6-Aminouracils as precursors for the syntheses of fused di- and tricyclic pyrimidines

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The treatment of 1-benzyl-, or 1-methyl-6-chlorouracil **(1a,b)** with nucleophilic primary amines followed by nitrosation, reduction, formylation and dehydro-cyclisation lead to xanthines **5** and **7**. While, the treatment of uracil **8** with aromatic aldehydes **9a–f** leads to the formation of dipyrimidinopyridines **10a–f**, reaction with formalin and primary amines gives pyrimidopyrimidines **11a–d** via double Michael reactions.

Keywords: 6-aminouracils, bicyclic pyrimidines, tricyclic pyrimidines

Bicyclic and tricyclic fused pyrimidine derivatives have received much attention in connection with biologically significant systems such as purines,[1-7] pteridines[8-14] and alloxazines. The synthesis of the above categories has been accomplished by the cyclisation of 6-aminouracil derivatives and ring transformation of other fused pyrimidine-2,4-diones.[15,16] In extending our recent work on simple bicyclic xanthines,[6,7] tricyclic alloxazines[17,18] and pyridodi pyrimidines[19] this paper reports a novel synthesis of 3-benzyl-9-methylxanthine **(5)**, 3,9-dimethyl-8-phenylxanthine **(7)**,[7] dipyrimidopyridines **10a–f** and pyrimido[4,5-d]pyrimidines **11a–d** via Mannich reactions.

The synthesis of 3,9-disubstituted xanthines **5,7** has been performed by various approaches[20-22] and we report a more favoured sequence from the 1-substituted-6-chlorouracils **1a**, **b**[23,24] (Scheme 1) by reaction with methylamine and *N*-methyl benzylamine respectively where the 6-amino compounds **2** and **6** were obtained in a good yield. Nitrosation of **2** afforded the 5-nitroso compound **3**, which underwent reductive formylation to **4** which readily undergoes intramolecular cyclization with formamide to furnish the xanthine **5** or refluxing the tertiary amine **6** with sodium nitrite in the presence of acetic acid resulted in ring closure in one step giving the 3,9-dimethyl-8- phenylxanthine (**7**), probably via a 5-nitroso compound **6a** and its tautomer **6b**. All the products were assigned by ^{1}H NMR, UV spectra and microanalysis.

It was found that the intramolecular cyclisation of 6-(*N*-alkylanilino)uracils with dimethylformamide (DMF)-$POCl_3$[25] or with *o*-haloarylaldehydes[26] in DMF or with benzaldehydes in acetic acid[27,28] or 6-aminouracils with oxazinanes[29] afford 5-deazaflavins. We found that stirring a solution of 6-amino-1-(2-chlorobenzyl)uracil **(8)** with an aryl aldehyde **9** at room temperature in methanol containing a few drops of hydrochloric acid affords 5,10-dihydrodipyrido[2,3-d:6,5-d'] dipyrimidine (**10**) (Scheme 2). The structures of compounds **10a–f** were established on the basis of analytical data and of ^{1}H and ^{13}C NMR spectra. For example, for compound **10a** proton signals at δ 5.57 for H5 and at 7.60 for NH10 and 16 ^{13}C NMR lines were observed.

