Synthesis and antimicrobial studies of some acridinediones and their thiourea derivatives

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Dedicated to Professor S. Swaminathan on his 80\textsuperscript{th} 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\textsuperscript{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\textsuperscript{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\textsuperscript{3, 4, 5}.

Molecular recognition\textsuperscript{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 P₂O₅ 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
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 acridenediones 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 acridenediones, p-aminophenol and tyramine were reacted with tetraketones 1a-c to obtain compounds 10a-d.

**Scheme 3**

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>R'</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c, 7a</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>1d, 7b</td>
<td>Me</td>
<td>4-OH-3-OCH₃C₆H₃</td>
</tr>
</tbody>
</table>
Condensation of dimesdone with vanillin furnished 2,2′-(4-hydroxy-3-methoxybenzylidene) bisdimesdone 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 (9a-f).

Scheme 4

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>R′</th>
</tr>
</thead>
<tbody>
<tr>
<td>1e, 8a</td>
<td>Me</td>
<td>4-CH₃OC₆H₄</td>
</tr>
<tr>
<td>1f, 8b</td>
<td>Me</td>
<td>4-ClC₆H₄</td>
</tr>
</tbody>
</table>

Scheme 5

Table 3

<table>
<thead>
<tr>
<th>Compound</th>
<th>R″</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>H</td>
</tr>
<tr>
<td>b</td>
<td>CH₂COOH</td>
</tr>
<tr>
<td>c</td>
<td>4-CH₃-C₆H₄</td>
</tr>
<tr>
<td>d</td>
<td>4-CH₃-O-C₆H₄</td>
</tr>
<tr>
<td>e</td>
<td>Ph</td>
</tr>
<tr>
<td>f</td>
<td>3,4-(CH₃)₂C₆H₃</td>
</tr>
</tbody>
</table>
The NMR spectrum of 9-arylacridinediones 9a-f exhibited geminal coupling of C₂, C₇ & C₄, C₅ 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](image)

**Table 4**

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>R'</th>
<th>R''</th>
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<tbody>
<tr>
<td>10 a</td>
<td>H</td>
<td>H</td>
<td>4-(OH)C₆H₄</td>
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<tr>
<td>10 b</td>
<td>Me</td>
<td>H</td>
<td>4-(OH)C₆H₄</td>
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<tr>
<td>10 c</td>
<td>Me</td>
<td>H</td>
<td>4-(OH)C₆H₄CH₂CH₂</td>
</tr>
<tr>
<td>10 d</td>
<td>H</td>
<td>Me</td>
<td>4-(OH)C₆H₄CH₂CH₂</td>
</tr>
</tbody>
</table>

**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

\[
\% \text{ Inhibition} = \frac{\text{Diameter of the inhibition zone} \times 100}{\text{Diameter of the petri-plate}}
\]

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

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

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 P₂O₅ 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(2H, 5H)acridinedione (2b).** Yield 69 %; yellow; mp 210-212 ° C; IR (KBr) 1637, 1580, 1374, 1345 cm⁻¹ ; ¹H NMR (90 MHz, CDCl₃) δ 1.01 (d, 3H, J = 6.1 Hz), 1.80-2.06 (m, 8H, C₂, C₃, C₆ & C₇-CH₂), 2.25-2.40 (m, 4H, C₄ & C₅-CH₂), 4.13 (q, 1H, C₉-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). C₂₀H₂₀N₂O₄ 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(2H,5H)acridinedione (2c).**

