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A Facile and Catalyst-free Synthesis of Hexahydroacridine-1,8(2*H*,5*H*)-dione and Octahydroacridin-10(1*H*)-yl)thiourea Derivatives: Inter- and Intramolecular Aza-Michael addition

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Abstract: An easy and convenient technique for the one-pot synthesis of novel compounds of hexahydroacridine-1,8(2*H*,5*H*)-dione and octahydroacridin-10(1*H*)-yl) thiourea derivatives has been developed by the reaction of the octahydro-1*H*-xanthenes with hydroxylamine hydrochloride and thiosemicarbazide in ethylene glycol, which is a green solvent, under mild reaction conditions. IR, ^{1}H NMR, ^{13}C NMR spectrometry, and X-ray diffraction analysis were used to identify the structures of these compounds.

Keywords: Cyclohexanedione, Octahydro-1*H*-xanthene, Acridine, X-ray, *1*D-Polymeric H-bond

Introduction

Acridine derivatives have a significant location in medicinal chemistry because of their extensive applications in biology. These derivatives exhibit fungicidal [1,2], anti-cancer [3-5], anti-parasitic [6], anti-inflammatory, and anti-microbial activities [7,8]. In addition, they are important components of effective analgesics [9,10]. Mepacrine, azacrine, proflavine, and aminacrine, are some other pharmaceutically active acridine derivatives, which also show antimalarial and antibacterial activities [11]. One of the well-known classes of bioactive compounds is acridine derivatives [12]. Among this class, proflavine and 9-aminoacridine were previously used as antibacterial agents. However, many derivatives of 9-arylaminoacridines have been widely studied as anticancer drugs [13,14]. It should be mentioned that the biological activities of the acridines is mainly because of the ability of the acridine moiety to intercalate between base pairs of double-stranded DNA through π-π interactions. This matter causes alteration in the cellular machinery [15]. For 9-arylaminoacridines, the formation of ternary drug/DNA/enzyme complexes was investigated. Based on the results, it can be suggested that the acridine moiety and aniline ring should be used for the DNA-binding and the enzyme-binding domains, respectively [13,16].

In this study, an easy and efficient technique has been proposed for the one-pot synthesis of novel hexahydroacridine-1,8(2*H*,5*H*)-dione and octahydroacridin-10(1*H*)-yl) thiourea derivatives by the reaction of octahydro-1*H*-xanthenes with hydroxylamine hydrochloride and thiosemicarbazide in ethylene glycol, which is a green solvent.

Results and Discussion

This manuscript describes the synthesis of novel hexahydroacridine-1,8(2*H*,5*H*)-dione and octahydroacridin-10(1*H*)-yl)thiourea derivatives from reaction of octahydro-1*H*-xanthenes with hydroxylamine hydrochloride and thiosemicarbazide. Since the usage of simply available reagents is a meaningful target in organic synthesis and in order to extend synthetic methods for the synthesis of hexahydroacridine-1,8(2*H*,5*H*)-dione and octahydroacridin-10(1*H*)-yl) thiourea, this paper now establishes a simple and expedient method using hydroxylamine

