CH_{arom.}$), 2981–2870 w ($CH_{aliph.}$), 1739 vs ($C{=}O_{ester}$), 1648 s, 1630 s ($2C{=}O_{cyclic}$), 1593 s (C═C); ^{1}H-NMR (400 MHz, DMSO-d_6), δ ppm: 9.58 (s, 1H, OH, disappeared by D_2O), 6.99–6.66 (m, 4H, $CH_{arom.}$), 4.99 (s, 1H, CH–Ar), 4.83 (s, 2H, N–$\underline{CH_2}$–C═O), 4.28–4.22 (q, J = 8 Hz, 2H, O–$\underline{CH_2}$–CH_3), 2.90–2.86, 2.44–2.40 (t, J = 8 Hz, 4H, $2CH_2$–$\underline{CH_2}$–C═O), 2.29–2.27 (t, J = 8 Hz, 4H, $2CH_2$–C═C), 1.99–1.94, 1.82–1.79 (m, 4H, $2CH_2$–$\underline{CH_2}$–CH_2), 1.28–1.25 (t, J = 8 Hz, 3H, –CH_2–$\underline{CH_3}$); ^{13}C-NMR (100 MHz, DMSO-d_6), δ ppm: 198.00 (2–$C{=}O_{cyclic}$), 169.68 ($C{=}O_{ester}$), 156.03 (2–C), 153.47, 132.76 (2–C), 128.51, 127.93, 120.49, 117.22 (4–CH), 114.95 (2–C), 62.18 ($\underline{CH_2}$–CH_3), 47.75 (CH_2–N), 35.98 (CH), 26.07, 25.71, 20.95 (6–CH_2), 14.40 (CH_3); MS (*m/z*, ɪ%): 395 (95.82) (M^+), 377 (52.37), 339 (25.86), 308 (28.93), 302 (100.00), 290 (74.46), 274 (77.73), 262 (26.18), 199 (62.77); analysis: calculated for $C_{23}H_{25}NO_5$ (395.44): C, 69.85; H, 6.38; N, 3.54%. Found: C, 69.91; H, 6.43; N, 3.47%.

9(2-hydroxy-5-bromophenyl)-1,8-dioxo-2,3,4,5,6,7,8,9-octahydroacridine-10(1*H*)yl)ethyl acetate [18] (3b). Yellow crystal; yield 80%; mp 242°C; IR (λ_{max}, cm^{-1}): 3150 (OH), 3049 w ($CH_{arom.}$), 2980–2888 w ($CH_{aliph.}$), 1737 vs ($C{=}O_{ester}$), 1631 s ($C{=}O_{cyclic}$), 1593 s (C═C); ^{1}H-NMR (400 MHz, DMSO-d_6), δ ppm: 9.84 (s, 1H, OH, disappeared by D_2O), 7.14–6.65 (m, 3H, $CH_{arom.}$), 4.96 (s, 1H, CH–Ar), 4.85 (s, 2H, –N–CH_2–C═O), 4.28–4.23 (q, J = 8 Hz, 2H, –$\underline{CH_2}$–CH_3), 2.89–2.86, 2.46–2.42 (t, J = 8 Hz, 4H, $2CH_2$–$\underline{CH_2}$–C═O), 2.31–2.28 (t, J = 8 Hz, 4H, $2CH_2$–C═C), 2.00–1.94, 1.84–1.77 (m, 4H, 2 CH_2–$\underline{CH_2}$–CH_2), 1.28–1.26 (t, J = 8 Hz, 3H, –CH_2–$\underline{CH_3}$); ^{13}C-NMR (100 MHz, DMSO-d_6), δ ppm: 197.60

