Synthesis and antimicrobial studies of some acridinediones and their thiourea derivatives

T. Josephrajan,[a] V. T. Ramakrishnan,*[a] G. Kathiravan,[b] and J. Muthumary[b]

[a] *Department of Organic Chemistry*
[b] *CAS in Botany*
University of Madras, Guindy Campus, Chennai- 600 025, India
E-mail: vtrk28@yahoo.com

Dedicated to Professor S. Swaminathan on his 80th birthday occasion

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Abstract
Acridinediones containing thiourea and piperazine moieties, and vanilline derived acridinediones were synthesised. Antimicrobial activities of eight acridinediones were studied against four vibrio isolates.

Keywords: Acridinediones, thiourea, geminal coupling, antimicrobial

Introduction

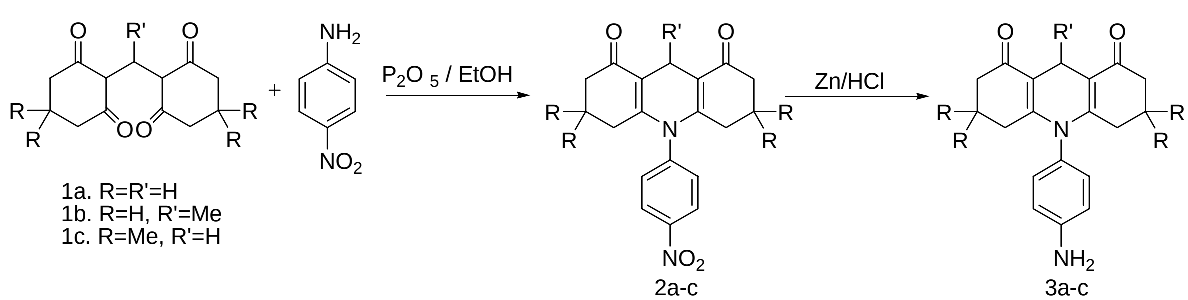
Anions play numerous fundamental roles in biological and chemical processes 1; for example, the majority of enzymes bind anions as either substrates or cofactors. In addition, the importance of being able to detect and or extract certain environmental anionic pollutants such as nitrate, phosphate and radioactive pertechnetate produced in the nuclear fuel cycle, has only recently been recognized. Recently a chromogenic azophenol- thiourea based anion sensor was reported 2.

Chromogenic receptors for biologically important substrates are one of the current areas of research. A wide variety of chromophores for cations such as alkali and alkaline earth metal ions have been reported. In contrast, only a few chromophores have been reported for the colorimetric determination of anions in the solution. The thiourea group as hydrogen bond donor has recently drawn much interest as a functional group for neutral receptors to recognize mono and dicarboxylate anions, halide ions, sulphates and dihydrogen phosphates 3, 4, 5.

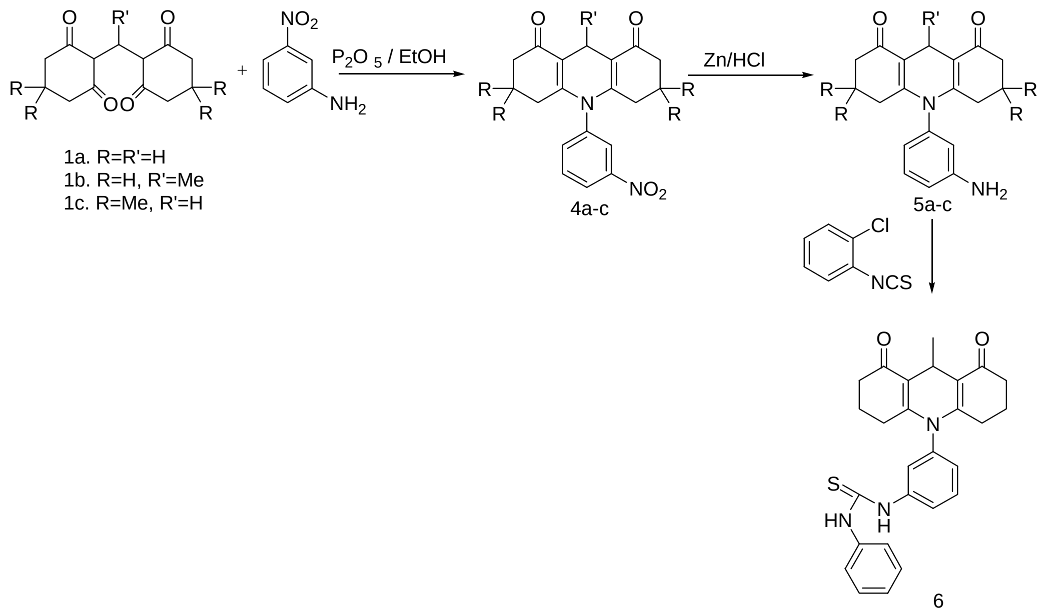
Molecular recognition 3 is a subject of considerable interest because of its implications in many fields: biology, medicine, environment, etc. In particular, the detection of metal cations involved in biological processes (e.g., sodium, potassium, calcium, magnesium), in clinical diagnostics (e.g., lithium, potassium, aluminium), or in pollution (e.g., lead, mercury, cadmium) has received considerable attention. Among the numerous methods employed, fluorescent sensors offer distinct advantages in terms of sensitivity and specificity. 4-Aryl-1, 4-dihydropyridines, also known as Hantzsch esters, have proved valuable as drugs for the treatment of cardiovascular disorders 6, 7 and constitute an important class of calcium channel blockers 8-11. The relationship between conformation and pharmacological effect in 1,4-dihydropyridines (1,4-DHPs) nifedipine-like compounds has been reported 12. Thus, 4-aryl substituted 1,4-DHPs with calcium antagonist properties exist as a boat conformation in which the aryl substituent is in pseudoaxial position, orthogonal to the dihydropyridine plane 13. Previous reports described the synthesis of 1,4-DHPs fused to one 14 or two 15 cyclohexanone rings, which present a positive ionotropic effect promoting (instead of blocking) the entry of calcium to the intracellular space (calcium antagonist effect) 16.

In continuation of our work 17-19 on the synthesis of acridinediones as laser dyes, we herein report the synthesis of acridinediones containing thiourea moiety and piperazine moiety as potential fluorescent chemosensors.

