A novel approach towards the synthesis of tricyclic systems based on pyridine, pyran, thiopyran, azepine, oxepin, thiepin, and pyrimidine rings under different solvent conditions

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Abstract: Synthesis of some oxygen, nitrogen, and sulfur based condensed heterocycles by the condensation of dimedone with aromatic monoaldehyde under different solvent conditions has been achieved.

Key words: dimedone, heterocyclization, dimerization.

Résumé : On a réalisé la synthèse de dérivés hétérocycliques à base d'oxygène, d'azote et de soufre par condensation de la dimédone avec un monoaldéhyde aromatique dans divers solvants.

Mots-clés : dimédone, hétérocyclisation, dimérisation.

[Traduit par la Rédaction]

Introduction

1,3-Dicarbonyl derivatives constitute important synthetic intermediates, incorporating multiple functionalities that can be either nucleophilic or electrophilic species in a large variety of synthetic transformations.[1] Their versatility and effectiveness as potential multicomponent substrates were first discovered and utilized by Arthur Hantzsch[2] in 1882. Since then, 1,3-dicarbonyl compounds have been playing increasingly significant roles in the development of modern synthetic organic chemistry. Keeping these facts in view, we are studying the synthesis of some novel heterocyclic systems by investigating the effect of a change in solvent on the ring size of heterocyclic moiety via the condensation of a 1,3-dicarbonyl compound (dimedone) with an aromatic monoaldehyde. A literature survey revealed that a fair amount of work has been published in the condensation reactions of dimedone.[3–8] Because of our laboratory's long standing interest in the condensation reactions of active methylene compounds,[9] we extend our synthetic activity along these lines to include the synthesis of some pyran, pyridine, thiopyran, oxepin, azepine, and thiepin based condensed heterocycles by the condensation of dimedone with aromatic monoaldehyde under different solvent conditions.[5,10–15] The intermediates and the final heterocyclic products have been found to be highly potent pharmacologically in recent years, revealing some important conclusions regarding structure–activity relationships.[16–19]

Results and discussion

When dimedone was treated with aromatic monoaldehyde in ethylene glycol under different sets of conditions (as detailed in the Experimental section); some novel pyran, pyridine, and thiopyran based condensed heterocycles have been generated with dimedone moiety on the periphery of the molecule. The reaction probably takes place via the concerted mechanism in which Knoevenagel condensation occurs between dimedone (**1**) and aromatic aldehydes (**2**), Michael addition of the second dimedone molecule on the 2-arylidenedimedone probably formed in situ as a result of Knoevenagel condensation, and cyclodehydration of the probable Michael product (**9**)[20,21] takes place in single step. The products (**10–14**)[20,22–25] were obtained in excellent yield but the intermediate products, arylidenedimedone of Knoevenagel condensation, and product (**9**) of Michael addition could not be isolated. In another method using acetic acid as solvent in the initial step, the yield of the final products (**10–14**) was not as good and hardly comparable with that in the case of ethylene glycol. The added advantage in this method was the isolation of the intermediate product (**9**) in a reasonably good yield, which was probably in dienol form, and subsequently produced the products (**10–14**) with different reagents using DMF as solvent. The yield falls slightly in all the conversions of **9** to **10**, **11**, **12**, **13**, and **14** using DMF as solvent. Using DMSO as solvent, some interesting results were obtained in which arylidenedimedone moiety initially formed and underwent reductive dimerization to give the dimer (**3**) (Scheme 1). In each case, the dimer (**3**) was obtained as a mixture of a racimate and the inactive meso compound. The racemic mixture (±) and the inactive meso compound could not be resolved and separated, respectively, by repeated efforts. The asymmetric synthesis of

Received 6 July 2009. Accepted 24 November 2009. Published on the NRC Research Press Web site at canjchem.nrc.ca on 15 April 2010.

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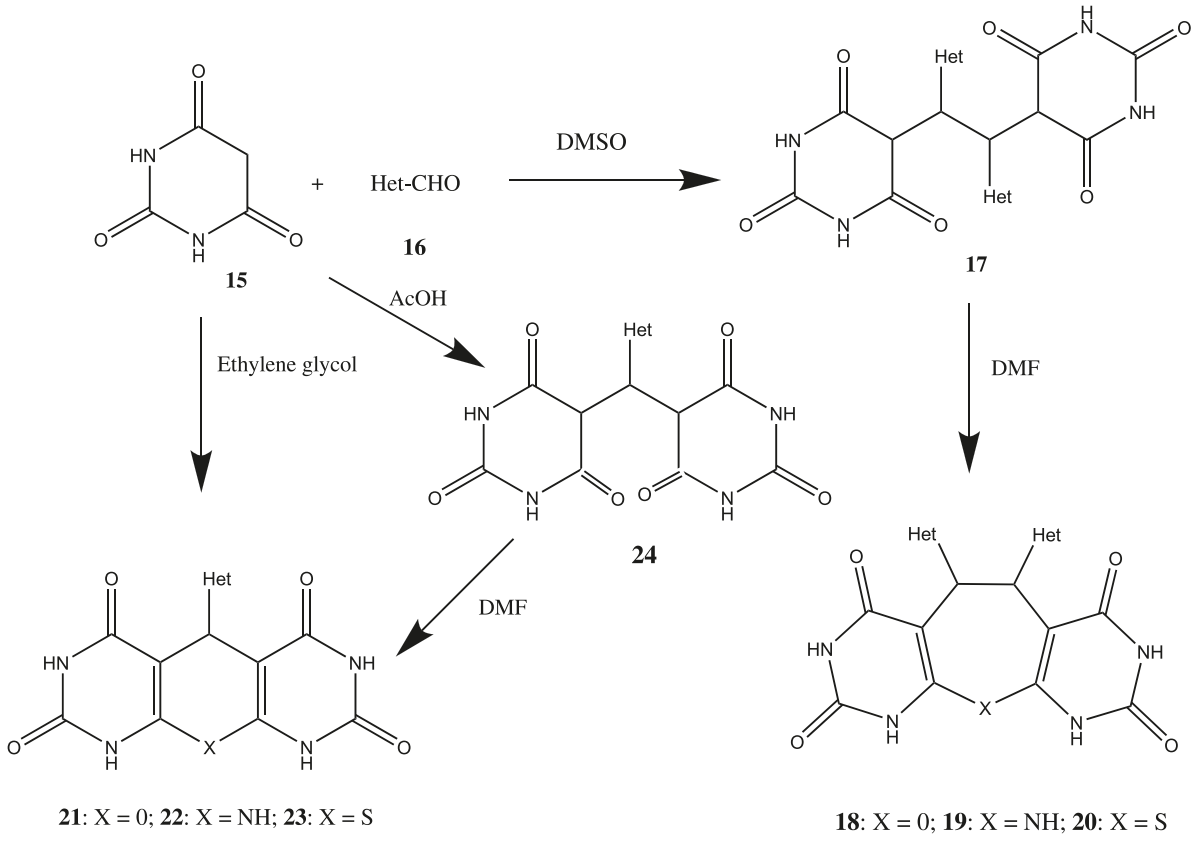
Scheme 1.



