Synthesis of Novel Bis-condensed Heterocyclic Ring Assembly Systems

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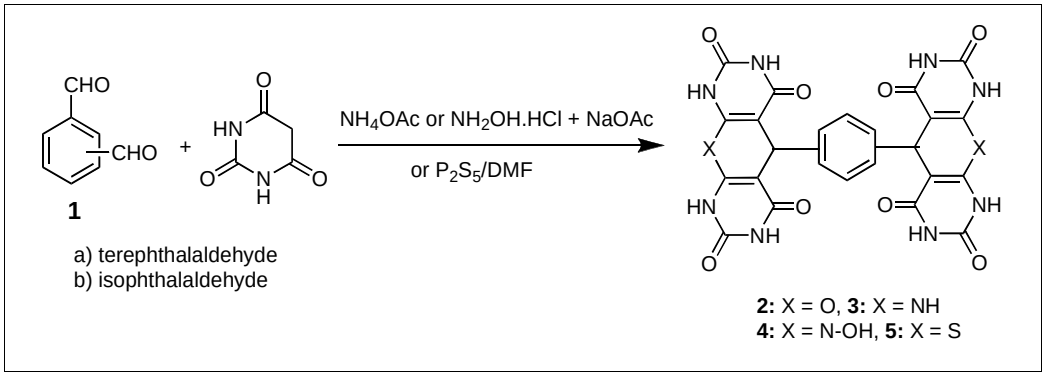

The novel bis-condensed heterocyclic systems with ring assemblies based on peripheral barbituric acid rings and central pyran, pyridine and thiine rings have been generated by the reaction of terephthalaldehyde and isophthalaldehyde with barbituric acid for comparison with the analogous systems generated with said dialdehydes and 1,3-cyclohexanedione.

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Carbonyl compounds especially the aldehydes and to large extent ketones also condense with cyclic reactive methylene compounds to produce olefins [1-2]. This is an excellent method for generation of carbon-carbon double bonds. These reactions are generally base or acid catalysed. Literature search reveals that a fair amount of work has been published on the reaction of aromatic monoaldehyde with active methylene compounds [3-9]. In the present article, we are reporting and highlighting the reaction of barbituric acid as an active methylene pyrimidine derivative with terephthalaldehyde and isophthalaldehyde in *N,N*-dimethyl formamide (DMF). When terephthalaldehyde and isophthalaldehyde were treated with barbituric acid under different conditions novel pyran, pyridine and thiine based heterocyclic ring assemblies were generated probably *via* the intermediacy of normal Knoevenagel reaction, Michael addition and cyclodehydratioon. With phthalaldehyde, a mixture of products was obtained and due to poor yield because of over crowding, the products could not be separated.

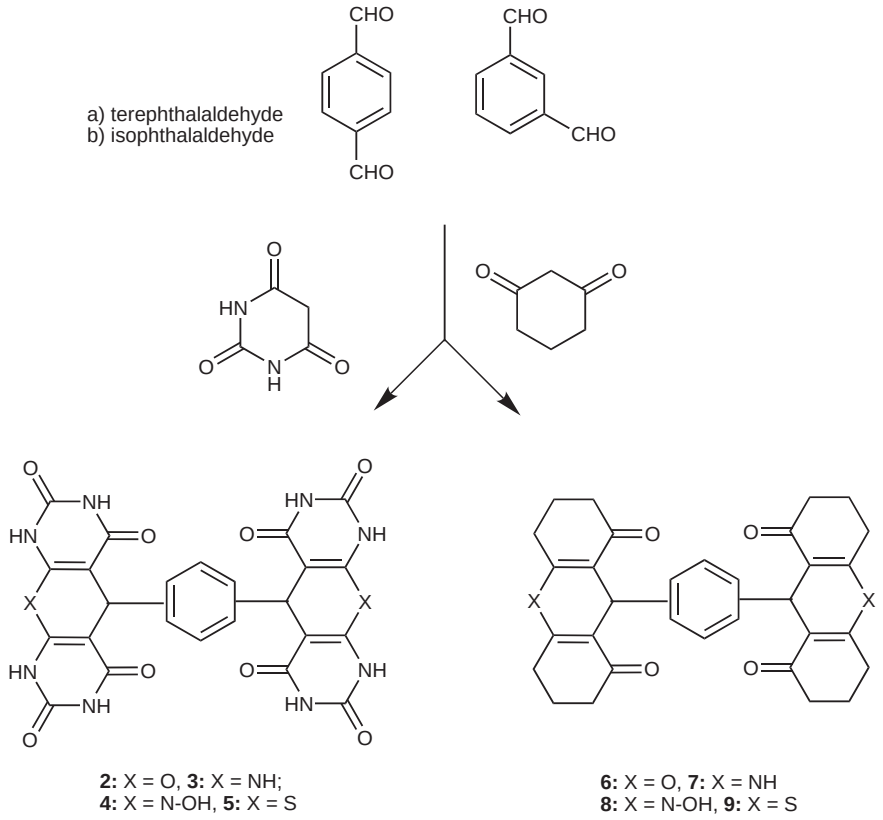
When the two aromatic dialdehydes were treated with 1,3-cyclohexanedione under different conditions in ethylene glycol as reported [10] with dimedone and [11] for the synthesis of bifunctional pyridine and quinoline derivatives under similar conditions; bis-xanthene, bis-acridine and bis-thioxanthene ring assemblies were generated as expected. Comparative yields in two different solvent systems for two sets of reactions have been recorded in Table 1. The reactions are shown in Scheme 1. All the compounds obtained gave analysis for C, H, N and S in good agreement with calculated values, and the structures were established on the basis of spectroscopic data.