Reaction of tetraketones **1a-c** with *p*-nitroaniline in ethanol with a catalytic amount of P_2O_5 afforded 10- (4-nitrophenyl)-3,4,6,7,9,10-hexahydro-1,8(2H, 5H) acridinediones (**2a-c**). The nitro compounds **2a-c** were reduced with zinc and HCl in refluxing ethanol to afford the corresponding 10-(4-aminophenyl)-3,4,6,7,9,10-hexahydro acridinediones **3a-c**. The reaction of 10-(*p*-aminophenyl) acridinediones **3a-c** with 2-chlorophenyl isothiocyanate in refluxing ethanol did not give the thiourea derivative. Various attempts with other base catalyzed conditions were also unsuccessful. The poor nucleophilicity of the amino group could be due to its position para to the acridine nitrogen in compounds **3a-c**. Hence, the tetraketones **1a-c** were condensed with 3-nitroaniline to afford the 10-(3-nitrophenyl) acridinediones **4a-c** which on reduction with Zn and HCl afforded the 10-(3-aminophenyl) acridinediones **5a-c**. Reaction of compound **5b** with *o*-chlorophenyl isothiocyanate in refluxing ethanol afforded N-(2-chlorophenyl)-N‘-[3-(9-methyl-3,4,6,7,9,10-hexahydro-1,8(2H,5H)acridinedione-10-yl)-phenyl] thiourea (**6)**.

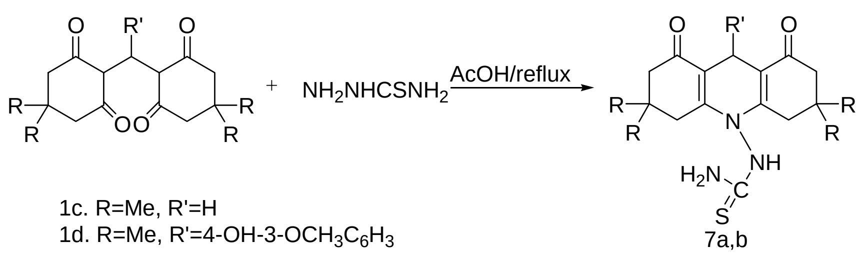


Scheme 1



Scheme 2

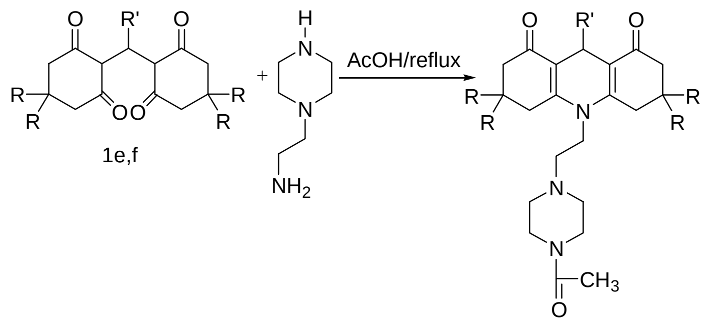
Next the reaction of tetraketone **1c** with thiosemicarbazide was carried out to afford N-(3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-1,8(2H,5H) acridinedione-10-yl)thiourea **(7a)**. Similarly tetraketone **1d** gave the product **7b**.The condensation of N-aminoethyl piperazine with the tetraketones **1e,f** in acetic acid was carried out to afford the acridinediones **8a,b** in which the N-acetylation of the piperazine ring has also occurred. The two products **8a,b** showed good fluorescence. Based on the importance of 4-aryl-dihydropyridines, the tetraketone **1d** was reacted with different amines to obtain 9-(4-hydroxy-3-methoxyphenyl acridinediones **9a-f**. As examples of hydroxyl group substituted acridinediones, *p*-aminophenol and tyramine were reacted with tetraketones **1a-c** to obtain compounds **10a-d**.



Scheme 3

Table 1

Compound	R	R′
1c, 7a	Me	H
1d, 7b	Me	4-OH-3-OCH_3 C_6H_3

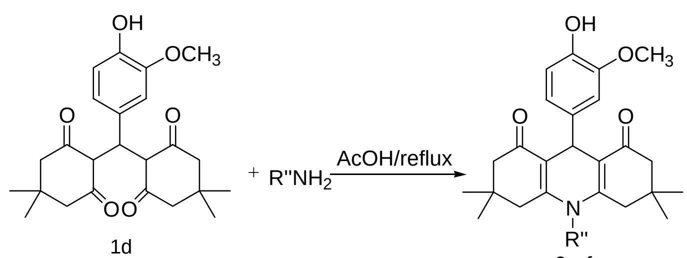


Scheme 4

Table 2

Compound	R	R′
1e, 8a	Me	4-$CH_3OC_6H_4$
1f, 8b	Me	4-ClC_6H_4

Condensation of dimedone with vanillin furnished 2,2’-(4-hydroxy-3-methoxybenzylidene) bisdimedone 20 (**1d**), which on reaction with ammonium acetate or amines afforded the respective 9- (4-hydroxy-3-methoxyphenyl)-10-substituted-3, 3, 6, 6-tetramethyl-3, 4, 6, 7, 9, 10-hexahydro-1, 8 (2H, 5H) acridinedione (9**a-f**).



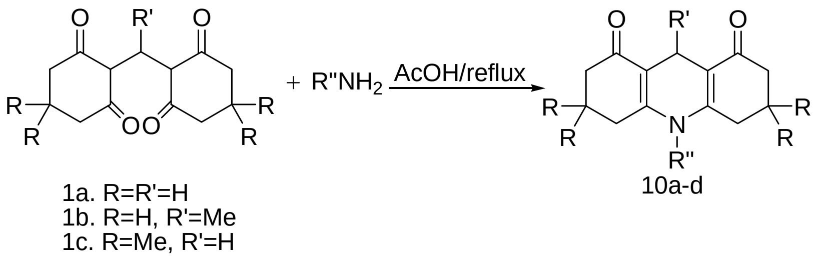
Scheme 5

Table 3

Compound **9**	R″
a	H
b	CH_2COOH
c	4-CH_3-C_6H_4
d	4-CH_3-O-C_6H_4
e	Ph
f	3,4-$(CH_3)_2$ C_6H_3

The NMR spectrum of 9-arylacridinediones **9a-f** exhibited geminal coupling of C_2, C_7 & C_4, C_5 methylene protons; two sets of two doublets were seen for all the compounds **9a-f** for the methylene protons. In the IR spectra, all the acridinediones showed absorptions in the 1650 Cm^{-1} region for the carbonyl group due to the vinylogous amide nature.

