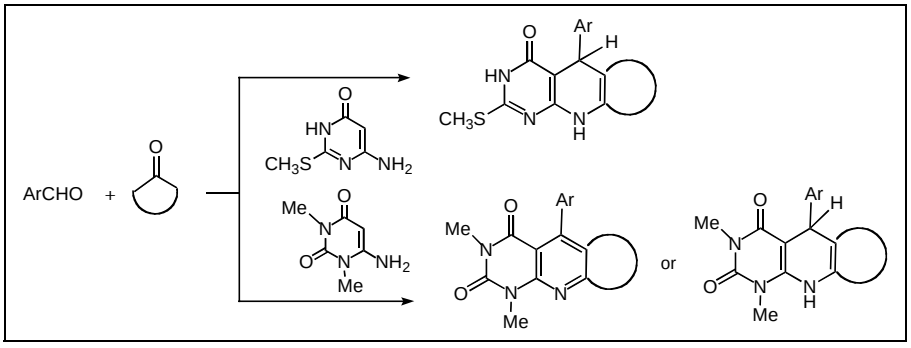
Three-Component, One-Pot Synthesis of Pyrimido[4,5-*b*]-quinoline and Pyrido[2,3-*d*]pyrimidine Derivatives

N. A. Hassan[a]*, M. I. Hegab [a], A. I Hashem[b], F. M. Abdel-Motti [a], S. H. A. Hebah [a], F. M. E. Abdel-Megeid[a]

[a] National Research Centre, Dokki, Cairo, Egypt,
[b] Faculty of Science, Ain Shams University, Cairo, Egypt

Received March 14, 2006



Reaction of 6-amino-2-methylthiouracil and 6-amino-1,3-dimethyluracil with equimoler amounts of cyclic ketones or cyclic 1,3-diketones and the appropriate aromatic aldehydes yielded regioselectivity a series of polycyclic pyrimido[4,5-*b*]quinoline and pyrido[2,3-*d*]pyrimidine derivatives in good yields.

J. Heterocyclic Chem., **44**, 775 (2007).

INTRODUCTION

The design and synthesis of 1,4-diyhdropyridines (1,4-DHPs) are of current research interest due to their exceptional properties as calcium antagonists [1-3] and as powerful arteriolar vasodilators [4]. Substitution on C2-C3 and C5-C6 positions of 1,4-DHP ring has been widely studied because of the important effects that some substituents induce on the biological properties of these systems [5-10]. Nifedipine, amlodipine, nimodipine, felodipine, clinidipine and nitrendipine are famous examples of DHP-calcium antagonists (see Chart 1). In addition, very recent papers have reported different biological activities of novel 1,4-DHP derivatives that are not connected with their calcium channel modulator properties, such as neurotropic [11] antidiabetic [12] antibacterial [13] and antiviral activity [14].

In order to gain a better understanding of the effect of the substitution pattern of the 1,4-DHP for biological activity, in this paper we describe the synthesis of novel pyrimido[4,5-*b*]quinoline derivatives in which the 1,4-DHP is fused to a cyclohexanone, indanone, cyclo-heptane, cyclohexane, cyclopentane and tetraline ring on C2-C3 positions and uracil or thiouracil moiety on C5-C6 positions. Also, the other objective of the present study is to prepare pyrido[2,3-*d*]pyrimidines. The interest in the synthesis of the later compounds is due to the fact that various derivatives of pyrido[2,3-*d*]pyrimidine were reported to be useful as antitumor [15], antimicrobial [16], antibacterial [17], antifolate [18], anticonvulsants [19], antileishmanial [20], antiinflammatory [21], diuretic, antiaggressive activity [22] and antiviral activity [23].

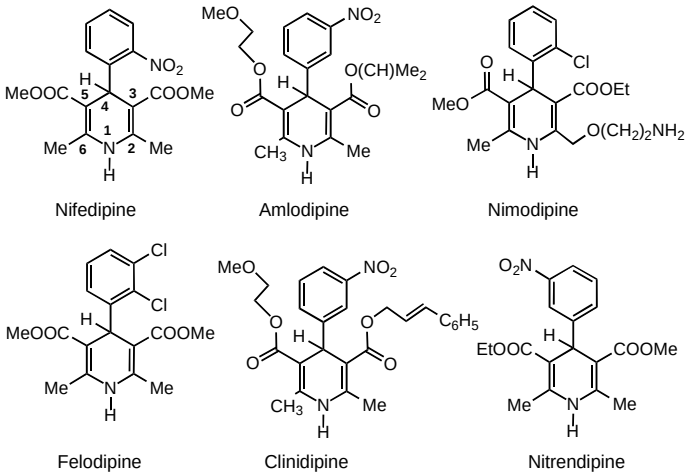


Chart 1: Representative examples of DHP-calcium antagonists

RESULTS AND DISCUSSION

In this study 6-amino-2-methylthiouracil (**1**), and 6-amino-1,3-dimethyluracil (**2**), which are important synthons required for annulation of pyrimidine ring onto other heterocyclic rings to form fused tricyclic and tetracyclic derivatives, were used as starting materials. The preparation of polycyclic pyrimido[4,5-*b*]quinoline derivatives were synthesized by refluxing equimolar amounts of 6-amino-2-methylthiouracil **1** in DMF with cyclic ketones like dimedone **3**, 1,3-cyclohexanedione **4**, α-tetralone **5** and appropriate benzaldehyde derivative, whereas, the use of other cyclic ketones such as 1,3-indandione **6**, 1-benzosuberone **7**, cyclopentanone **8**, 1-

indandione **15**, cycloheptanone **16** led to the formation of dihydropyrido[2,3-*d*]pyrimidine derivatives under the same experimental conditions (Scheme 1). The structural assignments of these products are based on their elemental analyses and the spectral data (*cf.* Experimental). As a representative example, compound **9a** revealed a molecular formula $C_{22}H_{26}N_4O_2S$ (m/z 410). Its ^{1}H NMR spectrum revealed the presence of two singlets at δ 12.33 ppm and 9.82 ppm assignable to the 2 NH protons. Signals attributable to the aromatic protons observed at δ 7.18-7.26 ppm. The signal assigned to the C_5H-aryl proton appeared as a singlet at 4.85 ppm. Signals attributable to the -SCH_3 and -$N(CH_3)_2$ protons observed at 2.50 ppm and 3.46 ppm, respectively. The two methyl groups of the cyclohexanone ring on C-2 appeared as singlets at δ 0.90 ppm and 1.09 ppm while the two protons on C-1 and C-3 appeared as AB system.

This reaction is assumed to proceed initially *via* the intermediacy of the condensation product (α,β-unsaturated ketone intermediate) resulted from the nucleophilic attack of the active methylene group of the ketone on the carbonyl group of the aldehyde. Then, subsequent nucleophilic attack by the amino group of the uracil derivative on the carbonyl carbon, of the α,β-unsaturated ketone intermediate, followed by cyclization and elimination of water could give the linear structure (route A). However, alternative attack of the amino group of the uracil derivative on the methylenic carbon of the α,β-unsaturated ketone followed by cyclization could lead to the angular structure (route B). The first case would correspond to the Quiroga *et al* [24] who investigated the reaction of 6-amino-2,3-dihydrothioxo-4(1*H*)-pyrimidinone with chalcones and the latter case would correspond to the Skraup synthesis and Doebner-Miller synthesis of pyridines and quinolines. Theoretically, this cyclo-condensation reaction can afford a linear structure (route A) and/or an angular structure (route B) as products (Figure. 1).

