Synthesis and Biological Testing of 3-Phenyloctahydro-pyrimido[1,2-*a*]-*s*-triazine Derivatives

Line Lucry [a], Ferdinand Enoma [a], François Estour [a], Hassan Oulyadi [b], Sabine Ménager [a], Olivier Lafont* [a]

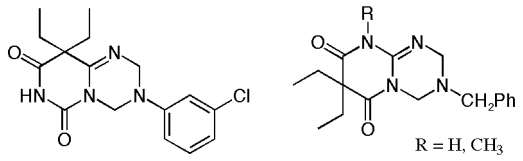
[a] Laboratoire de Pharmacochimie, Département de Chimie Organique, Faculté de Médecine et de Pharmacie de Rouen, 22 Boulevard Gambetta, 76183 Rouen Cedex 1, France
[b] Laboratoire de R.M.N., I.R.C.O.F., U.M.R. 6014 C.N.R.S., Université de Rouen, 76821 Mont Saint-Aignan Cedex, France.
Received November 15, 2001

A series of 46 3-phenyloctahydropyrimido[1,2-*a*]-*s*-triazine derivatives were synthesized. This synthesis was performed *via* iminodimethylation of dialkylated 2-aminopyrimidinedione synthons by substituted primary arylamines. *In vitro* pharmacological evaluation of these compounds is reported. One of them exhibited antifungal activity against *Microsporum canis* ($10^{-6}<IC_{50}<10^{-5}$ mol/L), and another showed affinity for serotoninergic 5-HT_{1A} and 5-HT_{2B} receptors ($10^{-8}<IC_{50}<10^{-7}$ mol/L).

J. Heterocyclic Chem., **39**, 663 (2002).

The well known antimalarial drug cycloguanide is a dihydro-*s*-triazine which interacts with the reduction of 7,8-dihydrofolates leading to 5,6,7,8-tetrahydrofolates. Tetrahydro-*s*-triazines could then be able to interact with the following metabolic reactions of folates metabolism [1,2]. Substituted triazines exhibited antimalarial activity [3] and bicyclic derivatives with a pentahydro-*s*-triazine heterocycle linked to a dihydropyrimidinone had shown good activity against fungi [4]. This prompted us to design tetrahydro-*s*-triazines in order to test their antiparasitic and antifungal activities. In the series of 3-phenyloctahydropyrimido[3,4-*a*]-*s*-triazines, a 3-chloro derivative (Scheme 1) proved to be active against *Epidermophyton floccosum* and *Trichophyton rubrum* (MIC = 1 μg/mL) [5,6]. Few octahydropyrimido[1,2-*a*]-*s*-triazines had already been synthesized (Scheme 1), but for all, nitrogen in position 3 was substitued by an aliphatic group [7].

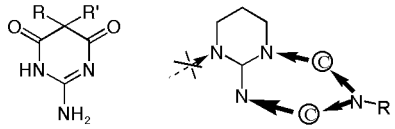
Scheme 1



We then decided to prepare a series of phenyloctahydropyrimido [1,2-*a*]-*s*-triazines bearing in position 3 a substituted phenyl nucleus, in order to test their antifungal activity. Various alkyl groups were introduced in position 7 to modify lipophilicity [8-10].

When a compound presents several mobile hydrogen atoms, it can undergo several aminomethylation reactions [11]. 2-Aminopyrimidine-4,6-diones present three positions sensible to this reaction, but only two of them reacted with primary amines. This allows an iminodimethylation reaction leading to a partially saturated triazine ring (Scheme 2) [12].

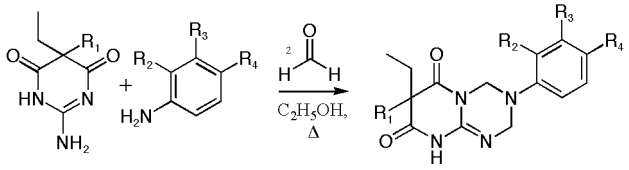
Scheme 2



Reactive positions of 2-aminopyrimidine-4,6-diones.

Despite the fact that aliphatic amines are more nucleophilic than aromatic amines, the latter can also undergo this kind of reaction. Anilines variously substituted by Cl (one or two atoms in position 2, 3 and/or 4) or CF_3 (in position 2, 3 or 4) were used. In all cases, one of the substituents in position five on 2-aminopyrimidine-4,6-diones was ethyl, the other substituent being different alkyl groups of increasing lipophilicities Me; Et; Pr; Bu. Two moles of formaldehyde for one mole of 2-aminopyrimidine-4,6-dione and one mole of substituted aniline were used in ethanol to yield octahydropyrimido[1,2-*a*]-*s*-triazines (Scheme 3 and Table 1).

Scheme 3



Synthesis of octahydropyrimido[1,2-*a*]-*s*-triazines.