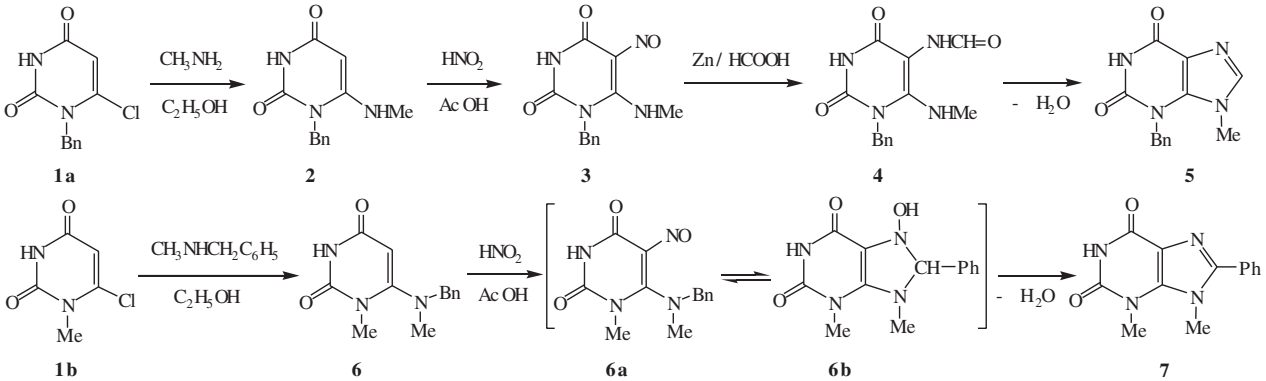
Recently, we noted that the reactions of 6-amino-1,3-dimethyluracil with primary amines and formaldehyde have been used for preparations of pyrimido[4,5-d]pyrimidine-2,4-diones.[30] It was found that stirring a mixture of 6-amino-1-(2-chlorobenzyl)uracil **8** with an equimolar amount of a primary aromatic or aliphatic amine and excess of formalin in the presence of acetic acid at room temperature affords 5,6,7,8-tetrahydropyrimido[4,5-d] pyrimidine-2,4(1*H*,3*H*)-dione (**11**) in good yield (Scheme 3) but 8-hydroxymethyl derivative of **11** was not obtained as reported earlier.[29] This conclusion was supported by the following evidence, in the ^{1}H NMR spectra of compounds **11a–d** no signals for an 8-CH_2OH group were found. The ^{13}C NMR spectrum of **11a** exhibited 17 lines, rather than the 18 peaks expected for the corresponding molecule with an 8-CH_2OH group.

Experimental

Melting points were determined with an Electrothermal Mel.-Temp. II apparatus and are uncorrected. The ^{1}H and ^{13}C NMR were recorded on a Bruker AC 250 spectrometer in DMSO-d_6 as a solvent and TMS as an internal standard (Chemical shift in δ, ppm). The UV spectra were determined with a Perkin Elmer, Lambda 5 or 15 spectrophotometer: λ_{max} in nm (logε). Elemental analysis was performed at the Micro Analytical Centre, Cairo University, Giza, Egypt. TLC was performed on silica gel G for TLC (Merck).

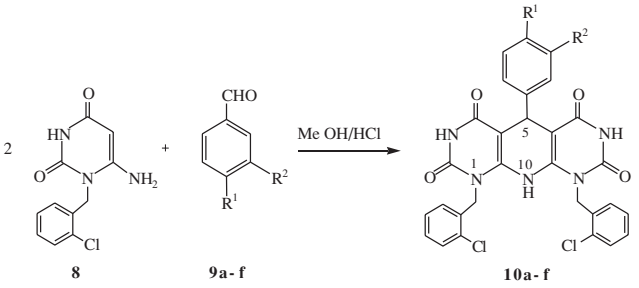
1-Benzyl- and 1-methyl-6-chlorouracil (**1a**[23,24] *and* **1b**[23]): Compounds **1a** and **1b** were prepared according to the reported method.[23]

1a: Yield 74%; m.p. 161°C lit. [159–161°C][23]; ^{1}H NMR: δ 11.76 (s,1H,NH), 7.34–7.23 (m, 5H, *J*= 7.4 Hz , ar.), 5.99 (s, 1H, CH(5)),



Scheme 1

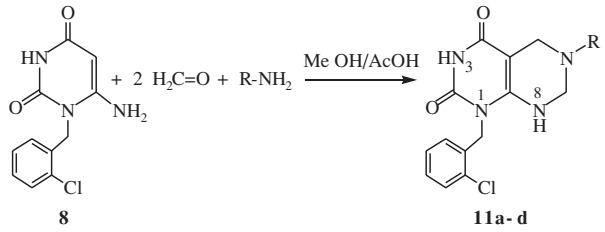
* Correspondence.



