A Facile One-pot Synthesis of Tetrahydropyrimidines Part 3 [1]: Synthesis of [Alkanediylbis(3-alkyl/aralkyl/aryl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis(arylmethanones) and [1,4-Phenylenebis(3-phenyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis(phenylmethanone)

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A facile one-pot synthetic strategy has been developed for novel [alkanediylbis(3-alkyl/aralkyl/ aryl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis(arylmethanones) **2a-c, 2e-m** and [1,4-phenylenebis(3-phenyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis(phenylmethanone) **2d** by refluxing enaminones **1a-f** in methanol with diamines and formaldehyde.

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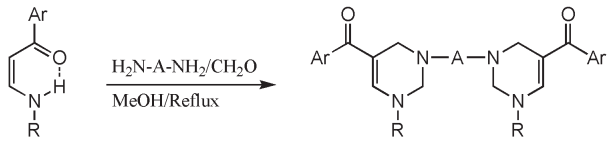
A few tetrahydropyrimidines are known in the literature [2]. However, in the course of our ongoing program aimed at developing synthetic strategies for 1,2,3,4-tetrahydropyrimidines in view of their biological properties, we have recently reported simple and convenient routes to 1-aralkyl/aryl-3-alkyl/aralkyl/aryl-5-aroyl-1,2,3,4-tetrahydropyrimidines [1] and 1-aralkyl/aryl-3-alkyl/aralkyl/aryl-5-aroyl-6-methylthio-1,2,3,4-tetrahydropyrimidines [3]. As a part of this investigation, we now report a facile one-pot synthesis of [alkanediylbis(3-alkyl/aralkyl/aryl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis(arylmethanones) and [1,4-phenylenebis(3-phenyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis(phenylmethanone) envisaging that molecules with two tetrahydropyrimidine rings linked through flexible aliphatic chains or through rigid aromatic chains could have enhanced biological activities. Our literature survey at this stage revealed that bis-1,2,3,4-tetrahydropyrimidines are unknown in the literature except for our preliminary report [4] and hence their biological properties remain unexplored.

Thus, when a mixture of enaminone **1a**, ethylenediamine and formaldehyde (2:1:4) was refluxed in methanol, work up of the reaction mixture gave **2a** in 79% yield, the structure of which was proposed to be [ethane-1,2-diylbis(3-phenyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis-(phenylmethanone) on the basis of spectral and analytical data. The reaction of **1a** with other diamines (A= $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-C_6H_4-$) and formaldehyde took place under similar conditions to give the respective bis-tetrahydropyrimidines **2b-d** in 54-70% overall yields. Similarly, the reaction of **1b-f** with appropriate diamines (see Scheme) and formaldehyde proceeded smoothly under identical conditions yielding the respective products **2e-g, 2h, 2i-k, 2l** and **2m** in moderate to high yields. The infrared spectra of **2a-m** showed strong peaks in the region of 1543-1626 cm^{-1} due to extensively delocalized double bonds and carbonyl groups. In the pmr spectra of **2a-m**, two singlets due to methylene protons at C_2 and C_6 appeared between 3.96-5.08 ppm and 3.64-4.43 ppm respectively. The benzylic methylene protons in **2e-g** and **2i-k** gave singlets in the range of 3.61-3.66 ppm whereas N-Me protons of **2m** appeared as a singlet at 2.94 ppm. The protons corresponding to the ethylene chain are observed as singlets resonating between 2.53-2.79 ppm for compounds **2a, 2e, 2h, 2i** and **2l**. In the case of **2b, 2f** and **2j** the NCH_2 protons of propylene chain exhibited triplets in the range of 2.41-2.68 ppm while the CH_2 protons of position 2 of the chain gave multiplets between 1.48-1.79 ppm. In compounds **2c, 2g, 2k** and **2m**, the NCH_2 protons of the butylene chain appeared as multiplets in the range of 2.34-2.59 ppm, while the CH_2 protons of positions 2 and 3 of the chain gave multiplets in the range of 1.33-1.65 ppm. The proton at C_4 was highly deshielded and its signal remained buried among the aromatic protons in the range of 6.73-7.57 ppm with the exception of **2m** in which it was visible as a singlet (for two protons) at 7.03 ppm.