(2–C═O_{cyclic}), 169.62 (C═O_{ester}), 156.16 (2–C), 153.55, 135.48, 131.05 (3–C), 130.66, 119.58, 114.34 (3–CH), 111.63 (2–C), 62.02 ($\underline{CH_2}$–CH_3), 47.77 (CH_2–N), 36.02 (CH), 26.53, 26.12, 20.98 (6–CH_2), 14.51 (CH_3); MS (*m*/*z*, ɪ%): 479 (0.56), 478 (0.86) (M^+ + 2), 477 (4.68), 476 (25.75) (M^+ + 1), 475 (90), 474 (30.26) (M^+), 433 (1.44), 404 (4.46), 384 (0.9), 300 (1.59), 281 (1.02), 253 (1.56), 206 (4.95), 91 (5.9), 91.95 (3.4), 52 (0.91), 51 (1.42), 50 (0.62); analysis: calculated for $C_{23}H_{24}NO_5Br$ (474.34): C, 58.23; H, 5.11; N, 2.95%. Found: C, 58.15; H, 5.23; N, 2.83%.

Synthesis of *N′*-[3-cyano-9-(4-chlorophenyl)-1-(4-methyl phenyl)-5-oxo-1,4,5,6,7,8-hexa hydroquinolin-2-yl]-*N,N*-dimethy limidoformamide (4). A solution of compound **4b** (3.12 g, 0.008 mol) and DMF/DMA (1.1 mL, 0.008 mol) in DMF (40 mL) was refluxed for 5 h, cooled, and then poured into ice-cold water. The formed precipitate was collected by filtration and recrystallized from ethanol as pale brown crystal yield 93%; mp 228°C; IR (λ_{max}, cm^{-1}): 3039 w ($CH_{arom.}$), 2970–2807 w ($CH_{aliph.}$), 2182 m (C≡N), 1635 s (C═$O_{cyclic\ ketone}$), 1610 s (C═N); ^{1}H-NMR (400 MHz, DMSO-d_6), δppm: 7.67 (s, 1H, CH═N), 7.38–7.13 (m, 8H, $CH_{arom.}$), 4.62 (s, 1H, CH–Ar), 2.90 (s, 3H, CH_3–N), 2.34 (s, 3H, CH_3–N), 2.20 (s, 3H, CH_3–Ph), 2.04–1.99 (t, 2H, $CH_2CH_2\underline{CH_2}$–C═O), 1.83–1.80 (t, 2H, $\underline{CH_2}CH_2CH_2$–C═O),1.67–1.63 (m, 2H, $CH_2\underline{CH_2}CH_2$–C═O); ^{13}C-NMR (100 MHz, DMSO-d_6), δ ppm: 195.39 (C═O), 157.68, 155.64, 153.92, 145.69, 137.99, 136.37, 131.45, 130.11, 129.64, 129.34, 128.85, 122.06, 111.60 (C≡N), 70.71 (C), 39.96 (CH), 37.97, 36.55, 34.28 (3–CH_2), 28.31 (CH_3–Ar), 21.27, 21.13 (2–CH_3–N); analysis: calculated for $C_{26}H_{25}N_4OCl$ (444.95): C, 70.17; H, 5.67; N, 12.59%. Found: C, 70.21; H; 5.61; N, 12.47%.

