HETEROCYCLES, Vol. 71, No. 4, 2007, pp. 925 - 932. © The Japan Institute of Heterocyclic Chemistry
Received, 11th December, 2006, Accepted, 1st February, 2007, Published online, 9th February, 2007. COM-06-10970

AN EFFICIENT TWO-STEP SYNTHESIS OF 4-METHYL-1,2,3,5,6,10b-HEXAHYDROPYRIMIDO[5,4-*c*]QUINOLINE-2,5-DIONES *VIA* BIGINELLI REACTION

Lhassane Ismaili,[a] Sophie Ubaldi,[b] Jean-Francois Robert,[a] Alain Xicluna,[a] Bernard Refouvelet*[a]

(a) Equipe Sciences séparatives et Biopharmaceutique (2SB), Laboratory of medicinal chemistry, Faculty of Pharmacy, 4, place Saint Jacques - 25030 Besançon Cedex, France
(b) SERAC / UT LCE, Faculty of Sciences – Building O -16, route de Gray - 25030 Besançon Cedex, France
e-mail : bernard.refouvelet@univ-fcomte.fr

Abstract - An efficient two-step synthesis of 4-methyl-1,2,3,5,6,10b-hexahydropyrimido[5,4-*c*]quinoline-2,5-diones is presented. It consists of the reactions of appropriate aldehyde, urea and ethyl acetoacetate according to Biginelli reaction, followed by cyclisation with ammonia.

INTRODUCTION

Within the framework of the prevention of the ageing, a lot of heterocyclic compounds either natural (phytoestrogens) or obtain by synthesis, having coumarin or quinoline rings, was studied for their biological activity. They are used specialy as antioxidizers like in Alzheimer disease by chelating iron or copper such as clioquinol[1,2] or as antagonists of the human oestrogenics receptors.[3-5]

After first biological studies realized in our laboratory[4-6] on new compounds with quinoline and coumarin structures, we intended to synthesize new potential antioxidizers having quinoline ring using the Biginelli reaction.

RESULTS AND DISCUSSION

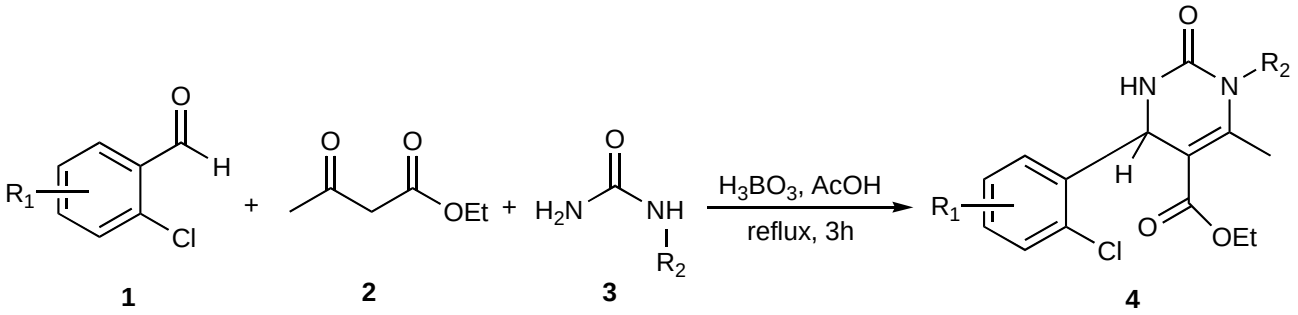
The Biginelli reaction is one of the multicomponent reactions (MCRs) and the most often used for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)ones. In general, Biginelli reaction is simple one pot using

condensations of β-dicarbonyl compound with aldehyde and urea and catalyst like strong acids, mild acids such as boric acid or Lewis acids such as $FeCl_3$.[7-9]

The interest of this reaction is that it allows obtaining directly the precursors to the wished molecules.