Reaction of tetraketone **1a,c** with *p*-aminophenol afforded the acridinedione **10a,b**. Likewise, tetraketones **1c,b** afforded the acridinediones **10c,d** on reaction with tyramine.



Scheme 6

Table 4

Compound **10**	R	R′	R″
a	H	H	4-(OH)C_6H_4
b	Me	H	4-(OH)C_6H_4
c	Me	H	4-(OH)$C_6H_4CH_2CH_2$
d	H	Me	4-(OH)$C_6H_4CH_2CH_2$

Biological studies of synthesized acridinediones

In human pathogenic bacteria, diseases attributed to *Vibrio* spp. (Vibriosis) 21 are considered to be the most common and significant infectious problems.

Acridines, the earliest known antibiotics, 22-24 are toxic towards bacteria and particularly towards malarial parasite due to their ability to inhibit DNA and RNA synthesis. The eight compounds listed in the tables (**3b, 3c, 4a, 9a, 9b, 9d, 10c, 10d**) were screened for the antimicrobial activity against different Vibrio isolates under the following conditions.

Method: Well diffusion method, Medium: The nutrient agar medium, Solvent: Chloroform. Concentrations:50µM and 100 µM. Condition: 24 hours at 24-28°C, Standard: The antibiotic Streptomycin

The nutrient agar medium, 20 mL was poured into the sterile petri dishes. To the solidified plates, wells were made using a sterile cork borer 10 mm in diameter. The 24 hour subcultured bacteria was inoculated in the petri-plates, with a sterile cotton swab dipped in the nutrient broth medium. After inoculating, the compounds were dissolved separately with the chloroform solvent and poured into the wells with varying concentrations ranging from 50 & 100 µM using a micropipette.

The plates were left over for 24 hours at 24-28 °C. The antibiotic Streptomycin was used as a standard for comparative study. The percentage of inhibition was calculated by the formula

$$\% \text{ Inhibition} = \frac{\text{Diameter of the inhibition zone x 100}}{\text{Diameter of the petri-plate}}$$

From this data, it has been found that all the compounds tested showed broad spectrum of inhibitory properties. The compound **9b** & **9d** showed good inhibition zone on the pathogen *Vibrio* isolate-I and moderate activity against the other isolates. The rest of the compounds have moderate activity against *Vibrio* isolate-I. The activity of compounds were diminished with *Vibrio* isolate-IV. Compounds **9a** & **10c** showed good activity against *Vibrio* isolate-II.

Table 5. Effect of acridinediones (50,100uM) concentrations on Vibrio isolates I-IV

Vibrio Isolate	Standard A uM (%I)	**3b**	**3c**	**4a**	**9a**	**9b**	**9d**	**10c**	**10d**
I		55	41	58	53	66	70	49	48
	27.5	(64	54	63	62	71	81	58	60)
II		50	47	69	72	63	53	84	55
	23.1	(62	54	77	80	70	62	90	67)
III		39	44	39	38	48	42	53	38
	19.3	(47	65	50	52	54	55	59	46)
IV		38	55	36	44	31	29	33	39
	21.8	(49	68	52	60	46	38	44	52)

A: Antibiotic streptomycin; I: Inhibition zone; %I: Percentage of Inhibition

Experimental Section

General Procedures. Melting points were determined by using a Toshniwal melting point apparatus in an open capillary tube and are uncorrected. IR spectra were recorded in Nicolet Impact 400 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR were recorded on Jeol GSX 400 MHz using TMS as internal standard. GC/MS data were obtained from a Jeol-DX-303 spectrometer. Microanalyses were performed in a Perkin-Elmer 240B element analyzer.

Preparation of 4- hydroxy-3-methoxybenzylidene bisdimedone (1d). To a solution of dimedone (4.0 g, 0.029 mol) in aq. methanol was added vanillin (2.17 g, 0.014 mol) and warmed until the solution became cloudy. The 4-hydroxy-3-methoxybenzylidene bisdimedone (1d) started to separate out. The reaction mixture **was diluted with water** (50 ml) and allowed to

stand overnight; the tetraketone 1d was collected by filtration and dried and recrystallized from methanol.
Yield: 5.56 g, 94 %; mp; 181-183° C (Lit. mp. 195.5-196.5° C) [20]
All other tetraketones were prepared as per literature procedure. [20]

General procedure for the synthesis of nitroacridines 2b,c & 4b,c

A mixture of tetraketone 1(a-c) (3.4 mmol) and nitroaniline (3.4 mmol) in ethanol (40 ml) was stirred at room temperature with a catalytic amount of P_2O_5 for 10 hours. The reaction mixture was concentrated and poured into cold water (100 ml). The yellow solid obtained was filtered, dried and recrystallized from chloroform-methanol to obtain the respective acridinedione. Syntheses of compounds 2a [17] and 4a [19] were reported earlier.

9-Methyl-10- (4-nitrophenyl)-3,4,6,7,9,10-hexahydro-1,8(2*H*, 5*H*)acridinedione (2b). Yield 69 %; yellow; mp 210-212 ° C; IR (KBr) 1637, 1580, 1531, 1374, 1345 cm^{-1} ; ^1H NMR (90 MHz, $CDCl_3$) δ 1.01 (d, 3H, J = 6.1 Hz), 1.80-2.06 (m, 8H, C_2, C_3, C_6 & C_7-CH_2), 2.25-2.40 (m, 4H, C_4 & C_5-CH_2), 4.13 (q, 1H, C_9-CH), 7.51 (d, 2H, J = 9.5 Hz, Ar-H), 8.38 (d, 2H, J = 9.5 Hz, Ar-H); MS (%) 352 (M^+,10.1), 338 (83.3), 337 (100),336 (3.1), 335 (3.6), 321 (4.7), 309 (3.2), 307 (20.4), 291(89.7), 55 (48). $C_{20}H_{20}N_2O_4$ requires: C, 68.16; H, 5.72; N, 7.94; found: C, 68.07; H., 5.46; N, 7.68.

10-(4-Nitrophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-1,8(2*H*,5*H*)acridinedi one (2c). Yield 85 %; yellow; mp 265-267 ° C; IR (KBr) 1660, 1580, 1530, 1375, 1350 cm^{-1} ; ^1H NMR (90 MHz, $CDCl_3$) δ 0.97 (s, 12H, *gem*-dimethyl), 1.80 (s, 4H, C_2 & C_7-CH_2), 2.25 (s, 4H, C_4 & C_5-CH_2), 3.21 (s, 2H, C_9-CH_2), 7.52 (d, 2H, J=9.8 Hz, Ar-H), 8.41 (d, 2H, J=9.8 Hz, Ar-H); MS (%) 394 (M^+, 38.2), 393 (8.2), 377(9.6), 364(10.3), 257(13.8), 256(8.7), 138 (13.2), 105 (100), 83 (26.8), 69 (40). $C_{23}H_{26}N_2O_4$ requires: C, 70.03; H, 6.64; N, 7.10; found: C, 69.76;H, 6.47; N, 6.93.