the enantiomers has almost been achieved in a separate study with good variety. Though it is still under active study, it may soon be submitted for publication. The dimers seemed to be very interesting for ring closure and as such were subjected to heterocyclization under different sets of conditions (as detailed in the Experimental section) in DMF to give some condensed heterocycles based on central oxepin, azepine, and thiepin moiety and the peripheral dimedone moiety. The condensed heterocyclic products (**4**–**8**) bearing seven membered central heterocyclic moiety were all obtained, again as single and pure meso compounds since the possibility of cyclization of the enantiomers of the racemic mixture of **3** resulting in the formation of a mixture of racemic (**4**–**8**) is not only highly difficult but almost impossible.

Exact quantities of $NH_2OH{\cdot}HCl$ in the synthesis of *N*-hydroxy compounds, $NH_2{\cdot}NH_2$ in the synthesis of *N*-amino compounds, and P_2S_5 in the synthesis of thio compounds should be used lest their higher quantities should form corresponding oximino, hydrazino, and thioxo derivatives, respectively, of the respective carbonyl products (**6**–**8**, **12**–**14**, **20**, and **23**).

To generalize these transformations and to derive the conclusions more confidently, reactions between a heterocyclic active methylene compound, barbituric acid (replacing dimedone), and heteroaromatic aldehydes, furfural and indole-3-carboxaldehyde (both replacing aromatic aldehydes), were also studied (Scheme 2). The results were exactly the same as expected under different conditions of solvents and reagents.

All the compounds obtained (**17**–**24**) were analyzed for C, H, N, and S and were found to be in good agreement with the calculated values, which have been presented in Table 1, along with mps and yield. The structures were established on the basis of spectroscopic data and elemental analysis.

Experimental

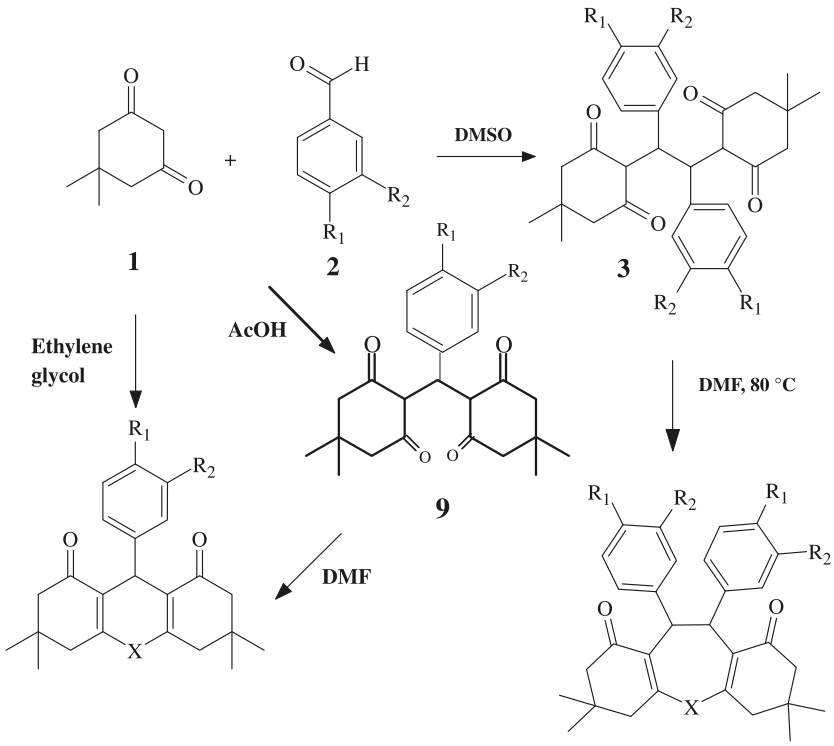
General

Thin layer chromatography was used to establish the homogeneity of the compounds. Column chromatography was performed over silica gel (60–120 mesh) using the ethyl acetate – petroleum ether system as eluent. All other reagents were commercially available and used without further purification. Melting points were determined in a capillary tube and are uncorrected. IR spectra were recorded on a PerkinElmer IR spectrometer using potassium bromide pellets. The ^1H and ^{13}C NMR spectra were run on Varian Unity 500 MHz NMR spectrometer using TMS as an internal standard (chemical shift in δ ppm). Elemental analyses were performed on simple a CHNS analyzer.

General procedure for the synthesis of 3

Dimedone (2 mmol) and aromatic aldehyde (2 mmol) were dissolved in dimethyl sulfoxide (1 mL) and the reaction mixture was refluxed for 30–40 min. The clear reaction

Scheme 2.