In this paper, we report the synthesis of 4-methyl 1,2,3,5,6,10b-hexahydropyrimido[5,4-*c*]quinoline-2,5-diones in two steps. The first step (Scheme 1) consists in a Biginelli reaction[8,10] and the second step is the cyclisation in the presence of ammonia.[11-13]

As shown in Scheme 1, the condensation of the derivatives of 2-chlorobenzaldehyde **1**, ethyl acetoacetate **2**, urea and its derivatives **3** and boric acid according to Biginelli reaction gives ethyl 4-phenyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates **4a-i**. For the compounds **4a-g** prepared with monosubstituted urea, we obtained exclusively the regioisomer *N*1-substituted 4-phenyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate according to the mechanisms and the regiochemistry described by Sweet and Fissekis[14] or described by Kappe.[15] All the compounds summarized in Table 1 were obtained in moderate to good yields ranging from 48 to 94%. All these products were isolated from reaction mixture by recrystallization from ethanol, and their structures were characterized by ^1H NMR, IR spectra and elementary analysis.

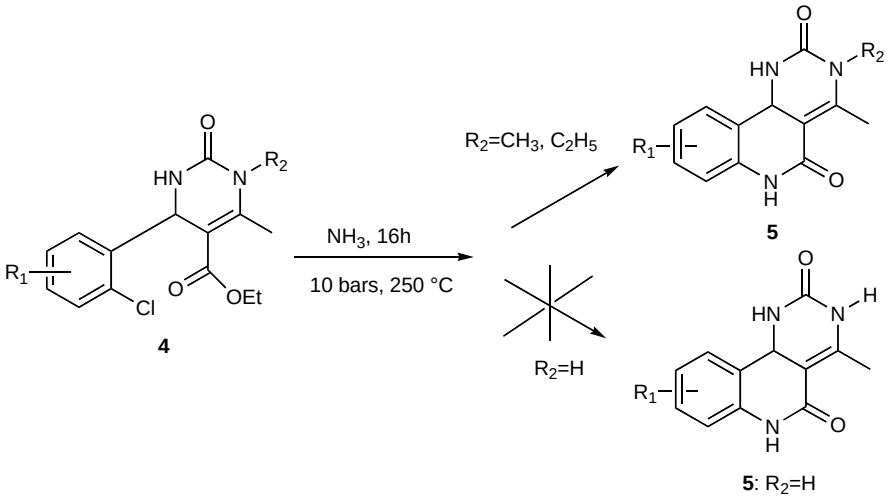


Scheme 1

Table 1. Synthesis of 3,4-dihydropyrimidin-2(1*H*)ones **(4a-i)**

Compounds	R1	R2	Yields %
4a	H	CH_3	70
4b	H	C_2H_5	73
4c	6-F	C_2H_5	75
4d	5-NO_2	CH_3	48
4e	3-Cl	C_2H_5	56
4f	6-Cl	CH_3	88
4g	3-Cl	CH_3	90
4h	H	H	94
4i	4-Cl	H	69

Scheme 2 reports cyclisation procedure of **4a-i** to new compounds **(5a-g).** This cyclisation is realised with ammonia under pressure except for compounds **4h** and **4i** with no substituted urea.



Scheme 2

According to the literature[16] the unreactivity of the ester group may be attributed to its strong conjugation with the lone pair of N-1 unsubstituted derivatives. The products **5a-g** obtained with good yields from 70 % to 90 % are presented in the (Table 2).

Table 2. Synthesis of hexahydropyrimidoquinolinedions **(5a-g)**

Compounds	R_1	R_2	Yields %
5a	H	CH_3	70
5b	H	C_2H_5	73
5c	10-F	C_2H_5	80
5d	9-NO_2	CH_3	85
5e	7-Cl	C_2H_5	73
5f	10-Cl	CH_3	90
5g	7-Cl	CH_3	81

All new products were characterized by ^{1}H NMR, IR spectra and elementary analysis. The ^{1}H NMR spectra of compounds **5a-g** show the disappearance of the triplet and quartet of ester group and appearance of additional NH signal.