8 **9a-f** **10a-f**

a, $R^1=R^2=H$;
b, $R^1=Cl$, $R^2=H$;
c, $R^1=OH$, $R^2=H$;
d, $R^1=NO_2$, $R^2=H$;
e, $R^1=OMe$, $R^2=H$;
f, $R^1=OMe$, $R^2=OH$

Scheme 2



8 **11a-d**

a, R = phenyl;
b, R =4-Me-C_6H_4;
c, R = 4-HO-C_6h_4;
d, R =cyclohexyl

Scheme 3

5.14 (s, 2H, CH_2); Anal. Calcd. for $C_{11}H_9ClN_2O_2$: C,55.82; H,3.83; N,11.83. Found: C,55.69; H,3.74; N,11.78.

1b: Yield 68%; m.p. 186°C lit. [192–194°C][23]; UV (methanol): 207 (3.85), 268 (3.99).

Anal. Calcd. for $C_5H_5ClN_2O_2$: C, 37.40; H, 3.14; N, 17.45. Found: C, 37.32; H, 3.11; N, 17.29.

1-Benzyl-6-methylaminouracil **(2)**: A mixture of 1-benzyl-6-chlorouracil **(1a)** (25 mmol) and ethanolic methylamine (40%, 10 ml) in abs. ethanol (10 ml) was heated under reflux for 15 minutes. After cooling, the resulting precipitate was collected and recrystallised from ethanol to give **2**.

2: Yield: 94%; m.p. 256°C; UV (methanol): λ 266 (logε 4.34), 204 (4.27); ^{1}H NMR: δ 10.58 (s, 1H ,NH(3)), 7.29 (m, 3H, *J*= 7.3 Hz, ar.), 7.15 (m, 2H, *J*= 6.88 Hz, ar.), 6.84 (q,1H, *J*= 5.5 Hz, NH(6)), 5.03 (s, 2H, CH_2), 4.48 (s, 1H, CH(5)), 2.60 (d, 3H, *J*= 5.5 Hz, CH_3(6)). Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C,62.32; H,5.66; N,18.17. Found: C,62.04; H,5.84; N,17.05.

1-Benzyl-6-methylamino-5-nitrosouracil **(3)**: A suspension solution of **2** (20 mmoles) in water (30 ml) was cooled in an ice bath to 0–5°C and then sodium nitrite (20 mmoles) in water (5 ml) was added. Dropwise addition of acetic acid (60 mmoles) with stirring caused nitrosation with a separation of light violet crystals. The resulting precipitate was washed by ether and dried in a vacuum desiccator for 24 h to give **3**.

Yield 85%; m.p. 170°C (decomposes); UV (methanol): λ 315 (4.23), 229 (4.45), 205 (4.25); ^{1}H NMR: δ 13.85 (s, 1H, NH(3)), 7.35 (m, 5H, ar.), 6.86 (q, 1H, NH(6)), 5.32 (s, 2H, CH_2), 2.94 (d, 3H, CH_3). Anal. Calcd. for $C_{12}H_{12}N_4O_3$: C,55.39; H,4.64; N,21.52. Found: C,55.02; H,4.59; N,21.63.

1-Benzyl-6-methylamino-5-formylaminouracil **(4)**: Zinc dust (30 mmoles) was gradually added to a mixture of **3** (10 mmoles) and formic acid (25 ml) with stirring. The mixture was heated under reflux for 15 min and the excess of zinc and zinc formate were removed by filtration of the hot solution. The filtrate was evaporated under vacuum to dryness. The residue was washed with a little ethanol and recrystallised from water to give **4**.