Synthesis of 2-methyl-9-(4-chlorophenyl)-10-(4-methylphenyl)-5,8,9,10-tetrahydropyr-imido[4,5-*b*]quinoline-4,6(3*H,7H*)-dione (5). A solution of compound **2b** (0.78 g, 0.002 mol) in dry acetic anhydride (20 mL) was refluxed for 3 h; the solvent was evaporated under reduced pressure, and the formed precipitate was collected and recrystallized from DMF as off white crystal, yield 68%; mp >320°C; IR (λ_{max}, cm^{-1}): 3395 m (NH), 3042 w ($CH_{arom.}$), 2951–2859 w ($CH_{aliph.}$), 1682 s (C═O_{amidic}), 1641 s (C═$O_{cyclic\ ketone}$), 1594 s (C═N); ^{1}H-NMR (400 MHz, DMSO-d_6), δ ppm: 12.06 (s, 1H, NH, disappeared by D_2O),7.97 (s, 1H, CH DMF molecule in the crystal lattice),7.37–7.17 (m, 8H, $CH_{arom.}$), 5.17 (s, 1H, CH–Ar), 2.9, 2.75 (s, 6H, $2CH_3$ DMF molecule in the crystal lattice), 2.40 (s, 3H, $\underline{CH_3}$–Ph), 2.24–2.10 (m, 4H, $\underline{CH_2}CH_2\underline{CH_2}$–C═O), 2.03 (s, 3H, CH_3–C═N), 1.87–1.68 (m, 4H, $2CH_2$);^{13}C-NMR (100 MHz, DMSO-d_6), δ ppm: 195.29 (C═$O_{cyclic\ ketone}$), 162.74 (HC═$O_{DMF\ molecule}$), 162.07 (C═O_{amidic}), 157.06, 154.57,153.66, 145.55, 138.14, 136.21, 131.00 (7–C), 130.17,130.05, 129.73, 128.39 (8–CH), 112.54, 101.18 (2–C), 36.21, 31.27 (2–$CH_{3DMF\ molecule}$), 36.68 (CH), 32.67, 28.41, 21.60 (3–CH_2), 21.31, 21.18 (2–CH_3); MS (*m*/*z*, ɪ %): 433 (1.61) (M^+ + 2), 431 (5.79) (M^+), 336 (1.24), 320 (23.81), 279 (1.03), 91.05 (8.46), 65 (6.37); analysis: calculated for $C_{25}H_{22}N_3O_2Cl$ (431.91): C, 69.51; H, 5.14; N, 9.73%. Found: C, 69.63; H, 5.07; N, 9.68%.

Synthesis of 4-(4-chlorophenyl)-1-(4-methylphenyl)-2,5-dioxo-1,2,3,4,5,6,7,8-octahydro-quinolone-3-carboxylic acid (6). A solution of compound **2b** (2.0 g, 0.0051 mol) in concd H_2SO_4 (20 mL) was stirred for 4 h at room temperature, and the reaction mixture was poured into ice-cold water. The formed precipitate was collected, filtered of, washed with water, and recrystallized from ethanol as pale yellow crystal, yield; 89%; mp 245°C; IR (λ_{max}, cm^{-1}): 3192 br (OH_{acid}), 3034 w ($CH_{arom.}$), 2948–2867 w ($CH_{aliph.}$), 1705 s (C═O_{acidic}), 1671 s (C═O_{amidic}), 1631 s (C═O_{cyclic}), 1601 s (C═C);^{1}H-NMR (400 MHz, DMSO-d_6), δ ppm: 7.76 (s, 1H, OH_{acid}, disappeared by D_2O), 7.41–7.10 (m, 8H, $CH_{arom.}$), 4.61 (d, *J* = 4 Hz, 1H, $\underline{CH}$–COOH), 3.59 (d, *J* = 4 Hz, 1H, $\underline{CH}$–Ar), 2.37 (s, 3H, CH_3–Ph), 2.30–2.26 (t, *J* = 8 Hz, 2H, $CH_2CH_2\underline{CH_2}$–C═O), 2.10–2.05 (t, 2H, $\underline{CH_2}CH_2CH_2$–C═O), 1.92–1.87 (m, 2H, $CH_2\underline{CH_2}CH_2$–C═O); ^{13}C-NMR (100 MHz, DMSO-d_6), δ ppm: 195.51 (C═O_{cyclic}), 169.64 (C═O_{acid}), 167.62 (C═O_{amidic}), 156.78, 140.06, 138.53, 135.06, 132.00 (5–C), 130.26, 130.04, 129.31, 129.10 (8–CH), 114.82 (C), 56.04 (C), 37.88 (CH), 36.36, 28.08, 21.88 (3–CH_2), 21.12 (CH_3); MS (*m*/*z*, ɪ%): 409 (0.27) (M^+), 405 (0.76), 380 (0.61), 366 (9.14), 364 (29.15), 91 (16.91); analysis: calculated for $C_{23}H_{20}NO_4Cl$ (409.86): C, 67.39; H, 4.92; N, 3.41%. Found: C, 67.31; H, 4.80; N, 3.48%.

