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Synthesis of fused dihydropyrimidinones from cyclic-1,3-dicarbonyl compounds: Modified Biginelli synthesis of 1,2,3,4,5,6,7,8-octahydroquinazolinediones and 3,4-dihydro-1*H*-indeno[1,2-*d*]pyrimidine-2,5-diones

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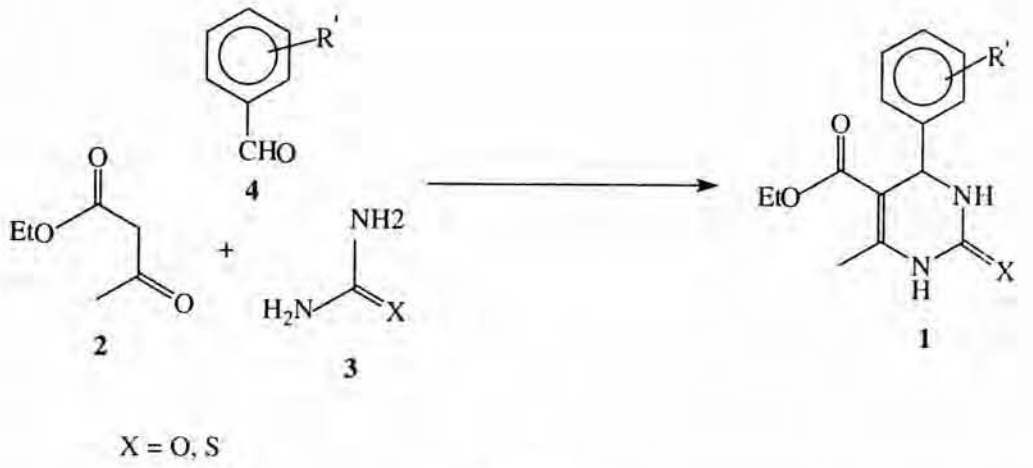
Syntheses of bicyclo-3,4-dihydropyrimidinediones from cyclic 1,3-diketones such as 5,5-dimethyl-1,3-cyclohexanedione (dimedone) and 1,3-indanedione have been attempted. During the multicomponent coupling of dimedone with (thio)urea and aldehydes, the unprecedented products of 9-aryl xanthene derivatives are obtained instead of the expected 4-aryl-1,2,3,4,5,6,7,8-octahydroquinazolinediones. Also, this reaction is senstive to solvent and the mole ratio of the ingredients used. High yields of bicyclic and tricyclic DHPMs with good selectivity are obtained using excess of urea and 1,3-dicarbonyl compounds. Interestingly, DHPMs are also formed in good to excellent yields by neat stirring of 1,3-dicarbonyl compounds, aldehydes and urea, keeping oil-bath temperature at 110°C. The mechanistic aspects of the reaction are also mentioned.

Recently, the focus on synthesis of 4-aryl (alkyl)-3,4-dihydropyrimidinones (DHPMs) has increased to manifold through a one-pot cyclocondensation of corresponding starting materials viz. ethyl acetoacetate, urea and aryl (alkyl) aldehydes employing both solvent and solvent-free conditions (**Scheme I**).[1-5] Being the structural resemblance with 1,4-dihydropyridines and exhibition of the wide range of medicinal applications, the DHPM chemistry has gained importance in organic chemistry.[6] Several marine alkaloids with interesting biological activities possessing DHPM nucleus have also been isolated.[7] However, the synthesis of fused DHPMs from cyclic 1,3-dicarbonyl compounds is relatively unknown.