However, in the present study, this one-step cyclocondensation reaction was found to give only, and regioselectively, one product for which two isomeric structures are possible, the linear structure and the angular structure. The linear structure is favored over the angular structure as judged from the ^{1}H NMR spectra, in particular with respect to the chemical δ shifts of the C_5H-aryl and signal of the N-H protons. The ^{1}H NMR spectra of the prepared dihydropyrido[2,3-*d*]pyrimidine derivatives **9**-**14** contain two relatively sharp singlets at δ 4.80-5.60, and δ 6.5-10.2 for the C_5H-aryl and N-H protons, respectively [24-26]. The fact that C_5H-aryl and N-H protons are not coupled is a good evidence for the linear structure and discards the angular structure. In the last structure, coupling between methylenic proton and NH would have been observed. The linear structure is in accordance with the previously reported analogous results

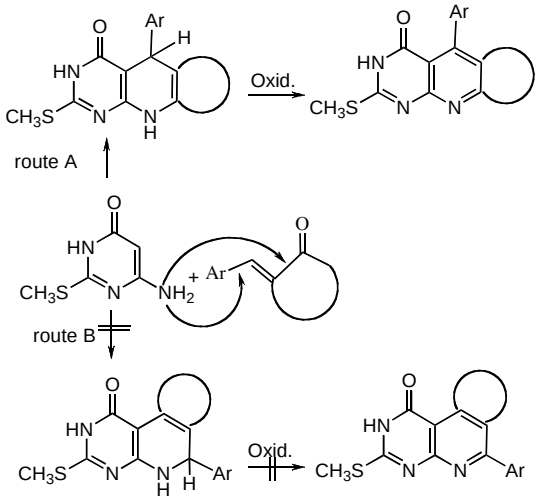


Figure 1

[21] where the C_5-H and N-H protons appeared at δ 4.81-5.00 and δ 9.71-9.98 ppm, respectively. In addition to that, several authors have extended the ^{1}H NMR investigation to the use of the NOE technique [24] and the assignment of the signals in the ^{1}H- and ^{13}C NMR by the ^{1}H,^{1}H COSY technique and ^{1}H,^{13}C shift correlation, as well as, by comparison with data previously reported for similar systems which all supported the linear structure [25-27]. Moreover, X-ray crystal studies and two dimensional H, C correlated NMR spectroscopic studies of products of similar cyclocondensation reactions indicated that linear rather than angular products are formed [28]. So, single crystal X-ray structure determination which failed to have it would be an additional tool to confirm the structure of some of the newly prepared dihydropyrido- and pyrido[2,3-*d*]pyrimidine derivatives. The recent results of Elgemeie *et al* [29] and others [30-33] represent an additional support for the linear structure.

Analogously, the stable dihydropyrimido[4,5-*b*]-quinolines **18** were isolated as the main products only in the reaction of 6-amino-1,3-dimethyluracil (**2**) with 1,3-cyclohexanedione **4** and appropriate benzaldehyde derivatives. On the other hand pyrimido[4,5-*b*]quinolines **19** and **20** were isolated upon using α-tetralone **5** and cyclohexanone **17** instead of 1,3-cyclohexanedione. Furtheromre, the reaction of **2** with cycloheptanone **16**, 1-indanone **15**, 1,3-indandione **6**, in the presence of appropriate benzaldehyde derivatives led to the formation of pyrido[2,3-*d*]-pyrimidine derivatives **21-23** respectively, as the main products (Scheme 1). The formation of the pyrido[2,3-*d*]-pyrimidines are compitable with the literature [20] which revealed that the dihydropyrido[2,3-*d*]pyrimidine-2,4-diones derivatives were unstable to air and could be easily

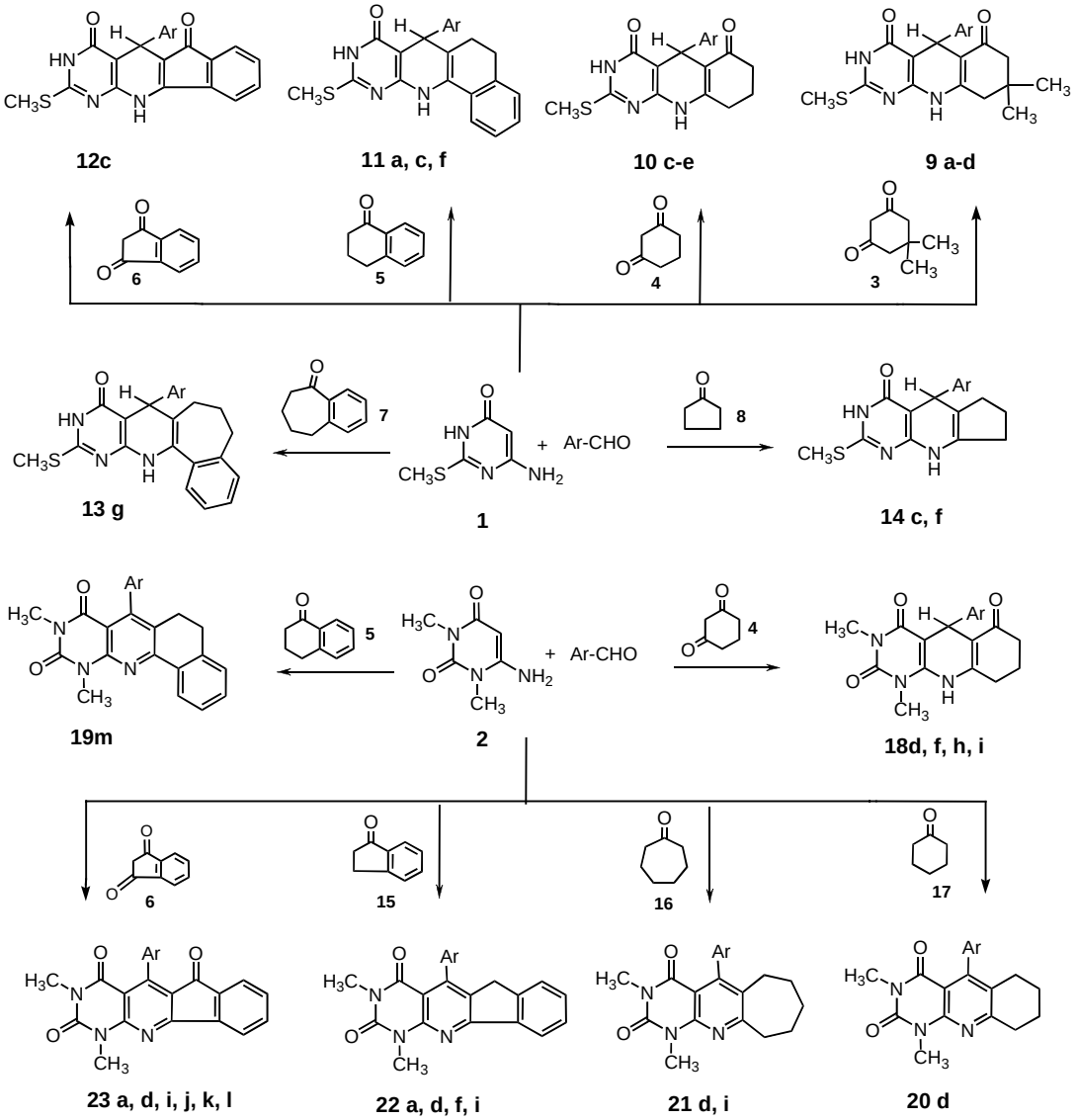
oxidized to corresponding aromatization products. We tried to gain the intermediate dihydropyridopyrimidine of products **21-23** by carrying out the same reactions under dry condition and under nitrogen, but the same products were obtained.

The structures of the all products were confirmed by elemental analyses and spectral data (MS, IR, ^{1}H NMR and ^{13}C NMR) (c.f. Experimental).

EXPERIMENTAL

All melting points are uncorrected and measured using Electro-thermal IA 9100 apparatus. IR spectra were recorded as potassium bromide pellets on a Nexus 670 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were run on a Brucker AC-250 NMR spectrometer, using d_6-DMSO as solvent at konstanz university (Germany) and on a Jeol-Ex-270 NMR spectro-photometer at the National Research Centre and chemical shifts were expressed as part per million; ppm (δ values) against TMS as internal reference. Mass spectra were recorded on EI + Q1 MSLMR UPLR. Microanalytical data were performed by Vario El Elmentar apparatus at Organic Microanalysis Section, National Research Centre.

General procedure for the preparation of pyrido[2,3-*d*]-pyrimidine and pyrimido[4,5-*b*]quinoline derivatives (9-23). A mixture of of 6-amino-2-methylthiouracil **1** (10 mmol) or 6-amino-1,3-dimethyluracil **2** (10 mmol), cyclic ketone (10 mmol) and (10 mmol) of the appropriate aldehyde in DMF (30 ml) was refluxed under stirring for 2-5 h. The solid product, so formed, was collected by filtration, washed with ethanol, dried and finally recrystallized from the proper solvent.