9-Methyl-10- (3-nitrophenyl)-3,4,6,7,9,10-hexahydro-1,8(2*H*, 5*H*) acridinedione (4b). Yield 79 %; yellow; mp 197-199 ° C; IR (KBr) 1665, 1575, 1535, 1368, 1340 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.06 (d, 3H, J = 7.35 Hz,CH_3), 1.9-2.06 (m, 8H, C_2, C_3, C_6 & C_7-CH_2), 2.30-2.51 (m, 4H, C_4 & C_5-CH_2), 4.11(q, 1H, C_9-CH), 7.51-8.53 (m, 4H, Ar-H); MS (%) 352 (M^+, 4.1), 350 (4.3), 337 (77.6), 336 (7.4), 335 (27.8), 321 (3.3), 307 (10.8), 291 (24), 217 (100), 215 (25.6), 189 (5.6), 175 (7.5), 161 (4.5), 159 (3.7), 145 (4.8), 138 (9.4), 105 (5.2), 55 (23.9). $C_{20}H_{20}N_2O_4$ requires: C, 68.16; H, 5.72; N, 7.94; found: C, 68.02; H, 5.84; N,7.78.

10-(3-Nitrophenyl)-3,3,6,6-tetramethyl--3,4,6,7,9,10-hexahydro-1,8(2*H*,5*H*)acridine dione (4c). Yield 78 %; yellow; mp above 300 ° C; IR (KBr) 1632, 1545, 1534, 1387, 1365 cm^{-1} ; ^1H NMR (90 MHz, $CDCl_3$) δ 0.94 (s, 12H, *gem*-dimethyl), 1.75 (br s, 4H, C_2 & C_7-CH_2), 2.10-2.40 (2d, 4H, C_4 & C_5-CH_2), 3.25 (s, 2H, C_9-CH_2), 7.66-8.41(m, 4H,Ar-H); MS (%) 394 (M^+, 100), 393 (23.4), 379 (18), 378 (11.5), 377 (36.2), 365 (7.9), 364 (14.1), 363 (9.2), 351(6.9), 349 (16), 348 (12.8), 347 (26.8), 337 (9.7), 331 (12.4), 323 (9.7), 256 (8.8), 83 (21.6), 69 (10.2), 55 (34.4). $C_{23}H_{26}N_2O_4$ requires: C, 70.03; H, 6.64; N, 7.10; found: C, 69.80; H, 6.85; N, 7.32.

General procedure for the synthesis of aminoacridinediones3a-c & 5a-c

The nitroacridinedione **2a** (1.0 g, 2.95 mmol) was dissolved in ethanol (40 ml) and 5 g of zinc dust was added; a few drops of con. HCl was added and.the mixture refluxed for 5 hours. After the completion of the reaction, the zinc dust was filtered off, the filtrate concentrated, and water (50ml) added. The solid was filtered, dried, and purified by column chromatography using neutral alumina and eluting with chloroform to isolate the amino compound **3a**.

10-(4-Aminophenyl)-3,4,6,7,9,10-hexahydro-1,8(2*H*, 5*H*) acridinedione (3a). Yield 71 %; brown; mp 251-253 ° C; IR (KBr) 3433, 3351, 1631, 1514, 1384 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.80-2.10 (m, 8H, C_2, C_3, C_6 & C_7), 2.20-2.40 (m, 4H, C_4, C_5), 3.22 (s, 2H, C_9-CH_2), 4.01 (br s, 2H, NH_2, exchanged with D_2O), 6.73-7.03 (2d, 4H, Ar-H); MS (%) 308(M^+, 100), 307 (100), 306 (46), 292 (4.8), 291 (13.5), 279 (7.3), 277(8.4), 265 (6), 251 (11), 249 (8.8), 223 (5.2), 214 (4), 202 (7.4), 195 (10.6), 154 (3), 106 (49.8). $C_{19}H_{20}N_2O_2$ requires: C, 74.00; H, 6.53; N, 9.08; found: C, 74.43; H, 6.86; N, 8.80.

10-(4-Aminophenyl)-9-methyl-3,4,6,7,9,10-hexahydro-1,8(2*H*,5*H*)acridinedione (3b). Yield 77 %; greenish yellow; mp 260-262 ° C; IR (KBr) 3420, 3340, 1680, 1560, 1380 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, 3H, *J* = 6.3 Hz, CH_3), 1.75-2.44 (m, 12H, C_2, C_3, C_4, C_5, C_6 & C_7-CH_2), 4.12-4.17 (q, 1H, *J* = 6.26 Hz, C_9-CH), 6.74 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.10 (d, 2H, *J* = Hz, Ar-H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 21.3 (CH_2), 21.5 (CH), 22.8, (CH_3), 28.0 (CH_2), 36.8 (CH_2), 115.5 (CH), 116.7 (C), 129.2 (C), 129.9 (C), 130.4 (CH), 147.1 (C), 196.6 (C); .MS (%) 307 (M^+-CH_3, 100). $C_{20}H_{22}N_2O_2$ requires: C, 74.50; H, 6.87; N 8.68; found: C, 74.09; H, 6.73; N, 8.47.

10-(4-Aminophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-1,8(2*H*,5*H*) acridine dione (3c). Yield 76 %; brown; mp 290-292°C; IR (KBr) 3432, 3320, 1631, 1555, 1385 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 12H, *gem*-dimethyl), 1.85 (s, 4H, C_2, C_7-CH_2), 2.21 (s, 4H, C_4, C_5-CH_2), 3.21 (s, 2H, C_9-CH_2), 4.03 (s, 2H, NH_2), 6.74 (d, 2H, *J* = 8.3 Hz, Ar-H), 6.89 (d, 2H, *J* = 8.3 Hz, Ar-H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 18.5 (C_9-CH_2), 28.3 (CH_3), 32.1 (C), 41.7 (C_2-CH_2), 49.9 (C_4-CH_2), 110.6 (C), 115.5 (CH), 129.4 (C), 130.4 (CH), 146.9 (C), 151.9 (C), 196.8 (C); MS (%) 364(M^+, 98.2), 363 (33.8), 349(17.4), 348 (14.7), 347 (29.8), 333 (9.8), 320 (10.8), 280 (10.1), 195 (15.1), 106 (9.3). $C_{23}H_{28}N_2O_2$ requires C, 75.79; H, 7.74; N, 7.68; found C, 75.44; H, 7.69; N, 7.49.