Yield 85 %; yellow; mp 265-267 ° C; IR (KBr) 1660, 1580, 1375, 1350 cm⁻¹ ; ¹H NMR (90 MHz, CDCl₃) δ 0.97 (s, 12H, gem-dimethyl), 1.80 (s, 4H, C₂ & C₇-CH₂), 2.25 (s, 4H, C₄ & C₅-CH₂), 3.21 (s, 2H, C₉-CH₂), 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). C₂₃H₂₆N₂O₄ 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(2H, 5H)acridinedione (4b).** Yield 79 %; yellow; mp 197-199 ° C; IR (KBr) 1632, 1545, 1534, 1387, 1365 cm⁻¹ ; ¹H NMR (90 MHz, CDCl₃) δ 1.06 (d, 3H, J = 7.35 Hz,CH₃), 1.9-2.06 (m, 8H, C₂, C₃, C₆ & C₇-CH₂), 2.30-2.51 (m, 4H, C₄ & C₅-CH₂), 4.11(q, 1H, C₉-CH), 7.51-8.53 (m, 4H, Ar-H); MS (%) 394 (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). C₂₀H₂₀N₂O₄ 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(2H, 5H)acridinedione (4c).**

Yield 78 %; yellow; mp above 300 ° C; IR (KBr) 1632, 1545, 1534, 1387, 1365 cm⁻¹ ; ¹H NMR (90 MHz, CDCl₃) δ 0.94 (s, 12H, gem-dimethyl), 1.75 (br s, 4H, C₂ & C₇-CH₂), 2.10-2.40 (2d, 4H, C₄ & C₅-CH₂), 3.25 (s, 2H, C₉-CH₂), 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). C₂₃H₂₆N₂O₄ 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 aminoacridinediones 3a-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 conc. 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 (50 ml) 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(2H,5H)acridinedione (3a). Yield 71%; brown; mp 251-253 °C; IR (KBr) 3433, 3351, 1631, 1514, 1384 cm⁻¹; ¹H NMR (90 MHz, CDCl₃) δ 1.80-2.10 (m, 8H, C₂, C₃, C₆ & C₇), 2.20-2.40 (m, 4H, C₄, C₅), 3.22 (s, 2H, C₉-CH₂), 4.01 (br s, 2H, NH₂, exchanged with D₂O), 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). C₁₉H₂₀N₂O₂ 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(2H,5H)acridinedione (3b). Yield 77%; greenish yellow; mp 260-262 °C; IR (KBr) 3420, 3340, 1680, 1560, 1380 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.99 (d, 3H, J = 6.3 Hz, CH₃), 1.75-2.44 (m, 12H, C₂, C₃, C₄, C₅, C₆ & C₇-CH₂), 4.12-4.17 (q, 1H, J = 6.26 Hz, C₉-CH), 6.74 (d, 2H, J = 7.8 Hz, Ar-H), 7.10 (d, 2H, J = Hz, Ar-H); ¹³C NMR (100.4 MHz, CDCl₃) δ 21.3 (CH₂), 21.5 (CH), 22.8, (CH₃), 28.0 (CH₂), 36.8 (CH₂), 115.5 (CH), 116.7 (C), 129.2 (C), 129.9 (C), 130.4 (CH), 147.1 (C), 196.6 (C); MS (%) 307 (M⁺-CH₃, 100). C₂₀H₂₂N₂O₂ 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(2H,5H)acridinedione (3c). Yield 76%; brown; mp 290-292 °C; IR (KBr) 3432, 3320, 1631, 1555, 1385 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.94 (s, 12H, gem-dimethyl), 1.85 (s, 4H, C₂, C₇-CH₂), 2.21 (s, 4H, C₄, C₅-CH₂), 3.21 (s, 2H, C₉-CH₂), 3.98 (br s, 2H, Ar-NH₂), 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). C₁₉H₂₀N₂O₂ requires: C, 75.79; H, 7.44; N, 7.74; found C, 75.44; H, 7.69; N, 7.49.