Ar = (a) 4-$(CH_3)_2$N-C_6H_4, (b) 1-naphthyl, (c) thiophen-2-yl, (d) 4-F-C_6H_4, (e) anthracen-9-yl, (f) 4-Cl-C_6H_4, (g) piperonyl, (h) 4-CH_3-C_6H_4, (i) 4-NO_2-C_6H_4, (j) 4-Br-C_6H_4 (k) 4-CH_3O-C_6H_4, (l) 2-CH_3O-C_6H_4, (m) C_6H_5

Scheme 1

8,8-Dimethyl-5-(4-*N*,*N*-dimethylaminophenyl)-2-methylsulfanyl-5,8,9,10-tetrahydro-3*H*,7*H*-pyrimido[4,5-*b*]-quinoline-4,6-dione (**9a**). From 6-amino-2-methylthiouracil **1** (1.57 g, 10 mmol), 5,5- dimethyl-1,3-cyclohexanedione **3** (1.40 g, 10 mmol) and *N*,*N*-dimethylaminobenzldehyde (1.49 g, 10 mmol) and as described for the general procedure, reaction time 2 h, the solid product was recrystallized from EtOH to give colorless powder (3.28 g, 66%); mp 313-15 ˚C; ir: 3470, 3222 (NH), 1652 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 3H, SCH_3), 0.90 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 2.01, 2.37 (dd, 2H, CH_2), 2.47, 2.53 (dd, 2H, CH_2), 3.46 (s, 6H, $N(CH_3)_2$), 4.85 (s, 1H, -C_5H-aryl), 7.18-7.26 (m, 4H, ArH), 9.82 (s, 1H, NH, D_2O exchangeable), 12.33 (s, 1H, -NHCO, D_2O exchangeable); ms: *m*/*z* 410 (M^+, 91.9 %), 395 (27.1), 326 (30.6), 290 (100), 242 (20.7), 121 (57.2), 206 (15.5), 77 (18.9). *Anal*. Calcd. for $C_{22}H_{26}N_4O_2S$: C, 64.39; H, 6.34; N, 13.65; S, 7.80. Found: C, 64.51; H, 6,44; N, 13.76; S, 7.56.

8,8-Dimethyl-2-methylsulfanyl-5-(1-naphthyl)-5,8,9,10-tetrahydro-3*H*,7*H*-pyrimido[4,5-*b*]quinoline-4,6-dione (**9b**). From 6-amino-2-methylthiouracil **1** (1.57 g, 10 mmol), 5,5-dimethyl-1,3-cyclohexanedione **3** (1.40 g, 10 mmol) and 1-naphthaldehyde (1.56 g, 10 mmol) and as described for the general procedure, reaction time 2 h, the solid product was recrystallized from EtOH to give colorless powder (3.28 g, 79%); mp 350-52 ˚C; ir: 3440, 3290 (NH), 1642 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 0.90 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 2.01, 2.37 (dd, 2H, CH_2), 2.49 (s, 3H, SCH_3) 2.50, 2.55 (dd, 2H, CH_2), 4.90 (s, 1H, -C_5H-aryl), 7.20-7.86 (m, 7H, ArH), 9.62 (s, 1H, NH, D_2O exchangeable), 12.30 (s, 1H, -NHCO, D_2O exchangeable); ms: *m*/*z* 417 (M^+, 22.3 %), 290 (100), 242 (10.2). *Anal*. Calcd. for $C_{24}H_{23}N_3O_2S$: C, 69.04; H, 5.55; N, 10.06; S, 7.67. Found: C, 69.22; H, 5.64; N, 10.09; S, 7.38.

8,8-Dimethyl-2-methylsulfanyl-5,8,9,10-tetrahydro-3*H*,7*H*-5-(thiophen-2-yl)pyrimido[4,5-*b*]quinoline-4,6-dione (**9c**). From 6-amino-2-methylthiouracil **1** (1.57 g, 10 mmol), 5,5-dimethyl-1,3-cyclohexanedione **3** (1.40 g, 10 mmol) and thiophene-2-carboxaldehyde (1.12 g, 10 mmol) and as described for the general procedure, reaction time 2 h, the solid product was recrystallized from DMF to give colorless powder (2.87 g, 77%); mp 347-49 ˚C; ir: 3466, 3319 (NH), 1612, 1643 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 0.97 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 2.50 (s, 3H, SCH_3), 2.00, 2.20 (dd, 2H, CH_2), 2.51, 2.53 (dd, 2H, CH_2), 4.80 (s, 1H, -C_5H-aryl), 6.60-7.2 (m, 3H, ArH), 9.70 (s, 1H, NH, D_2O exchangeable), 12.60 (s, 1H, -NHCO, D_2O exchangeable); ms: *m*/*z* 373 (M^+, 100 %). *Anal*. Calcd. for $C_{18}H_{19}N_3O_2S_2$: C, 57.89; H, 5.13; N, 11.25; S, 17.14. Found: C, 57.98; H, 5.20; N, 11.47; S, 17.01.

8,8-Dimethyl-5-(4-fulorophenyl)-2-methylsulfanyl-5,8,9,10-tetrahydro-3*H*,7*H*-pyrimido[4,5-*b*]quinoline-4,6-dione (**9d**). From 6-amino-2-methylthiouracil **1** (1.57 g, 10 mmol), 5,5-dimethyl-1,3-cyclohexanedione **3** (1.40 g, 10 mmol) and 4-fluorobenzaldehyde (1.24 g, 10 mmol) and as described for the general procedure, reaction time, 2 h, the solid product was recrystallized from EtOH to give colorless powder (3.28 g, 79%); mp 365-67 ˚C; ir: 3470, 3290 (NH), 1642 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 0.80 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 2.01, 2.40 (dd, 2H, CH_2), 2.457, 2.53 (dd, 2H, CH_2), 2.50 (s, 3H, SCH_3), 4.90 (s, 1H, -C_5H-aryl), 7.18-7.26 (m, 4H, ArH), 9.80 (s, 1H, NH, D_2O exchangeable), 12.35 (s, 1H, -NHCO, D_2O exchangeable); ms: *m*/*z* 385 (M^+, 100 %). *Anal*. Calcd. for $C_{20}H_{20}FN_3O_2S$: C, 62.32; H, 5.23; N, 10.90; S, 8.31. Found: C, 62.14; H, 5.24; N, 11.00; S, 8.46.

2-Methylsulfanyl-5,8,9,10-tetrahydro-3*H*,7*H*-5-(thiophen-2-yl)pyrimido[4,5-*b*]quinoline-4,6-dione (**10c**). From 6-amino-2-methylthiouracil **1** (1.57 g, 10 mmol), 1,3-cyclohexanedione **4** (1.12 g, 10 mmol) and thiophene-2-carboxaldehyde (1.12 g, 10 mmol) and as described for the general procedure, reaction time, 2 h, the product was recrystallized from DMF to give colorless powder (3.00 g, 87%); mp 353-55˚C; ir: 3450, 3290 (NH), 1650 (C=O) (cm^{-1}); ms: *m*/*z* 345 (M^+, 100), 330 (38), 288 (12), 262 (79), 214 (23), 73.9 (22). *Anal*. Calcd. for $C_{16}H_{15}N_3O_2S_2$: C, 55.63; H, 4.38; N, 12.16; S, 18.56. Found: C, 55.79; H, 4.30; N, 12.19; S, 18.61.