10: X = O; **11**: X = NH; **12**: X = NOH
13: X = NNH_2; **14** : X = S

4: X = O; **5**: X = NH; **6**: X = NOH
7: X = NNH_2; **8**: X = S

a: $R_1 = R_2 = OCH_3$
b: $R_1 = NO_2$, $R_2 = H$

mixture was diluted with methanol (20 mL). The insoluble product was separated by filtration, washed with methanol (3 × 20 mL), and then finally dried at 100 °C for 1 h.

General procedure for the synthesis of 4–8

Compound **3** (0.01 mol) was stirred at 80° in DMF for 30 min (for **4**: as such; for **5**: 3 mmol NH_4OAc; for **6**: 2 mmol $NH_2OH{\cdot}HCl$ and 2 mmol NaOAc; for **7**: 2 mmol $NH_2{\cdot}NH_2{\cdot}HCl$ and 2 mmol NaOAc; and for **8**: 2 mmo1 P_2S_5 was added). The reaction mixture was cooled to room temperature, diluted with water, the insoluble product filtered and then the solid obtained was washed with water, dried, and crystallized from ethanol. Further purification was accomplished by running it through a short column of silica gel followed by recrystallization from hot ethanol.

General method for the synthesis[20,21] of 9a and 9b

Dimedone (0.02 mol) and an aromatic aldehyde (0.01 mol) were dissolved in glacial acetic acid (30 mL) and stirred at room temperature until TLC showed the disappearance of the starting material. The insoluble product was separated by filtration, washed with water (3 × 20 mL), dried, and crystallized from 95% ethanol. Further purification was accomplished by running it through a short column of silica gel followed by recrystallization from ethanol.

General procedure for the synthesis[20,22–25] of 10–14

Dimedone (4 mmol) and an aldehyde (2 mmol) were refluxed in an ethylene glycol (1 mL) for 8–10 min (for **10**: as such; for **11**: 3 mmol NH_4OAc; for **12**: 2 mmol $NH_2OH{\cdot}HCl$ and 2 mmol NaOAc; for **13**: 2 mmol $NH_2{\cdot}NH_2{\cdot}HCl$ and 2 mmol NaOAc; and for **14**: 2 mmo1 P_2S_5 was added). The reaction mixture was allowed to cool at room temperature, then poured into 50 mL of water. The solid that was separated was filtered and washed with water. The crude solid after drying was purified by recrystallization from 95% EtOH to give **10**, **11**, **12**, **13**, and **14**.

2-[1,2-Bis(3,4–dimethoxyphenyl)-2-(4,4-dimethyl-2,6-dioxocyclohexyl)ethyl]-5,5-dimethylcyclohexane-1,3-dione (3a)

Recrystallized from methanol, mp 232–236 °C. IR (KBr, cm^{-1}): 3410, 3040, 2944, 2860, 2594, 1580, 1460, 1410, 1370, 1296, 1235, 1132, 1050, 972, 870, 790. ^{1}H NMR (DMSO-d_6) δ: 1.10 (s, 6H, 2 × CH_3), 1.20 (s, 6H, 2 × CH_3), 2.30–2.52 (m, 8H, 4 × CH_2), 3.82 (s, 6H, OCH_3), 3.86 (s, 6H, OCH_3), 5.47 (d, 2H, J = 6.0 Hz), 5.70 (d, 2H, J = 6.0 Hz), 6.96–7.28 (m, 6H, ArH). ^{13}C NMR (DMSO-d_6) δ: 15.9, 19.3, 27.1, 29.4, 47.4, 54.2, 58.3, 112.6, 115.2, 121.4, 133.5, 144.4, 147.5, 151.0, 160.0, 197.6. Anal. calcd. for $C_{34}H_{42}O_8$: C 70.56, H 7.31; found: C 70.51, H 7.25.

Table 1. Physical and analytical data of compounds **17–24.**

Compound	Mp (°C)[a]	Yield (%)	Molecular formula	Analysis (% calcd./found)			
				C	H	N	S
17a	282–284	82	$C_{26}H_{20}N_6O_6$	60.93	3.90	16.40	
				60.89	3.88	16.35	
17b[26]	278–282	78	$C_{18}H_{14}N_4O_8$	52.17	3.38	13.52	
				52.12	3.34	13.48	
18a	276–282	80	$C_{26}H_{18}N_6O_5$	63.15	3.64	17.0	
				63.09	3.62	16.94	
18b[26]	286–290	82	$C_{18}H_{12}N_4O_7$	54.54	3.03	14.14	
				54.51	3.01	14.09	
19a	284–288	80	$C_{26}H_{19}N_7O_4$	63.28	3.85	19.87	
				63.23	3.84	19.82	
19b	282–286	82	$C_{18}H_{13}N_5O_6$	54.68	3.29	17.72	
				54.62	3.26	17.67	
20a	280–284	76	$C_{26}H_{18}N_6O_4S$	61.17	3.52	16.47	6.27
				61.11	3.51	16.40	6.24
20b	286–290	74	$C_{18}H_{12}N_4O_6S$	52.42	2.91	13.59	6.27
				52.36	2.88	13.52	6.25
21a	292–296	80	$C_{17}H_{11}N_5O_5$	55.89	3.01	19.17	
				55.84	2.98	19.11	
21b[26]	>300	78	$C_{13}H_8N_4O_6$	49.36	2.53	17.72	
				49.32	2.49	17.65	
22a	>300	80	$C_{17}H_{12}N_6O_4$	56.04	3.29	23.07	
				56.00	3.28	23.01	
22b	>300	82	$C_{13}H_9N_5O_5$	49.52	2.85	22.22	
				49.32	2.49	19.11	
23a	>300	78	$C_{17}H_{11}N_5O_4S$	53.54	2.88	18.37	8.39
				53.49	2.84	18.31	8.35
23b	>300	76	$C_{13}H_8N_4O_5S$	46.98	2.40	16.86	9.63
				46.92	2.36	16.81	9.61
24a	>300	80	$C_{17}H_{13}N_5O_6$	53.26	3.39	18.27	
				53.21	3.36	18.22	
24b	>300	84	$C_{13}H_{10}N_4O_7$	46.70	2.99	16.76	
				46.66	2.97	16.70	

Note: a: Het = 3-indolyl; **b**: Het = 2-furyl (Scheme 2).