Results and Discussion.

Using only terephthalaldehyde and barbituric acid in DMF as such; in presence of NH_4OAc, $NH_2OH.HCl$, and NaOAc and P_2S_5, the condensed ring assembly compounds **2a**, **3a**, **4a** and **5a** respectively were obtained in good yield under thermal conditions. Using isophthalaldehyde and barbituric acid under exactly similar conditions the novel compounds **2b**, **3b**, **4b** and **5b** were obtained. With 1,3-cyclohexanedione and terephthalaldehyde under analogues conditions using ethylene glycol solvent, the ring assembly compounds **6a**,**7a**, **8a and 9a** were obtained. 1,3-Cyclohexanedione and isophthalaldehyde under different conditions in the ethylene glycol furnished the compounds **6b**, **7b** ,**8b and 9b.**

It has been summarised under the present exposition that DMF is suitable solvent for barbituric acid as a synthon and ethylene glycol is the most suitable solvent for cyclohexanedione as the synthon. P_2S_5 in the synthesis of thio compunds **5a**, **5b**, **9a** and **9b**; and NH_2OH HCl in the synthesis of *N*-hydroxy compounds **4a**, **4b**, **8a** and **8b** should be used exactly quantitatively lest the higher quantities of the reagents should form the corresponding thioxo and oximino derivatives respectively.

Scheme-1



2: X = O, **3:** X = NH;
4: X = N-OH, **5:** X = S

6: X = O, **7:** X = NH
8: X = N-OH, **9:** X = S

Table 1

Synthesis of Target Compound

Product	Reaction Time (min.)	Yield using Ethylene glycol (%)	Yield using DMF (%)
2a	10	50	82
3a	12	52	84
4a	12	50	86
5a	11	48	80
2b	13	54	84
3b	14	56	86
4b	15	56	88
5b	14	54	82
6a	22	90	48
7a	21	92	52
8a	20	94	54
9a	23	90	56
6b	25	96	52
7b	24	92	56
8b	25	90	54
9b	23	92	48

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. The ^{1}H and ^{13}C-NMR spectra were run on Varian unity 500 MHz NMR spectrophotometer with DMSO-d_6 as solvent and TMS as internal standard. IR spectra were recorded on a Perkin Elmer Infrared Model S99-B and Zeiss IMTS spectrometer. Elemental analyses were performed on a simple CHNS analyzer.