10-(3-Aminophenyl)-3,4,6,7,9,10-hexahydro-1,8(2*H*,5*H*) acridinedione (5a). Yield 71 %; brown; mp 247-249 ° C; IR (KBr) 3435, 3350, 1665, 1575, 1360 cm^{-1} **;** ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 12H, *gem*-dimethyl), 1.82-2.56 (m, 12H, C_2, C_3, C_4, C_5, C_6 & C_7-CH_2), 3.21 (s, 2H, C_9-CH_2), 3.98 (br s, 2H, Ar-NH_2), 6.45-7.27 (m, 4H, Ar-H); MS (%) 308 (M^+, 80), 307 (28), 292 (8.4), 251 (20), 214 (10), 195 (15), 154 (7), 106 (65). $C_{19}H_{20}N_2O_2$ requires: C, 74.00; H, 6.53; N, 9.08 ; found C,73.72; H, 6.68; N, 8.87.

10-(3-Aminophenyl)-9-methyl-3,4,6,7,9,10-hexahydro-1,8(2*H*,5*H*)acridinedione (5b). Yield 75 %; brown; mp 274-276 °C; IR (KBr) 3420, 3378, 1675, 1550, 1360 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ 0.91 (d, 3H, *J*=6.35 Hz, CH_3), 1.78-1.91 (m, 4H, C_3, C_6-CH_2), 2.06-2.35 (m, 8H, C_2, C_4, C_5 & C_7-CH_2), 3.99 (q, 1H, *J* = 6.8 Hz, C_9-CH), 4.96 (br s, 2H, NH_2), 6.43-7.89

(m, 4H, Ar-H). $C_{20}H_{22}N_2O_2$ requires: C, 74.50; H, 6.87; N, 8.68; found C, 74.37; H, 6.92; N, 8.54.

10-(3-Aminophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-1,8(2*H*,5*H*) acridine dione (5c). Yield 71 %; brown; mp 252-254 ° C; IR (KBr) 3432, 3351, 2949, 1631, 1385 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 12H, gemdimethyl), 1.90 (s, 4H, C_2 & C_7-CH_2), 2.21 (s, 4H, C_4 & C_5-CH_2), 3.21 (s, 2H, C_9-CH_2), 3.98 (s, 2H, Ar-NH_2); 6.45-7.27 (m, 4H, Ar-H); ^{13}C NMR (100.4 MHz, $CDCl_3$) : δ 18.5 (C_9-CH_2), 28.3 (CH_3), 32.3 (C), 41.5 (C_2-CH_2), 50.0 (C_4-CH_2), 110.6 (C), 115.5 (CH), 115.7 (CH), 119.4 (CH), 130.5 (CH), 140.1 (C), 148.0 (C), 151.2 (C), 196.7 (C); MS (%) 364 (M^+, 100), 363 (14), 349 (17.1), 348 (13), 280 (6), 134 (35.9). $C_{23}H_{28}N_2O_2$ requires: C, 75.79; H, 7.74; N, 7.68; found: C, 75.47; H, 7.83; N, 7.52.

***N*-(2-Chlorophenyl)-N'-[3-(9-methyl-3,4,6,7,9,10-hexahydro-1,8(2*H*,5*H*)acridinedi one-10-yl)-phenyl] thiourea (6).** The acridinedione 5b (1.0g, 3.1mmol) and 2-chlorophenyl isothiocyanate (0.52 g, 3.1mmol) on refluxing in ethanol for 9 hours furnished the thiourea 6.Yield 72 %; brown; mp 238-240 ° C; IR (KBr) 3425, 3378, 1665, 1441, 1372 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, 3H, J=7.8 Hz, CH_3), 1.81-2.43 (m, 12H, C_2, C_3,C_4, C_5, C_6 & C_7-CH_2), 3.48 (br s, 2H, NH, exchanged with D_2O), 4.12 (q, 1H, J=7.6Hz, C_9-CH), 6.51-7.81 (m, 8H, Ar-H); MS (%) 380 (7.1), 379 (27.5) , 322 (5.5), 307 (100), 216 (3.4), 214 (4.7). $C_{27}H_{26}N_3O_2SCl$ requires: C, 65.90; H, 5.32; N, 8.53; found: C, 65.59; H, 5.30; N, 8.32.

General procedure for the synthesis of thioureas 7a,b

A mixture of the tetraketone **1c** (**1d**) (3.4 mmol) and thiosemicarbazide (3.4 mmol) was refluxed in acetic acid (15ml) for 14 hours. The reaction mixture was cooled and poured into crushed ice. The solid obtained was $CHCl_3$-MeOH (8:2), to isolate the thiourea **7a** (**7b**).

***N*-(3,3,6,6-Tetramethyl-3** filtered and purified by column chromatography over silica gel and eluted with**,4,6,7,9,10-hexahydro-1,8(2*H*,5*H*)acridinedione-10-yl)-thiourea (7a).** Yield 74 %; brown; mp 130-132 ° C; IR (KBr) 3420, 3350, 1670, 1445, 1375 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ 1.08 (s, 12H, gem-dimethyl), 2.29 (br s, 8H, C_2, C_4, C_5 & C_7, CH_2), 3.16 (s, 2H,C_9-CH_2), 6.6 (s, NH_2, exchanged with D_2O); MS (%) 313 (14.1), 296 (7.2), 272 (18.1), 271 (68.9), 257 (11.7), 256(35.8), 216 (32.8), 214 (100), 91 (22), 83 (27.1), 69 (29.6). $C_{18}H_{25}N_3O_2S$ requires: C, 62.21; H, 7.25; N, 12.09. found C, 61.93; H, 7.43; N, 11.93.