Scheme



1 **2**

Comp	Ar	R	Comp	Ar	R	A
1a	Ph	Ph	**2a**	Ph	Ph	$-(CH_2)_2-$
	-	-	**2b**	Ph	Ph	$-(CH_2)_3-$
	-	-	**2c**	Ph	Ph	$-(CH_2)_4-$
	-	-	**2d**	Ph	Ph	$-C_6H_4-$
1b	Ph	Bz	**2e**	Ph	Bz	$-(CH_2)_2-$
	-	-	**2f**	Ph	Bz	$-(CH_2)_3-$
	-	-	**2g**	Ph	Bz	$-(CH_2)_4-$
1c	4-ClPh	Ph	**2h**	4-ClPh	Ph	$-(CH_2)_2-$
1d	4-ClPh	Bz	**2i**	4-ClPh	Bz	$-(CH_2)_2-$
	-	-	**2j**	4-ClPh	Bz	$-(CH_2)_3-$
	-	-	**2k**	4-ClPh	Bz	$-(CH_2)_4-$
1e	4-MePh	4-MePh	**2l**	4-MePh	4-MePh	$-(CH_2)_2-$
1f	Ph	Me	**2m**	Ph	Me	$-(CH_2)_4-$

EXPERIMENTAL

Melting points were recorded by open capillary method and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer 983 spectrometer. ^{1}H nmr (90 MHz) spectra were recorded on Varian EM-390 spectrometer. High-resolution ^{1}H nmr and ^{13}C nmr (300 MHz) spectra were recorded on Bruker ACF-300 spectrometer. The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in the standard fashion with reference to TMS as internal reference. FAB-mass spectra (MS) were measured on JEOL SX 102/DA-6000 Mass spectrometer using Argon as the FAB gas and *m*-nitrobenzylalcohol as the matrix. Elemental analyses were performed on a Vario-EL III instrument.

The starting materials **1a** [5], **1b** [6], **1c** [7] and **1e-f** [8] were prepared by reported procedures. The unknown starting material **1d** was prepared by reported procedure [8] and its analytical and spectral data are given below.

(2*Z*)-3-(Benzylamino)-1-(4-chlorophenyl)prop-2-en-1-one (**1d**).

This compound was obtained as a pale yellow solid in 74% yields, mp 83-84 °C; ir (KBr): 1585, 1615, 1657, 3430 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 4.46 (d, 2H, J=6.2 Hz), 5.71 (d, 1H, C_2-H, J=7.4 Hz), 6.99-7.05 (dd, 1H, C_3-H, J=7.4 & 12.5 Hz), 7.27-7.38 (m, 7H), 7.79-7.82 (m, 2H), 10.63 (broad m, 1H, exchangeable with D_2O).

Anal. Calcd. for $C_{16}H_{14}ClNO$ (271.75): C, 70.72; H, 5.19; N, 5.15. Found: C, 70.51; H, 5.16; N, 5.21.

[Alkanediylbis(3-alkyl/aralkyl/aryl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis(arylmethanones) (**2a-c**) and (**2e-m**) and [1,4-Phenylenebis(3-phenyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis(phenylmethanone) (**2d**).

General Procedure.

A mixture of diamine (1 mmol) and formaldehyde (4 mmol, 40% solution) in 2 mL methanol was stirred at room temperature for 10 minutes. To this was added a solution of enaminone **1** (2 mmol) in 5-6 mL methanol and the resulting mixture was refluxed for 4-5 hours in case of **2a-d, 2h** and **2l** and 20-24 hours in case of **2e-g, 2i-k** and **2m**. After the completion of the reaction (monitored by tlc), the reaction mixture was cooled in ice-water and the precipitated product was collected by filtration, washed with cold methanol (3x1 mL) and dried to give analytically pure **2a-d, 2h** and **2l** which were recrystallized from methanol.