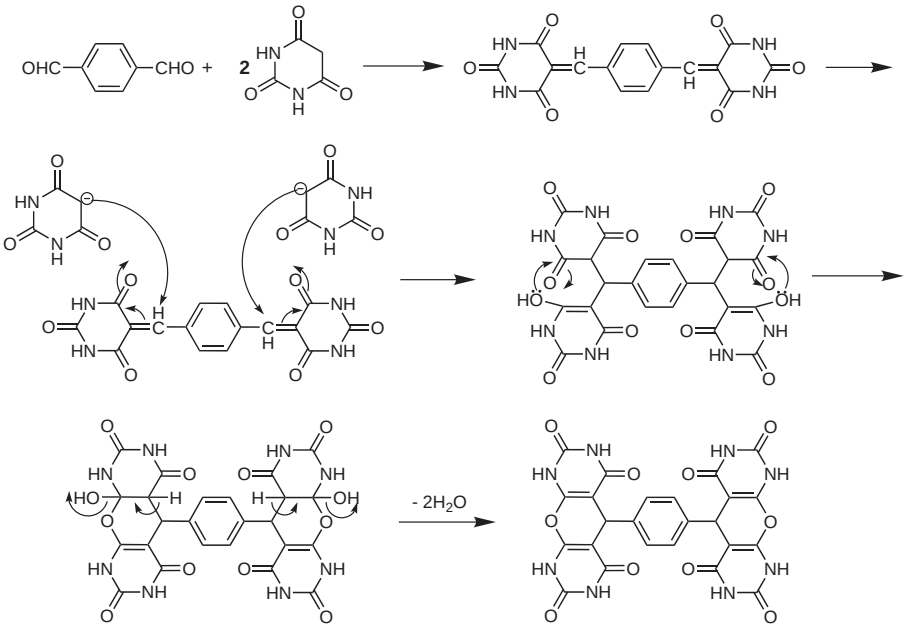
General Procedure for the Synthesis of Compunds **2-5**.

A mixture of aromatic dialdehyde **1a** or **1b** as appropriate (1 mmol), barbituric acid (4 mmol), DMF (1 ml) was refluxed in a flask of 25 ml (for **3**: 3 mmol NH_4OAc; for **4**: 2mmol $NH_2OH.HCl$ and 2 mmol NaOAc and for **5**: 2 mmo1 P_2S_5 was added). After monitoring over TLC for about 10- 15 min the reaction mixture was cooled, poured into 50 ml water. The soild was collected by filtration, washed with water and then recrystallized from EtOH to give **2**, **3**, **4** or **5**.

General Procedure for the Synthesis of Compounds **6-9**.

A mixture of aromatic dialdehyde **1a** or **1b** as appropriate (1 mmol), cyclohexanedione (4 mmol), ethylene glycol (1 ml) was refluxed in a flask of 25 ml (for **3**: 3 mmol NH_4OAc; for **4**: 2 mmol $NH_2OH.HCl$ and 2 mmol NaOAc; and for **5**: 2 mmo1 P_2S_5 was added). After monitoring over TLC for about 20-25 min the reaction mixture was cooled, poured into 50 ml water. The soild was collected by filtration, washed with water and then recrystallized from EtOH to give **6**, **7**, **8**, or **9**.

Scheme 2



(Mechanism of formation of **2a**)

5,5'-(1,4-phenylene)bis(5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetrone) (**2a**).

M.P. 274-275°C; IR (KBr, ν, cm^{-1}): 3440, 3360, 2960, 3870,1648, 1660, 1599, 1511, 1450, 1373, 1304, 1255, 1168, 1148, 1045, 851, 810, 733, 663, 592, 503; ^{1}H - N MR (DMSO-d_6 ,δ ppm): 5.84 (2H s, 2 x CH), 6.86 (4H, s, ArH), 11.14 (4H, s, NH's); 11.22 (4H, s, NH's) ^{13}C - NMR: δ43.15 (barbituric acid C-5 carbon), 60.2 (barbituric acid C-6 carbon), 86.25 (benzyl carbon), 130.15, 135.11, 138.06, 146.33, 153.72, 154.40 (six carbons for benzene ring), 161.96, 165.57 (two sets of barbituric acid carbonyls of two carbon each).

Anal. Calcd. for $C_{24}H_{14}N_8O_{10}$: C, 50.18; H, 2.45; N, 19.50. Found: C, 50.12; H, 2.34; N, 19.40.

5,5'-(1,4-phenylene)bis(5,10-dihydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetrone) (**3a**).

M.P. > 300°C; IR (KBr, ν, cm^{-1}): 3465, 3370, 3234, 3068, 2950, 2870, 1640, 1650, 1475, 1390, 1360, 1250, 1215, 1170, 1143, 1016, 980, 942, 890, 864, 746. 708, 630, 599, 566, 527; ^{1}H - N MR (DMSO-d_6, δ ppm): 4.73 (2H s, 2 x CH), 6.89 (4H, s, ArH); 9.12 (4 H, s, NH's), 9.24 (4H, s, NH's); ^{13}C - NMR: δ 42.10 (barbituric acid C-5 carbon), 58.6 (barbituric acid C-6 carbon), 87.46 (benzyl carbon) 130.15, 133.12, 134.23, 146.33, 153.27, 154.29 (six carbons for benzene ring), 167.76, 165.29 (two sets barbituric acid carbonyls of two carbon each).