***N*-[9-(4-Hydroxy-3-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-1,8(2*H*, 5*H*) acridinedione –10-yl] thiourea (7b).** Yield 81%; pale brown; mp 212-214 °C ; IR (KBr) 3450, 3320, 1658, 1434, 1385 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$) δ 0.84 & 1.01 (2s, 12H, gem-dimethyl), 1.95-2.17 (2d, 4H,J=16.1, C_2,C_7-CH_2), 2.21-2.42 (2d, 4H, *J*=17.33, C_4, C_5-CH_2), 3.68(s, 3H, OCH_3), 3.71 (s, 2H, NH_2, exchanged with D_2O), 4.76 (s, 1H, C_9-CH), 6.48-7.0 (m, 3H, Ar-H), 8.1 & 8.2 (br s, NH, exchanged with D_2O); MS (%) 393 (35.9), 272 (26.5), 216 (24.9), 91 (23.8), 83 (54.2), 69 (25.7).

General procedure for the synthesis of acridinedione 8a,b

A mixture of the tetraketone 1e (1f) (2.49 mmol) and *N*-aminoethyl piperazine (2.49 mmol) was refluxed in acetic acid (15ml) for 14 hours. The reaction mixture was cooled and poured into crushed ice. The solid obtained was filtered and purified by column chromatography over silica gel and eluted with $CHCl_3$-MeOH (9:1), to isolate the respective acridinedione 8a (8b).

10-[2-(4-Acetylpiperazin-1-yl)ethyl]-9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6, 7, 9,10-hexahydro-1,8(2*H*, 5*H*) acridinedione (8a). Yield 63%; pale brown; mp 198-200 °C; IR (KBr) 1685, 1665, 1547, 1374 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.00 &1.08 (2s, 12H, gem-dimethyl), 2.09-3.63 (m, 23H, C_2, C_4, C_5, C_7-CH_2, N-CH_2, CH_3CO), 3.71(s, 3H, OCH_3), 5.19 (s, 1H, C_9CH), 6.68 (d, 2H, J=8.7Hz, Ar-H), 7.65 (d, 2H, J=8.3Hz, Ar-H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 21.2, 28.0, 29.2, 30.8, 32.4, 40.5, 42.1, 45.9, 49.8, 53.1, 55.1, 113.2, 115.7, 128.4, 138.1, 149.8, 157.5, 168.9, 195.6; MS 533 (M^+,13.6),491 (35.9), 395 (40.9), 393 (6), 378 (7.3), 362 (4.1), 272 (13.6), 271 (5), 256 (3.4), 83 (13.7), 69 (6.4), 55 (14.4).

10-[2-(4-Acetylpiperazin-1-yl)ethyl]-9-(4-chlorophenyl)-3,3,6,6-tetramethyl-3,4,6, 7,9,10-hexahydro-1,8(2*H*, 5*H*) acridinedione (8b). Yield 75 %; brown; mp 212-214 °C; IR (KBr) 1680, 1658, 1574, 1380 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.00 & 1.09 (2s, 12H,gem-dimethyl), 2.04-2.22 (m, 10H, CH_2), 2.36-2.57 (m, 11H, CH_2), 5.22 (s, 1H, C_9-H), 7.11 (d, 2H, J = 6.3Hz, Ar-H), 7.18 (d, 2H, J = 6.3Hz, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$):21.8, 28.6, 29.9, 32.0, 33.1, 41.7, 42.8, 46.6, 50.4, 54.7, 115.9, 128.6, 129.6, 144.9, 150.6, 169.6, 196.1.MS 537 (M^+, 48), 384 (21.9), 369 (20.6), 272 (34.2), 270 (40.8), 256 (17.9), 83 (28.9), 69 (16.1), 55 (11.3). $C_{31}H_{40}N_3O_3Cl$ requires: C, 69.19; H, 7.49; N, 7.80; found: C, 68.95; H, 7.28; N, 7.62.

9- (4- Hydroxy- 3- methoxyphenyl)- 3, 3, 6, 6-tetramethyl- 3, 4, 6, 7, 9, 10-hexa- hydro-1, 8(2*H*, 5*H*) acridinedione (9a). General procedure.

A mixture of the tetraketone **1d** (2.41 mmol) and the respective amine (2.41 mmol) was refluxed in acetic acid (15ml) for 5-6 hours. The reaction mixture was cooled and poured into crushed ice. The solid obtained was filtered and purified by column chromatography over silica gel and eluting with $CHCl_3$-MeOH (9:1), to isolate the respective acridinedione **9a-f**.

Yield 84 %; yellow; mp 296-298 °C; IR (KBr) 3273, 3167, 1634, 1499 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$-DMSO-d_6) δ 0.95 and 1.07 (2s, 12H, *gem*-dimethyl), 2.06-2.21 (2d, 4H, J = 16.3 Hz, C_4 & C_5 -CH_2), 2.30-2.42 (2d, 4H, J = 17 Hz, C_2 & C_7 -CH_2,), 3.77(s, 3H, OCH_3), 4.85 (s, 1H, C_9-CH), 6.61 (s, 2H, Ar-H), 6.85 (s, 1H, Ar-H), 8.08 (br s, 1H, OH), 8.94 (s, 1H, NH); ^{13}C NMR (100.4 MHz, $CDCl_3$-DMSO-d_6) δ 25.6 (CH_3), 28.3 (CH_3), 31.1 (C), 31.3 (CH), 49.5 (CH_2), 54.4 (OCH_3), 110.9 (CH),111.4 (C), 113.5 (CH), 118.8 (CH), 137.6(C), 142.9 (C),145.4 (C), 147.8(C), 194.0 (CO). MS 395 (93.3, M^+), 394 (16.9), 380 (10.9), 379 (4.1), 378(9), 350 (3.9), 273 (46), 272 (100), 271 (14.3), 256 (9.3), 228 (4.4), 217 (3.2), 189 (3.6), 124 (8.9), 109 (5.8), 81 (4.5), 53 (3); $C_{24}H_{29}NO_4$ requires: C, 72.88; H, 7.39; N, 3.54; found: C, 73.11; H, 7.53; N, 3.26.