[a]All compounds were recrystallized from hot ethanol.

10,11-Bis(3,4-dimethoxyphenyl)-3,3,7,7-tetramethyl-1,2,3,4,6,7,8,9,10,11-decahydrodibenzo[*b*,*f*]oxepin-1,9-dione (4a)

Recrystallized from hot ethanol, mp 240–244 °C. IR (KBr, cm^{-1}): 3422, 3046, 2950, 2868, 2694, 1588, 1470, 1422, 1376, 1298, 1244, 1150, 1066, 972, 880, 700. ^{1}H NMR (DMSO-d_6) δ: 1.11 (s, 6H, 2 × CH_3), 1.24 (s, 6H, 2 × CH_3), 2.34–2.54 (m, 8H, 4 × CH_2), 3.80 (s, 6H, OCH_3), 3.86 (s, 6H, OCH_3), 5.44 (d, 2H, J = 6.0 Hz), 7.02–7.28 (m, 6H, ArH). ^{13}C NMR (DMSO-d_6) δ: 15.9, 19.4, 27.1, 29.7, 47.7, 54.2, 56.3, 112.6, 115.0, 121.2, 133.4, 147.5, 160.4, 197.7. Anal. calcd. for $C_{34}H_{40}O_7$: C 72.83, H 7.19; found: C 72.78, H 7.14.

10,11-Bis(3,4-dimethoxyphenyl)-3,3,7,7-tetramethyl-2,3,4,5,6,7,8,9,10,11-decahydro-1*H*-dibenzo[*b*,*f*]azepine-1,9-dione (5a)

Recrystallized from hot ethanol, mp 260–264 °C. IR (KBr, cm^{-1}): 3420, 3056, 2950, 2862, 2684, 1578, 1475, 1422, 1366, 1290, 1248, 1155, 1068, 976, 880, 704. ^{1}H NMR (DMSO-d_6) δ: 1.12 (s, 6H, 2 × CH_3), 1.26 (s, 6H, 2 × CH_3), 2.30–2.50 (m, 8H, 4 × CH_2), 3.84 (s, 6H, OCH_3), 3.88 (s, 6H, OCH_3), 5.46 (d, 2H, J = 6.0 Hz), 7.02–7.26 (m, 6H, ArH), 8.20 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6) δ: 15.4, 19.6, 27.7, 29.7, 47.7, 54.2, 56.3, 112.6, 115.0, 121.4, 134.4, 148.5, 160.2, 196.4. Anal. calcd. for $C_{34}H_{41}NO_6$: C 72.96, H 7.38, N 2.50; found: C 72.78, H 7.34, N 2.46.

10,11-Bis(3,4-dimethoxyphenyl)-5-hydroxy-3,3,7,7-tetramethyl-2,3,4,5,6,7,8,9,10,11-decahydro-1*H*-dibenzo[*b*,*f*]azepine-1,9-dione (6a)

Recrystallized from hot ethanol, mp 240–242 °C. IR (KBr, cm^{-1}): 3400, 3058, 2964, 2866, 2674, 1576, 1476, 1424, 1368, 1288, 1246, 1156, 1064, 976, 886, 710. ^{1}H NMR (DMSO-d_6) δ: 1.12 (s, 6H, 2 × CH_3), 1.26 (s, 6H, 2 × CH_3), 2.30–2.50 (m, 8H, 4 × CH_2), 3.84 (s, 6H, OCH_3), 3.88 (s, 6H, OCH_3), 5.46 (d, 2H, J = 6.0 Hz), 7.02–7.26 (m, 6H, ArH), 10.73 (bs, 1H, OH). ^{13}C NMR (DMSO-d_6) δ: 15.4, 19.6, 27.4, 29.2, 47.8, 54.2, 56.3, 112.6, 115.1, 121.2, 132.4, 144.5, 161.1, 197.4. Anal. calcd. for $C_{34}H_{41}NO_7$: C 70.93, H 7.17, N 2.43; found: C 72.89, H 7.14, N 2.38.

5-Amino-10,11-bis(3,4-dimethoxyphenyl)-3,3,7,7-tetramethyl-2,3,4,5,6,7,8,9,10,11-decahydro-1*H*-dibenzo[*b*,*f*]azepine-1,9-dione (7a)

Recrystallized from hot ethanol, mp 270–272 °C. IR (KBr, cm^{-1}): 3410, 3050, 2954, 2865, 2676, 1578, 1466, 1416, 1366, 1286, 1242, 1158, 1066, 976, 880, 716. ^{1}H NMR (DMSO-d_6) δ: 1.14 (s, 6H, 2 × CH_3), 1.22 (s, 6H, 2 × CH_3), 2.34–2.54 (m, 8H, 4 × CH_2), 3.82 (s, 6H, OCH_3), 3.86 (s, 6H, OCH_3), 5.42 (d, 2H, J = 6.0 Hz), 7.02–7.24 (m, 6H, ArH), 8.25 (d, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 15.4, 19.2, 26.1, 29.6, 47.4, 54.2, 56.1, 112.6, 115.0, 121.2, 133.6, 147.2, 160.4, 197.4. Anal. calcd. for $C_{34}H_{42}N_2O_6$: C 71.05, H 7.36, N 4.87; found: C 72.01, H 7.31, N 4.81.