MATERIALS AND METHODS

All compounds were characterized using the methods of elementary analyses, IR spectroscopy and NMR spectroscopy. Infrared spectra were recorded on a Shimadzu FTIR-8201 PC spectrometer in KBr (ν in cm^{-1}). Proton NMR spectra were recorded on a Bruker AC 300 spectrometer. Chemical shift values and IR data for all compounds are summarized in the experimental part and in agreement with the proposed structures.

Melting points (mp) were obtained with a kofler and were not corrected. All reactions were monitoring with Thin Layer Chromatography (TLC) and carried out on Alugram Sil G/UV_{254} plate with appropriate solvents. Microanalyses were carried out by the service Central d'Analyses. Centre National de la Recherche Scientifique, Vernaison, France.

EXPERIMENTAL

Synthesis of Ethyl 4-(2-Chlorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a).

A solution of *o*-chlorobenzaldehyde (3 mmol), ethyl acetoacetate (3 mmol), urea (3,6 mmol) and H_3BO_3 (0,6 mmol), in glacial acetic acid (10 mL) is heated at 100°C, while stirring for 2h. Then it is cooled to rt, and poured into ice water (50 mL). The product collected by filtration was recrystallised from EtOH (95%), to give the pure product, **4a** in 70% yield, mp 215°C, ir ν(C=O) ester 1708, ν(C=O) amide 1615, ν(NH) 2990. ^{1}H NMR (DMSO-d_6) 1.15 ppm (3H, t, J = 7.1 Hz, CH_3 ester), 2.6 ppm (3H, s, CH_3), 3.2 ppm (3H, s, N-CH_3), 3.9 ppm (2H, q, J = 7.1 Hz, CH_2 ester) 5.7 ppm (1H, d, J = 2.9 Hz, CH), 7.3-7.5 ppm (4H, m, aromH), 7.9 ppm (1H, s, NH). Anal. Calcd for $C_{15}H_{17}N_2O_3Cl$: C, 58.35; H, 5.55; Cl, 11.48; N, 9.07. Found: C, 58.24; H, 5.59; Cl, 11.49; N, 9.12.

Ethyl 4-(2-Chlorophenyl)-1-ethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b).

Compound **4b** was prepared with the same procedure as **4a** in 52 % yield, mp 210°C, ir ν(C=O) ester 1705, ν(C=O) amide 1670, ν(NH) 3300. ^{1}H NMR (DMSO-d_6) 1.1 ppm (3H, t, J = 7.1 Hz, CH_3 ethyl), 1.2 ppm (3H, t, J = 7.0 Hz, CH_3 ester), 2.6 ppm (3H, s, CH_3), 3.8 ppm (1H, m, CH ethyl), 3.9 ppm (1H, m, CH ethyl), 3.95 ppm (2H, q, J = 7.1 Hz, CH_2 ester), 5.7 ppm (1H, d, J = 2.9 Hz, CH), 7.3-7.4 ppm (4H, m, aromH), 7.9 ppm (1H, s, NH). Anal. Calcd for $C_{16}H_{19}N_2O_3Cl$: C, 59.54; H, 5.93; Cl, 10.98; N, 8.68. Found: C, 60.03; H, 5.87; Cl, 10.92; N, 8.60.

Ethyl 4-(2-Chloro-6-fluorophenyl)-1-ethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c).

Compound **4c** was prepared with the same procedure as **4a** in 75 % yield, mp 158°C, ir ν(C=O) ester 1703, ν(C=O) amide 1670, ν(NH) 3342. ^{1}H NMR (DMSO-d_6) 1.0 ppm (3H, t, J = 7.0 Hz, CH_3 ethyl), 1.2 ppm (3H, t, J = 7.1 Hz, CH_3 ester), 2.6 ppm (3H, s, CH_3), 3.7 ppm (1H, m, CH ethyl), 3.8 ppm (1H, m, CH ethyl), 3.9 ppm (2H, q, J = 7.1 Hz, CH_2 ester), 5.7 ppm (1H, d, J = 3.1 Hz, CH), 7.2-7.4 ppm (2H, m, aromH), 7.5 ppm (1H, m, aromH), 8 ppm (1H, s, NH). Anal. Calcd for $C_{16}H_{18}N_2O_3ClF$: C, 56.39; H, 5.32; Cl, 10.40; F, 5.58; N, 8.22. Found: C, 56.42; H, 5.27; Cl, 10.37; F, 5.52; N, 8.27.