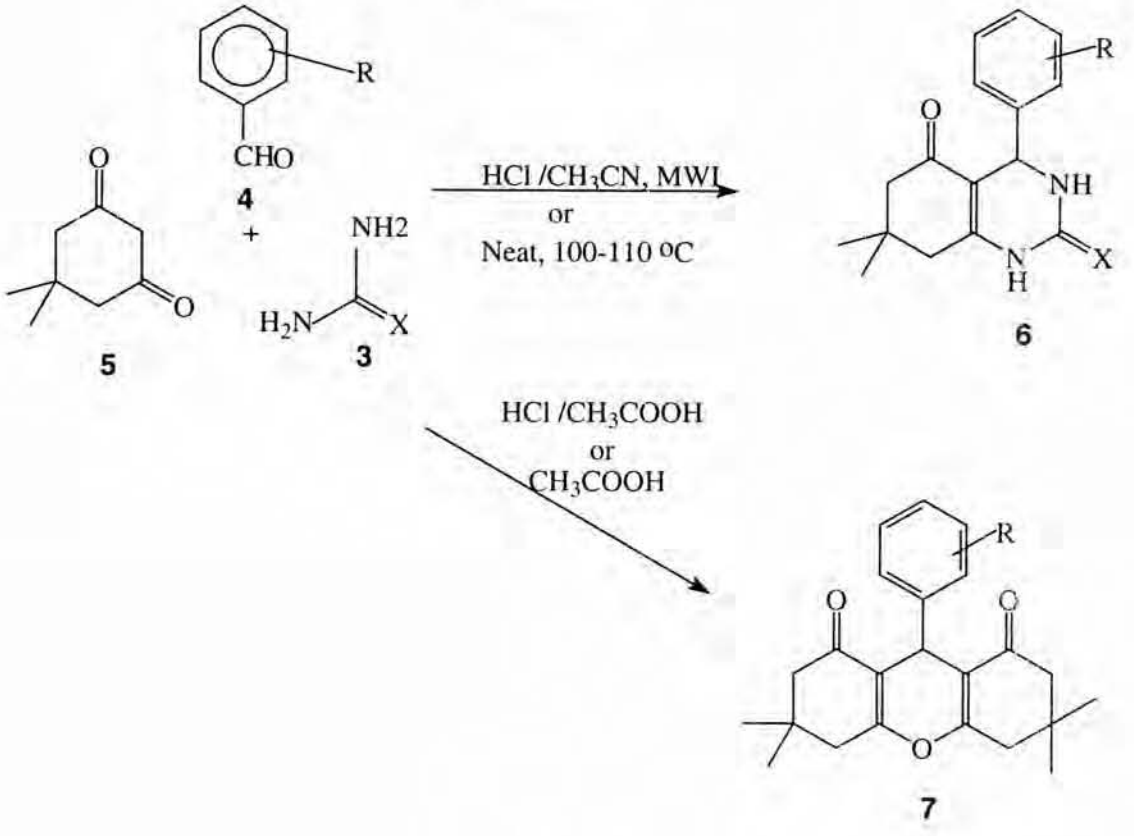
The literature on the chemistry of partially hydrogenated quinazolines **6** is scanty.[8,9] In the present work, we describe the synthesis of cyclohexanone fused DHPM **6** and indenone fused DHPM **9**. For a model reaction, we have attempted to prepare **6a** by condensing dimedone **5**, urea **3** and benzaldehyde **4** under both thermal and microwave irradiation in acetic acid medium. The product shows a singlet at δ 4.5 ppm and a multiplet at δ 2 - 2.5 ppm in ^{1}H NMR but does not contain NH absorptions in ^{1}H NMR and IR spectra. Mass spectral data unfolded the structure of the compound formed in the reaction mixture; i.e. the mass peak observed at m/z 350 (**7a**) with major peak at m/z 273 in contrast to the expected m/z 270. Therefore, the anticipated product of the reaction **6a** has not formed under typical acetic acid medium instead dimethone anhydride (9-aryl xanthene derivative) **7a** was obtained and the formation of **7a** indicates that the urea component has not been incorporated in the product (**Scheme II**).