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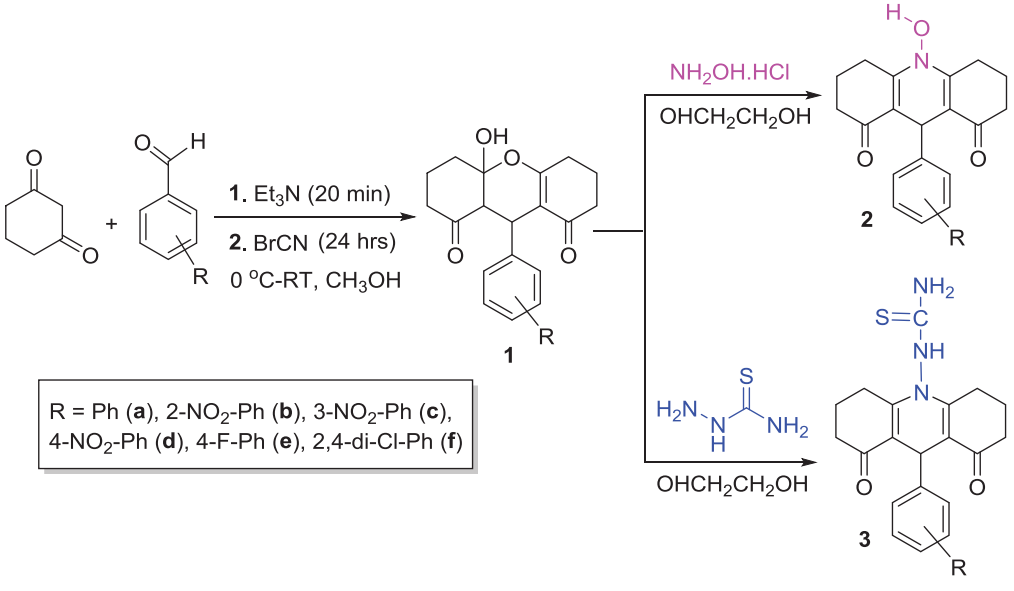
hydrochloride and thiosemicarbazide as a worthy nitrogen source in ethylene glycol, which is a green solvent. In an easy reaction work-up mixture and in a short period of the reaction time, high yields of products are achieved under mild reaction conditions with no catalyst (Scheme 1).

Firstly, the reaction of octahydro-1*H*-xanthenes **1** [17] with hydroxylamine hydrochloride or thiosemicarbazide in different solvents and at various temperatures was examined. The obtained results disclose that the usage of ethylene glycol at 100 °C is the optimal temperature for the one-pot reaction of octahydro-1*H*-xanthenes with hydroxylamine hydrochloride and thiosemicarbazide. Table 1 represents the results of the reactions of several octahydro-1*H*-xanthenes with hydroxylamine hydrochloride or thiosemicarbazide.

The reaction mechanism is shown in Scheme 2. In the course of the reaction, dehydration of **1a,** in the presence of hydroxylamine, obtained compound **A**. Then aza-Michael addition [18-20] of hydroxylamine to the β position of the α,β-unsaturated ketone generated an intermediate **B**. The ethereal ring opening of intermediate **B** led to the generation of intermediate **C**. Intramolecular aza-Michael addition of hydroxylamine to the β-position of the other α,β-unsaturated ketone in the intermediate **C** moiety, resulted in conversion into an intermediate **D**. This intermediate gave **2a** with the loss of a water molecule (Scheme 2).

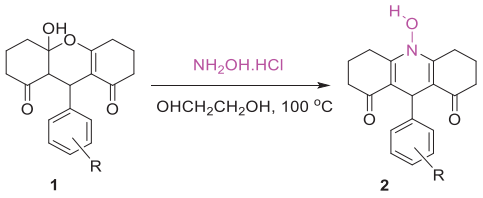
The ketone carbonyl group in **1b** has a stretching frequency at 1723 cm^{-1}. This peak is lost in the compounds **2b** and **3b**. Instead, the peak of α,β-unsaturated carbonyl stretching frequency of **1b**, **2b** and **3b** are shown at 1653, 1699 and 1662 cm^{-1}, respectively. These observations confirmed the expansion of the conjugation in compounds **2** and **3**. A peak at δ 10.76 ppm is seen in ^{1}H NMR spectrum of **2a** which corresponded to a hydroxylamine proton (see Supplementary Data). The ^{13}C NMR spectrum of **1a** also displayed a peak at δ 205.17 ppm which corresponded to a saturated ketone carbonyl group instead, this peak disappeared in the ^{13}C NMR spectrum of **2a** and shifted to up field position and showed a distinct peak at δ 194.92 ppm (see Supplementary Data). This distinct peak confirmed the presence of a plane of symmetry in **2**.