Yield: 74%; m.p. 243°C; UV (methanol): λ 272 (3.95), 210 (3.69); ^{1}H NMR: δ 10.91 (s, 1H, NH(3)), 8.38 (s, 1H, NH(5)), 8.06 (d, 1H, CHO(5)), 7.29 (m, 3H, ar.), 7.16 (m, 2H, ar.), 6.46 (q, 1H, *J*= 4.4 Hz, NH(6)), 5.11 (s, 2H, NCH_2), 2.79 (d, 3H, CH_3(6)); Anal. Calcd. for $C_{13}H_{14}N_4O_3$: C,56.92; H,5.14; N,20.42. Found: C, 57.02; H,5.22; N,20.55.

1-Benzyl-9-methylxanthine **(5)**: A mixture of **4** (5 mmoles) in formamide (5 ml), water (0.25 ml) and formic acid (0.25 ml) was heated under reflux for 30 minutes. It was evaporated to dryness *in vacuo* and the precipitate recrystallised from water to give **5**.

Yield: 78%; m.p. 145°C; UV (methanol): λ 266 (4.37), 234 (4.31),209 (4.49); ^{1}H NMR: δ 10.98 (s, 1H, NH(3)), 7.57 (s, 1H, CH(8)), 7.25 (m, 5H, ar.), 5.08 (s, 2H, CH_2(1)), 3.83 (s, 3H ,CH_3). Calcd. for $C_{13}H_{12}N_4O_2$: C,60.92; H,4.72; N,21.86. Found: C,60.78; H,4.91; N,21.89.

1-Methyl-6-N-methylbenzylaminouracil **(6)**: A mixture of 1-methyl-6-chlorouracil[23] **(1b)** (25 mmols) and *N*-methylbenzylamine (25 mmoles) in abs. ethanol (10 ml) was heated under reflux for 36 hrs in an oil bath. After cooling, the resulting precipitate was collected and recrystallised from ethanol to give **6**.

Yield: 89%; m.p. 152°C; ^{1}H NMR: δ 10.94 (s, 1H, NH(3)), 7.31 (m, 5H, ar.), 4.96 (s, 1H, CH(5)), 4.15 (s, 2H, CH_2(6)), 3.27 (s, 3H, NCH_3(1)), 2.54 (s, 3H, NCH_3(6)); Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C,63.65; H,6.16; N,17.13. Found: C,63.33; H,6.20; N,17.33.

3,9-Dimethyl-8-phenylxanthine **(7)**[7]: A mixture of **6** (20 mmoles) in water (30 ml), sodium nitrite (20 mmoles) in water (5 ml) and acetic acid (60 mmoles) was heated with stirring for 1/2h. The reaction mixture was kept in refrigerator overnight, the resulting precipitate was collected by filtration and recrystallised from methanol to give **7** in 77% yield with m.p. 309–311°C, lit [7] 312–313 °C. ^{1}H NMR: δ 11.13 (s, 1H, NH(1)), 7.56 (m, 5H, ar.), 3.84 (s, 3H, NMe(9)), 3.65 (s, 3H, NMe(3)); Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C,60.92; H,4.72; N,21.86. Found: C,60.88; H, 4.68; N,21.82.

6-Amino-1-(2-chlorobenzyl)uracil **(8):** Ethyl cyanoacetate (0.13 mol) was added to a hot solution of sodium ethoxide [Na (9.0g) in abs. ethanol (116 ml)] with stirring. N-(2-Chlorobenzyl)urea (0.13 mol) was added to the above solution. The reaction mixture was heated under reflux for 6h. Conc. HCl was added to the mixture till pH= 6, the precipitate product was filtered, washed with water then ethanol and recrystallised from water, dried to give 68% yield with m.p. 295°C. ^{1}H NMR: δ 10.93 (s, 1H, NH), 7.60 (s, 2H, NH_2), 7.49 (d, 1H, J_o=8.2, ar.), 7.32 (t, 2H, *J*= 3.5 Hz, ar.), 6.86 (s, 1H, ar.), 5.08 (s, 2H, CH_2), 4.61 (s, H, CH(5)). ^{13}C NMR: δ 43.14 (CH_2), 85.28, 125.31, 127.37, 128.50, 129.28, 131.53, 133.60, 149.90, 154.53, 164.18. Anal. Calcd. for $C_{11}H_{10}ClN_3O_2$: C,52.49; H,4.00; N,16.69. Found: C,52.13; H,4.09; N,16.48.