10-(3-Aminophenyl)-3,4,6,7,9,10-hexahydro-1,8(2H,5H)acridinedione (5a). Yield 71%; brown; mp 247-249 °C; IR (KBr) 3435, 3350, 1665, 1575, 1360 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.94 (s, 12H, gem-dimethyl), 1.80-2.56 (m, 12H, C₂, C₃, C₄, C₅, C₆ & C₇-CH₂), 3.11 (s, 2H, C₉-CH₂), 3.21 (s, 2H, NH₂), 3.74 (d, 2H, J = 8.3 Hz, Ar-H), 6.89 (d, 2H, J = 8.3 Hz, Ar-H); ¹³C NMR (100.4 MHz, CDCl₃) δ 18.5 (C₉-CH₂), 28.3 (CH₃), 32.1 (C), 41.7 (C₂-CH₂), 49.9 (C₄-CH₂), 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). C₂₃H₂₈N₂O₂ requires C, 75.79; H, 7.74; N, 7.68; found C, 75.44; H, 7.69; N, 7.49.

10-(3-Aminophenyl)-9-methyl-3,4,6,7,9,10-hexahydro-1,8(2H,5H)acridinedione (5b). Yield 75%; brown; mp 274-276 °C; IR (KBr) 3430, 3378, 1675, 1550, 1360 cm⁻¹; ¹H NMR (400 MHz, CDCl₃-DMSO-d₆): δ 0.91 (d, 3H, J = 6.35 Hz, CH₃), 1.78-1.91 (m, 4H, C₃, C₅-CH₂), 2.06-2.35 (m, 8H, C₂, C₄, C₅ & C₇-CH₂), 3.99 (q, 1H, J = 6.8 Hz, C₉-CH), 4.96 (br s, 2H, NH₂), 6.43-7.89
10-(3-Aminophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-1,8(2H,5H) acridine dione (5c).

Yield 71 %; brown; mp 252-254 °C; IR (KBr) 3432, 3351, 2949, 1631, 1385 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.94 (s, 12H, gem-dimethyl), 1.90 (s, 4H, C₂ & C₇-CH₂), 2.21 (s, 4H, C₄ & C₅-CH₂), 3.21 (s, 2H, C₉-CH₂), 3.98 (s, 2H, Ar-NH₂); 6.45-7.27 (m, 4H, Ar-H); ¹³C NMR (100.4 MHz, CDCl₃) : δ 18.5 (C₉-CH₂), 28.3 (CH₃), 32.3 (C), 41.5 (C₂-CH₂), 50.0 (C₄-CH₂), 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). C₂₂H₂₂N₂O₂ requires: C, 74.50; H, 6.87; N, 8.68; found C, 74.37; H, 6.92; N, 8.54.