5-(4-Fluorophenyl)-2-methylsulfanyl-5,8,9,10-tetrahydro-3*H*,7*H*-pyrimido[4,5-*b*]quinoline-4,6-dione (**10d**). From 6-amino-2-methylthiouracil **1** (1.57 g, 10 mmol), 1,3-cyclohexanedione **4** (1.12 g, 10 mmol) and 4-florobenzaldehyde (1.24 g, 10 mmol) and as described for the general procedure, reaction time 2 h, the product was recrystallized from DMF to give colorless powder (2.47 g, 69%); mp 316-18 ˚C; ir: 3470, 3280 (NH), 1645 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H, SCH_3), 2.4-2.6 (m, 6H, CH_2), 4.95 (s, 1H, -C_5H-aryl), 7.0-7.30 (m, 4H, ArH), 9.90 (s, 1H, NH, D_2O exchangeable), 12.40 (s, 1H, -NHCO, D_2O exchangeable); ms: *m*/*z* 357 (M^+, 100 %). *Anal*. Calcd. for $C_{18}H_{16}FN_3O_2S$: C, 60.49; H, 4.51; N, 11.76; S, 17.14. Found: C, 60.66; H, 4.73; N, 11.77; S, 17.01.

5-(Anthracen-9-yl)-2-methylsulfanyl-5,8,9,10-tetrahydro-3*H*,7*H*-pyrimido[4,5-*b*]quinolin-4,6-dione (**10e**). From 6-amino-2-methylthiouracil **1** (1.57 g, 10 mmol), 1,3-cyclohexanedione **4** (1.12 g, 10 mmol) and 9-anthracene-carboxaldehyde (2.06 g, 10 mmol) and as described for the general procedure, reaction time 5 h, the product was recrystallized from DMF to give pale yellow powder (2.59 g, 59%); mp 349-52C°(decomp.); ir: 3470, 3290 (NH), 1642 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 1.50-2.20 (m, 6H, CH_2), 2.5 (s, 3H, SCH_3), 6.50 (s, 1H, -C_5H-aryl), 7.40-9.0 (m, 9H, ArH), 10.20 (s, 1H, NH, D_2O exchangeable), 12.0 (s, 1H, -NHCO, D_2O exchangeable); ms: *m*/*z* 439 (M^+, 48.3 %), 262 (100), 214 (26.3), 178 (56.5). *Anal*. Calcd. for $C_{26}H_{21}N_3O_2S$: C, 71.05; H, 4.82; N, 9.56, S, 7.29. Found: C, 71.23; H, 4.66; N, 9.73. S, 7.11.

7-(4-Dimethylaminophenyl)-10-methylsulfanyl-5,6,7,12-tetrahydro-9*H*-benzo[*h*]pyrimido[4,5-*b*]quinolin-8-one (**11a**). From 6-amino-2-methylthiouracil **1** (1.57 g, 10 mmol), 1-tetralone **5** (1.46 g, 10 mmol) and *N*,*N*-dimethylamino-benzaldehyde (1.49 g, 10 mmol) and as described for the general procedure, reaction time 5 h, the solid product was recrystallized from DMF to give colorless powder (3.95 g, 95%); mp 278-80 ˚C; ir: 3345, 3180(NH), 1643 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 2.52-2.54 (m, 4H, CH_2), 2.56 (s, 3H, SCH_3), 3.48 (s, 6H, $N(CH_3)_2$) , 5.50 (s, 1H, -C_7H-aryl), 6.30-6.90 (m, 9H, ArH + NH, D_2O exchangeable), 11.80 (s, 1H, -NHCO, D_2O exchangeable). *Anal*. Calcd. for $C_{24}H_{24}N_4OS$: C, 69.20; H, 5.81; N, 13.45; S, 7.70. Found: C, 69.31; H, 5.77; N, 13.67, S, 7.59.

10-Methylsulfanyl-7-(thiophen-2-yl)-5,6,7,12-tetrahydro-9*H*-benzo[h]pyrimido[4,5-b]quinolin-8-one (**11c**). From 6-amino-2-methylthiouracil **1** (1.57 g, 10 mmol), 1-tetralone **5** (1.46 g, 10 mmol) and thiophene-2-carboxaldehyde (1.12 g, 10 mmol) and as described for the general procedure, reaction time 5 h. The solid product was recrystallized from dioxane to give colorless powder (2.77 g, 73%); mp 352-54˚C; ir: 3345, 3180(NH), 1655 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 2.30-2.60 (m, 4H, CH_2), 2.45 (s, 3H, SCH_3), 5.60 (s, 1H, -C_7H-aryl), 6.50-7.25 (m, 8H, ArH+ NH, D_2O exchangeable), 12.00 (s, 1H, -NHCO, D_2O exchangeable). *Anal*. Calcd. for $C_{20}H_{17}N_3OS_2$: C,

63.30; H, 4.52; N, 11.07; S, 16.90. Found: C, 63.54; H, 4.49; N, 11.07; S, 16.86.

7-(4-Chlorophenyl)-10-methylsulfanyl-5,6,7,12-tetrahydro-9*H*-benzo[*h*]pyrimido[4,5-*b*]quinolin-8-one (**11f**). From 6-amino-2-methylthiouracil **1** (1.57 g, 10 mmol), 1-tetralone **5** (1.46 g, 10 mmol) and 4-chlorobenzaldehyde (1.41g, 10 mmol) and as described for the general procedure, reaction time 5 h, the solid product was recrystallized from DMF in colorless powder (3.43 g, 84%); mp 270-72˚C; ir: 3445, 3245(NH), 1646 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 2.30-2.60 (m, 4H, CH_2), 2.48 (s, 3H, SCH_3), 5.48 (s, 1H, -C_7H-aryl), 6.40-7.56 (m, 8H, ArH), 9.54 (s, 1H, NH, D_2O exchangeable), 11.80 (s, 1H, -NHCO, D_2O exchangeable). *Anal.* Calcd. for $C_{22}H_{18}ClN_3OS$: C, 64.78; H, 4.45; N, 10.30; S, 7.86. Found: C, 64.64; H, 4.39; N, 10.20; S, 7.91.

2-Methylsulfanyl-5-(thiophen-2-yl)-5,11-dihydro-3*H*-indeno[2',1':5,6]pyrido[2,3-*d*]pyrimidine-4,6-dione (**12c**). From 6-amino-2-methylthiouracil **1** (1.57 g, 10 mmol), 1,3-indandione **6** (1.46 g, 10 mmol) and thiophene-2-carboxaldehyde (1.12 g, 10 mmol) and as described for the general procedure, reaction time 5 h. The product was recrystallized from dioxane to give pale yellow powder (2.92 g, 77%); mp 346-48 ˚C; ir: 3451, 3444 (NH), 1642 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 2.60 (s, 3H, SCH_3), 5.10 (s, 1H, -C_5H-aryl), 6.90-7.80 (m, 7H, ArH), 11.20 (br, IH, NH, D_2O exchangeable), 12.60 (br, IH, NH, D_2O exchangeable). *Anal.* Calcd. for $C_{19}H_{13}N_3O_2S_2$: C, 60.14; H, 3.45; N, 11.07. S, 16.90. Found: C, 60.30; H, 3.56; N, 11.18, S, 16.79.

8-(Benzo[1,3]dioxol-5-yl)-11-methylsulfanyl-6,7,8,13-tetrahydro-10*H*-10,12,13-triaza-benzo[3,4]cyclohepta[1,2-*b*]-naphthalen-9-one (**13g**). From 6-amino-2-methylthiouracil **1** (1.57 g, 10 mmol), 1-benzosuberone **7** (1.60 g, 10 mmol) and 3,4-methylenedioxybenzaldehyde (piperonal) (1.50 g, 10 mmol) and as described for the general procedure reaction time 5 h, the solid product was recrystallized from EtOH to give colorless powder (3.49 g, 81%); mp 350-52 ˚C; ir: 3470, 3290 (NH), 1655 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 1.85-2.20 (m, 6H, CH_2), 2.48 (s, 3H, SCH_3), 5.40 (s, 1H, -C_8H-aryl), 5.87 (s, 2H, -OCH_2O), 6.50-7.25 (m, 7H, ArH), 9.20 (s, 1H, NH, D_2O exchangeable), 12.00 (s, 1H, -NHCO, D_2O exchangeable). *Anal.* Calcd. for $C_{24}H_{21}N_3O_3S$: C, 66.80; H, 4.91; N, 9.74; S, 7.43. Found: C, 66.69; H, 4.99; N, 9.87, S, 7.50.