9- (4-Hydroxy-3-methoxyphenyl)-10-carboxymethyl-3, 3, 6, 6- tetramethyl-3, 4, 6, 7,9, 10-hexahydro-1, 8(2*H*, 5*H*) acridinedione (9b). Yield 64 %; yellow; mp 237-239 °C; IR (KBr)

3150, 2982, 1720, 1640, 1371 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$-DMSO-d_6) δ 0.97 and 1.07 (2s,12H, *gem*-dimethyl), 2.12-2.22 (2d, 4H, J = 16 Hz, C_4 & C_5-CH_2), 2.35-2.49 (2d, 4H, J = 17 Hz, C_2 & C_7-CH_2), 3.35 (s, 2H, N-CH_2), 3.79 (s, 3H, OCH_3), 5.05 (s, 1H, C_9-CH), 6.61-6.93 (m, 3H, Ar-H); MS 380 (1, M^+-73), 124 (85), 109 (100), 81 (45), 53 (15). The X-ray diffraction studies established the structure of 9b.[25]

9- (4- Hydroxy- 3- methoxyphenyl)-10- (4- methylphenyl)- 3, 3, 6, 6- tetramethyl-3, 4, 6, 7,9, 10- hexahydro-1, 8(2*H*, 5*H*) acridinedione (9c). Yield 77 %; dark brown; mp 176-178°C; IR (KBr) 3404, 2956, 1635, 1364 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$-DMSO-d_6) δ 0.81 and 0.94 (2s, 12H, *gem*-dimethyl), 1.81-2.10 (2d, 4H, J=17.58 Hz, C_4 & C_5-CH_2), 2.10-2.21 (2d, 4H, J=16.6 Hz, C_2 & C_7-CH_2), 2.47 (s, 3H, Ar-CH_3), 3.88 (s, 3H, OCH_3), 5.16 (s, 1H, C_9-CH), 6.50 (s, 1H, OH), 6.75-7.36 (m, 7H, Ar-H); ^{13}C NMR (100.4 MHz, $CDCl_3$-DMSO-d_6) δ 20.9 (Ar-CH_3), 26.3 (CH_3), 29.4 (CH_3), (CH), 32.0 (C), 41.4 (CH_2), 49.9 (CH_2), 55.5 (OCH_3), 111.5 (CH), 114.0 (CH), 114.2 (C), 119.1 (CH), (129.3 (CH) and 130.4 (CH) signals were distorted), 135.9 (C), 138.1 (C), 139.1 (C), 143.6 (C), 146.0 (C), 149.6 (C), 195.7 (CO); MS 485 (56.8, M^+), 362 (66.2). $C_{31}H_{35}NO_4$ requires: C, 76.67; H, 7.26; N, 2.88; found: C, 76.77; H, 7.54; N, 2.29.

9- (4- Hydroxy- 3- methoxyphenyl)- 10-(4-methoxyphenyl)- 3, 3, 6, 6- tetramethyl- 3, 4, 6, 7,9, 10- hexahydro-1, 8(2*H*, 5*H*) acridinedione (9d). Yield 79 %; brown; mp 253-255°C; IR (KBr) 3390, 2967, 1660, 1342 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$-DMSO-d_6) δ 0.82 and 0.95 (2s, 12H, gem-dimethyl), 1.83-2.09 (2d, 4H, J = 17.6 Hz, C_4 & C_5-CH_2), 2.12-2.22 (2d, 4H, J = 16.3 Hz, C_2 & C_7-CH_2), 3.90 & 3.91 (2s, 6H, Ar-OCH_3), 5.18 (s, 1H, C_9-CH), 5.57 (s, 1H, Ar-OH), 6.73-7.13 (m, 7H, Ar-H); ^{13}C NMR (100.4 MHz, $CDCl_3$-DMSO-d_6) δ 26.7 (CH_3), 29.7 (CH_3), 32.0 (CH), 32.2 (C), 41.7 (CH_2), 50.1 (CH_2), 55.5 (OCH_3), 55.7 (OCH_3), 111.8 (CH), 113.8 CH), 114.6 (C), 119.2 (CH), 129.9 (CH), 130.8 (CH), 131.4 (C), 138.6 (C), 143.6 (C), 145.8 (C), 150.0 (C), 159.7 (C), 195.9 (CO); MS 501 (100, M^+), 500 (14), 486 (12.3), 485 (11.3), 473 (7.2), 416 (7.7), 379 (79), 378 (100), 363 (8.2), 362 (19.5), 348 (7.7), 334 (7.9), 322 (10.5), 320 (5.7), 250.5 (31.6). $C_{31}H_{35}NO_5$ requires: C, 74.22; H, 7.03; N, 2.79; found C, 73.91; H, 6.99; N, 2.48.

9- (4- Hydroxy- 3- methoxyphenyl)- 10- phenyl- 3, 3, 6, 6- tetramethyl- 3, 4, 6, 7,9, 10- hexahydro-1, 8(2*H*, 5*H*) acridinedione (9e). Yield 75 %; brown; mp 232-234° C; IR(KBr)3410,2967,1645, 1350 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$-DMSO-d_6) δ 0.81 and 0.94 (2s,12H, *gem*-dimethyl), 1.79-2.09 (2d, 4H, J=17.3 Hz, C_4 & C_5-CH_2), 2.12-2.22 (2d, 4H, J=16.8 Hz, C_2 & C_7-CH_2), 3.89 (s, 3H, OCH_3), 5.20 (s, 1H, C_9-CH), 5.65 (s, 1H, Ar-OH), 6.77-7.56 (m, 8H, Ar-H); ^{13}C NMR (100.4 MHz, $CDCl_3$-DMSO-d_6) δ 26.6 (CH_3), 29.6 (CH_3), 31.9 (CH), 32.3 (C), 41.7 (CH_2), 50.1 (CH_2), 55.8 (OCH_3), 111.8 (CH), 113.9 (CH), 114.7 (C), 119.2 (CH), (129.3 (CH), and 130.1 (CH) signals were distorted) 138.5 (C),138.9 (C), 143.6 (C), 145.8 (C), 149.5 (C), 196.0 (CO); MS471 (69.9, M^+), 456 (5.4), 454 (4.3), 348 (100), 333 (3.9), 332 (13.5). $C_{30}H_{33}NO_4$ requires: C, 76.40; H, 7.05; N, 2.94; found C, 76.21; H, 6.99; N, 2.78.