Synthesis of ethyl [4-(4-chlorophenyl)-1-(4-methylphenyl)-2,5-dioxo-1,2,3,4,5,6,7,8-octa hydroquinoline]-3-carboxylate (7).

Method 1. To a solution of compound **2b** (2.0 g, 5.13 mmol) in absolute ethanol (50 mL), concd H2SO4 (2 mL) was added then allowed to heat under reflux for 4 h, cooled, and poured into ice-cold water. The formed precipitate was collected, filtered, and recrystallized from ethanol as white crystal, yield 70%; mp 1600°C.

Method 2. To a solution of compound **6** (1.58 g, 0.004 mol) in absolute ethanol (40 mL) was added concd H_2SO_4 (1.5 mL). The reaction mixture was refluxed for 4 h, cooled, and then poured into ice-cold water. The formed precipitate was collected, filtered, and recrystallized from ethanol as white crystal, yield 77%; mp 160°C; IR (λ_{max}, cm^{-1}): 3252 m (NH), 3032 w ($CH_{arom.}$), 2995–2868 w ($CH_{aliph.}$), 1739 vs (C═O_{ester}), 1703 s (C═O_{amidic}), 1647 s (C═O_{cyclic}), 1614 s (C═C); ^{1}H-NMR (400 MHz, DMSO-d_6), δppm: 7.40–7.07 (m, 8H, $CH_{arom.}$), 4.68 (d, *J* = 4 Hz, 1H, $\underline{CH}$–COOEt), 4.25–4.22 (q, *J* = 4 Hz, 2H, O–$\underline{CH_2}$–CH_3), 3.92 (d, *J* = 4 Hz, 1H, CH–Ar), 2.37 (s, 3H, CH_3–Ph), 2.30 (t, 2H, $CH_2CH_2\underline{CH_2}$–C═O), 2.10–2.06 (t, 2H, $\underline{CH_2}CH_2CH_2$–C═O), 1.92–1.86 (m, 2H, $CH_2\underline{CH_2}CH_2$–C═O), 1.25–1.22 (t, 3H, –CH_2–$\underline{CH_3}$); ^{13}C-NMR

(100 MHz, DMSO-d_6), δ ppm: 195.35 (C═O_{cyclic}), 168.02 (C═O_{ester}), 165.91 (C═O_{amidic}), 156.56, 138.80, 138.47, 134.51, 132.30 (5–C), 130.43, 129.33, 129.28, 128.77 (8–CH), 115.36 (C), 62.14 ($\underline{CH_2}$–CH_3), 55.06, 37.04 (2–CH), 36.28, 27.96, 21.97 (3–CH_2), 21.13 (CH_3Ar), 14.46 ($\underline{CH_3}$–CH_2); analysis: calculated for $C_{25}H_{24}NO_4Cl$ (437.91): C, 68.56; H, 5.53; N, 3.19%. Found: C, 68.41; H, 5.65; N, 3.23%.