Crystal structure of 10-hydroxy-9-(4-nitro-phenyl)-3,4,6,7,9,10-hexahydro-2*H*,5*H*-acridine-1,8-dione (**2d**) with the atom labeling scheme is depicted in Figure 1a. Compounds **2d** crystallize in the monoclinic space groups $P2_1/n$ with the four molecules in the unit cell. 3,4,6,7,9,10-Hexahydro-2*H*,5*H*-acridine-1,8-dione ring system is substituted at the central methine C7 atom with a 4-nitro-phenyl. In addition, it carries a hydroxy substituent on the acridine N atom. C-C (cyclohexene) distances are in the range of typical single bond range [1.461(3)–1.521(3) Å]. The C7 carbon atom is not a stereocenter since the structure is symmetric. For the thirteen C atoms and one N atom of the acridine unit, the acridinedione ring system deviates meaningfully from planarity with an r.m.s. deviation of 0.614 Å. Such a plane is not quite orthogonal to the benzene ring plane [dihedral angle = 89.3°], a stable conformation is obtained by a strong intermolecular O5–H···O_2 hydrogen bond between the two adjacent molecules (Figure 1b). It is worth mentioning that in the reverse direction, both

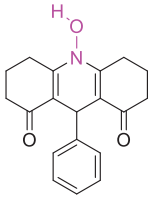
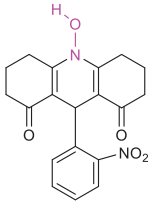
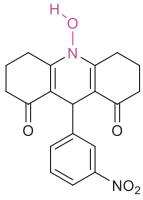
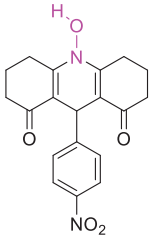
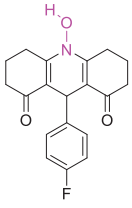


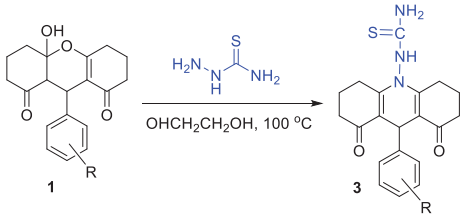
Scheme 1

Table 1 One-pot synthesis of hexahydroacridine-1,8(2*H*,5*H*)-dione **2** and octahydroacridin-10(1*H*)-yl)thiourea derivatives **3**.



1 2

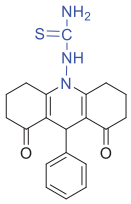
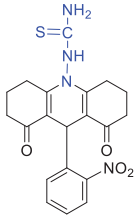
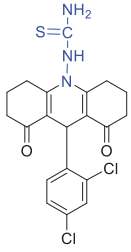
Entry	Product	Time (h)	Yield (%)[a]	Mp (°C)
1	(**a**) 	2	73	238–239
2	(**b**) 	3	76	225
3	(**c**) 	3	69	–
4	(**d**) 	0.5	62	245
5	(**e**) 	6	68	210



1 3

(*Continued*)

Table 1 Continued.

Entry	Product	Time (h)	Yield (%)[a]	Mp (°C)
6	**(a)** 	3	88	257
7	**(b)** 	2	54	231–234
8	**(f)** 	2	45	229–231

[a]Isolated yield.