10,11-Bis(3,4-dimethoxyphenyl)-3,3,7,7-tetramethyl-1,2,3,4,6,7,8,9,10,11-decahydrodibenzo[*b*,*f*]thiepin-1,9-dione (8a)

Recrystallized from hot ethanol, mp 240–244 °C. IR (KBr, cm^{-1}): 3426, 3056, 2960, 2864, 2694, 1588, 1470, 1422, 1376, 1298, 1244, 1156, 1068, 976, 880, 700. ^{1}H NMR (DMSO-d_6) δ: 1.11 (s, 6H, 2 × CH_3), 1.24 (s, 6H, 2 × CH_3), 2.34–2.54 (m, 8H, 4 × CH_2), 3.82 (s, 6H, OCH_3), 3.86 (s, 6H, OCH_3), 5.44 (d, 2H, J = 6.0 Hz), 7.02–7.28 (m, 6H, ArH). ^{13}C NMR (DMSO-d_6) δ: 15.7, 19.2, 27.2, 29.4, 47.1, 54.2, 56.3, 112.6, 115.0, 121.2, 132.4, 147.4, 160.2, 197.6. Anal. calcd. for $C_{34}H_{40}O_6S$: C 70.80, H 6.99, S 5.66; found: C 70.74, H 6.92, S 5.61.

2-[(4,4-Dimethyl-2,6-dioxocyclohexyl)(3,4-dimethoxyphenyl)methyl]-5,5-dimethylcyclohexane-1,3-dione (9a)[20]

Recrystallized from ethanol, mp 172–176 °C. IR (KBr, cm^{-1}): 3440, 3090, 2844, 2866, 2564, 1590, 1470, 1440, 1300, 1292, 1232, 1144, 1040, 972, 870, 790. ^{1}H NMR (DMSO-d_6) δ: 1.12 (s, 6H, 2 × CH_3), 1.20 (s, 6H, 2 × CH_3), 2.30–2.52 (m, 8H, 4 × CH_2), 3.82 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.47 (d, 2H, J = 6.0 Hz), 5.70 (1H, s, CH), 6.96–7.28 (m, 3H, ArH). ^{13}C NMR (DMSO-d_6) δ: 15.4, 17.7, 26.2, 53.7, 56.4, 68.3, 112.8, 114.4, 119.2, 142.1, 144.4, 147.7, 208.4. Anal. calcd. for $C_{24}H_{30}O_5$: C 72.33, H 7.58; found: C 72.29, H 7.53.

9-(3,4-Dimethoxyphenyl)-3,3,6,6-tetramethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthene-1,8-dione (10a)[20]

Recrystallized from 95% ethanol, mp 186–188 °C. IR (KBr, cm^{-1}): 3222, 3066, 2956, 2866, 2664, 1586, 1474, 1424, 1378, 1288, 1246, 1160, 1064, 976, 856, 740. ^{1}H NMR (DMSO-d_6) δ: 1.10 (s, 6H, 2 × CH_3), 1.22 (s, 6H, 2 × CH_3), 2.34–2.52 (m, 8H, 4 × CH_2), 3.82 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.42 (d, 1H, J = 6.0 Hz), 7.02–7.28 (m, 3H, ArH). ^{13}C NMR (DMSO-d_6) δ: 15.4, 25.2, 27.1, 47.4, 54.2, 56.1, 108.0, 114.4, 130.6, 159.7, 160.6, 198.4. Anal. calcd. for $C_{25}H_{34}O_5$: C 72.43, H 8.26; found: C 72.37, H 8.22.

9-(3,4-Dimethoxyphenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (11a)[22]

Recrystallized from 95% ethanol, mp 252–256 °C. IR (KBr, cm^{-1}): 3424, 3066, 2954, 2864, 2686, 1576, 1478, 1422, 1366, 1290, 1248, 1166, 1070, 956, 840, 704. ^{1}H NMR (DMSO-d_6) δ: 1.12 (s, 6H, 2 × CH_3), 1.24 (s, 6H, 2 × CH_3), 2.30–2.50 (m, 8H, 4 × CH_2), 3.84 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.46 (d, 1H, J = 6.0 Hz), 7.04–7.24 (m, 3H, ArH), 8.26 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6) δ: 16.4, 25.3, 27.7, 47.1, 54.2, 56.1, 108.0, 114,1, 130.2, 159.2, 161.6, 197.4. Anal. calcd. for $C_{25}H_{35}NO_4$: C 72.60, H 8.53, N 3.38; found: C 72.53, H 8.48, N 3.34.

9-(3,4-Dimethoxyphenyl)-10-hydroxy-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (12a)[24]

Recrystallized from 95% ethanol, mp 260–262 °C. IR (KBr, cm^{-1}): 3410, 3068, 2954, 2866, 2674, 1566, 1466, 1428, 1364, 1280, 1260, 1146, 1074, 944, 880, 740. ^{1}H NMR (DMSO-d_6) δ: 1.16 (s, 6H, 2 × CH_3), 1.22 (s, 6H, 2 × CH_3), 2.34–2.54 (m, 8H, 4 × CH_2), 3.84 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.46 (d, 1H, J = 6.0 Hz), 7.02–7.26 (m, 3H, ArH), 10.73 (bs, 1H, OH). ^{13}C NMR (DMSO-d_6) δ: 15.1, 25.5, 27.2, 47.6, 54.4, 56.1, 108.0, 114.2, 130.2, 159.4, 160.4, 198.4. Anal. calcd. for $C_{25}H_{35}NO_5$: C 69.90, H 8.21, N 3.26; found: C 69.84, H 8.16, N 3.22.