Synthesis of ethyl[4-(4-chlorophenyl)-1-(4-methylphenyl)-(5*E*)-2-oxo-5-(2-phenyl-hydrazinylidene)-1,2,3,4,5,6,7,8-octahydro quinoline]-3-carboxylate (8). A mixture of compound **7** (0.65 g, 0.0015 mol), phenyl hydrazine (0.15 mL, 0.0015 mol), and catalytic amount of trifloroacetic acid in ethanol (20 mL) was heated under reflux for 4 h. The solvent was evaporated under reduced pressure, and the formed precipitate was collected by filtration and recrystallized from ethanol as green crystal, yield 76%; mp 138–140°C; IR (λ_{max}, cm^{-1}): 3252 m (NH), 3099–3024 w ($CH_{arom.}$), 2981–2836 w ($CH_{aliph.}$), 1730 vs (C═O_{ester}), 1666 s (C═O_{amidic}), 1630 s (C═N), 1596 s (C═C); ^{1}H-NMR (400 MHz, DMSO-d_6), δppm: 8.97 (s, 1H, NH, disappeared by D_2O), 7.44–6.68 (m, 13H, $CH_{arom.}$), 5.06 (d, J = 4 Hz, 1H, CH–COOEt), 4.25–4.20 (q, J = 4 Hz, 2H, O–$\underline{CH_2}$–CH_3), 3.83 (d, J = 4 Hz, 1H, CH–Ar), 2.36 (s, 3H, CH_3–Ph), 2.62–2.58 (t, 2H, $CH_2CH_2\underline{CH_2}$–C═O), 1.89–1.86 (t, 2H, $\underline{CH_2}CH_2CH_2$–C═O), 2.12, 1.69 (m, 2H, $CH_2\underline{CH_2}CH_2$–C═O), 1.21–1.19 (t, J = 4 Hz, 3H, –CH_2–$\underline{CH_3}$); ^{13}C-NMR (100 MHz, DMSO-d_6), δ ppm:168.67 (C═O_{ester}),165.27 (C═O_{amidic}),146.60, 142.01, 139.56, 139.45, 137.94, 135.15, 131.93, 115.87 (8–C), 130.14, 129.96, 129.53, 129.21, 128.68, 118.91, 112.86 (13–CH), 61.72 ($\underline{CH_2}$–CH_3), 55.56, 38.54 (2–CH), 26.78, 23.35, 21.30 (3–CH_2), 21.12 (CH_3Ar), 14.52 ($\underline{CH_3}$–CH_2); analysis: calculated for $C_{31}H_{30}N_3O_3Cl$ (528.04): C, 70.50; H, 5.73; N, 7.95%. Found: C, 70.46; H, 5.78; N, 7.89%.

Synthesis of [9-(3-bromophenyl)-2,3,4,5,6,7,8,9-octahydro acridin-10(1*H*)-yl]acetic acid (9). To a solution of compound **3b** (2.37gm, 0.005 mol) in ethanol (40 mL) was added NaOH solution (0.4gm, 0.01 mol in 5 mL water). The reaction mixture was heated under reflux for 5 h, cooled, poured to cold water, and acidified with concd HCl. The separated solid was filtered off, dried, and recrystallized from ethanol, yield 97%; mp 237–239° C; IR (λ_{max}, cm^{-1}): 3444 br (OH_{acid}), 3110 br ($OH_{phenolic}$), 3015 w ($CH_{arom.}$), 2972–2882 w ($CH_{aliph.}$), 1707 s (C═O_{acid}), 1625 s (C═O_{cyclic}), 1585 s (C═C); ^{1}H-NMR (400 MHz, DMSO-d_6), δ ppm: 13.29 (br, 1H, OH_{acidic}, disappeared by D_2O), 9.77 (s, 1H, $OH_{phenolic}$, disappeared by D_2O), 7.10–6.67 (m, 3H, $CH_{arom.}$), 4.98 (s, 1H, CH–Ar), 4.71 (s, 1H, N–CH_2–C═O), 4.47 (q, 2H, CH_2 ethanol molecule in the crystal lattice), 3.2 (s, 1H, OH disappeared by D_2O,ethanol molecule in the crystal lattice), 2.9, 2.5 (t, 4H, $2CH_2CH_2\underline{CH_2}$–C═O), 2.30 (t, 4H, $2\underline{CH_2}CH_2CH_2$–C═O), 1.98, 1.84 (m, 4H, $2CH_2\underline{CH_2}CH_2$–C═O), 1.08 (t, 3H,$CH_3$ ethanol molecule in the crystal lattice); ^{13}C-NMR (100 MHz, DMSO-d_6), δ ppm: 197.46 (2–C═O_{cyclic}), 170.98 (C═O_{acid}), 156.15,153.56, 135.66 (6–C), 131.19, 130.56, 119.50 (3–CH), 114.40, 111.67 (4–C), 56.52 (CH_2 ethanol molecule), 47.83 (CH_2–N), 36.08 (CH), 26.55, 26.22, 21.05 (6–CH_2), 19.01 (CH_3 ethanol molecule); analysis: calculated for $C_{21}H_{20}NO_5Br$ (446.29): C, 56.51; H, 4.52; N, 3.13%. Found: C, 56.38; H, 4.43; N, 3.27%.