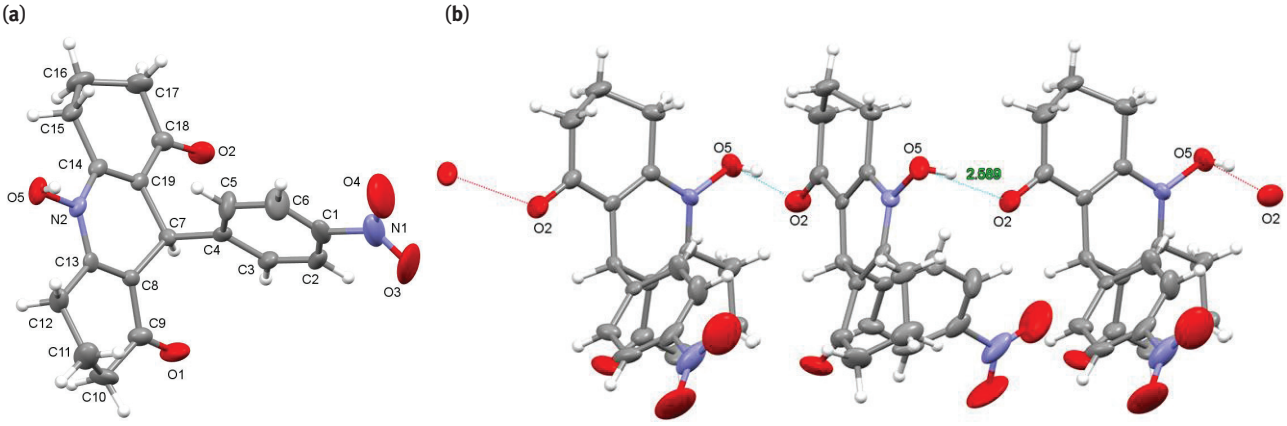
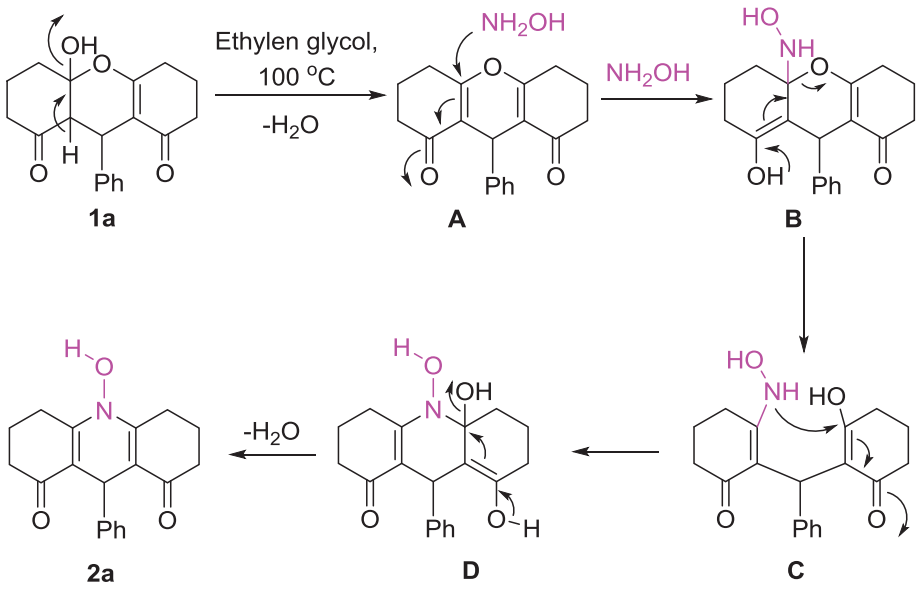


Figure 1 (a) Molecular structure of the compound **2d**. Thermal ellipsoids are depicted at the 40% probability, (b) *1*D-polymeric H-bonding geometry.

outer cyclohexenone rings adopt flattened chair configurations with the C11 and C16 atoms each about 0.320(4) Å from the best-fit planes through the remaining five C atoms. On the other hand, from the best-fit plane through the other four C atoms, the central C13/N2/C7-C8/C14/C19 ring could be perfectly described as a flattened boat with N2 and C7, 0.048(4) and 0.109(4) Å, respectively. Note that the bond angles and lengths in the molecule of **2d** agree well with ones found in closely related molecules [21,22].