2-Methylsulfanyl-5-(thiophen-2-yl)-3,5,6,7,8,9-hexahydro-cyclopenta[5,6]pyrido[2,3-*d*]pyrimidin-4-one (**14c**). From 6-amino-2-methylthiouracil **1** (1.57 g, 10 mmol), cyclopentanone **8** (0.84 g, 10 mmol) and thiophene-2-carboxyaldehyde (1.12 g, 10 mmol) and as described for the general procedure, reaction time, 5 h. The product was recrystallized from dioxane to give pale yellow powder (2.44 g, 77%); mp 350-52 ˚C; ir: 3443, 3249 (NH), 1642, 1630 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 2.30-2.55 (m, 6H, CH_2), 2.40 (s, 3H, SCH_3), 5.60 (s, 1H, -C_5H-aryl), 6.55-7.45 (m, 4H, ArH + NH, D_2O exchangeable), 12.00 (s, 1H, -NHCO, D_2O exchangeable); ms: *m/z* 317 (M^+, 100 %). *Anal.* Calcd. for $C_{15}H_{15}N_3OS_2$: C, 56.76; H, 4.76; N, 13.24; S, 20.20. Found: C, 56.71; H, 4.80; N, 13.47; S, 19.99.

5-(4-Chlorophenyl)-2-methylsulfanyl-3,5,6,7,8,9-hexahydro-cyclopenta[5,6]pyrido[2,3-*d*]pyrimidin-4-one (**14f**). From 6-amino-2-methylthiouracil **1** (1.57 g, 10 mmol), cyclopentanone **8** (0.84 g, 10 mmol) and 4-chlorobenzaldehyde (1.4 g, 10 mmol) and as described for the general procedure, reaction time, 5 h. The product was recrystallized from dioxane to give pale yellow powder (2.44 g, 77%); mp 347-49 ˚C; ir: 3420, 3355 (NH), 1649 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 2.33-2.60 (m, 6H, CH_2), 2.48 (s, 3H, SCH_3), 5.02 (s, 1H, -C_5H-aryl), 6.80 (d, *J*= 9 Hz, 2H, ArH), 7.40 (d, *J*= 9 Hz, 2H, Ar H), 6.55-6.60 (br, IH, NH, D_2O exchangeable), 12.00 (s, 1H, -NHCO, D_2O exchangeable); ms: *m/z* 347 (M^+, Cl^{37}, 36 %) 345, (M^+, Cl^{35}, 100). *Anal.* Calcd. for $C_{17}H_{16}ClN_3OS$: C, 59.04; H, 4.66; N, 12.15; S, 9.27. Found: 59.24; H, 4.7 6; N, 12.28; S, 9.11.

1,3-Dimethyl-5-(4-fluorophenyl)-5,8,9,10-tetrahydro-1*H*, 7*H*-pyrimido[4,5-*b*]quinoline-2,4,6-trione (**18d**). From 6-amino-1,3-dimethyluracil **2** (1.55 g, 10 mmol), 1,3-cyclo-hexanedione **4** (1.12 g, 10 mmol) and 4-fluorobenzaldehyde (1.24 g, 10 mmol) and as described for the general procedure, reaction time 2 h, the product was recrystallized from EtOH in colorless crystals (3.01g, 85%); mp 311-13 ˚C; ir: 1642, 1713 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 2.52-2.59 (m, 2H, CH_2), 2.61-2.65 (m, 2H, CH_2), 2.72-2.88 (m, 2H, CH_2), 3.17 (s, 3H, CH_3), 3.19 (s, 3H, CH_3), 4.95 (s, 1H, -C_5H-aryl), 6.95, 7.24 (m, 4H, ArH), 9.00 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 20.71 (C-8), 26.59 (C-5), 27.53 (CH_3-N3), 30.14 (CH_3-N1), 33.02 (C-9), 36.65 (C-7), 90.07 (C-4a), 112.77 (C-5a); C-3`, Ph, doublet at 114.06, 114.39, *J* = 82 Hz; C-2`, Ph, doublet at 129.17, 129.30, *J* = 8 Hz; C-1`, Ph, doublet at 142.67, 142.71, *J* = 3 Hz; 143.83 (C-10a), 150.61 (C-9a), 151.57 (C-2), 158.66 (C-4); C-4`, Ph, doublet at 160.78, 162.50, *J* = 108 Hz; 194.61 (C-6); ms: *m/z* 355 (M^+, 14 %), 260 (100), 203 (20). *Anal.* Calcd. for $C_{19}H_{18}FN_3O_3$: C, 64.22; H, 5.11; N, 11.82. Found: C, 64.34; H, 5.20; N, 11.73.

5-(4-Chlorophenyl)-1,3-dimethyl-5,8,9,10-tetrahydro-1*H*, 7*H*-pyrimido[4,5-*b*]quinoline-2,4,6-trione (**18f**). From 6-amino-1,3-dimethyluracil **2** (1.55 g, 10 mmol), 1,3-cyclohex-anedione **4** (1.12 g,10 mmol) 4-chlorobenzaldehyde (1.40 g, 10 mmol) and as described for the general procedure, reaction time 2 h, the product was recrystallized from EtOH in colorless crystals (3.33 g, 90%); mp 310-13 ˚C; ir: 1652, 1718(C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 1.98-2.04, 2.40-2.58 (m, 6H, $3CH_2$), 3.09 (s, 3H, CH_3), 3.45 (s, 3H, CH_3), 4.98 (s, 1H, -C_5H-aryl), 7.19 (d, 2H, *J* = 11.2 Hz, ArH), 7.23 (d, 2H, *J* = 11.2 Hz, Ar H), 9.09 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 20.62 (C-8), 26.43 (C-5), 27.56 (CH_3-N3), 30.19 (CH_3-N1), 33.29 (C-9), 36.54 (C-7), 89.63 (C-4a), 112.33 (C-5a), 127.59 (C-3`, Ph), 129.44 (C-2`, Ph), 130.34 (C-4`, Ph), 143.77 (C-1`, Ph), 145.40 (C-10a), 150.47 (C-9a), 151.66 (C-2), 160.67 (C-4), 194.71 (C-6). ms: *m/z* 371 (M^+, Cl^{35}, 12.80 %), 373 (M^+, Cl^{37}, 4.4), 260 (100), 203 (14.5). *Anal.* Calcd. for $C_{19}H_{18}ClN_3O_3$: C, 61.38; H, 4.88; N, 11.30. Found: C, 61.50; H, 4.80; N, 11.43.

1,3-Dimethyl-5-(4-tolyl)-5,8,9,10-tetrahydro-1*H*,7*H*-pyrimido[4,5-*b*]quinoline-2,4,6-trione (**18h**). From 6-amino-1,3-dimethyluracil **2** (1.55 g, 10 mmol), 1,3-cyclohexanedione **4** (1.12 g,10 mmol) and 4-toluoldehyde (1.20 g, 10 mmol) and as described for the general procedure, reaction time 2 h. The product was recrystallized from EtOH to give colorless crystals (3.08 g, 88%); mp 274-76 ˚C; ir: 3350 (NH), 1690, 1652, (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 1.79-1.97 (m, 4H, $2CH_2$), 2.18 (s, 3H, CH_3), 2.22-2.24 (m, 2H, CH_2), 3.09 (s, 3H, CH_3), 3.46 (s, 3H, CH_3), 4.89 (s, 1H, -C_5H-aryl), 6.94 (d, *J*=10.8 Hz, 2H, ArH), 7.09 (d, *J*= 10.8 Hz, 2H, ArH), 9.10 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 20.47 (CH_3-Ph), 20.66 (C-8), 26.43 (C-5), 27.53 (CH_3-N3), 30.18 (CH_3-N1), 32.98 (C-9), 36.61 (C-7), 90.21 (C-4a), 112.88 (C-5a), 126.34 (C-3`, Ph), 127.39 (C-2`, Ph), 128.24 (C-4`, Ph), 134.66 (C-1`, Ph), 143.60 (C-10a), 150.49 (C-9a), 151.35 (C-2), 160.67 (C-4), 194.67 (C-6); ms: *m/z* 351 (M^+, 15.5 %), 260 (100), 203 (16). *Anal.* Calcd.

for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.57; H, 6.10; N, 11.78.