Ethyl 4-(2-Chloro-5-nitrophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d).

Compound **4d** was prepared with the same procedure as **4a** in 48 % yield, mp 128°C, ir ν(C=O) ester 1685, ν(C=O) amide 1631, ν(NH) 3213. ^{1}H NMR (DMSO-d_6) 0.9 ppm (3H, t, J = 7.0 Hz, CH_3 ester), 2.6 ppm (3H, s, CH_3), 3.15 ppm (3H, s, N-CH_3), 3.9 ppm (2H, q, J = 7.0 Hz, CH_2 ester) 5.7 ppm (1H, d, J = 3.0 Hz, CH), 7.8 ppm (1H, d, J = 8.6 Hz, aromH), 8.1 ppm (1H, s, NH) 8.2 ppm (2H, m, aromH). Anal. Calcd for $C_{15}H_{16}N_3O_5Cl$: C, 50.93; H, 4.56; Cl, 10.02; N, 11.88. Found: C, 50.85; H, 4.59; Cl, 10.09; N, 11.95.

Ethyl 4-(2,3-Dichlorophenyl)-1-ethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e).

Compound **4e** was prepared with the same procedure as **4a** in 56 % yield, mp 116°C, ir ν(C=O) ester 1678, ν(C=O) amide 1624, ν(NH) 3344. ^{1}H NMR (DMSO-d_6) 1.0 ppm (3H, t, J = 7.1 Hz, CH_3 ethyl), 1.2 ppm (3H, t, J = 7.0 Hz, CH_3 ester), 2.5 ppm (3H, s, CH_3), 3.7 ppm (1H, m, CH ethyl), 3.8 ppm (1H, m, CH ethyl), 3.9 ppm (2H, q, J = 7.0 Hz,CH_2 ester) 5.6 ppm (1H, d, J = 3.0 Hz, CH), 7.3-7.4 ppm (2H, m, aromH), 7.6 ppm (1H, d, J = 8.9 Hz, aromH), 7.9 ppm (1H, s, NH). Anal. Calcd for $C_{16}H_{18}N_2O_3Cl_2$: C, 53.79; H, 5.08; Cl, 19.85; N, 7.84. Found: C, 53.75; H, 5.12; Cl, 19.77; N, 7.88.

Ethyl 4-(2,6-Dichlorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f).

Compound **4f** was prepared with the same procedure as **4a** in 88 % yield, mp 130°C, ir ν(C=O) ester 1683, ν(C=O) amide 1630, ν(NH) 3322. ^{1}H NMR (DMSO-d_6) 0.9 ppm (3H, t, J = 7.0 Hz, CH_3 ester), 2.4 ppm (3H, s, CH_3), 3.2 ppm (3H, s, N-CH_3), 3.9 ppm (2H, q, J = 7.0 Hz, CH_2 ester); 6.2 ppm (1H, d, J = 3.0 Hz, CH), 7.2-7.6 ppm (3H, m, aromH), 7.8 ppm (1H, s, NH). Anal. Calcd for $C_{15}H_{16}N_2O_3Cl_2$: C, 52.49; H, 4.70; Cl, 20.66; N, 8.16. Found: C, 52.34; H, 4.74; Cl, 20.48; N, 8.22.

4-(2,3-Dichlorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g).

Compound **4g** was prepared with the same procedure as **4a** in 90 % yield, mp 118°C, ir ν(C=O) ester 1672, ν(C=O) amide 1621, ν(NH) 3350. ^{1}H NMR (DMSO-d_6) 0.9 ppm (3H, t, J = 7.1 Hz, CH_3 ester), 2.5 ppm (3H, s, CH_3), 3.1 ppm (3H, s, N-CH_3), 3.9 ppm (2H, q, J = 7.0 Hz, CH_2 ester); 5.6 ppm (1H, d, J = 3.2 Hz, CH), 7.2-7.5 ppm (3H, m, aromH), 7.9 ppm (1H, s, NH). Anal. Calcd for $C_{15}H_{16}N_2O_3Cl_2$: C, 52.49; H, 4.70; Cl, 20.66; N, 8.16. Found: C, 52.37; H, 4.73; Cl, 20.69; N, 8.19.