Anal. Calcd. for $C_{24}H_{16}N_{10}O_8$: C, 50.35; H, 2.81; N, 24.46. Found: C, 50.28; H, 2.76; N, 24.42.

5,5'-(1,4-phenylene)bis(10-hydroxy-5,10-dihydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetrone) (**4a**).

M.P. > 300°C; IR (KBr, ν, cm^{-1}): 3463, 3358, 3210, 2940, 2870,1660, 1648, 1620, 1505, 1462, 1400, 1369, 1230, 1150, 1010, 808, 660, 590, 582; ^{1}H - N MR (DMSO-d_6, δ ppm): 4.46 (2H s, 2 x CH), 6.95 (4H, s, ArH), 10.73 (2H, s, 2 x OH), 11.10 (4H, s, NH's), 11.28 (4H, s, NH's); ^{13}C - NMR: δ 42.26 (barbituric acid C-5 carbon), 56.8 (barbituric acid C-6 carbon), 87.30 (benzyl carbon), 130.20, 132.50, 134.40, 146.70, 152.40, 155.28 (six carbons for benzene ring), 167.76, 165.28 (two sets of barbituric acid carbonyls of two carbon each).

Anal. Calcd.for $C_{24}H_{16}N_{10}O_{10}$: C, 47.69; H, 2.66; N, 23.17. Found: C, 47.62; H, 2.64; N, 23.10.

5,5'-(1,4-phenylene)bis (5,9-dihydro-2*H*-thiopyrano[2,3-*d*:6,5-*d*']-dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetrone) (**5a**).

M.P. > 300°C; IR (KBr, ν, cm^{-1}): 3488, 3342, 3240, 2950, 2840, 1670, 1648, 1470, 1340, 1204. 1167, 1142, 1003, 702, 580; ^{1}H - N MR (DMSO-d_6, δ ppm): 4.46 (2H s, 2 x CH), 6.81-7.05 (4H, s, ArH); 11.14 (4H, s, NH's), 11.26 (4H, s, NH's); ^{13}C - NMR: δ 42.20 (barbituric acid C-5 carbon), 57.2 (barbituric acid C-6 carbon), 87.22 (benzyl carbon), 130.22, 132.70, 134.42, 146.20, 151.20, 155.16 (six carbons for benzene ring), 167.60, 165.30 (two sets of barbituric acid carbonyls of two carbon each).

Anal. Calcd. for $C_{24}H_{14}N_8O_8S_2$: C, 47.52; H, 2.32; N, 18.47 S, 10.57. Found: C, 47.50; H, 2.28; N, 18.40; S, 10.50

5,5'-(1,3-phenylene)bis(5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetrone) (**2b**).

M.P. 260-275°C; IR (KBr, ν, cm^{-1}): 3467, 3382, 2962, 2783, 1660, 1646, 1450, 1367, 1200, 1170, 1140, 1005, 810, 707, 680, 575, 483; ^{1}H - N MR (DMSO-d_6, δ ppm): 5.82 (2H s, 2 x CH), 7.20 (4H, m, ArH), 11.10 (4H, s, NH's), 11.28 (4H,s, NH's); ^{13}C - NMR: δ 43.10 (barbituric acid C-5 carbon), 60.1 (barbituric acid C-6 carbon), 87.67 (benzyl carbon), 130.10, 134.10, 138.0, 147.20, 152.20, 154.40 (six carbons for benzene ring), 161.90, 164.90 (two sets of barbituric acid carbonyls of two carbon each).

Anal. Calcd. for $C_{24}H_{14}N_8O_{10}$: C, 50,18; H, 2.45; N, 19.50. Found: C, 50.16; H, 2.30; N, 19.35.

5,5'-(1,3-phenylene)bis(5,10-dihydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetrone) (**3b**).

M.P. > 300°C; IR (KBr, ν, cm^{-1}): 3452, 3367, 3230, 3070, 2960, 2865, 1648, 1470, 1400, 1360, 1250, 1210, 1170, 1140, 1016, 990, 840, 890, 864, 748, 705. 630, 566, 526; ^{1}H - NMR (DMSO-d_6, δ ppm): 4.72 (2H s, 2 x CH), 6.90 (4H, m, ArH); 9.16 (4H, s, NH's), 9.28 (4H, s, NH's); ^{13}C - NMR: δ 42.10 (barbituric acid 5-C carbon), 57.7 (barbituric acid C-6 carbon), 87.28 (benzyl carbon), 130.10, 132.40, 134.20, 145.70, 152.20, 155.10 (six carbons for benzene ring), 167.76, 165.28 (two sets of barbituric acid carbonyls of two carbon each).