In case of **2e-g, 2i-k** and **2m** where no precipitation occurred, the solvent was removed by distillation, the residue dissolved in chloroform (5 mL), the solution washed with water (3x3 mL), dried over anhydrous Na_2SO_4 and the solvent evaporated to give crude bis-tetrahydropyrimidines which were purified by passing through a neutral alumina column using ethylacetate as eluant.

[Ethane-1,2-diylbis(3-phenyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis(phenylmethanone) (**2a**).

This compound was obtained as a white solid in 79% yield, mp 230 °C (decomp); ir (KBr): 1564, 1580, 1613 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 2.63 (s, 4H, 2 CH_2), 3.64 (s, 4H, 2 CH_2), 4.44 (s, 4H, 2 CH_2), 6.73-6.95 (m, 7H), 7.12-7.35 (m, 15H); ^{13}C nmr ($CDCl_3$): δ 47.1, 50.2, 68.0, 108.5, 118.0, 123.9, 127.7, 127.8, 129.3, 129.8, 139.2, 143.8, 144.8, 193.4.

Anal. Calcd. for $C_{36}H_{34}N_4O_2$ (554.68): C, 77.95; H, 6.18; N, 10.10 . Found: C, 77.71; H, 6.31; N, 10.22.

[Propane-1,3-diylbis(3-phenyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis(phenylmethanone) (**2b**).

This compound was obtained as a white solid in 59% yield, mp 165-67 °C; ir (KBr): 1563, 1580, 1615 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.79 (m, 2H), 2.68 (t, 4H, 2 CH_2), 3.80 (s, 4H, 2 CH_2), 4.51 (s, 4H, 2 CH_2), 6.90-7.28 (m, 6H), 7.31-7.82 (m, 16H); ^{13}C nmr ($CDCl_3$): δ 26.3, 47.8, 50.3, 67.9, 109.5, 118.4, 124.2, 128.0, 128.3, 129.6, 130.0, 139.7, 144.3, 145.2, 193.8.

Anal. Calcd. for $C_{37}H_{36}N_4O_2$ (568.71): C, 78.14; H, 6.38; N, 9.85. Found: C, 77.92; H, 6.26; N, 9.98.

[Butane-1,4-diylbis(3-phenyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis(phenylmethanone) (**2c**).

This compound was obtained as a pale yellow solid in 70% yield, mp 176-77 °C; ir (KBr): 1563, 1577, 1618 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.64 (m, 4H, 2 CH_2), 2.59 (m, 4H, 2 CH_2), 3.80 (s, 4H, 2 CH_2), 4.52 (s, 4H, 2 CH_2), 6.91-7.12 (m, 6H), 7.26-7.57 (m, 16H); ^{13}C nmr ($CDCl_3$): δ 25.6, 47.5, 52.5, 68.2, 109.6, 118.5, 124.2, 128.2, 128.4, 129.7, 130.1, 139.8, 144.4, 145.2, 193.9.

Anal. Calcd. for $C_{38}H_{38}N_4O_2$ (582.73): C, 78.32; H, 6.57; N, 9.61. Found: C, 78.60; H, 6.46; N, 9.46.

[1,4-Phenylenebis(3-phenyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis(phenylmethanone) (**2d**).

This compound was obtained as a yellow solid in 54% yield, mp 118-20 °C; ir (KBr): 1507, 1580 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 4.43 (s, 4H, 2 CH_2), 5.08 (s, 4H, 2 CH_2), 6.84-7.55 (m, 26H); ^{13}C nmr ($CDCl_3$): δ 47.3, 66.2, 110.6, 118.6, 119.3, 121.5, 124.5, 125.7, 128.2, 128.4, 129.8, 130.3, 142.9, 146.0, 193.9.