This view supports that the incorporation of urea is the crucial step in the formation of **6**. However, by adapting acetonitrile as the solvent with catalytic amount of conc. HCl, the reaction yields mixture of **6** and **7**. The selective formation of **6** can be achieved by using excess of urea (3 mole). Repetition of the reaction with various aldehydes and different Lewis acid catalysts ($InCl_3$, $ZnCl_2$), it is understood that the formation of acyliminium ion is crucial to prepare **6**. The high acidity of **5**, anomaly over other 1,3-dicarnbonyl compounds, favours the Knoevenagel condensation to form **7**. This observation discloses the evidence that the formation of benzal urea (acyliminium ion equivalent) is vital for the formation of DHPMs and can be achieved by using excess of urea (**Scheme III**).

Recently, DHPMs were prepared through solvent-free and without catalyst under conventional and microwave heating for linear 1,3-dicarbonyl compounds.[10a,b] In an attempt to extend the same to cyclic-1,3-dicarbonyl compounds, we have heated the neat mixture in a small test tube under microwave



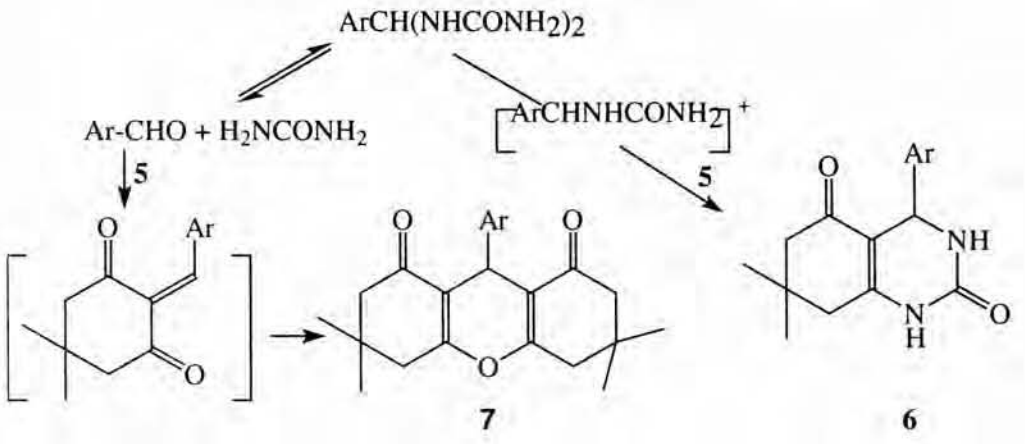
Scheme I



Scheme II

irradiation for 5 min. But the TLC of the reaction shows mixture of products. In contrast, the oil-bath stirring of neat reaction mixture at 100-110°C for 3 hr afforded high yields of **6a-f**. It is expected from the product formation that the reaction mixture forms a low melting eutectic mixture which upon heating for 3hr afforded the desired product[10c] (**Table I**).

We have also explored the possibility of utilizing the acetonitrile - conc. HCl for coupling with bicyclo-1,3-dione system such as, indane-1,3-dione **8**, with **3** and **4**. The mixture was heated for 20 min in a microwave oven with excess of indane-1,3-dione (**8**, 2-3 moles). The unreacted **8** recovered from column chromatography can be reused for the succeeding



Scheme III

Table I — Synthesis of quinazoline derivatives using Biginelli condensation by the reaction of dimedone, urea components and aldehydes.

Entry	R	X	Product (Yield) [a]			
			Method A [b]	Method B [c]	Method C [d]	Method D [e]
1	H	O	**6a** (72)[d]	**6a** (47)	**7a** (93)	**6a** (78)
2	4- OH	O	**6b** (77)	**6b** (35)	-	**6b** (81)
3	4-Cl-	O	**6c** (75)	**6c** (63)	**7d** (98)	**6c** (77)
4	2-Cl-	O	**6d** (82)	**6d** (49)	-	**6d** (80)
5	4-CH_3O-	O	**6e** (82)	**6e** (71)	**7e** (97)	**6e** (79)
6	4-CH_3-	S	**6f** (79)	**6f** (22)	**7f** (95)	**6f** (75)