On a four-circle Rigaku R-AXIS RAPID-S diffractometer which was equipped with a two-dimensional area IP detector, a single-crystal of the compound **2d** was employed to collect data for the crystal structure determination. In addition, Graphite-monochromated Mo-K_α radiation (l = 0.71073 Å) and oscillation scans technique with D*w* = 5° for one image were also utilized for collecting some data. Using the least-squares (LS) methods on the basis of reflections with $F^2 > 2s(F^2)$, the lattice parameters



Scheme 2

were estimated. CrystalClear (Rigaku/MSC Inc., 2005) software was applied for integration of the intensities, correction for Lorentz and polarization effects, and cell refinement [23]. Direct methods using SHELXS-97 were used to solve the structures [24], which permitted for the location of the heaviest atoms. In this case, the remaining non-hydrogen atoms were located from different Fourier maps which were calculated using some successive full-matrix least squares refinement cycles on F^2 using SHELXL-97 [24]. Anisotropic displacement parameters were utilized to refine all non-hydrogen atoms. Appropriate HFIX instructions in SHELXL were employed to attach hydrogens to carbons located at their geometric positions. It should be reported that no peaks of chemical significance were observed in the final difference Fourier maps. Crystal data for **2d**: $C_{19}H_{18}N_2O_5$, crystal system, space group: monoclinic, $P2_1/n$; (no:14); unit cell dimensions: a = 9.213(2), b = 16.571(4), c = 12.034(2) Å, α = 90, β = 112.059(6), γ = 90°; volume: 1721.2(6) Å^3; Z = 4; calculated density: 1.367 g/cm^3; absorption coefficient: 0.10 mm^{-1}; F(000)= 744; θ-range for data collection 2.1–25.5°; refinement method: full matrix least-square on F^2; data/parameters: 3171/239; goodness-of-fit on F^2: 1.168; final R-indices [I > 2s(I)]: R_1 = 0.076, wR_2 = 0.182; largest diff. peak and hole: 0.366 and –0.311 e Å^{-3}. The Cambridge Crystallographic Data Center as supplementary publication no. CCDC-1841461 was used to deposit crystallographic data for the structure **2d**. Copies of these utilized data are available by application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; FAX: (+44) 1223 336033, or online via www.ccdc.cam.ac.uk/data_request/cif, or by sending emails to data_request@ccdc.cam.ac.uk

Conclusion

In closing, an easy and efficient technique has been proposed for the one-pot synthesis of novel compounds of hexahydroacridine-1,8(2*H*,5*H*)-dione and octahydroacridin-10(1*H*)-yl) thiourea derivatives by the reaction of octahydro-1*H*-xanthenes with hydroxylamine hydrochloride and thiosemicarbazide in ethylene glycol, which is a green solvent. The main advantages of this protocol are as follows: (i) it is a simple procedure under mild reaction conditions; (ii) high yields of the products are obtained; (iii) reaction times are short; (iv) it uses hydroxylamine hydrochloride and thiosemicarbazide as commercially available, inexpensive, and easy-to-handle reagents; especially in comparison with a large number of nitrogen sources.

Experimental

Materials and apparatus

The 1,3-cyclohexanedione, aldehyde derivatives, triethylamine, hydroxylamine hydrochloride, thiosemicarbazide, and solvents were purchased from Merck and Aldrich. They were used without any further purification. Cyanogen bromide was also synthesized using reported literature [25]. Thin-layer chromatography (TLC), carried out on silica gel plates (SILG/UV 254, Merk) using UV light as the visualizing agent, was used to monitor the reactions.

Electrothermal 9100 apparatus were employed to measure the melting points. On a Nexus 670 model Bruker FT-IR spectrophotometer, KBr pellets were used to record IR spectra. A Bruker Advance 300 MHz (300 MHz for ^{1}H) was also used to record ^{1}H NMR and ^{13}C NMR spectra. Chemical shifts were recorded in ppm downfield from tetramethylsilane and coupling constants *J* are reported in Hz. Abbreviations used in ^{1}H NMR are s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet).

General reaction procedure

Synthesis of the 4a-hydroxy-9-aryl-3,4,4a,5,6,7,9,9a-octahydro-1*H*-xanthene-1,8(2H)-dione 1 Triethylamine (2.6 mmol) was added to a stirring mixture of 1,3-cyclohexanedione (4.0 mmol) and aldehyde derivative (2.0 mmol) in methanol (10.0 mL) and stirred for 20 min. Then, the reaction mixture was added dropwise to cyanogen bromide (2.0 mmol) in methanol (4.0 mL) and the mixture was stirred in an ice bath. Monitoring of the reaction with TLC analysis (*n*-hexane/EtOAc (10/8) showed the reaction was completed within 24 h. After the reaction had reached completion, the solvent was removed under reduced pressure and afforded the octahydro-1*H*-xanthene products in good to excellent yields. Reaction products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectrometry.