Synthesis of 2-[9-(2-hydroxyphenyl)-1,8-dioxo-1,2,3,4,5,6,7,8,9,10 decahydroacridin-10-yl]acetohydrazide and 2-[9-(3-bromo-2-hydroxyphenyl)-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-acridin-10-yl]acetohydrazide (10a,b) (general procedure). A solution of compound **3a**,**b** (0.005 mol) in hydrazine hydrate (20 mL) was refluxed for 2 h, cooled, and then triturated with ethanol. The precipitated solid obtained was filtered off, dried, and recrystallized from DMF to furnish compound **10a**,**b**.

2-[9-(2-Hydroxyphenyl)-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-deca hydroacridin-10-yl]acetohyd-razide (10a). Yellow powder from DMF; yield 90%; decomposed at 264°C; IR (λ_{max}, cm^{-1}): 3362 br (OH), 3339 m, 3251 m (NH_2, NH), 3051 w ($CH_{arom.}$), 2926–2867 w ($CH_{aliph.}$), 1668 s (C═O_{amide}), 1627 s (C═O_{cyclic}) 1582 s (C═C); ^{1}H-NMR (400 MHz, DMSO-d_6), δppm: 11.05 (br, 1H, NH, disappeared by D_2O), 9.07 (s, 1H, OH, disappeared by D_2O), 6.98–6.56 (m, 4H, $CH_{arom.}$), 5.63 (broad, 2H, NH_2, disappeared by D_2O), 5.20 (s, 1H, CH–Ar), 4.22 (s, 2H, –N–CH_2–C═O), 2.51, 2.38–2.34 (t, 4H, $2CH_2CH_2\underline{CH_2}$–C═O), 2.31–2.29, 2.07–2.01 (t, 4H, $2\underline{CH_2}CH_2CH_2$–C═O), 1.82–1.78, 1.63–1.60 (m, 4H, $2CH_2\underline{CH_2}CH_2$–C═O); ^{13}C-NMR (100 MHz, DMSO-d_6), δ ppm: 195.74 (2–C═O_{cyclic}), 169.35 (C═O_{amidic}), 154.85, 148.49, 140.22, 134.62 (4–C), 128.55, 126.72, 119.29, 116.95 (4–CH), 110.92 (2–C), 46.77 (CH_2–N), 27.93 (CH), 25.23, 22.47, 20.82 (6–CH_2); MS (*m*/*z*, ı%): 381 (0.18) (M^+), 269 (0.96), 199 (1.07), 180 (2.13), 167 (1.06), 94 (100.00), 66 (33.85); analysis: calculated for $C_{21}H_{23}N_3O_4$ (381.42): C, 66.12; H, 6.09; N, 11.01%. Found: C, 66.02; H, 6.23; N, 11.18%.

2-[9-(3-Bromo-2-hydroxyphenyl)-1,8-dioxo-1,2,3,4,5,6,7,8, 9,10decahydroacridin-10-yl] acetohydrazide (10b). Yellow powder from DMF; yield 92%; decomposed at 254°C; IR (λ_{max}, cm^{-1}): 3534 br (OH), 3333 m, 3209 m (NH_2, NH), 3087–3046 w ($CH_{arom.}$), 2951–2870 w ($CH_{aliph.}$), 1679 s (C═O_{amide}), 1637 s (C═O_{cyclic}), 1617 s (C═C); ^{1}H-NMR (400 MHz, DMSO-d_6), δppm: 11.65 (br, 1H, NH, disappeared by D_2O), 9.13 (s, 1H, OH, disappeared by D_2O), 7.01–6.50 (m, 3H, $CH_{arom.}$), 5.65 (br, 2H, NH_2, disappeared by D_2O), 5.14 (s, 1H, CH–Ar), 4.25 (s, 2H, N–CH_2–C═O), 2.58–2.54, 2.40–2.36 (t, 4H, $2CH_2CH_2\underline{CH_2}$–C═O), 2.29–2.21, 2.07–2.02 (t, 4H, $2\underline{CH_2}CH_2CH_2$–C═O), 1.82–1.79, 1.62–1.60 (m, 4H, $2CH_2\underline{CH_2}CH_2$–C═O); ^{13}C-NMR (100 MHz, DMSO-d_6),