N-(2-Chlorophenyl)-N'-[3-(9-methyl-3,4,6,7,9,10-hexahydro-1,8(2H,5H)acridinedione-10-yl)-phenyl] thiourea (6). The acridinedione 5b (1.0g, 3.1 mmol) 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, CDCl₃) δ 1.01 (d, 3H, J=7.8 Hz, CH₃), 1.81-2.43 (m, 12H, C₂, C₃,C₄, C₅, C₆ & C₇-CH₂), 3.48 (br s, 2H, NH, exchanged with D₂O), 4.12 (q, 1H, J=7.6Hz, C₉-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). C₂₇H₂₆N₃O₂SCl 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 CHCl₃-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(2H,5H)acridinedione-10-yl)-thiourea (7a). Yield 74 %; brown; mp 130-132 °C; IR (KBr) 3420, 3350, 1645, 1375 cm⁻¹. ¹H NMR (90 MHz, CDCl₃) δ 1.08 (s, 12H, gem-dimethyl), 2.29 (br s, 8H, C₂, C₄, C₅ & C₇, CH₂), 3.16 (s, 2H, C₉-CH₂), 6.6 (s, NH₂, exchanged with D₂O); 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). C₁₈H₂₅N₃O₂S 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(2H, 5H) 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, CDCl₃) δ 0.84 & 1.01 (2s, 12H, gem-dimethyl), 1.95-2.17 (2d, 4H,J=16.1, C₃,C₇-CH₂), 2.21-2.42 (2d, 4H, J=17.33, C₄, C₅-CH₂), 3.68(s, 3H, OCH₃), 3.71 (s, 2H, NH₂, exchanged with D₂O), 4.76 (s, 1H, C₉-CH), 6.48-7.0 (m, 3H, Ar-H), 8.1 & 8.2 (br s, NH, exchanged with D₂O); 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 CHC13-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(2H, 5H) acridinedione (8a). Yield 63%; pale brown; mp 198-200 °C; IR (KBr) 1685, 1665, 1547, 1374 cm -1. 1H NMR (400 MHz, CDCl3) δ 1.00 &1.08 (2s, 12H, gem-dimethyl), 2.09-3.63 (m, 23H, C 2, C4, C5, C7-CH2, N-CH2, CH3CO), 3.71(s, 3H, OCH3), 5.19 (s, 1H, C9CH), 6.68 (d, 2H, J=8.7Hz, Ar-H), 7.65 (d, 2H, J=8.3Hz, Ar-H); 13C NMR (100.4 MHz, CDCl3) 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(2H, 5H) acridinedione (8b). Yield 75 %; brown; mp  212-214 °C; IR (KBr) 1680, 1658, 1574, 1380 cm -1. 1 H NMR (200 MHz, CDCl 3): δ 1.00 & 1.09 (2s, 12H,gem-dimethyl), 2.04-2.22 (m, 10H, CH2), 2.36-2.57 (m, 11H, CH2), 5.22 (s, 1H, C9-H), 7.11 (d, 2H, J = 6.3Hz, Ar-H), 7.18 (d, 2H, J = 6.3Hz, Ar-H); 13C 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). C31H40N3O3Cl 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, 6, 7, 9, 10-hexa- hydro-1, 8(2H, 5H) 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 CHCl3-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, CDCl3-DMSO-d6) δ 0.95 and 1.07 (2s, 12H, gem-dimethyl), 2.06-2.21 (2d, 4H, J = 16.3 Hz, C4 & C5 -CH2), 2.30-2.42 (2d, 4H, J = 17 Hz, C2 & C7 -CH2,), 3.77(s, 3H, OCH3), 4.85 (s, 1H, C9-CH), 6.61 (s, 2H, Ar-H), 6.85 (s, 1H, Ar-H), 8.08 (br s, 1H, OH), 8.94 (s, 1H, NH); 13C NMR (100.4 MHz, CDCl3-DMSO-d6) δ 25.6 (CH3), 28.3 (CH3), 31.1 (C), 31.3 (CH), 49.5 (CH2), 54.4 (OCH3), 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); C24H29NO4 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,-tetramethyl-3, 4, 6, 7, 9, 10-hexahydro-1, 8(2H, 5H) acridinedione (9b). Yield 64 %; yellow; mp 237-239°C; IR (KBr)