10-Amino-9-(3,4-dimethoxyphenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (13a)

Recrystallized from 95% ethanol, mp 270–272 °C. IR (KBr, cm^{-1}): 3420, 3042, 2960, 2864, 2672, 1562, 1462, 1424, 1360, 1284, 1242, 1158, 1066, 946, 882, 727. ^{1}H NMR (DMSO-d_6) δ: 1.14 (s, 6H, 2 × CH_3), 1.22 (s, 6H, 2 × CH_3), 2.34–2.54 (m, 8H, 4 × CH_2), 3.84 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.44 (d, 1H, J = 6.0 Hz), 7.06–7.26 (m, 3H, ArH), 8.28 (d, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 15.2, 25.4, 27.2, 47.5, 54.1, 56.2, 108.0, 114.4, 132.6, 159.4, 160.2, 197.4. Anal. calcd. for $C_{25}H_{36}N_2O_4$: C 70.06, H 8.46, N 6.53; found: C 70.01, H 8.48, N 6.48.

9-(3,4-Dimethoxyphenyl)-3,3,6,6-tetramethyl-2,3,4,5,6,7,8,9-octahydro-1*H* thioxanthene-1,8-dione (14a)

Recrystallized from 95% ethanol, mp 234–238 °C. IR (KBr, cm^{-1}): 3426, 3056, 2960, 2864, 2694, 1588, 1470, 1422, 1376, 1298, 1244, 1156, 1068, 976, 880, 700. ^{1}H NMR (DMSO-d_6) δ: 1.11 (s, 6H, 2 × CH_3), 1.24 (s, 6H, 2 × CH_3), 2.34–2.54 (m, 8H, 4 × CH_2), 3.80 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.44 (d, 1H, J = 6.0 Hz), 7.02–7.28 (m, 3H, ArH). ^{13}C NMR (DMSO-d_6) δ: 15.2, 22.2, 27.4, 47.2, 54.2, 56.1, 108.0, 114.4, 130.6, 159.2, 160.4, 194.4. Anal. calcd. for $C_{25}H_{34}O_4S$: C 69.73, H 7.95, S 7.44; found: C 69.68, H 7.88, S 7.38.

2-[1,2-Bis(4-nitrophenyl)-2-(4,4-dimethyl-2,6-dioxocyclohexyl)ethyl]-5,5-dimethylcyclohexane-1,3-dione (3b)

Recrystallized from methanol, mp 238–240 °C. IR (KBr, cm^{-1}): 3400, 3000, 2966, 2840, 2584, 1560, 1468, 1416, 1360, 1296, 1235, 1144, 1080, 976, 840, 786. ^{1}H NMR (DMSO-d_6) δ: 1.10 (s, 6H, 2 × CH_3), 1.20 (s, 6H, 2 × CH_3), 2.30–2.52 (m, 8H, 4 × CH_2), 5.46 (d, 2H, J = 6.0 Hz), 5.72 (d, 2H, J = 6.0 Hz), 6.96–7.28 (m, 8H, ArH). ^{13}C NMR (DMSO-d_6) δ: 16.9, 20.3, 28.6, 30.4, 47.5, 112.5, 115.2, 122.4, 131.5, 142.4, 147.5, 150.2, 160.4, 198.6. Anal. calcd. for $C_{30}H_{32}N_2O_8$: C 65.68, H 5.87, N 5.10; found: C 65.62, H 5.81, N 5.06.

10,11-Bis(4-nitrophenyl)-3,3,7,7-tetramethyl-1,2,3,4,6,7,8,9,10,11-decahydro-dibenzo[*b*,*f*]oxepin-1,9-dione (4b)

Recrystallized from hot ethanol, mp 240–244 °C. IR (KBr, cm^{-1}): 3422, 3046, 2950, 2868, 2694, 1588, 1470, 1422, 1376, 1298, 1244, 1150, 1066, 972, 880, 700. ^1H NMR (DMSO-d_6) δ: 1.11 (s, 6H, 2 × CH_3), 1.24 (s, 6H, 2 × CH_3), 2.34–2.54 (m, 8H, 4 × CH_2), 5.42 (d, 2H, J = 6.0 Hz), 7.02–7.28 (m, 8H, ArH). ^{13}C NMR (DMSO-d_6) δ: 15.9, 19.4, 27.1, 29.7, 47.7, 54.2, 112.6, 115.0, 121.2, 133.4, 147.5, 160.4, 197.7. Anal. calcd. for $C_{30}H_{30}N_2O_7$: C 67.91, H 5.69, N 5.28; found: C 67.87, H 5.64, N 5.23.

10,11-Bis(4-nitrophenyl)-3,3,7,7-tetramethyl-2,3,4,5,6,7,8,9,10,11-decahydro-1*H*-dibenzo[*b*,*f*]azepine-1,9-dione (5b)

Recrystallized from hot ethanol, mp 260–264 °C. IR (KBr, cm^{-1}): 3420, 3056, 2960, 2862, 2684, 1578, 1475, 1422, 1366, 1290, 1248, 1155, 1068, 976, 880, 704 . ^1H NMR (DMSO-d_6) δ: 1.12 (s, 6H, 2 × CH_3), 1.26 (s, 6H, 2 × CH_3), 2.30–2.50 (m, 8H, 4 × CH_2), 5.46 (d, 2H, J = 6.0 Hz), 7.02–7.26 (m, 8H, ArH), 8.24 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6) δ: 15.4, 19.6, 27.7, 29.7, 47.7, 54.2, 112.6, 115.0, 121.4, 134.4, 148.5, 160.2, 196.4. Anal. calcd. for $C_{30}H_{31}N_3O_6$: C 68.03, H 5.90, N 7.93; found: C 67.98, H 5.84, N 7.88.