General procedure for the synthesis of 9-substituted 1,3,6,8,9,10-hexahydro-1,8-di(2-chlorobenzyl)pyrido[2,3-d:6,5-d']pyrimidine-2,4,5,7-tetraone **10a–f :** To 6-amino-1-(2-chlorobenzyl)uracil **(7)** (2.0 mmol) in MeOH (10 ml) and Conc. HCl (0.4 ml) was added the appropriate aromatic aldehydes **9a–f** (1.0 mmol) with stirring at room temperature for 0.5–4.0 hs. The resulting precipitate was collected by filtration and recrystallised from aqueous acetic acid.

10a: Yield: 48%; m.p. 300°C; reaction time 1.0h; ^{1}H NMR: δ 10.96 (s, 2H, NH(3,6)), 7.60 (sb, 1H, NH), 7.61 (d, 2H, J_o= 8.5 Hz, ar.), 7.33 (m, 9H, *J*= 1.5 Hz, ar.), 6.99 (d, 2H, J_o= 8.5 Hz, ar.), 5.57 (s, 1H, CH), 5.13 (s, 4H, $2CH_2$); ^{13}C NMR: δ 34.26 (CH), 43.28 (CH_2), 124.88, 125.33, 126.54, 127.36, 127.59, 128.31, 128.57, 129.04, 129.35, 131.63, 132.89, 133.56, 139.27, 149.93; Anal. Calcd. for $C_{29}H_{21}Cl_2N_5O_4$: C,60.63; H,3.68; N,12.19. Found: C,60.23; H,3.59; 12.01.

10b: Yield: 52%; m.p. 190°C; reaction time 1/2h; ^{1}H NMR: δ 11.00 (s, 2H, 2NH(3,6)), 7.67 (sb, 1H, NH), 7.50 (d, 2H, J_o=8.10,ar.), 7.35 (m, 8H, ar.), 6.99 (d, 2H, J_P= 7.9, ar.), 5.54 (s, 1H, CH), 5.14 (s, 4H, $2CH_2$); ^{13}C NMR: δ 33.92 (CH), 43.37 (CH_2), 125.39, 127.39, 128.51, 128.57, 128.61, 129.26, 129.33, 129.44, 131.60, 133.49, 133.63, 138.47, 149.80, 149.90; Anal. Calcd. for $C_{29}H_{20}Cl_3N_5O_4$: C, 57.20; H,3.31, N,11.50. Found: C, 56.98; H, 3.19; N, 11.23.

10c: Yield: 47%; m.p. 260°C; reaction time 2.5h; ^{1}H NMR: δ 10.92 (s, 2H, 2NH(3,6)), 8.99 (s, 1H, OH), 7.69 (sb, 1H, NH), 7.50 (d, 2H, J_o= 7.4, ar.), 7.37 (m, 4H, ar.), 6.98 (m, 4H, ar.), 6.64 (d, 2H, J_o= 8.6, ar.), 5.47 (s, 1H, CH), 5.13 (s, 4H, $2CH_2$); ^{13}C NMR: δ 33.49 (CH), 43.24 (CH_2), 114.45, 118.92, 123.18, 125.33, 127.41, 128.56, 128.95, 129.34, 129.83, 131.63, 133.59, 149.94, 154.67. Anal. Calcd. for $C_{29}H_{21}Cl_2N_5O_5$: C, 58.99; H,3.50; N,11.86. Found: C, 58.72; H, 3.44; N, 11.64.