[a] The reaction mixture was microwave irradiated for 8 –12 min for Method A, Method B and Method C. [b] 1.5: 1: 1 mole ratio of **3**, **4** and **5** respectively in acetonitrile and conc. HCl. [c] 3: 1: 1 mole ratio of **3**, **4** and **5** respectively in acetic acid and conc. HCl. [d] 1.2: 1: 1 ratio of **3**, **4** and **5** respectively in acetic acid and conc. HCl. [e] 1.2:1:1 mole ratio of **3**, **4** and **5** was stirred on an oil-bath at 110°C for 4 hr.

experiments and moderate yield of the corresponding indenone fused DHPM (**9a-d**) were obtained by this reaction (**Scheme IV**). The formation of **9** was confirmed by absorption peak at 3250 – 3350 cm^{-1} in IR spectra, and two NH protons resonating around 10 ppm and 8 ppm and a methine proton around 5.5 ppm. Interestingly, no detectable amount of **9** is formed on prolonged refluxing in acetic acid or CH_3CN – HCl. In this case as well, the neat heating of the reaction mixture over oil bath stirring is rather better than microwave neat heating of the reactants as the later causes the sublimation of 1,3-indanedione (**Table II**).

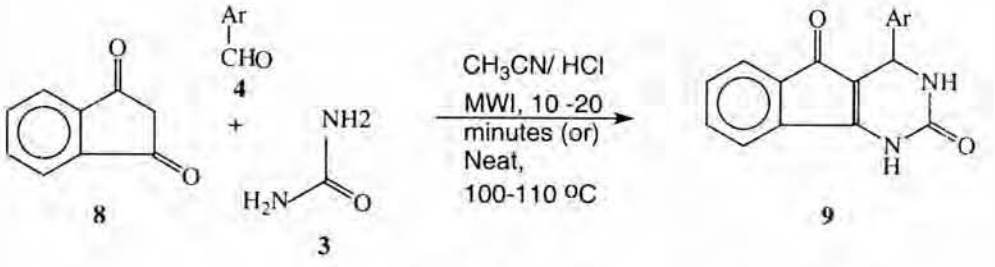
The general mechanism of the reaction is depicted in **Scheme V**.

In conclusion, this work has widened the scope of Biginelli reaction, and provided an efficient method for 4-aryl-octahydroquinazoline **6** and 4-aryl-indeno-[1,2-*d*] pyrimidines **9**. The usage of acetonitrile- HCl mixture has enabled the preparation of a variety of 3,4-dihydropyrimidine derivatives. Surprisingly, it was found that solvent-free and without catalyst reaction conducted at 100 -110°C over an oil-bath stirring is superior to the other methods.

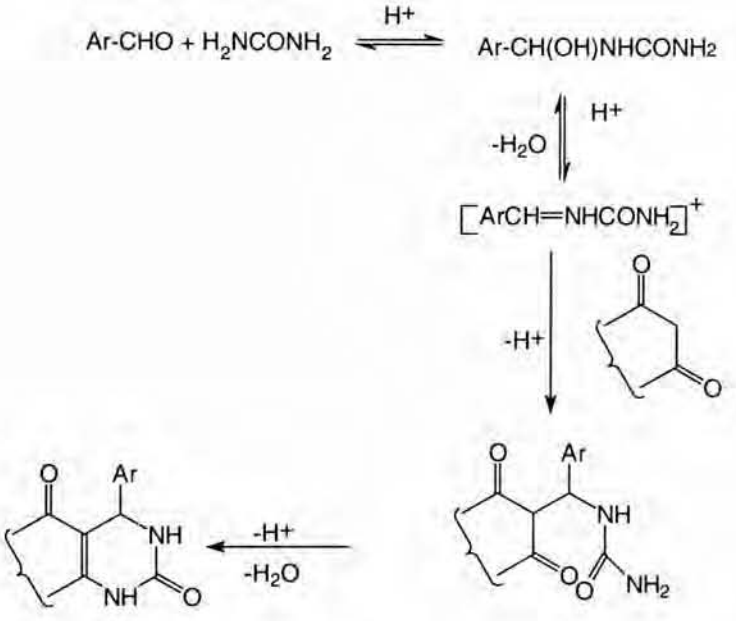
Table II — Synthesis of 4-arylindeno[1,2-*d*]pyrimidinones by cyclizing indane-1,3-dione, urea and various aldehydes