Anal. Calcd. for $C_{40}H_{34}N_4O_2$ (602.72): C, 79.71; H, 5.69; N, 9.30. Found: C, 79.98; H, 5.80; N, 9.18.

[Ethane-1,2-diylbis(3-benzyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis(phenylmethanone) (**2e**).

This compound was obtained as a pale yellow solid in 75% yield, mp 103-04 °C; ir (KBr): 1541, 1580, 1613 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 2.55 (s, 4H, 2 CH_2), 3.66 (s, 4H, 2 CH_2), 3.96 (s, 4H, 2 CH_2), 4.23 (s, 4H, 2 CH_2), 7.17-7.49 (m, 22H); ms: m/z 583 (MH^+).

Anal. Calcd. for $C_{38}H_{38}N_4O_2$ (582.73): C, 78.32; H, 6.57; N, 9.61. Found: C, 78.61; H, 6.66; N, 9.48.

[Propane-1,3-diylbis(3-benzyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis(phenylmethanone) (**2f**).

This compound was obtained as a pale yellow gum in 70% yield; ir (KBr): 1543,1573, 1613 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.49 (m, 2H), 2.42 (t, 4H, 2 CH_2), 3.66 (s, 4H, 2 CH_2), 3.88 (s, 4H, 2 CH_2), 4.22 (s, 4H, 2 CH_2), 7.16-7.49 (m, 22H); ^{13}C nmr ($CDCl_3$): δ 25.8, 47.7, 50.8, 58.1, 65.7, 107.1, 127.5, 128.6, 128.9, 129.2, 129.7, 130.5, 135.7, 140.2, 150.3, 192.6.

Anal. Calcd. for $C_{39}H_{40}N_4O_2$ (596.76): C, 78.49; H, 6.76; N, 9.39. Found: C, 78.30; H, 6.64; N, 9.30.

[Butane-1,4-diylbis(3-benzyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis(phenylmethanone) (**2g**).

This compound was obtained as a pale yellow solid in 80% yield, mp 99-100 °C; ir (KBr): 1551, 1580, 1617 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.33 (m, 4H, 2 CH_2), 2.36 (m, 4H, 2 CH_2), 3.66 (s, 4H, 2 CH_2), 3.90 (s, 4H, 2 CH_2), 4.24 (s, 4H, 2 CH_2), 7.19-7.29 (m, 6H), 7.31-7.45 (m, 10H), 7.48-7.51 (m, 6H); ms: m/z 611 (MH^+).

Anal. Calcd. $C_{40}H_{42}N_4O_2$ (610.79): C, 78.66; H, 6.93; N, 9.17. Found: C, 78.39; H, 7.06; N, 9.25.

[Ethane-1,2-diylbis(3-phenyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis-[(4-chlorophenyl)methanone] (**2h**).

This compound was obtained as a pale yellow solid in 64% yield, mp 176-77 °C; ir (KBr): 1544, 1570, 1613 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.79 (s, 4H, 2 CH_2), 3.81 (s, 4H, 2 CH_2), 4.61 (s, 4H, 2 CH_2), 6.90-6.93 (m, 4H), 7.10-7.15 (m, 3H), 7.31-7.46 (m, 8H), 7.49-7.57 (m, 5H); ^{13}C nmr ($CDCl_3$): δ 47.4, 50.7, 68.6, 108.8, 116.4, 118.5, 118.9, 124.5, 128.4, 128.6, 129.7, 144.2, 145.1, 192.4.

Anal. Calcd. for $C_{36}H_{32}Cl_2N_4O_2$ (623.57): C, 69.34; H, 5.17; N, 8.98. Found: C, 69.62; H, 5.25; N, 8.85.

[Ethane-1,2-diylbis(3-benzyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis-[(4-chlorophenyl)methanone] (**2i**).

This compound was obtained as a white solid in 83% yield, mp 95-96 °C; ir (KBr): 1547, 1575, 1611 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.53 (s, 4H, 2 CH_2), 3.64 (s, 4H, 2 CH_2), 3.96 (s, 4H, 2 CH_2), 4.24 (s, 4H, 2 CH_2), 7.16-7.44 (m, 20H); ms: m/z 652 (MH^+), 654 (MH^++2), 656 (MH^++4).