1,3-Dimethyl-5-(4-nitrophenyl)-5,8,9,10-tetrahydro-1*H*,7*H*-pyrimido[4,5-*b*]quinoline-2,4,6-trione (**18i**). From 6-amino-1,3-dimethyluracil **2** (1.55 g, 10 mmol), 1,3-cyclohexanedione **4** (1.12 g, 10 mmol) and 4-nitrobenzaldehyde (1.51 g, 10 mmol) and as described for the general procedure, reaction time 2 h, the product was recrystallized from EtOH to give colorless crystals (3.44 g, 90%); mp 301-3 ˚C; ir: 3349 (NH), 1698, 1662 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 1.79-1.96 (m, 2H, CH_2), 2.02-2.37 (m, 2H, CH_2), 2.76-2.85 (m, 2H, CH_2), 3.40 (s, 3H, CH_3), 3.47 (s, 3H, CH_3), 5.03 (s, 1H, -C_5H-aryl), 7.51 (d, *J*=8.6, Hz, 2H, ArH), 8.05 (d, *J*=8.6 Hz, 2H, ArH), 9.22 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 20.58 (C-8), 26.47 (C-5), 27.57 (CH_3-N3), 30.28 (CH_3-N1), 34.39 (C-9), 36.46 (C-7), 80.99 (C-4a), 111.67 (C-5a), 122.95 (C-3`, Ph), 128.94 (C-2`, Ph), 144.05 (C-1`, Ph), 145.71 (C-4`, Ph), 150.46 (C-9a), 152.25 (C-10a), 153.90 (C-2), 160.67 (C-4), 194.74 (C-6); ms: *m/z* 382 (M^+, 11 %), 260 (100), 203 (15). *Anal.* Calcd. for $C_{19}H_{18}N_4O_5$: C, 59.68; H, 4.71; N, 14.65. Found: C, 59.87; H, 4.61; N, 14.86.

9,11-Dimethyl-5,6-dihydro-7-phenyl-11*H*-benzo[*h*]-pyrimido-4,5-*b*]quinoline-8,10-dione (**19m**). From 6-amino-1,3-dimethyluracil **2** (1.55 g, 10 mmol), 1-tetralone **5** (1.46 g, 10 mmol) and benzaldehyde (1.06 g, 10 mmol) and as described for the general procedure, reaction time 5 h. The product was recrystallized from dioxane to give pale yellow powder (1.88 g, 51%); mp 350-52˚C; ir: 1679(C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 2.83 (t, *J*= 6.8 Hz, 2H, CH_2), 3.28 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 3.64 (t, *J*= 6.8 Hz, 2H, CH_2), 7.00-7.10 (m, 2H, ArH), 7.40-7.85 (m, 5H, ArH) 7.85-7.95 (m, 2H, Ar H); ^{13}C NMR (DMSO-d_6): δ 24.12 (C-6), 26.98 (CH_3-N9), 27.87 (C-5), 29.37 (CH_3-N11), 106.85 (C-7a), 125.93 (C-2`, Ph), 126.03 (C-2), 127.00 (C-1, C-3), 127.33 (C-4), 127.78 (C-6a), 130.66 (C-3`, 4`, Ph), 133.18 (C-1`, Ph), 138.11 (C-4a), 139.20 (C-4b), 149.89 (C-7), 150.72 (C-10), 151.72 (C-12a), 154.45 (C-11a), 159.72 (C-8); ms: *m/z* 369 (M^+, 100 %), 341 (4), 311 (3), 292 (10), 254 (11), 184 (10). *Anal.* Calcd. for $C_{23}H_{19}N_3O_2$: C, 74.79; H, 5.15; N, 11.38. Found: C, 74.52; H, 5.28; N, 11.62.

1,3-Dimethyl-5-(4-fluorophenyl)-6,7,8,9-tetrahydro-1*H*-pyrimido[4,5-*b*]quinoline-2,4-dione (**20d**). From 6-amino-1,3-dimethyluracil **2** (1.55 g, 10 mmol), cyclohexanone **17** (1.41, 10 mmol) and 4-fluorobenzaldehyde (1.24, 10 mmol) and as described for the general procedure, reaction time 5 h. The product was recrystallized from dioxane to give pale yellow powder (2.03 g, 60%); mp 350-52 ˚C; ir: 1689(C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 1.85 (m, 4H, $2CH_2$), 2.83 (t, *J*= 6.8 Hz, 2H, CH_2), 3.37 (s, 3H, CH_3), 3.60 (s, 3H, CH_3), 3.65 (t, *J*= 6.8 Hz, 2H, CH_2), 7.00-7.10 (m, 2H, ArH), 7.85-7.95 (m, 2H, ArH); ms: *m/z* 339 (M^+, 100 %). *Anal.* Calcd. for $C_{19}H_{18}FN_3O_2$: C, 67.25; H, 5.35; N, 12.38. Found: C, 67.32; H, 5.38; N, 12.49.

1,3-Dimethyl-5-(4-fluorophenyl)-1,6,7,8,9,10-hexahydrocyclohepta[5,6]pyrido[2,3-*d*]pyrimidine-2,4-dione (**21d**). From 6-amino-1,3-dimethyluracil **2** (1.55 g, 10 mmol), cycloheptanone **16** (1.12 g, 10 mmol) and 4-fluorobenzaldehyde (1.24 g, 10 mmol) and as described for the general procedure, reaction time 5 h. The product was recrystallized from dioxane to give pale yellow powder (2.57 g, 73%); mp 182-84 ˚C; ir: 1702, 1658(C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 1.50-1.85 (m, 6H, $3CH_2$), 2.83 (t, *J*= 6.8 Hz, 2H, CH_2), 3.37 (s, 3H, CH_3), 3.60 (s, 3H, CH_3), 3.65 (t, *J*= 6.8 Hz, 2H, CH_2), 7.00-7.10 (m, 2H, ArH), 7.85-7.95 (m, 2H, ArH); ms: *m/z* 353 (M^+, 100 %), 338 (22), 324 (32), 310, 15, 259 (17). *Anal.* Calcd. for $C_{20}H_{20}FN_3O_2$: C, 67.97; H, 5.70; N, 11.89. Found: C, 67.75; H, 5.66; N, 11.99.

1,3-Dimethyl-5-(4-nitrophenyl)-1,6,7,8,9,10-hexahydrocyclohepta[5,6]pyrido[2,3-*d*]pyrimidine-2,4-dione (**21i**). From 6-amino-1,3-dimethyluracil **2** (1.55 g, 10 mmol), cycloheptanone **16** (1.12 g, 10 mmol) and 4-nitrobenzaldehyde (1.51 g, 10 mmol) and as described for the general procedure, reaction time, 5 h. The product was recrystallized from dioxane to give pale yellow powder (2.28 g, 60%); mp 345-47 ˚C; ir: 1689(C=O) (cm^{-1}). ^{1}H NMR (DMSO-d_6) δ 1.85 (m, 6H, CH_2), 2.83 (t, *J*= 6.8 Hz, 2H, CH_2), 3.37 (s, 3H, CH_3), 3.60 (s, 3H, CH_3), 3.65 (t, *J*= 6.8 Hz, 2H, CH_2), 7.00-7.10 (m, 2H, ArH), 7.85-7.95 (m, 2H, ArH); ms: *m/z* 380 (M^+, 100 %). *Anal.* Calcd. for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.21; H, 5.40; N, 14.64.

1,3-Dimethyl-5-(4-*N*,*N*-dimethylaminophenyl)-l,6-dihydro-indeno[2',1':5,6]pyrido[2,3-d]pyrimidine-2,4-dione (22a). From 6-amino-1,3-dimethyluracil **2** (1.55 g, 10 mmol), 1-indanone **15** (1.46 g, 10 mmol) and 4-*N*,*N*-dimethylamino-benzaldehyde (1.49 g, 10 mmol) and as described for the general procedure, reaction time 5 h. The product was recrystallized from DMF to give pale yellow powder (3.31 g, 83%); mp 309-11˚C; ir: 1642(C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 2.88 (s, 6H, NMe_2), 3.45 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 3.81 (s, 2H, CH_2), 6.68-7.96 (m, 8H, Ar H); ms: *m/z* 398 (M^+, 1 %).155 (45), 82 (91), 56 (100). *Anal.* Calcd. for $C_{24}H_{22}N_4O_2$: C, 72.34; H, 5.57; N, 14.06. Found: C, 72.12; H, 5.67; N, 14.27.