Entry	Ar	Product	Method A (Yield)[a]	Method B (Yield)[b]
1	C_6H_5	**9a**	63	77
2	4-Cl-C_6H_4	**9b**	67	73
3	2-Cl-C_6H_4	**9c**	60[c]	64
4	3-NO_2-C_6H_4	**9d**	73	74

[a] Yield of the product obtained by using mole ratio of 2:1.2:1 indane-1,3-dione, urea and aldehydes respectively. [b] Yield of the product obtained by stirring 2:1.2:1 mole ratio of indane-1,3-dione, urea and aldehydes on an oil-bath at 110°C. [c] Yield of the product obtained using 3 moles of indane-1,3-dione.



Scheme IV



Scheme V

Experimental Section

General procedure. A mixture of dimedone (**5**, 0.012 mole), aryl aldehyde (**4**, 0.010 mole) and (thio)urea (**3**, 0.015 mole) was irradiated in acetonitrile along with 0.1 mL of conc.HCl under BPL – SANYO domestic microwave oven operating at 80 W for 20 min with a pulse rate of 10 sec and 30 % of power. The same reaction in acetic acid gave **7**. However, 30 mmoles of urea led to mixture of **6** and **7**. Then the reaction mixture was poured into crushed ice and subjected to usual work-up followed by column chromatography to give **6**. The same procedure is followed for the preparation of **9** by using excess of indane-1,3-dione (**8**, 3 equivalents) and the unreacted **8** recovered from column chromatography.

A mixture of 1,3-dicarbonyl compound (0.010 mole for dimedone system and 0.020 mole for indane-1,3-dione), aryl aldehyde (**4**, 0.010 mole) and (thio)urea (**3**, 0.012 mole) were taken in 100 mL RB flask, and stirred at 100-110°C on an oil-bath for 3 hr. Then the mixture was cooled to room temperature. The solid obtained was washed with ethanol and column chromatographed with ethyl acetate: petroleum ether (1:3) to afford **6/9**.

7,7-Dimethyl-4-phenyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one 6a: m.p. 184-86°C; IR (KBr): 3342, 2959, 1697, 1631, 1374 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO - d_6): δ 0.98 (s, 3H, 7-Me), 1.01 (s, 3H, 7-Me), 2.04 (ABq, 2H, J = 16.03 Hz, CH_2), 2.25 (ABq, 2H, J = 17.18 Hz, CH_2) 5.15 (d, 1H, J = 2.7 Hz, 1H, 4 - CH), 7.20 -7.31 (m, 5H, Ph-), 7.85 (s, 1H, NH (3)), 9.42 (s, 1H, NH (1)); ^{13}C NMR: δ 27.40, 29.32, 32.85, 40.04, 50.38, 53.11, 107.97, 126.79, 127.70, 128.88, 145.18, 152.49, 152.99, 193.50. Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.11; H, 6.66; N, 10.37. Found: C, 71.50; H, 6.92; N, 9.73%.