δ ppm: 194.86 (2–C═O_{cyclic}) 168.97 (C═O_{amide}), 154.49, 149.10, 140.86, 137.41 (4–C), 130.96, 130.03, 129.55 (3–CH), 119.26, 110.58 (2–C), 46.72 (CH_2–N), 28.56 (CH), 25.33, 22.52, 20.82 (6–CH_2); analysis: calculated for $C_{21}H_{22}N_3O_4Br$ (460.32): C, 54.79; H, 4.82; N, 9.13%. Found: C, 54.64; H, 4.75; N, 9.27%.

Synthesis of 1-{*N′*-(4-chlorobenzylidine)[9-(2-hydroxyphenyl)-1,8-dioxo-2,3,4,5,6,7,8,9-octahydroacridin-10(1*H*)-yl]}acetohydrazide (11). A mixture of compound **10a** (0.38 g, 0.001 mol), *p*-chlorobenzaldehyde (0.14 g, 0.001 mol), and DMF (4 mL) in dioxane (20 mL) were heated under reflux for 5 h. The solvent was evaporated under reduced pressure, and the formed precipitate was filtered off and recrystallized from ethanol as brown crystal in yield 50%; mp 288–290°C; IR (λ_{max}, cm^{-1}): 3351 br (OH), 3283 m (NH), 3050 w ($CH_{arom.}$), 2932–2864 w ($CH_{aliph.}$), 1622 s (C═O_{amide}) and (C═O_{cyclic}), 1561 s (C═N); ^{1}H-NMR (400 MHz, DMSO-d_6), δppm: 10.47 (s, 1H, OH, disappeared by D_2O), 8.47 (s, 1H, N═CH–Ph), 7.87–7.85, 7.53–7.51 (d, 4H, $CH_{arom.}$), 6.97–6.65 (m, 4H, $CH_{arom.}$), 5.34 (s, 2H, N–CH_2–C═O), 5.29 (s, 1H, CH–Ar), 4.3 (q, 2H, CH_2, an ethanol molecule in the crystal lattice), 3.46 (s, 1H, NH, disappeared by D_2O), 3.2 (s, 1H, OH an ethanol molecule in the crystal lattice), 3.17–3.04, 2.70–2.56 (t, 4H, 2$CH_2CH_2\underline{CH_2}$–C═O), 2.33–2.29, 2.26–2.23 (t, 4H, 2$\underline{CH_2}CH_2CH_2$–C═O), 2.03–1.93, 1.86–1.59 (m, 4H, 2$CH_2\underline{CH_2}CH_2$–C═O), 1.06 (t, 3H, CH_3 an ethanol molecule in the crystal lattice); ^{13}C-NMR (100 MHz, DMSO-d_6), δ ppm: 195.94 (2–C═O_{cyclic}), 168.68 (C═O_{amide}), 157.96 (C), 155.71 (CH═N), 154.02, 151.54, 135.71, 134.02, 133.88 (5–C), 130.05, 129.42, 128.28, 127.63, 120.04, 117.32 (8–CH), 111.64, 110.56, 56.50 (3–C), 36.46 (CH_2–N), 26.88 (CH), 25.89, 25.80, 25.49, 21.01, 20.40, 19.01 (6–CH_2); analysis: calculated for $C_{28}H_{26}N_3O_4Cl$ (503.97): C, 66.72; H, 5.21; N, 8.33%. Found: C, 66.84; H, 5.17; N, 8.46%.

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