1,3-Dimethyl-5-(4-fluoropheny)-l,6-dihydro-indeno-[2',1':5,6]pyrido[2,3-*d*]pyrimidine-2,4-dione (**22d**). From 6-amino-1,3-dimethyluracil **2** (1.32 g, 10 mmol), 1-indanone **15** (1.46 g, 10 mmol) and 4-fluorobenzaldehyde (1.24 g, 10 mmol) and as described for the general procedure, reaction time 5 h, the product was recrystallized from dioxane to give pale yellow powder (3.06 g, 82%); mp 257-59 ˚C; ir: 1642(C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 3.14 (s, 3H, CH_3), 3.17 (s, 3H, CH_3), 3.34 (s, 2H, CH_2), 6.94-7.35 (m, 8H, ArH); ms: *m/z* 373 (M^+, 1.71 %), 260 (100), 203 (25), 155 (24). *Anal.* Calcd. for $C_{22}H_{16}FN_3O_2$: C, 70.77; H, 4.32 N, 11.25. Found: C, 70.65; H, 4.38; N, 11.12.

1,3-Dimethyl-5-(4-chloropheny)-l,6-dihydro-indeno-[2',1':5,6]pyrido[2,3-*d*]pyrimidine-2,4-dione (**22f**). From 6-amino-1,3-dimethyluracil **2** (10 mmol), 1-indanone **15** (10 mmol) and 4-chlorobenzaldehyde (1.40 g, 10 mmol) and as described for the general procedure, reaction time 5 h, the product crystallized from dioxane to give pale yellow powder (75%); mp 285-87˚C; ir: 1642(C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 3.45 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 3.81 (s, 2H, CH_2), 6.68-7.96 (m, 8H, ArH); ms: *m/z* 391 (M^+, Cl^{37}, 34 %), 389 ($M,^+$ Cl^{35}, 100). *Anal.* Calcd. for $C_{22}H_{16}ClN_3O_2$: C, 67.86; H, 4.11; N, 10.79. Found: C, 67.58; H, 4.28; N, 10.57.

1,3-Dimethyl-5-(4-nitrophenyl)-l,6-dihydro-indeno-[2',1':5,6]pyrido[2,3-*d*]pyrimidine-2,4-dione (**22i**). From 6-amino-1,3-dimethyluracil **2** (1.55 g, 10 mmol), 1-indanone **15** (1.46 g, 10 mmol) and 4-nitrobenzaldehyde (1.51g, 10 mmol) and as described for the general procedure, reaction time 5 h, the product was recrystallized from DMF to give pale yellow powder (2.64 g, 66%); mp 255-57˚C; ir: 1642(C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 3.09 (s, 3H, CH_3), 3.11 (s, 3H, CH_3), 3.20 (s, 2H, CH_2), 7.37 (d, *J*= 12 Hz, 2H, ArH), 7.62 (m, 4H, ArH). 8.21 (d, *J*= 12 Hz, 2H, ArH); ms: *m/z* 400 (M^+, 34 %). *Anal.* Calcd. for $C_{22}H_{16}N_4O_2$: C, 66.00; H, 4.03; N, 13.99. Found: C, 66.26; H, 4.08; N, 13.69.

5-(4-*N*,*N*-Dimethylaminophenyl)-1,3-dimethyl-1*H*-indeno-[2',1':5,6]pyrido[2,3-*d*]pyrimidine-2,4,6-trione (**23a**). From of 6-amino-1,3-dimethyluracil **2** (1.55 g, 10 mmol), 1,3-indandione **6** (1.46 g, 10 mmol) and 4-*N*,*N*-dimethyl-aminobenzaldhyde (1.49 g, 10 mmol) and as described for the general procedure, reaction time, 5 h, the product was crystallized from DMF to give pale yellow powder (3.30 g, 80%); mp 350-53 °C; ir: 1689, 1725 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 2.88 (s, 6H, $N(CH_3)_2$), 3.45 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 6.90-7.85 (m, 8H, ArH); ms: *m*/*z* 412 (M^+, 100 %), 395 (6), 368 (3). *Anal*. Calcd. for $C_{22}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58. Found: C, 69.68; H, 4.88; N, 13.70.

1,3-Dimethyl-5-(4-fluorophenyl)-1*H*-indeno[2',1':5,6]-pyrido-[2,3-*d*]pyrimidine-2,4,6-trione (**23d**). From 6-amino-1,3-dimethyluracil **2** (1.55 g, 10 mmol), 1,3-indandione **6** (1.46 g, 10 mmol) and 4-fluorobenzaldhyde (1.24 g, 10 mmol) and as described for the general procedure, reaction time, 5 h. The product was recrystallized from DMF in pale yellow powder (2.90 g, 75%); mp 303-5 °C; ir: 1637, 1715 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 3.20 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 7.27-7.34 (m, 4H, ArH), 7.66-7.85 (m, 3H, ArH), 8.05 (d, 1H, *J*= 12 Hz, ArH); ms: *m*/*z* 387 (M^+, 75 %), 386 (M^+-1, 100), 372 (5), 329 (4), 273 (14), 245 (7) 193 (19). *Anal*. Calcd. for $C_{22}H_{14}N_3O_3$: C, 68.21; H, 3.64; N, 10.85. Found: C, 68.33; H, 3.76; N, 10.93.

1,3-Dimethyl-5-(4-nitrophenyl)-1*H*-indeno-[2',1':5,6]-pyrido-[2,3-*d*]pyrimidine-2,4,6-trione (**23i**). From 6-amino-1,3-dimethyluracil **2** (1.55 g, 10 mmol), 1,3-indandione **6** (1.46 g, 10 mmol) 4-nitrobenzaldehyde (1.51g, 10 mmol) and as described for the general procedure, reaction time 5 h. The product was recrystallized from DMF in pale yellow powder (75%); mp 249-51°C; ir: 1689, 1725 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 3.45 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 7.41-8.30 (m, 8H, ArH); ms: *m*/*z* 414 (M^+, 100 %), 384 (5), 367 (15), 329 (9), 283 (120). *Anal*. Calcd. for $C_{22}H_{14}N_4O_5$: C, 63.77; H, 3.41; N, 13.52. Found: C, 63.91; H, 3.48; N, 13.34.

5-(4-Bromophenyl)-1,3-dimethyl-1*H*-indeno-[2',1':5,6]-pyrido[2,3-*d*]pyrimidine 2,4,6-trione (**23j**). From 6-amino-1,3-dimethyluracil **2** (1.55 g, 10 mmol), 1,3-indandione **6** (1.46 g, 10 mmol) and 4-bromobenzaldhyde (1.85 g, 10 mmol) and as described for the general procedure, reaction time 5 h. The product was recrystallized from dioxane in pale yellow powder (3.40 g, 76%); mp 310-12 °C; ir: 1666, 1711 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 3.45 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 7.25-7.45 (m, 4H, ArH), 7.65-7.85 (m, 4H, ArH); ms: *m*/*z* 449 (M^+, Br^{81} 98 %), 447 ($M,^+$ Br^{79} 100). *Anal*. Calcd. for $C_{22}H_{14}BrN_3O_3$: C, 58.95; H, 3.15; N, 9.37. Found: C, 59.20; H, 3.26; N, 9.28.