Ethyl 4-(2-Chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4h).

Compound **4h** was prepared with the same procedure as **4a** in 94 % yield, mp 215°C, ir ν(C=O) ester 1690, ν(C=O) amide 1640, ν(NH) 3360. ^{1}H NMR (DMSO-d_6) 1.1 ppm (3H, t, J = 7.1 Hz, CH_3 ester), 2.3 ppm (3H, s, CH_3), 3.9 ppm (2H, q, J = 7.0 Hz, CH_2 ester); 5.6 ppm (1H, d, J = 3.0 Hz, CH), 7.1-7.2 ppm (4H, m, aromH), 7.7 ppm (1H, s, NH), 9.3 ppm (1H, s, NH). Anal. Calcd for $C_{14}H_{15}N_2O_3Cl$: C, 57.05; H, 5.13; Cl, 12.03; N, 9.50. Found: C, 57.11; H, 5.11; Cl, 11.97; N, 9.45.

Ethyl 4-(2,4-Dichlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i).

Compound **4i** was prepared with the same procedure as **4a** in 69 % yield, mp 249°C, ir ν(C=O) ester 1699 ν(C=O) amide 1641, ν(NH) 3415. ^{1}H NMR (DMSO-d_6) 1 ppm (3H, t, J = 7.0 Hz, CH_3 ester), 2.3 ppm (3H, s, CH_3), 3.9 ppm (2H, q, J = 7.1 Hz, CH_2 ester); 5.6 ppm (1H, d, J = 3.0 Hz, CH), 7.3-7.5 ppm (3H, m, aromH), 7.8 ppm (1H, s, NH), 9.3 ppm (1H, s, NH). Anal. Calcd for $C_{14}H_{14}N_2O_3Cl_2$: C, 51.08; H, 4.29; Cl, 21.54; N, 8.51. Found: C, 51.12; H, 4.27; Cl, 21.49; N, 8.62.

3,4-Dimethyl-1,2,3,5,6,10b-hexahydropyrimido[5,4-*c*]quinoline-2,5-dione (5a).

A solution of *o*-chloro-3,4-dihydropyrimidin-2-(1 H) one. **4a** (1g, 3,2mmol) and 80ml of ammonia at 32% was heated at 250°C under 10 bars for 16h. The solvent was removed in vacuum to afford a solid which was dissolved in water and neutralized with 5M hydrochloric acid. The precipitate obtained was recuperated by filtration and recrystallised from ethanol to give the pure product **6a** in 70 % yield, mp 236°C, ir ν(C=O) amide 1680, 1636, ν(NH) 3120. ^{1}H NMR (DMSO-d_6) 2.6 ppm (3H, s, CH_3), 3.1 ppm (3H, s, N-CH_3), 5.6 ppm (1H, d, J = 3.2 Hz, CH), 7.2-7.6 ppm (4H, m, aromH), 7.9 ppm (1H, s, NH), 12 ppm (1H, s, NH). Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.25; H, 5.34; N, 17.21.

3-Ethyl-4-methyl-1,2,3,5,6,10b-hexahydropyrimido[5,4-*c*]quinoline-2,5-dione (5b).

Compound **5b** was prepared with the same procedure as **5a** in 73 % yield, mp 244°C, ir ν(C=O) amide 1679, 1622, ν(NH) 2990. ^{1}H NMR (DMSO-d_6) 1.1 ppm (3H, t, J = 6.9 Hz, CH_3 ethyl), 2.6 ppm (3H, s, CH_3), 3.6 ppm (1H, m, N-CH ethyl), 3.8 ppm (1H, m, N-CH ethyl), 5.7 ppm (1H, d, J = 3.3 Hz, CH), 7.2-7.5 ppm (4H, m, aromH), 7.8 ppm (1H, s, NH), 12 ppm (1H, s, NH). Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.31; H, 5.91; N, 16.35.