10,11-Bis(4-nitrophenyl)-5-hydroxy-3,3,7,7-tetramethyl-2,3,4,5,6,7,8,9,10,11-decahydro-1*H*-dibenzo[*b*,*f*]azepine-1,9-dione (6b)

Recrystallized from hot ethanol, mp 240–242 °C. IR (KBr, cm^{-1}): 3400, 3088, 2964, 2866, 2676, 1576, 1478, 1424, 1368, 1288, 1246, 1156, 1064, 976, 886, 710. ^1H NMR (DMSO-d_6) δ: 1.12 (s, 6H, 2 × CH_3), 1.26 (s, 6H, 2 × CH_3), 2.32–2.54 (m, 8H, 4 × CH_2), 5.44 (d, 2H, J = 6.0 Hz), 7.02–7.24 (m, 8H, ArH), 10.72 (bs, 1H, OH). ^{13}C NMR (DMSO-d_6) δ: 15.4, 19.6, 27.4, 29.2, 47.8, 54.2, 112.6, 115.1, 121.2, 132.4, 144.5, 161.1, 197.4. Anal. calcd. for $C_{30}H_{31}N_3O_7$: C 66.04, H 5.72, N 7.70; found: C 65.98, H 5.65, N 7.63.

5-Amino-10,11-bis(4-nitrophenyl)-3,3,7,7-tetramethyl-2,3,4,5,6,7,8,9,10,11-decahydro-1*H*-dibenzo[*b*,*f*]azepine-1,9-dione (7b)

Recrystallized from hot ethanol, mp 266–268 °C. IR (KBr, cm^{-1}): 3410, 3050, 2954, 2865, 2676, 1578, 1466, 1416, 1366, 1286, 1242, 1158, 1066, 976, 880, 716. ^1H NMR (DMSO-d_6) δ: 1.14 (s, 6H, 2 × CH_3), 1.22 (s, 6H, 2 × CH_3), 2.34–2.54 (m, 8H, 4 × CH_2), 5.46 (d, 2H, J = 6.0 Hz), 7.02–7.24 (m, 8H, ArH), 8.22 (d, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 15.4, 19.2, 26.1, 29.6, 47.4, 54.2, 112.6, 115.0, 121.2, 133.6, 147.2, 160.4, 197.4. Anal. calcd. for $C_{30}H_{32}N_4O_6$: C 66.16, H 5.92, N 10.28; found: C 66.08, H 7.86, N 10.21.

10,11-Bis(4-nitrophenyl)-3,3,7,7-tetramethyl-1,2,3,4,5,6,7,8,9,10,11-decahydro-dibenzo[*b*,*f*]thiepin-1,9-dione (8b)

Recrystallized from hot ethanol, mp 240–244 °C. IR (KBr, cm^{-1}): 3426, 3056, 2960, 2864, 1588, 1470, 1422, 1376, 1298, 1244, 1156, 1068, 976, 880, 700. ^1H NMR (DMSO-d_6) δ: 1.11 (s, 6H, 2 × CH_3), 1.24 (s, 6H, 2 × CH_3), 2.34–2.54 (m, 8H, 4 × CH_2), 5.42 (d, 2H, J = 6.0 Hz), 7.02–7.28 (m, 8H, ArH). ^{13}C NMR (DMSO-d_6) δ: 15.7, 19.2, 27.2, 29.4, 47.1, 54.2, 112.6, 115.0, 121.2, 132.4, 147.4, 160.2, 197.6. Anal. calcd. for $C_{30}H_{30}N_2O_6S$: C 65.91, H 5.53, N 5.12, S 5.86; found: C 65.85, H 5.48, N 5.05, S 5.80.

2-[(4,4-Dimethyl-2,6-dioxocyclohexyl)(4-nitrophenyl)methyl]-5,5-dimethylcyclohexane-1,3-dione (9b)[21]

Recrystallized from ethanol, mp 188 °C (decomp), 252 °C. IR (KBr, cm^{-1}): 3440, 3090, 2834, 2868, 2544, 1590, 1472, 1446, 1320, 1282, 1230, 1146, 1060, 974, 870, 790. ^1H NMR (DMSO-d_6) δ: 1.14 (s, 6H, 2 × CH_3), 1.22 (s, 6H, 2 × CH_3), 2.34–2.52 (m, 8H, 4 × CH_2), 5.47 (d, 2H, J = 6.0 Hz), 5.70 (1H, s, CH), 7.02–7.24 (m, 4H, ArH). ^{13}C NMR (DMSO-d_6) δ: 15.4, 17.7, 26.2, 68.3, 112.8, 114.4, 119.2, 142.1, 144.4, 147.7, 208.4. Anal. calcd. for $C_{23}H_{27}NO_6$: C 66.81, H 6.58, N 3.38; found: C 66.76, H 6.54, N 3.34.

9-(4-Nitrophenyl)-3,3,6,6-tetramethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthene-1,8-dione (10b)

Recrystallized from 95% ethanol, mp 236–238 °C. IR (KBr, cm^{-1}): 3222, 3066, 2956, 2866, 2664, 1586, 1474, 1424, 1378, 1288, 1246, 1160, 1064, 976, 856, 740. ^1H NMR (DMSO-d_6) δ: 1.10 (s, 6H, 2 × CH_3), 1.22 (s, 6H, 2 × CH_3), 2.34–2.52 (m, 8H, 4 × CH_2), 5.44 (d, 1H, J = 6.0 Hz), 7.02–7.26 (m, 4H, ArH). ^{13}C NMR (DMSO-d_6) δ: 15.4, 25.2, 27.1, 47.4, 54.2, 108.0, 114.4, 130.6, 159.7, 160.6, 198.4. Anal. calcd. for $C_{23}H_{25}NO_5$: C 69.85, H 6.37; found: C 69.78, H 6.31.

9-(4-Nitrophenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (11b)[23]

Recrystallized from 95% ethanol, mp 252–256 °C. IR (KBr, cm^{-1}): 3424, 3066, 2954, 2864, 2686, 1576, 1478, 1422, 1366, 1290, 1248, 1166, 1070, 956, 840, 704. ^1H NMR (DMSO-d_6) δ: 1.12 (s, 6H, 2 × CH_3), 1.24 (s, 6H, 2 × CH_3), 2.30–2.50 (m, 8H, 4 × CH_2), 5.46 (d, 1H, J = 6.0 Hz), 7.04–7.24 (m, 4H, ArH), 8.26 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 16.4, 25.3, 27.7, 47.1, 54.2, 108.0, 114.1, 130.2, 159.2, 161.6, 197.4. Anal. calcd. for $C_{23}H_{26}N_2O_4$: C 70.03, H 6.64, N 7.10; found: C 69.98, H 6.58, N 7.04.