3150, 2982, 1720, 1640, 1371 cm⁻¹; ¹H NMR (400 MHz, CDCl₃-DMSO-d₆) δ 0.97 and 1.07 (2s, 12H, gem-dimethyl), 2.12-2.22 (2d, 4H, J = 16 Hz, C₄ & C₅-CH₂), 2.35-2.49 (2d, 4H, J = 17 Hz, C₂ & C₇-CH₂), 3.35 (s, 2H, N-CH), 3.79 (s, 3H, OCH₃), 5.05 (s, 1H, C₉-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(2H, 5H) acridinedione (9c). Yield 77%; dark brown; mp 176-178°C; IR (KBr) 3404, 2956, 1635, 1364 cm⁻¹; ¹H NMR (400 MHz, CDCl₃-DMSO-d₆) δ 0.97 and 1.07 (2s, 12H, gem-dimethyl), 2.12-2.22 (2d, 4H, J = 16 Hz, C₄ & C₅-CH₂), 2.35-2.49 (2d, 4H, J = 17 Hz, C₂ & C₇-CH₂), 3.35 (s, 2H, N-CH), 3.79 (s, 3H, OCH₃), 5.05 (s, 1H, C₉-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-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-1,8(2H, 5H) acridinedione (9d). Yield 79%; brown; mp 253-255°C; IR (KBr) 3390, 2967, 1660, 1342 cm⁻¹; ¹H NMR (400 MHz, CDCl₃-DMSO-d₆) δ 0.82 and 0.95 (2s, 12H, gem-dimethyl), 1.83-2.09 (2d, 4H, J = 17.6 Hz, C₄ & C₅-CH₂), 2.12-2.22 (2d, 4H, J = 16.3 Hz, C₂ & C₇-CH₂), 3.90 & 3.91 (2s, 6H, Ar-OCH₃), 5.18 (s, 1H, C₉-CH), 5.57 (s, 1H, Ar-OH), 6.73-7.13 (m, 7H, Ar-H); ¹³C NMR (100.4 MHz, CDCl₃-DMSO-d₆) δ 26.7 (CH₃), 29.7 (CH₃), 32.0 (CH), 32.2 (C), 41.7 (CH₂), 50.1 (CH₂), 55.5 (OCH₃), 55.7 (OCH₃), 111.8 (CH), 113.8 (CH), 114.6 (C), 119.2 (CH), 129.3 (CH), 130.8 (CH), 131.4 (C), 138.6 (C), 145.8 (C), 150.0 (C), 159.7 (C), 195.9 (CO); MS 485 (56.8, M⁺), 362 (66.2). C₃₁H₃₅NO₅ 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(2H, 5H) acridinedione (9e). Yield 75%; brown; mp 232-234°C; IR (KBr) 3410, 2965, 1645, 1350 cm⁻¹; ¹H NMR (400 MHz, CDCl₃-DMSO-d₆) δ 0.81 and 0.94 (2s, 12H, gem-dimethyl), 1.79-2.09 (2d, 4H, J = 17.3 Hz, C₄ & C₅-CH₂), 2.12-2.22 (2d, 4H, J = 16.3 Hz, C₂ & C₇-CH₂), 3.89 (s, 3H, OCH₃), 5.20 (s, 1H, C₉-CH), 5.65 (s, 1H, Ar-OH), 6.77-7.56 (m, 8H, Ar-H); ¹³C NMR (100.4 MHz, CDCl₃-DMSO-d₆) δ 26.7 (CH₃), 29.7 (CH₃), 32.0 (CH), 41.7 (CH₂), 50.1 (CH₂), 55.5 (OCH₃), 55.7 (OCH₃), 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⁺), 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). C₃₁H₃₅NO₄ 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-(3,4-dimethylphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-1,8(2H, 5H) acridinedione (9f). Yield 76%; brown; mp 260-262°C; IR(KBr) 3430, 2955, 1634, 1364 cm⁻¹; ¹H NMR (400 MHz, CDCl₃-DMSO-d₆) δ 0.82 and 0.96
(2s, 12H, gem-dimethyl), 1.82-2.14 (2d, 4H, J = 17.6 Hz, C4 & C5-CH2), 2.10-2.20 (2d, 4H, J = 16.12 Hz, C2 & C7-CH2), 2.36 (s, 3H, Ar-CH3), 2.37 (s, 3H, Ar-CH3), 3.84 (s, 3H, OCH3), 5.08 (s, 1H, 9-CH), 6.71-8.03 (m, 7H, Ar-H and OH); 13C NMR (100.4 MHz, CDCl3-DMSO-d6) δ 19.0 (CH3), 19.4 (CH3), 26.0 (CH3), 29.2 (CH3), 31.0 (CH), 31.7 (C), 40.9 (CH2), 49.7 (CH2), 55.1 (OCH3), 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). C32H37NO2 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 (2H, 5H) acridinedione (10a).