10d: Yield: 61%; m.p. 230°C; reaction time 4h; ^{1}H NMR: δ 11.10 (sb, 2H, 2NH(3,6)), 8.12 (d, 2H, ar.), 7.73 (sb, 1H, NH), 7.53 (m, 4H, ar.), 7.38 (m, 4H, ar.), 7.04 (d, 2H, ar.), 5.65 (s, 1H, CH), 5.13 (s, 4H, $2CH_2$); ^{13}C NMR: δ 34.84 (CH), 43.47 (CH_2), 122.76, 124.88, 125.43, 127.46, 127.68, 128.03, 128.61, 129.34, 130.77, 131.61,

133.41, 145.23, 148.58, 149.90; Anal. Calcd. for $C_{29}H_{20}Cl_2N_6O_6$: C, 56.23; H,3.25; N,13.56. Found: C,56.01; H, 3.13; N, 13.27.

10e: Yield: 37%; m.p. 205°C; reaction time 2h; ^{1}H NMR: δ 10.94 (s, 2H, 2NH(3,6)), 7.50 (d, 2H, ar.), 7.36 (m, 4H, ar.), 7.11 (d, 2H, ar.), 6.98 (d, 2H, ar.), 6.80 (d, 2H, ar.), 5.51 (s, 1H, CH), 5.13 (s, 4H, $2CH_2$), 3.71 (s, 3H, OCH_3); ^{13}C NMR: δ 33.53 (CH), 43.25 (CH_2), 54.85 (OMe), 113.03, 125.33, 126.84, 127.37, 127.52, 128.56, 128.78, 129.34, 129.65, 130.90, 131.62, 133.57, 149.93, 156.82; Anal. Calcd. for $C_{30}H_{23}Cl_2N_5O_5$: C, 59.61; H,3.83; N,11.59. Found: C, 59.43; H,3.70; N,11.36.

10f: Yield: 40%; m.p. 175°C; reaction time 1h; ^{1}H NMR: δ 10.93 (s, 2H, 2NH(3,6)), 8.56 (s, 1H, OH), 7.73 (sb, 1H, NH), 7.50 (d, 4h, ar.), 7.35 (t, 4H, ar.), 6.99 (s, 1H, ar.), 6.66 (m, 2H, ar.), 5.52 (s, 1H, CH), 5.15 (s, 4H, $2CH_2$), 3.69 (s, 3H, OCH_3); ^{13}C NMR: δ 33.75 (CH), 43.24 (CH2), 55.63 (OCH3), 111.26, 113.94, 115.02, 118.43, 119.08, 125.25, 127.28, 128.58, 128.83, 129.37, 129.99, 131.63, 133.62, 143.93, 146.91, 149.94; Anal. Calcd. for $C_{30}H_{23}Cl_2N_5O_6$: C,58.07; H,3.73; N,11.28. Found: C,57.93; H,3.66; N,11.00.

General procedure for the synthesis of 1-(2-chlorobenzyl)-6-substituted-3,5,7,8-tetrahydro-2,4-dioxopyrimido[4,5-d]pyrimidines **(11a–d)**: A mixture of **8** (2 mmoles) in methanol (20ml) and acetic acid (2 ml) was heated to 40°C and then primary aromatic amines in methanol (5 ml) and formalin (4 mmoles, 40%) were added dropwise with stirring until a clear solution was obtained. The resulting precipitate was filtered washed with ethanol and dried to give **11a–d**.

11a: Yield:34%; m.p. 195°C; ^{1}H NMR: δ 10.92 (s, 1H, NH), 7.60 (s, 1H, NH), 7.50 (d, 1H, ar.), 7.32 (m, 5H, ar.), 7.24 (t, 1H, ar.), 7.14 (t, 1H, ar.), 6.95 (d, 1H,ar.), 5.08 (s, 2H, CH_2), 3.89 (d, 2H, CH_2), 3.54 (s, 2H, CH_2). ^{13}C NMR: 43.14 (CH_2), 45.58 (CH_2), 58.70 (CH_2), 125.31, 125.63, 127.37, 128.50, 129.27, 130.77, 131.52, 132.56, 133.60, 134.33, 149.90, 154.52, 162.30, 164.18. Anal. Calcd. for $C_{19}H_{17}ClN_4O_2$: C,61.87; H,4.64; N,15.19. Found: C, 61.54, H, 4.62; N, 14.98.