Synthesis of the compounds 2

A mixture of octahydro-1*H*-xanthene **1** (0.31 mmol) and hydroxylamine hydrochloride (0.31 mmol, 0.02 g) in ethylene glycol (8 mL) was stirred at 100°C, for an appropriate time. The reaction progress was monitored by TLC analysis (*n*-hexane/EtOAc (6/3). After the reaction had reached completion, the reaction mixture was cooled to room temperature and then, it was extracted with H_2O and CH_2Cl_2. Under reduced pressure, the organic layer was evaporated and then, it afforded the xanthene oxime **2** products in good to excellent yields. Reaction products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectrometry.

10-Hydroxy-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione 2a [18] (Table 1, entry 1): Green solid, mp: 238–239 °C.

FT-IR (KBr): υ (cm^{-1}) = 3402, 2943, 2880, 1618, 1362, 1302, 1234, 1177, 1127, 943, 903, 770. ^{1}H NMR (300 MHz in $CDCl_3$): δ (ppm) = 10.75 (s, 1H, OH), 7.20-7.04 (m, 5H), 5.06 (s, 1H, OH), 2.85-2.79 (m, 2H), 2.64-2.49 (m, 2H), 2.26-2.08 (m, 4H), 2.01-1.99 (m, 1H), 2.01-1.78 (m, 4H). ^{13}C NMR (75 MHz in DMSO-d_6): δ (ppm) = 194.92, 154.62, 146.44, 129.44, 129.38, 128.54, 127.48, 127.41, 126.44, 125.15, 110.89, 110.83, 36.67, 30.52, 30.48, 26.11, 25.23, 24.00, 21.21, 20.74, 19.56.

10-Hydroxy-9-(2-nitrophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione 2b (Table 1, entry 2): Brown solid, mp: 225 °C.

FT-IR (KBr): υ (cm^{-1}) = 3405, 2946, 2884, 1698, 1527, 1447, 1345, 1240, 1168, 1129, 1060, 940, 866, 785, 757, 700, 637,543. ^{1}H NMR (300 MHz in DMSO-d_6) δ (ppm) = 10.58 (s, 1H, OH), 8.17-7.77 (m, 3H), 7.74-6.92 (m, 10H), 4.8 (s, 1H, OH), 4.01-3.90 (m, 2H), 3.10-2.86 (m, 3H), 2.37-2.74 (m, 17H), 1.73-1.02 (m, 12H). ^{13}C NMR (75 MHz in DMSO-d_6): δ (ppm) = 197.80, 173.06, 163.64, 160.61, 159.95, 158.71, 158.856, 154.27, 152.09, 150.107, 149.78, 149.17, 148.708, 148.12, 147.56, 146.71, 137.70, 136,63, 135.288, 133.646, 133.236, 132.17, 130.34, 129.80, 128.88, 128. 412, 127.89, 127.433, 126.88, 126.68, 126.59, 126.369, 126.59, 126.37, 125.87, 124.79, 124.60, 124.43, 123.39, 122.82, 122.25, 108.16, 107.823, 107, 67.86, 66.11, 65, 64.36, 63.84, 63.11, 61.21, 59.42, 57.61.

10-Hydroxy-9-(4-nitrophenyl)-3,4,6,7,9,10-hexahydroacridine 1,8(2*H*,5*H*)-dione 2d (Table 1, entry 4): Yellow solid, mp: 245 °C.