General procedure to give the acridinedione. 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 to give 10a. Yield 69%; brown; mp 255-257° C; IR (KBr) 3280, 1655, 1536, 1373 cm-1; 1H NMR (300 MHz, CDCl3-DMSO-d6) δ 1.6-2.2 (m, 12H, C2, C3, C4, C5, C6 & C7-CH2), 2.93 (s, 2H, C9-CH2), 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); 13C NMR (300 MHz, CDCl3-DMSO-d6) 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). C19H19NO3 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(2H,5H) acridinedione (10b).

Yield 76%; pale green; mp above 300° C; IR (KBr) 3180, 1640, 1555, 1390 cm-1; 1H NMR (300 MHz, CDCl3-DMSO-d6) δ 0.88 (s, 12H, gem-dimethyl), 2.12 (s, 4H, C2 & C7-CH2), 2.25 (s, 4H, C4 & C5-CH2), 2.98 (s, 2H, C9-CH2), 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); 13C NMR (300 MHz, CDCl3-DMSO-d6) δ 18.5, 27.7, 31.8, 45.4, 49.4, 108.7, 109.0, 116, 130.5, 151.8, 195.5; MS 365 (M+, 9), 348 (31), 337 (1), 323 (2), 309 (1), 273 (100), 272 (8). C23H27NO3 requires: C, 75.59; H, 7.45; N, 3.83; found C, 75.40; H, 6.26; N, 4.25.

10 - (4-Hydroxyphenethyl) 3,3,6,6-tetramethyl - 3, 4, 6, 7, 9, 10 – hexahydro -1, 8 (2H, 5H) acridinedione (10c).

Yield 85%; brown; mp 236-238° C; IR (KBr) 3197, 1643, 1561, 1395 cm-1; 1H NMR (400 MHz, CDCl3-DMSO-d6) δ 1.03 (s, 12H, gem-dimethyl), 2.18 (s, 4H, C2, & C4-CH2), 2.36 (s, 4H, C5 & C7-CH2), 2.77 (t, 2H, J = 7.3 Hz, Ar-CH2), 3.76 (d, 2H, J = 6.5 Hz, N-CH2), 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); 13C NMR (100.4 MHz, CDCl3-DMSO-d6) δ 17.5 (CH2), 28.2 (CH3), 31.9 (C), 36.3 (CH2), 40.1 (CH2), 45.9 (CH2), 49.3 (CH2), 111.6 (C), 115.5 (CH), 127.3 (C), 129.6 (CH), 151.6 (C), 156.2 (C), 196.2 (CO); MS 393 (M+, 27), 300 (41), 272 (58), 131 (16), 120 (60), 117 (44), 94 (27), 91 (48), 84 (81). C25H31NO3 requires: C, 76.30; H, 7.93; N, 3.56; found C, 76.39; H, 7.57; N, 3.76.

10 - (4-Hydroxyphenethyl)-9-methyl-3, 4, 6, 7, 9, 10 – hexahydro -1, 8 (2H, 5H) acridinedione (10d).

Yield 71%; yellow; mp 271-273° C; IR (KBr) 3210, 1657, 1580, 1398 cm-1; 1H NMR (400 MHz, CDCl3-DMSO-d6) δ 1.03 (s, 12H, gem-dimethyl), 2.18 (s, 4H, C2, & C4-CH2), 2.36 (s, 4H, C5 & C7-CH2), 2.77 (t, 2H, J = 6.5 Hz, Ar-CH2), 3.05 (s, 2H, C9-CH2), 3.76 (t, 2H, J = 6.5 Hz, N-CH2), 6.79 (d, 2H, J = 8.3 Hz, Ar-H), 6.99 (d, 2H, J = 8.3 Hz, Ar-H), 7.06 (d, 2H, J = 7.5 Hz, Ar-H), 9.87 (s, 1H, Ar-OH); 13C NMR (100.4 MHz, CDCl3-DMSO-d6) δ 120.0, 20.4, 21.0, 25.5, 29.9, 35.4, 45.4, 116.3, 126.5, 128.7, 151.4, 155.3, 195.0; MS 336 (100), 216 (21). C22H25NO3 requires: C, 75.18; H, 7.17; N, 3.98; found C, 74.98; H, 7.18; N, 3.64.
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References