7,7-Dimethyl-4-(hydroxyphenyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one 6b: m.p. 199 - 200°C; IR (KBr): 3414, 3271, 1683, 1652, 1514 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO - d_6): δ 0.97 (s, 3H, 7-Me), 1.07 (s, 3H, 7-Me), 2.04 (ABq, 2H, J = 13 Hz, CH_2), 2.35 (m, 2H, CH_2), 5.15 (d, 1H, J = 3.9 Hz, CH (4)), 6.68 (d, 2H, J = 12.6 Hz), 7.07 (d, 2H, J = 12.9 Hz), 7.49 (s, 1H, NH (3)), 9.35 (s, 1H, NH (1)), 9.62 (s, 1H, OH); ^{13}C NMR: δ 25.67, 27.53, 30.94, 40.70, 50.07, 52.13, 106.29, 113.12, 113.65, 126.10, 131.48 150.68, 154.99, 192.20.

7,7-Dimethyl-4-(4-chlorophenyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one 6c: m.p. 196 - 98°C; IR (KBr): 3255, 3092, 2956, 1707, 1651, 1612, 1465 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO - d_6): δ 0.91 (s, 3H, 7-Me), 1.02 (s, 3H, 7-Me), 2.04 (m, 4H, 2×CH_2), 5.28 (d, 1H, J = 3.9 Hz, 1H, 4 - CH), 7.52 (d, 2H, J = 9.0 Hz, Ar-H), 7.75 (s, 1H, NH (3)), 7.83 (d, 2H, J = 9.0 Hz, Ar-H), 9.35 (s, 1H, NH (1)); ^{13}C NMR: δ 27.37, 29.21, 32.82, 40.11, 50.29, 52.00, 107.55, 129.27, 131.67, 132.15, 144.10, 152.27, 155.12, 193.46.

7,7-Dimethyl-4-(2-chlorophenyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one 6d: m.p. 230°C; IR (KBr): 3257, 2953, 1714, 1634, 1513, 1440 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO - d_6): δ 0.99 (s, 3H, 7-Me), 1.02 (s, 3H, 7-Me), 2.07 (ABq, 2H, J = 8.7 Hz, CH_2), 2.34 (m, 2H, CH_2), 5.66 (s, 1H, CH (4)), 6.75 (s, 1H, NH (1)), 7.13 – 7.18 (m, 3H, Ar-H), 7.24 (d, 1H, J = 8.7 Hz, Ar-H), 9.32 (s, 1H, NH (1)); ^{13}C NMR: δ 26.77, 27.77, 31.57, 40.11, 49.33, 50.07, 105.29, 126.26, 127.97, 128.10, 128.78, 131.56, 150.01, 152.24, 192.57; Anal. Calcd for $C_{16}H_{17}N_2O_2Cl$: C, 63.05; H, 5.58; N, 9.19. Found: C, 63.05; H, 5.77; N, 8.91%.

7, 7-Dimethyl-4-(4-anisyl)-5-oxo-1,2,3,4,5,6, 7, 8-octahydroquinazolin-2-one 6e: m.p. 229°C; IR (KBr): 3270, 3015, 1720, 1654, 1521, 1445 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO - d_6): δ 0.95 (s, 3H, 7-Me), 1.06 (s, 3H, 7-Me), 2.05 (ABq, 2H, J = 9.0 Hz, CH_2), 2.52 (m, 2H, CH_2), 3.77 (s, 3H, Ar-OMe), 5.32 (s, 1H, CH (4)), 6.83 (d, 2H, J = 9.1 Hz), 7.23 (d, 2H, J = 9.1 Hz), 7.56 (s, 1H, NH (3)), 9.17 (s, 1H, NH (1)); ^{13}C NMR: δ 25.37, 27.26, 30.68, 40.11, 49.15, 49.95, 53.39, 106.27, 119.1, 125.88, 128.15, 135.05, 150.73, 156.78, 191.89.