Anal. Calcd. for $C_{24}H_{16}N_{10}O_8$: C, 50.35; H, 2.81; N, 24.46. Found: C, 50.26; H, 2.75; N, 24.40.

5,5'-(1,3-phenylene)bis(10-hydroxy-5,10-dihydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetrone) (**4b**).

M.P. > 260-262°C; IR (KBr, ν, cm^{-1}): 3442, 3354, 3310, 2960, 2870, 1660,1644, 1460, 1366, 1200, 1165, 1140, 1004, 704, 582; ^{1}H - N MR (DMSO-d_6, δ ppm): 4.46 (2H s, 2 x CH), 6.81-7.05 (4H, m, ArH), 10.71 (2H, s, 2 x OH), 11.18 (4 H, s, NH's), 11.22 (4H, s, NH's); ^{13}C - NMR: δ 42.26 (barbituric acid C-5 carbon), 58.8 (barbituric acid C-6 carbon), 87.30 (benzyl carbon), 130.24, 132.60, 134.44, 146.50, 151.10, 155.10 (six carbons for benzene ring), 167.66, 165.30 (two sets of barbituric acid carbonyls of two carbon each).

Anal. Calcd. for $C_{24}H_{16}N_{10}O_{10}$: C, 47.69; H, 2.66; N, 23.17. Found: C, 47.63; H, 2.62; N, 23.15.

5,5'-(1,3-phenylene)bis (5,9-dihydro-2*H*-thiopyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetrone) (**5b**).

M.P. > 300°C; IR (KBr, ν, cm^{-1}): 3452, 3354, 3220, 2960, 2845, 1640, 1480, 1370, 1200, 1167, 1140, 1002, 702, 580; ^{1}H - NMR (DMSO-d_6, δ ppm): 4.46 (2H s, 2 x CH), 6.9-7.06 (4H, m, ArH), 11.12 (4H, s, NH's), 11.26 (4H, s, NH's); ^{13}C - NMR: δ 42.28 (barbituric acid C-5 carbon), 58.8 (barbituric acid C-6 carbon), 87.22 (benzyl carbon), 130.20, 131.40, 133.70, 146.10, 150.76, 155.14 (six carbons for benzene ring), 167.60, 165.40 (two sets of barbituric acid carbonyls of two carbon each).

Anal. Calcd. for $C_{24}H_{14}N_8O_8S_2$: C, 47.52; H, 2.32; N, 18.47; S, 10.57. Found: C, 47.49; H, 2.27; N, 18.40; S, 10.50.

9,9'-(1,4-phenylene)bis(3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione) (**6a**).

M.P. 280-282°C; IR (KBr, ν, cm^{-1}) 2960, 2870, 2660, 1599, 1511, 1450, 1373, 1304, 1255, 1168, 1148, 1045, 851, 810, 733, 663, 592, 503; ^{1}H - NMR DMSO-d_6, δ ppm): 2.0-2.73 (24H, m, 12 x CH_2, 5.84(2H, s ,2 xCH); 6.86 (4H, s, ArH);

Anal. Calcd. for $C_{32}H_{30}O_6$: C, 75.27; H, 5.92. Found: C, 75.20; H, 5.85.

9,9'-(1,4-phenylene)bis(3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione) (**7a**).

M.P. >300°C; IR (KBr, ν, cm^{-1}): 3234, 3068, 2957, 2397, 2869, 1645, 1476, 1368, 1290, 1249, 1215, 1169, 1143, 1017, 979, 942, 890, 864, 746, 707, 631, 599, 556, 527; ^{1}H - NMR (DMSO-d_6, δ ppm): 1.90-2.72 (24H, m, 12 x CH_2), 4.73(2H, s, 2 x CH); 6.89 (4H, s, ArH); 9.22 (2H, s , 2 x NH).

Anal. Calcd. for $C_{32}H_{32}N_2O_4$: C, 75.56 ; H,6.34, N, 5.50. Found: C, 75.54; H, 6.32; N, 5.44.