9-(4-Nitrophenyl)-10-hydroxy-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (12b)[25]

Recrystallized from 95% ethanol, mp 260–262 °C. IR (KBr, cm^{-1}): 3410, 3068, 2954, 2866, 2674, 1566, 1466, 1428, 1364, 1280, 1260, 1146, 1074, 944, 880, 740. ^1H NMR (DMSO-d_6) δ: 1.16 (s, 6H, 2 × CH_3), 1.22 (s, 6H, 2 × CH_3), 2.34–2.54 (m, 8H, 4 × CH_2), 5.46 (d, 1H, J = 6.0 Hz), 7.02–7.26 (m, 4H, ArH), 10.73 (bs, 1H, OH). ^{13}C NMR (DMSO-d_6) δ: 15.1, 25.5, 27.2, 47.6, 54.4, 108.0, 114.2, 130.2, 159.4, 160.4, 198.4. Anal. calcd. for $C_{23}H_{26}N_2O_5$: C 67.30, H 6.38, N 6.82; found: C 67.24, H 6.31, N 6.77.

10-Amino-9-(4-nitrophenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydro acridine-1,8-dione (13b)

Recrystallized from 95% ethanol, mp 270–272 °C. IR (KBr, cm^{-1}): 3420, 3042, 2960, 2864, 2672, 1562, 1462, 1424, 1360, 1284, 1242, 1158, 1066, 946, 882, 727. ^1H NMR (DMSO-d_6) δ: 1.14 (s, 6H, 2 × CH_3), 1.22 (s, 6H, 2 × CH_3), 2.34–2.54 (m, 8H, 4 × CH_2), 5.44 (d, 1H, J = 6.0 Hz), 7.02–7.24 (m, 4H, ArH), 8.28 (d, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 15.2, 25.4, 27.2, 47.5, 54.1, 108.0, 114.4, 132.6, 159.4, 160.2, 197.4. Anal. calcd. for $C_{23}H_{27}N_3O_4$: C 67.46, H 6.64, N 10.26; found: C 67.41, H 6.58, N 10.21.

9-(4-Nitrophenyl)-3,3,6,6-tetramethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-thioxanthene-1,8-dione (14b)

Recrystallized from 95% ethanol, mp 234–238 °C. IR (KBr, cm^{-1}): 3426, 3056, 2960, 2864, 2694, 1588, 1470, 1422, 1376, 1298, 1244, 1156, 1068, 976, 880, 700. ^1H NMR (DMSO-d_6) δ: 1.11 (s, 6H, 2 × CH_3), 1.24 (s, 6H, 2 × CH_3), 2.34–2.54 (m, 8H, 4 × CH_2), 3.80 (s, 3H, OCH_3), 5.44 (d, 1H, J = 6.0 Hz), 7.02–7.28 (m, 4H, ArH). ^{13}C NMR (DMSO-d_6) δ: 15.2, 22.2, 27.4, 47.2, 54.2, 108.0, 114.4, 130.6, 159.2, 160.4, 194.4. Anal. calcd. for $C_{23}H_{25}NO_4S$: C 67.13, H 6.12, S 7.79; found: C 67.07, H 6.06, S 7.72.

5-[1,2-Di(2-furyl)-2-(2,4,6-trioxohexahydropyrimidin-5-yl)ethyl]-hexahydropyrimidine-2,4,6-trione (17b)[26]

^1H NMR (DMSO-d_6, 500 MHz) δ: 6.90–7.0 (6H, m, furan ring Hs), 8.45 (2H, d, J = 6.0 Hz), 8.48 (2H, d, J = 6.0 Hz), 11.26 (4H, s, NHs). ^{13}C NMR (DMSO-d_6, 500 MHz) δ: 43.1 (barbituric acid C-5 carbon), 86.6 (benzyl carbon), 136.2, 137.7, 139.9, 142.3 (four different carbons for two furan moieties), 161.4, 162.1, 165.4 (three different carbonyl carbons from barbituric acid).

5,6-Di(2-furyl)-5,6-dihydropyrimidino[5′,4’:6,7]oxepino[2,3-*d*]pyrimidine-2,4,7,9(1*H*,3*H*,8*H*,10*H*)-tetraone (18b)[26]

^1H NMR (DMSO-d_6, 500 MHz) δ: 6.95–6.70 (6H, m, furan ring Hs), 8.46 (2H, d, J = 6.0 Hz), 11.10 (s, 2H, NHs), 11.23 (2H, s, NHs). ^{13}C NMR (DMSO-d_6) δ: 43.2 (barbituric acid C-5 carbon), 139.9, 141.1, 144.2, 146.7 (four different carbons for two furan rings), 161.1, 163.4 (two different carbonyl carbons from barbituric acid).

5-(2-Furyl)–5*H*-pyrimidino[5′,4′:5,6]pyrano[2,3-*d*]pyrimidine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetraone (21b)[26]

^1H NMR (DMSO-d_6, 500 MHz) δ: 6.90–7.20 (3H, m, furan ring Hs), 8.68 (1H, s), 11.12 (s, 2H, NHs), 11.26 (s, 2H, NHs). ^{13}C NMR (DMSO-d_6, 500 MHz) δ: 41.4 (barbituric acid C-5 carbon), 86.1 (benzyl carbon), 136.6, 137.2, 138.8, 141.4 (for carbons for furan ring), 162.3, 169.4 (two different carbonyl carbons for the barbituric acid moieties).

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