Anal. Calcd. for $C_{38}H_{36}Cl_2N_4O_2$ (651.62): C,70.04; H, 5.57; N, 8.60. Found: C, 70.24; H, 5.41; N, 8.49.

[Propane-1,3-diylbis(3-benzyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis-[(4-chlorophenyl)methanone] (**2j**).

This compound was obtained as a pale yellow solid in 70% yield, mp 105-06 °C; ir (KBr): 1543, 1575, 1613 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.48 (m, 2H), 2.41 (t, 4H, 2 CH_2), 3.61 (s, 4H, 2 CH_2), 3.89 (s, 4H, 2 CH_2), 4.30 (s, 4H, 2 CH_2), 7.08-7.53 (m, 20H); ms: m/z 666 (MH^+), 668 (MH^++2), 670 (MH^++4).

Anal. Calcd. for $C_{39}H_{38}Cl_2N_4O_2$ (665.65): C, 70.37; H, 5.75; N, 8.42. Found: C, 70.10; H, 5.61; N, 8.56.

[Butane-1,4-diylbis(3-benzyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis-[(4-chlorophenyl)methanone] (**2k**).

This compound was obtained as a pale yellow solid in 80% yield, mp 105 °C; ir (KBr): 1555, 1575, 1620 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.33 (m, 4H, 2 CH_2), 2.34 (m, 4H, 2 CH_2), 3.64 (s, 4H, 2 CH_2), 3.93 (s, 4H, 2 CH_2), 4.25 (s, 4H, 2 CH_2), 7.17-7.45 (m, 20H); ms: m/z 680 (MH^+), 682 (MH^++2), 684 (MH^++4).

Anal. Calcd. for $C_{40}H_{40}Cl_2N_4O_2$ (679.68): C, 70.68; H, 5.93; N, 8.24. Found: C, 70.95; H, 5.82; N, 8.10.

[Ethane-1,2-diylbis(3-(4-methylphenyl)-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis-[(4-methylphenyl)methanone] (**2l**).

This compound was obtained as a white solid in 65 % yield, mp 225-26 °C; ir (KBr): 1575, 1590, 1619 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.30 (s, 6H, 2 CH_3), 2.38 (s, 6H, 2 CH_3), 2.79 (s, 4H, 2 CH_2), 3.82 (s, 4H, 2 CH_2), 4.59 (s, 4H, 2 CH_2), 6.80-6.83 (m, 4H), 7.10-7.26 (m, 9H), 7.42-7.51 (m, 5H); ^{13}C nmr ($CDCl_3$): δ 21.1, 21.8, 47.9, 51.1, 69.1, 109.0, 119.1, 128.9, 129.2, 130.6, 134.5, 137.4, 140.8, 142.5, 145.7, 194.2.

Anal. Calcd. for $C_{40}H_{42}N_4O_2$ (610.79): C, 78.66; H, 6.93; N, 9.17. Found: C, 78.42; H, 6.79; N, 9.02.

[Butane-1,4-diylbis(3-methyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis(phenylmethanone) (**2m**).

This compound was obtained as a yellow solid in 80% yield, mp 148-49 °C; ir (KBr): 1552, 1582, 1626 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.65 (m, 4H, 2 CH_2), 2.58 (m, 4H, 2 CH_2), 2.94 (s, 6H, 2 CH_3), 3.66 (s, 4H, 2 CH_2), 3.96 (s, 4H, 2 CH_2), 7.03 (s, 2H, 2 CH), 7.38-7.49 (m, 10H); ms: m/z 459 (MH^+).

Anal. Calcd. for $C_{28}H_{34}N_4O_2$ (458.60): C, 73.33; H, 7.47; N, 12.22. Found: C, 73.60; H, 7.62; N, 12.36.

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