FT-IR (KBr): υ (cm^{-1}) = 3432.9, 2930.9, 2702.9, 1643.2, 1514, 1351.6, 1231.6, 1175.4, 1126.9, 955.8, 909.5, 824.4, 699.6, 595.7, 537.6. ^{1}H NMR (300 MHz in DMSO-d_6) δ (ppm) = 10.84 (s, 1H, OH), 8.07 (d, 2H, *J* =8.1Hz), 7.48-7.36 (m, 3H), 5.15 (s, 1H, OH), 2.86-2.80 (m, 2H), 2.65-2.49 (m, 8H), 2.24-1.82 (m, 4H). ^{13}C NMR (75 MHz in DMSO-d_6): δ (ppm) = 196.73, 194.89, 165.80, 155.18, 153.93, 131.01, 129.94, 127.79, 124.82, 124.66, 122.73, 122.53, 114.84, 109.85, 36.50, 35.28, 31.55, 26.99, 26.07, 25.33, 24.17.

9-(4-Fluorophenyl)-10-hydroxy-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione 2e (Table 1, entry 5): White solid, mp: 210 °C.

FT-IR (KBr): υ (cm^{-1}) = 3414, 2943, 2885, 2705, 1643, 1602, 1510, 1364, 1308, 1232, 1177, 1133, 956, 907, 839, 688, 605, 545. ^{1}H NMR (300 MHz in DMSO-d_6) δ (ppm) = 10.77 (s, 1H, OH), 7.11-6.99 (m, 6H), 5.04 (s, 1H, OH), 2.83-2.78 (m, 2H), 2.62-2.48 (m, 2H), 2.22-1.94 (m, 6H), 1.94-1.77 (m, 7H). ^{13}C NMR (75 MHz in DMSO-d_6): δ (ppm) = 194.92, 154.66, 142.61, 131.32, 130.28, 128.13, 116.28, 116.05, 115.83, 114.06, 110.78, 36.61, 31.61, 30.04, 25.99, 24.64, 23.99, 31.30.

4.2.3 Synthesis of the 1-(1,8-dioxo-9-aryl-2,3,4,5,6,7,8,9-octahydroacridin-10(1*H*)-yl)thiourea derivatives 3 A mixture of octahydro-1*H*-xanthene **1** (0.25 mmol) and thiosemicarbazide (0.25 mmol, 0.02 g) in ethylene glycol (8 mL) was stirred at 100°C, for a suitable period of time. TLC analysis (*n*-hexane/EtOAc (9/3)

was used to monitor the reaction progress. After the reaction had reached completion, the reaction mixture was cooled to the room temperature and then it was filtered. The products were washed with deionized water and dried in air. This afforded the thiosemicarbazone **3** products in good to perfect yields. Reaction products were characterized by IR. But we could not take ^{1}H NMR and ^{13}C NMR spectrometry from thiosemicarbazone **3** products, because these compounds were insoluble in DMSO solvent.

1-(1,8-Dioxo-9-phenyl-2,3,4,5,6,7,8,9-octahydroacridin-10(1*H*)-yl)thiourea 3a (Table 1, entry 6): Yellow solid, mp: 257 °C. FT-IR (KBr): υ (cm^{-1}) = 3684, 3441, 3074, 2944, 2886, 1660, 1362, 1179, 1131, 958, 704, 622, 543.

1-(9-(2-Nitrophenyl)-1,8-dioxo-2,3,4,5,6,7,8,9-octahydroacridin-10(1*H*)-yl)thiourea 3b (Table 1, entry 7): Yellow solid, mp: 231–234 °C. FT-IR (KBr): υ (cm^{-1}) = 3428, 3256, 3146, 2984, 2811, 1590, 1530, 1461, 1370, 1284, 1094, 820, 468.

1-(9-(2,4-Dichlorophenyl)-1,8-dioxo-2,3,4,5,6,7,8,9-octahydroacridin-10(1*H*)-yl)thiourea 3f (Table 1, entry 8): Brown solid, mp: 229-231 °C. FT-IR (KBr): υ (cm^{-1}) = 3739, 3452, 3078, 2962, 2897, 1662, 1622, 1520, 1361, 1202, 1178, 1130, 1013, 962, 786, 616, 539.

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