1,3-Dimethyl-5-(4-methoxyphenyl)-1*H*-indeno[2',1':5,6]-pyrido[2,3-*d*]pyrimidine 2,4,6-trione (**23k**). From 6-amino-1,3-dimethyluracil **2** (1.55 g, 10 mmol), 1,3-indandione **6** (1.46 g, 10 mmol) and 4-methoxybenzaldehyde (1.36, 10 mmol) and as described for the general procedure, reaction time 5 h, the product was recrystallized from DMF in pale yellow powder (2.99 g, 75%); mp 289-91 °C; ir: 1668, 1718 (C=O), 1085 (OCH_3) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 3.15 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 6.96 (d, 2H, *J*= 9.2 Hz, ArH), 7.19 (d, 2H, *J*= 9.0 Hz, ArH), 7.58-7.77 (m, 3H, ArH), 7.93 (d, 1H, *J*= 9.2 Hz, ArH); ^{13}C NMR (DMSO-d_6): δ 28.50 (CH_3-N3), 30.58 (CH_3-N1), 55.59 (OCH_3), 110.47 (C-4a), 120.31 (C-3, Ph), 121.79 (C-5a), 123.60 (C-8), 123.75 (C-10), 127.89 (C-2`, Ph), 130.00 (C-7), 132.54 (C-1`, Ph), 134.76 (C-6a), 136.66 (C-9), 140.95 (C-10a), 149.84 (C-5), 151.13 (C-2), 155.41 (C-10b), 155.75 (C-4`, Ph), 159.97 (C-4), 168.57 (C-11a), 188.65 (C-6); ms: *m*/*z* 399 (M^+, 100 %), 384 (11), 285 (5), 214 (5). *Anal*. Calcd. for $C_{23}H_{17}N_3O_4$: C, 69.17; H, 4.29; N, 10.52. Found: C, 69.31; H, 4.43; N, 10.43.

5-(2-Methoxyphenyl)-1,3-dimethyl-1*H*-indeno[2',1':5,6]-pyrido[2,3-*d*]pyrimidine-2,4,6-trione (**23l**). From 6-amino-1,3-dimethyluracil **2** (1.55 g, 10 mmol), 1,3-indandione **6** (1.46 g, 10 mmol) and 2-methoxybenzaldehyde (1.36 g, 10 mmol) and as described for the general procedure, reaction time 5 h, the product was recrystallized from DMF to give pale yellow powder (2.80 g, 70%); mp 322-24 °C; ir: 1713, 1665 (C=O) (cm^{-1}); ^{1}H NMR (DMSO-d_6): δ 3.15 (s, 3H, CH_3), 3.32 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 6.98-7.15 (m, 4H, ArH), 7.35-7.85 (m, 3H, ArH), 7.90 (d, 1H, *J*= 10 Hz, ArH); ms: *m*/*z* 399 (M^+, 10 %), 368 (100). *Anal*. Calcd. for $C_{23}H_{17}N_3O_4$: C, 69.17; H, 4.29; N, 10.52. Found: C, 69.26; H, 4.35; N, 10.66.

REFERENCES

[1] Suarez, M.; Verdecia, Y.; Ochoa, E.; Martin, N.; Martinez, R.; Quinteiro, M.; Seoane, C.; Soto, J. L.; Novoa, H.; Blaton, N.; Peeters O. M.; De Ranter, G. *J. Heterocycl. Chem.* **2000**, *37*, 735.

[2] Trigle, D. J.; Langs, D. A.; Janis, R. A. *Med. Res. Rev.* **1989**, 9, 123.

[3] Bossert, F. *Med. Res. Rev.* **1989**, *9*, 291.

[4] Alajarin, R.; Alvarez-Builla, J.; Vaquero, J. J.; Sunkel, C.; Fau, J.; Statkow, P.; Sanz, J. *Tetrahedron Asymmetry* **1993**, *4*, 617.

[5] Kazda, S.; Toward, R. *Br. J. Pharmacol.* **1981**, *72*, 582.

[6] Arrowsmith, J. E.; Campell, S. F.; Cross, P. E.; Stubbs, J. K. *Pharmacologist* **1985**, 27, 290.

[7] Safak, C.; Sahin, I.; Sunal, R. *Arzneim-Forsch.* **1990**, *40*, 119.

[8] Rose, U. *Arch. Pharm.* **1990**, *323*, 281.

[9] Rose, U. *Pharm. Acta Helv.* **1991**, *66*, 68.

[10] Rose, U.; Drager, M. *J. Med. Chem.* **1992**, *35*, 2238.

[11] Minsane, I.; Klusa, V.; Dambrova, M.; Germane, S.; Duburs, G.; Bisennieks, E.; Roimondini, R.; Ogren, S. O. *Eur. Neuropsychopharmacol.* **1998**, *8*, 329.

[12] Krause, A.; Germane, S.; Eberlins, O.; Sturms, I.; Klusa, V.; Duburs, G. *Eur. J. Med. Chem.* **1999**, *34*, 301.

[13] Gunics, G.; Farkas, S.; Motohashi, N.; Shah, A.; Harsukh, G.; Kawase, M.; Molnar, J. *Int. J. Antimicrob. Agents* **2002**, *20*, 227.

[14] Pattan, S. R.; Parate, A. N. *Indian J. Heterocycl. Chem.* **2003**, *12*, 387.

[15] Gangjee, A.; Vasudevan, A.; Queener, F.; Kisliuk, R. *J. Med. Chem.* **1996**, *39*, 1438.

[16] Donkor, I. O.; Klein, C. L.; Liang, L.; Zhu, N.; Bradley, E.; Clark, A. M. *J. Pharm. Sci.* **1995**, *84*, 661.

[17] Nargund, L. V. G.; Reddy, Y. S. R.; Jose, R. *Indian Drugs* **1991**, *29*, 45.

[18] Rosowsky, A.; Mota, C. E.; Queener, S. F. *J. Heterocycl. Chem.* **1995**, *32*, 335.

[19] Deyanov, A. B.; Niyazov, R. K.; Nazmetdinov, F. Y.; Syropyatov, B. Y.; Kolla, V. E.; Konshin, M. E. *Khim.-Farm. Zh.* **1991**, *25*, 26.

[20] Satti, N. K.; Suri, K. A.; Sun, O. P.; Kapil, A. *Indian J. Chem., Sect. B*. **1993**, *32B*, 978.

[21] Kolla, V. E.; Deyanov, A. B.; Nazmetdinov, F. Y.; Kashina, Z. N.; Drovosekova, L. P. *Khim.-Farm. Zh.* **1993**, *27*, 29.

[22] Saladowska, H.; Bartoszko-Malik, A.; Zawisza, T. *Farmaco* **1990,** *45*, 101.

[23] Nasr, M. N.; Gineinah, M. M. *Arch. Pharm.* **2002**, *6*, 289.

[24] Qurioga, J.; Insuasty, B.; Sanchez, A.; Nogueras M, Meier; H. *J. Heterocycl. Chem.* **1992**, *29*, 1045.

[25] Quiroga, J.; Insuasty, B.; Pungo, M.; Mendoza, I.; Meier, H. *An. Quim.* **1994**, *90*, 300.

[26] Quiroga, J.; Hormaza, A.; Insuasty, B.; Nogueras, M.;

Sanches, A.; Hanolad, N.; Meier, H. *J. Heterocycl. Chem.* **1997**, *34*, 521.

[27] Qurioga, J; Hormaza, A; Insuasty, B; Ortiz, J. A; Sanchez, A; Nogueras, M. *J. Heterocycl. Chem.* **1998**, *35*, 231.

[28] Donkor, I. O.; Devraj, R.; Queener, S. F.; Barrows, L. R.; Gangjee, A. *J. Heterocycl. Chem.* **1996**, *33*, 1653.

[29] Elgemeie, G. E. H.; Fathy, N. M.; Hope, H., and Jones P. G. *Acta Crystallogr.* **1998**, *C54*, 1109.

[30] Qurioga, J.; Cisneros C.; Insuasty, B.; Abonia, R.; Nogueras, M.; Sanchez, A. *Tetrahedron Lett.* **2001**, *42*, 5625.

[31] Agarwal, A.; Chauhan, P. M. S. *Synth. Commun.* **2004**, *34*, 4447.

[32] Suarez, M.; De Armas, M.; Ramirez, O.; Alvarez, A.; Martinez, R.; Molero, D.; Seoane, C.; Liz, R.; De Armas, H. N.; Blaton, N.; Peeters, O. M.; Martin, N. *New J. Chem.* **2005**, *29*, 1567.

[33] Suarez, M.; Verdecia, Y.; Ochoa, E.; Salfran, E.; Moran, L.; Martin, N.; Martinez, R.; Quinteiro, M.; Seoane, C.; Sato, J. L.; Novoa, H.; Blaton, N.; Peeters, O.; De Ranter, C. *Eur. J. Org. Chem.* **2000**, 2079.