7,7-Dimethyl-5-thioxo-4-(4-tolyl)-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one 6f : m.p. 191 - 93°C; IR (KBr): 3281, 3064, 2901, 1687, 1643, 1631, 1450 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO - d_6): δ 0.95 (s, 3H, 7-Me), 1.08 (s, 3H, 7-Me), 2.03 (ABq, 2H, J = 9 Hz, CH_2), 2.13 (m, 5H, CH_2 & Ar-Me), 5.61 (s, 1H, CH (4)), 6.97 (d, 2H, J = 11.4 Hz, Ar-H), 7.06 (d, 2H, J = 11.4 Hz, Ar-H), 7.51 (s, 1H, NH (3)), 8.02 (s, 1H, NH (1)); ^{13}C NMR: δ 23.22, 25.24, 27.46, 30.40, 40.82, 50.12, 52.30, 113.06, 126.52, 126.91, 150.21, 152.16, 153.60, 161.10, 195.12.

3,6,8a,9a-Tetrahydro-2*H*,7*H*-3,3,6,6-tetramethyl-9-phenyl-xanthene-1,8-dione 7a: m.p. 199-200°C; IR (KBr): 2958, 1671, 1619, 1487 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.99 (s, 6H, 2×Me), 1.10 (s, 6H, 2×Me), 2.07 (ABq, 4H, J = 15.9 Hz, 2 × CH_2), 2. 46 (s, 4H, 2 × CH_2), 4.71 (s, 1H, CH (9)), 7.05 –7.22 (s, 5H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 27.56, 29.21, 31.41, 32.14, 40.79, 50.62, 115.20, 128.14, 129.72, 131.96, 142.63, 162.40, 196.30; MS (EI, m/z): 350 (M^+), 273 (100), and 193.

3, 6, 8a, 9a-Tetrahydro-2*H*,7*H*-3,3,6,6-tetramethyl-9-(4-chlorophenyl)-xanthene-1,8-dione 7c: m.p. 244- 46°C; IR (KBr): 2955, 1662, 1488, 1362 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.99 (s, 6H, 2×Me), 1.08 (s, 6H, 2×Me), 2.17 (ABq, 4H, J = 12.6 Hz, 2 × CH_2), 2.45 (s, 4H, 2 × CH_2), 4.65 (s, 1H, CH (9)), 6.55 (d, 2H, J = 9 Hz, Ar-H), 7.08 (d, 2H, J = 9 Hz, Ar-H); ^{13}C NMR ($CDCl_3$): δ 27.30, 29.07, 30.89, 32.18, 40.78, 50.64, 115.16, 115.81, 129.30, 135.51, 154.66, 162.43, 197.27; MS (EI, m/z): 384 (M^+), 349, 273 (100), 217.

3,6,8a,9a-Tetrahydro-2*H*,7*H*-3,3,6,6-tetramethyl-9-(4-anisyl)-xanthene-1,8-dione 7e: m.p. 234 - 236°C; IR (KBr): 2957, 1664, 1510, 1163 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.98 (s, 6H, 2×Me), 1.08 (s, 6H, 2×Me), 2.12 (ABq, 4H, J = 16.2 Hz, 2 × CH_2), 2.45 (s, 4H, 2 × CH_2), 3.72 (s, 3H, Ar-OMe), 4.68 (s, 1H, CH (9)), 6.72 (d, 2H, J = 9 Hz, Ar-H), 7.17 (d, 2H, J = 9 Hz, Ar-H); ^{13}C NMR ($CDCl_3$): δ 27.23, 29.17, 30.85, 32.09, 40.79, 50.69, 55.12, 113.38, 115.68, 129.21, 136.41, 157.86, 162.01, 196.37; Anal. Calcd for $C_{24}H_{28}O_4$: C, 75.78; H, 7.36. Found: C, 75.76; H, 7.36%.