9- (4- Hydroxy- 3- methoxyphenyl)- 10- (3,4-dimethylphenyl)- 3, 3, 6, 6-tetramethyl-3, 4, 6, 7,9, 10- hexahydro- 1, 8(2*H*, 5*H*) acridinedione (9f). Yield 76%; brown; mp 260-262° C; IR(KBr) 3403, 2955, 1634, 1364 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$-DMSO-d_6) δ 0.82 and 0.96

(2s, 12H, *gem*-dimethyl), 1.82-2.14 (2d, 4H, *J*=17.6 Hz, C_4 & C_5-CH_2), 2.10-2.20 (2d, 4H, *J*=16.12 Hz, C_2 & C_7-**CH_2),** 2.36 (s, 3H, Ar-CH_3), 2.37 (s, 3H, Ar- CH_3), 3.84 (s, 3H, OCH_3), 5.08 (s, 1H, 9-CH), 6.71-8.03 (m, 7H, Ar-H and OH); ^{13}C NMR (100.4 MHz, $CDCl_3$-DMSO-d_6) δ 19.0 (CH_3), 19.4 (CH_3), 26.0 (CH_3), 29.2 (CH_3), 31.0 (CH), 31.7 (C), 40.9 (CH_2), 49.7 (CH_2), 55.1 (OCH_3), 111.2 (CH), 113.6 (C),114.4 (CH), 119.1 (CH), (127,129 and 130 were distorted signals) 135.7 (C), 137.5 (C), 143.8 (C), 146.3 (C), 149.7 (C), 195.2 (CO); MS 499 (75.4, M^+), 376 (100). $C_{32}H_{37}NO_2$ requires: C, 76.92; H, 7.46; N, 2.80; found C, 76.56; H, 7.31; N, 2.63.

10 - (4 - Hydroxyphenyl) - 3, 4, 6, 7, 9, 10-hexahydro - 1, 8 (2*H*, 5*H*) acridinedione (10a). General procedure to give the acridinedio. The tetraketone 1a (1.0 g, 4.2 mmol) and *p*-aminophenol (0.46 g, 4.2 mmol) were refluxed in acetic acid for 12 hours. The reaction mixture was cooled, filtered and dried ne 10a.

Yield 69 %; brown; mp 255-257° C; IR (KBr) 3280, 1655, 1536, 1373 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$- DMSO-*d_6)* δ 1.6-2.2 (m, 12H, C_2,C_3,C_4,C_5,C_6 & C_7-CH_2), 2.93 (s, 2H, C_9- CH_2), 6.82 (d,2H, *J* = 8.8 Hz, Ar-H), 7.11 (d, 2H, *J* = 8.8 Hz, Ar- H), 9.89 (s, 1H, Ar-OH); ^{13}C NMR (300 MHz, $CDCl_3$- DMSO-*d_6)* δ 19.3, 21.6, 28.2, 36.5,110.6, 116.6, 130.5, 131.4, 154.6, 158.2, 196.6; MS 309 (M^+, 1). $C_{19}H_{19}NO_3$ requires: C, 73.76; H, 6.18; N, 4.52; found C, 73.40; H, 6.26; N, 4.25.

10-(4-Hydroxyphenyl)- 3,3,6,6-tetramethyl-3, 4,6,7,9,10-hexahydro-1,8(2*H*,5*H*) acridinedione (10b). Yield 76 %; pale green; mp above 300° C; IR (KBr) 3180, 1640, 1555, 1390 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$-DMSO-*d_6)* δ 0.88 (s, 12H, gem-dimethyl), 2.12 (s, 4H, C_2 & C_7- CH_2), 2.25 (s, 4H, C_4 & C_5-CH_2), 2.98 (s, 2H, C_9- CH_2), 6.85 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.06 (d, 2H, *J* = 7.5 Hz, Ar-H), 9.87(s, 1H, Ar-OH); ^{13}C NMR (300 MHz, $CDCl_3$-DMSO-*d_6)* δ 18.5, 27.7, 31.8, 45.4, 49.4, 108.7, 109.0, 116, 130.6, 151.8, 195.5; MS 365 (M^+, 9), 348 (31), 337 (1), 323 (2), 309 (1), 273 (100), 272 (8). $C_{23}H_{27}NO_3$ requires: C, 75.59; H, 7.45; N, 3.83; found C, 75.38; H, 7.57; N, 3.76.

10 - (4-Hydroxyphenethyl) 3,3,6,6-tetramethyl-- 3, 4, 6, 7, 9, 10 – hexahydro -1, 8 (2*H*, 5*H*) acridinedione (10c). Yield 85 %; brown; mp 236-238° C; IR (KBr) 3197, 1643, 1561, 1395cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-*d_6)* δ 1.03 (s, 12H, *gem*-dimethyl), 2.18 (s, 4H, C_2, & C_4-CH_2), 2.36 (s, 4H, C_5 & C_7-CH_2), 2.73 (t, 2H, *J* = 6.5 Hz, Ar-CH_2), 3.05 (s, 2H, C_9-CH_2), 3.76 (t, 2H, *J* = 6.5 Hz, N-CH_2), 6.79 (d, 2H, *J* = 8.3 Hz, Ar-H), 6.99 (d, 2H, *J* = 8.3 Hz, Ar- H), 8.72 (br s, 1H, Ar-OH); ^{13}C NMR (100.4 MHz, $CDCl_3$- DMSO-*d_6)* δ 17.5 (CH_2), 28.2 (CH_3), 31.9 (C), 36.3 (CH_2), 40.1 (CH_2), 45.9 (CH_2), 49.3 (CH_2), 111.6 (C), 115.5 (CH), 127.3 (C), 129.6 (CH), 151.6 (C), 156.2 (C), 196.2 (CO); MS 393 (M^+, 39), 300 (41), 272 (58),131 (16), 120 (60), 117 (44), 94 (27), 91(48), 84 (81). $C_{25}H_{31}NO_3$ requires: C, 76.30; H, 7.93; N, 3.56; found C, 76.39; H, 8.01; N, 3.23.

10 - (4-Hydroxyphenethyl)-9-methyl-3, 4, 6, 7, 9, 10-hexahydro -1, 8 (2*H*, 5*H*) acridinedione (10d). Yield 71 %; yellow; mp 271-273° C; IR (KBr) 3210, 1657, 1580, 1398cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-*d_6)* δ 0.82 (d, 3H, *J*=6.8 Hz, CH_3), 1.90-2.64 (m, 12H, C_2, C_3, C_4, C_5, C_6 & C_7-CH_2), 2.77 (t, 2H, *J* = 7.3 Hz, Ar-CH_2), 3.82 (t, 2H, *J* = 7.3 Hz, N-CH_2), 3.95 (q, 1H, CH_3), 6.76 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.02 (d, 2H, *J* = 8.3 Hz, Ar- H), 9.03 (br s, 1H, Ar-OH); ^{13}C NMR (100.4 MHz, $CDCl_3$-DMSO-*d_6)* δ 120.0, 20.4, 21.0, 25.5, 29.9, 35.4, 45.4, 114.6, 116.3, 126.5, 128.7, 151.4, 155.3, 195.0. MS 336 (100), 216 (21). $C_{22}H_{25}NO_3$ requires: C, 75.18; H, 7.17; N, 3.98; found C, 74.98; H, 7.18; N, 3.64.

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