3-Ethyl-10-fluoro-4-methyl-1,2,3,5,6,10b-hexahydropyrimido[5,4-*c*]quinoline-2,5-dione (5c).

Compound **5c** was prepared with the same procedure as **5a** in 80 % yield, mp 228°C, ir ν(C=O) amide 1683, 1630, ν(NH) 3100. ^{1}H NMR (DMSO-d_6) 1.1 ppm (3H, t, J = 7.3 Hz, CH_3 ethyl), 2.5 ppm (3H, s, CH_3), 3.7 ppm (1H, m, N-CH ethyl), 3.8 ppm (1H, m, N-CH ethyl), 5.9 ppm (1H, d, J = 3.6 Hz, CH), 7.3-

7.5 ppm (3H, m, aromH), 7.6 ppm (1H, s, NH), 11.9 ppm (1H, s, NH). Anal. Calcd for $C_{14}H_{14}N_3O_2F$: C, 61.08; H, 5.13; F, 6.90; N, 15.26. Found: C, 61.12; H, 5.06; F, 6.94; N, 15.18.

3,4-Dimethyl-9-nitro-1,2,3,5,6,10b-hexahydropyrimido[5,4-*c*]quinoline-2,5-dione (5d).

Compound **5d** was prepared with the same procedure as **5a** in 85 % yield, mp 253°C, ir ν(C=O) amide 1675, 1620, ν(NH) 2995. ^{1}H NMR (DMSO-d_6) , 2.5 ppm (3H, s, CH_3), 3.5 ppm (3H, s, N-CH_3), 5.6 ppm (1H, d, J = 3.6 Hz, CH), 7.1-7.5 ppm (3H, m, aromH), 7.7 ppm (1H, s, NH), 12.1 ppm (1H, s, NH). Anal. Calcd for $C_{13}H_{12}N_4O_4$: C, 54.17; H, 4.20; N, 19.44. Found: C, 54.28; H, 4.17; N, 19.37.

7-Chloro-3-ethyl-4-methyl-1,2,3,5,6,10b-hexahydropyrimido[5,4-*c*]quinoline-2,5-dione (5e).

Compound **5e** was prepared with the same procedure as **5a** in 73 % yield, mp 250°C, ir ν(C=O) amide 1671, 1618, ν(NH) 2998. ^{1}H NMR (DMSO-d_6) 1.0 ppm (3H, t, J = 6.9 Hz, CH_3 ethyl), 2.5 ppm (3H, s, CH_3), 3.7 ppm (1H, m, N-CH ethyl), 3.8 ppm (1H, m, N-CH ethyl), 5.6 ppm (1H, d, J = 3.3 Hz, CH), 7.2-7.4 ppm (3H, m, aromH), 7.6 ppm (1H, s, NH), 11.9 ppm (1H, s, NH). Anal. Calcd for $C_{14}H_{14}N_3O_2Cl$: C, 57.64; H, 4.84; Cl, 12.15; N, 14.40. Found: C, 57.42; H, 4.88; Cl, 12.10; N, 14.51.

10-Chloro-3,4-dimethyl-1,2,3,5,6,10b-hexahydropyrimido[5,4-*c*]quinoline-2,5-dione (5f).

Compound **5f** was prepared with the same procedure as **5a** in 90 % yield, mp 258°C, ir ν(C=O) amide 1666, 1619, ν(NH) 3005. ^{1}H NMR (DMSO-d_6) 2.5 ppm (3H, s, CH_3), 3.2 ppm (3H, s, N-CH_3), 6.1 ppm (1H, d, J = 3.2 Hz, CH), 7.2-7.5 ppm (3H, m, aromH), 7.6 ppm (1H, s, NH), 11.6 ppm (1H, s, NH). Anal. Calcd for $C_{13}H_{12}N_3O_2Cl$: C, 56.22; H, 4.36; Cl, 12.77; N, 15.13. Found: C, 56.25; H, 4.30; Cl, 12.65; N, 15.22.