3,6,8a,9a-Tetrahydro-2*H*,7*H*-3,3,6,6-tetramethyl-9-(4-tolyl)-xanthene-1,8-dione 7f: m.p. 220 - 23°C; IR (KBr): 2953, 1623, 1557, 1383 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.99 (s, 6H, 2×Me), 1.10 (s, 6H, 2×Me), 2.04 (ABq, 4H, J = 15.8 Hz, 2 × CH_2), 2.26 (s, 3H, Ar-Me), 2.45 (s, 4H, 2 × CH_2), 4.70 (s, 1H, CH (9)), 7.02 (d, 2H, J = 7.8 Hz, Ar-H), 7.15 (d, 2H, J = 7.8 Hz, Ar-H); ^{13}C NMR ($CDCl_3$): δ 21.15, 27.46, 29.36, 31.52, 32.29, 40.94, 50.83, 115.83, 128.32, 128.88, 135.86, 141.28, 162.21, 196.59.

4-Phenyl-3,4-dihydro-1*H*-indeno[1,2-*d*]pyrimidine-2,5-dione 9a: m.p. 240°C (dec.); IR (KBr): 3461, 3383, 2927, 1683, 1638, 1599 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO - d_6): δ 5.33 (s, 1H, CH (4)), 7.83 (m, 5H), 7.92 (s, 1H, NH (3)), 8.04 (m, 4H), 8.56 (s, 1H, NH (1)); ^{13}C NMR ($CDCl_3$ + DMSO - d_6): δ 53.07, 104.61, 120.28, 121.25, 126.96, 128.03, 128.95, 130.15, 131.19, 133.96, 135.1, 143.75, 151.91, 157.14, 189.07.

4-(4-Chlorophenyl)-3,4-dihydro-1*H*-indeno[1,2-*d*]pyrimidine-2,5-dione 9b: m.p. 262°C (dec.); IR (KBr): 3353, 3253, 3057, 2894, 1688, 1643 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO - d_6): δ 5.37 (d, 1H, J = 1.96 Hz, CH (4)), 7.29 (m, 1H), 7.30 (s, 1H), 7.33 (d, 2H, J = 8.34 Hz), 7.37 (d, 2H, J = 8.25 Hz), 7.59 (m, 2H), 7.98 (s, 1H, NH (3)), 10.77 (s, 1H, NH (1)); ^{13}C NMR ($CDCl_3$ + DMSO - d_6): δ 51.77, 103.46, 119.60, 120.58 128.13, 130.55, 131.71, 131.90, 133.13, 135.2, 141.74, 151.07, 156.58, 188.41.

4-(2-Chlorophenyl)-3,4-dihydro-1*H*-indeno[1,2-*d*]pyrimidine-2,5-dione 9c: m.p. 236°C (dec.); IR (KBr): 3361, 3280, 3064, 2921, 1688, 1643, 1631, 1450 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO - d_6): δ 5.73 (d, 1H, J = 1.96 Hz, CH (4)), 7.23 (d, 1H, J = 6.36 Hz), 7.29 (m, 3H), 7.38 (d, 1H, J = 1.96 Hz), 7.41 (d, 1H, J = 0.96 Hz), 7.42 (d, 1H, J = 2.4 Hz), 7.62 (d, 1H, J = 6.84 Hz), 7.86 (s, 1H, NH (3)), 10.81 (s, 1H, NH (1)).

4-(3-Nitrophenyl)-3,4-dihydro-1*H*-indeno[1,2-*d*]pyrimidine-2,5-dione (9d): m.p. >300°C(dec.); IR (KBr): 3359, 3264, 3063, 2925, 1689, 1643, 1637, 1451 cm^{-1};^1H NMR ($CDCl_3$ + DMSO - d_6): δ 5.39 (d, 1H, J = 1.95 Hz, CH (4)), 7.05 (m, 4H), 7.37 (m, 3H), 7.58 (d, 1H, J = 6.9 Hz), 7.65 (s, 1H, NH(3)), 7.79 (s, 1H, NH (1)); ^{13}C NMR ($CDCl_3$+ DMSO - d_6): δ 52.60, 103.44, 120.65, 121.51, 121.80, 123.20, 130.79, 131.55, 132.67, 133.89, 134.03, 135.77, 145.74, 148.29, 151.85, 157.75, 189.15.

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