9,9'-(1,4-phenylene)bis(10-hydroxy-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione) (**8a**).

M.P. >300°C; IR (KBr, ν, cm^{-1}): 3225, 1954, 1871, 1667, 1660, 1504, 1462, 1504, 1362, 1369, 1229, 1154, 1010, 808, 661, 582; ^{1}H - NMR (DMSO-d_6, δ ppm): 2.00-2.65 (24H, m, 12 x CH_2), 4.47 (2H, s, 2 x CH); 6.95 (4H, s, ArH); 10.73 (2H,s, 2 x OH).

Anal. Calcd. for $C_{32}H_{32}N_2O_6$: C, 71.09 ; H, 5.96, N, 5.18. Found: C, 71.0; H, 5.99; N, 5.14.

9,9'-(1,4-phenylene)bis(3,4,5,6,7,9-hexahydro-1*H*-thioxanthene-1,8(2*H*)-dione) (**9a**).

M.P. >300°C; IR (KBr, ν, cm^{-1}): 3240, 2860, 2810, 1640, 1420, 1360, 1200, 1160, 1140, 980, 704, 580; ^{1}H - N MR (DMSO-d_6, δ ppm): 2.03-2.61 (24H, m, 12 x CH_2), 4.46 (2H, s, 2 x CH); 6.98-7.30 (4H, m, ArH).

Anal. Calcd .for $C_{32}H_{30}O_4S_2$: C, 70.82; H, 5.57; S, 11.81. Found: C, 70.76; H, 5.51; S, 11.77.

9,9'-(1,3-phenylene)bis(3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione) (**6b**).

M.P. 272-273°C; IR (KBr, ν, cm^{-1}): 2963, 2782, 1658, 1449, 1367, 1207, 1170, 1143, 1004, 813, 707, 679, 575, 593; ^{1}H - NMR (DMSO-d_6, δ ppm): 1.99-2.57 (24H, m, 12 x CH_2), 4.47 (2H, s, 2 x CH); 6.88-7.04 (4H, s, ArH).

Anal. Calcd. for $C_{32}H_{30}O_6$: C, 75.27; H, 5.92. Found: C, 75.21; H, 5.86.

9,9'-(1,3-phenylene)bis(3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione) (**7b**).

M.P. >300°C; IR (KBr, ν, cm^{-1}): 3278, 3222, 3079, 2960, 1650, 1616, 1487, 1368, 1255, 1222, 1170, 1145, 1004, 978, 888, 700, 661, 558, 479; ^{1}H - NMR (DMSO-d_6, δ ppm): 1.93-2.42 (24H, m, 12 x CH_2), 4.75 (2H, s, 2 x CH), 6.88-6.92 (4H, s, ArH); 9.20 (2H, s, 2 x NH).

Anal. Calcd. for $C_{32}H_{32}N_2O_4$: C, 75.56 ; H,6.34, N, 5.50. Found: C, 75.54; H, 6.32; N, 5.44.

9,9'-(1,3-phenylene)bis(10-hydroxy-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione) (**8b**).

M.P. 256-258°C; IR (KBr, ν, cm^{-1}): 3310, 2958, 2874, 1660, 1460, 1366, 1201, 1165, 1143, 1004, 704, 582; ^{1}H - NMR (DMSO-d_6, δ ppm): 2.03-2.61 (24H, m, 12 x CH_2), 4.47(2H, s, 2 x CH); 6.81-7.06 (4H, m, ArH); 10.71 (2H, s, 2 x NH).

Anal. Calcd. for $C_{32}H_{32}N_2O_6$: C, 71.09; H, 5.96; N, 5.18. Found: C, 71.0; H, 5.99; N, 5.14.

9,9'-(1,3-phenylene)bis(3,4,5,6,7,9-hexahydro-1*H*-thioxanthene-1,8(2*H*)-dione) (**9b**).

M.P. >300°C; IR (KBr, ν, cm^{-1}): 3220, 2826, 2740, 1610, 1410, 1330, 1210, 1140, 980, 704, 580; ^{1}H - NMR (DMSO-d_6, δ ppm): 2.03-2.61 (24H, m, 12 x CH_2), 4.46 (2H, s, 2 x CH); 6.98-7.28 (4H,m, ArH).

Anal. Calcd. for $C_{32}H_{30}O_4S_2$: C, 70.82; H, 5.57; S, 11.81. Found: C, 70.76; H, 5.51; S, 11.77.

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