7-Chloro-3,4-dimethyl-1,2,3,5,6,10b-hexahydropyrimido[5,4-*c*]quinoline-2,5-dione (5g).

Compound **5g** was prepared with the same procedure as **5a** in 81 % yield, mp 254°C, ir ν(C=O) amide 1673, 1622, ν(NH) 2990. ^{1}H NMR (DMSO-d_6) 2.6 ppm (3H, s, CH_3), 3.2 ppm (3H, s, N-CH_3), 5.6 ppm (1H, d, J = 3.5 Hz, CH), 7.2-7.6 ppm (3H, m, aromH), 7.8 ppm (1H, s, NH), 11.9 ppm (1H, s, NH). Anal. Calcd for $C_{13}H_{12}N_3O_2Cl$: C, 56.22; H, 4.36; Cl, 12.77; N, 15.13. Found: C, 56.16; H, 4.39; Cl, 12.70; N, 15.24.

REFERENCES

1. V. Moret, Y. Laras, N. Pietrancosta, C. Garino, G. Quelever, A. Rolland, B. Mallet, J.-C. Norreel, and J.-L. Kraus, *Bioorg. Med. Chem. Lett*, 2006, **16,** 3298.

2. L. Benvenisti-Zarom, J. Chempand, and R.-F. Regan, *Neuropharmacology*, 2005, **49,** 687.
3. G. J. M. Ketcho Wanda, D. Njamen, E. Yankep, M. T. Fotsing, Z. T. Fomum, J. Wober, S. Starcke, O. Zierau, and G. Vollmer, *Phytomedicine*, 2006,**13**, 139.
4. B. Refouvelet, C. Guyon, Y. Jacquot, C. Girard, H. Fein, F. Bevalot, J.-F. Robert, B. Heyd, G. Mantion, L. Richert, and A. Xicluna, *Eur. J. Med. Chem*, 2004, **39,** 931.
5. Y. Jacquot, A. Cleeren, I. M. Y. Laios, A. Boulahdour, L. Bermont, B. Refouvelet, G. Adessi, G. Leclercq, and A. Xicluna, *Biol. Pharm. Bull*., 2002, **25,** 335.
6. Y. Jacquot, C. Rojas, B. Refouvelet, J. F. Robert, G. Leclercq, and A. Xicluna, *Mini Reviews in Medicinal Chemistry*, 2003, **3**, 159.
7. P. Biginelli, *Gazz. Chim. Ital.*, 1893, **23**, 360.
8. S. Tu, F. Fang, C. Miao, H. Jiang, Y. Feng, D. Shi, and X. Wang, *Tetrahedron Letters*, 2003, **44,** 6153.
9. Z.-T. Wang, L.-W. Xu, C.-G. Xia, and H.-Q. Wang, *Tetrahedron Lett.*, 2004, **45**, 7951.
10. D. Russwsky, R. F. S. Canto, S. A. A. Sanches, M. G. M. D'Oca, A. De Fatima, R. A. Pilli, L. K. Kohn, M. A. Antonio, and E. De Carvalho, *Bioorg. Chem*, 2006, **34**, 173.
11. L. Ismaili, B. Refouvelet, and A. Xicluna, *European Patent*, 2002, 0207177.
12. Y. Hashimoto, I. Ishizaki, K. Shudo, and T. Okamoto, *Chem. Pharm. Bull*., 1983, **31,** 3891.
13. T. Miki, M. Kori, A. Fujishima, H. Mabuchi, R. Tozawa, M. Nakamura, Y. Sugiyama, and H. Yukimasa, *Bioorg. Med. Chem*., 2002, **10,** 385.
14. F. Sweet and J. D. Fissekis, *J. Am. Chem. Soc.*, 1973, **95**, 8741.
15. C. O. Kappe, *J. Org. Chem.*, 1997, **62**, 7201.
16. C. O. Kappe, *Tetrahedron*, 1993, **49**, 6937.