11b: Yield: 63%; m.p. 210°C; ^{1}H NMR: δ 10.77 (s, 1H, NH), 7.46 (d, 2H, *J*= 8.2 Hz, ar.), 7.30 (t, 1H, *J*= 3.5 Hz, NH), 7.11 (t, 1H, *J*= 7.4 Hz, ar.), 6.98 (dd, 4H, *J*= 8.2 Hz, ar.), 6.56 (d, 1H, *J*= 7.4 Hz, ar.), 4.95 (s, 2H, CH_2), 4.59 (s, 2H, CH_2), 4.11 (s, 2H, CH_2), 2.22 (s, 3H, CH_3). ^{13}C NMR: 20 (CH_3), 41.63 (CH_2), 45.03 (CH_2), 59.48 (CH_2), 117.48, 125.19, 127.12, 128.49, 129.08, 129.35, 131.36, 133.55, 146.01, 149.45, 149.91, 150.07, 160.94, 164.20. Anal. Calcd. for $C_{20}H_{19}ClN_4O_2$: C,62.74; H,5.00; N,14.63. Found: C, 62.33; H,4.89: N,14.52.

11c: Yield: 49%; m.p., 200°C; ^{1}H NMR: δ 10.53 (s, 1H, NH), 8.72 (s, 1H, OH), 7.46 (t, 1H, *J*= 6.6 Hz, NH), 7.28 (t, 1H, *J*= 7.4 Hz, ar.), 7.13 (t, 1H, 7.4 Hz, ar.), 6.82 (d, 2H, *J*= 9.0 Hz, ar.), 6.65 (d, 2H, *J*= 9.0 Hz, ar.), 4.97 (s, 2H, CH_2), 4.48 (d, 2H, CH_2), 4.02 (s, 2H, CH_2); ^{13}C NMR: 41.58 (CH_2), 45.59 (CH_2), 60.84 (CH_2), 115.39, 119.45, 125.23, 127.12, 128.46, 129.22, 131.40, 133.6, 140.74, 149.42, 150.09, 151.64, 160.93, 164.20. Anal. Calcd. for $C_{19}H_{17}ClN_4O_3$: C, 59.30; H, 4.45; N, 14.55. Found: C, 59.01; H, 4.42: N, 14.59.

11d: Yield: 38%; m.p., 220°C; ^{1}H NMR: δ 10.68 (s, 1H, NH), 7.49 (m, 2H, J= 3.5 Hz, ar.), 7.31 (t, 1H, J= 3.1 Hz, ar.), 7.17 (s, 1H, NH), 6.83 (t, 1H, J= 3.9 Hz, ar.), 4.98 (s, 2H, CH_2), 4.02 (s, 2H, CH_2), 3.53 (s, 2H, CH_2), 2.38 (t, 1H, NCH), 1.46 (10H, cyclohexyl). ^{13}C NMR: 24.76 ($C^{3'}$, $C^{5'}$), 25.54 ($C^{4'}$), 30.17 ($C^{2'}$, $C^{6'}$), 41.67 (NCH), 43.67 (CH_2), 56.93 (CH_2), 59.20 (CH_2), 80.94, 125.18, 127.25, 128.55, 129.30, 131.44, 133.77, 149.72, 150.25, 161.01.

Anal. Calcd. For $C_{19}H_{22}ClN_4O_2$: C, 61.03; H, 5.93; N,14.98. Found: C, 59.79; H, 5.81: N, 14.68.

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