Iminodimethylation reaction yields were partly related to the nucleophilicity of the aromatic amine. When phenyl ring was *p*-subtituted by an electonwithdrawing group, only 21% of the octahydropyrimido[1,2-*a*]-*s*-triazine **44** were obtained (Table 2). With the same substituents in position 7 (Et, Et), compound **11** was obtained with a better yield with aniline (72%). But nucleophilicity was not the only factor, because when the nucleus of the aromatic

Table 1

Octahydropyrimido[1,2-*a*]-*s*-triazines Synthesized

No.	R_1	R_2	R_3	R_4	Yield (%)
1	CH_3	H	H	H	65
2	CH_3	Cl	H	H	27
3	CH_3	H	Cl	H	59
4	CH_3	H	H	Cl	75
5	CH_3	Cl	Cl	H	41
6	CH_3	Cl	H	Cl	36
7	CH_3	H	Cl	Cl	21
8	CH_3	CF_3	H	H	61
9	CH_3	H	CF_3	H	45
10	CH_3	H	H	CF_3	61
11	C_2H_5	H	H	H	72
12	C_2H_5	Cl	H	H	53
13	C_2H_5	H	Cl	H	76
14	C_2H_5	H	H	Cl	70
15	C_2H_5	Cl	Cl	H	38
16	C_2H_5	Cl	H	Cl	18
17	C_2H_5	H	Cl	Cl	38
18	C_2H_5	CF_3	H	H	15
19	C_2H_5	H	CF_3	H	50
20	C_2H_5	H	H	CF_3	33
21	C_2H_5	H	CF_3	Cl	77
22	C_3H_7	H	H	H	30
23	C_3H_7	Cl	H	H	36
24	C_3H_7	H	Cl	H	36
25	C_3H_7	H	H	Cl	36
26	C_3H_7	Cl	Cl	H	33
27	C_3H_7	Cl	H	Cl	6
28	C_3H_7	H	Cl	Cl	59
29	C_3H_7	CF_3	H	H	32
30	C_3H_7	H	CF_3	H	54
31	C_3H_7	H	H	CF_3	42
32	C_3H_7	H	CF_3	Cl	60
33	C_4H_9	H	H	H	69
34	C_4H_9	Cl	H	H	28
35	C_4H_9	H	Cl	H	53
36	C_4H_9	H	H	Cl	41
37	C_4H_9	Cl	Cl	H	38
38	C_4H_9	Cl	H	Cl	15
39	C_4H_9	H	Cl	Cl	61
40	C_4H_9	CF_3	H	H	54
41	C_4H_9	H	CF_3	H	20
42	C_4H_9	H	H	CF_3	15
43	C_4H_9	H	CF_3	Cl	71

amine was substituted by an electron-donor such as methyl, the yield of **45** was lower than with aniline (62%).

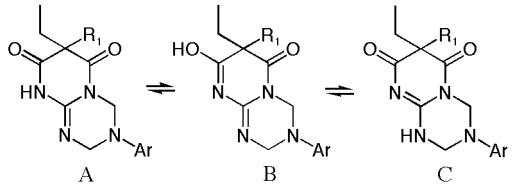
Table 2

Influence of the Nucleophilicity of the Aromatic Amine on Iminodimethylation Reaction Yield

No.	R_1	R_2	R_3	R_4	Yield (%)
11	C_2H_5	H	H	H	72
44	C_2H_5	H	H	NO_2	21
45	C_2H_5	H	H	CH_3	62

These kinds of compounds can be written in three tautomeric forms A, B and C (Scheme 4). A structural study was performed and the results for compound **4** are reported here. In the ^{1}H-NMR spectrum, a signal was observed at δ 11.77 ppm, which corresponded to an acidic proton, exchangeable by deuterium oxide. A ^{1}H-NMR nuclear Overhauser effect experiment by irradiation of this signal provided no response. If compound **4** had the tautomeric form C, an effect on the methylene in α-position would have been observed. For the tautomeric form B, an effect on the methylene of the ethyl group could have been observed. For the tautomeric form A, no effect could be expected. Even if it is not possible to draw firm conclusions from this experiment, this result is in agreement with the tautomeric form A.

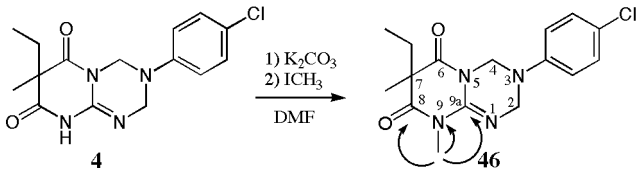
Scheme 4



Tautomeric forms of octahydropyrimido[1,2-*a*]-*s*-triazines.

Because no significant correlation was observed by inverse ^{1}H-^{13}C and ^{1}H-^{15}N correlation NMR experiments, possibilities to obtain a model of compound **4** for spectral studies were investigated. Compound **4** was directly submitted to the action of methyl iodide and of a base (Scheme 5). Only the monoalkylation on the N-9 nitrogen atom leading to the *s*-triazine **46** was observed.

Scheme 5



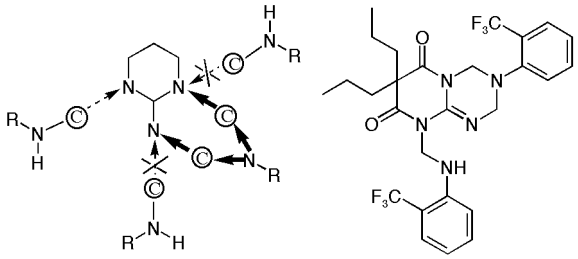
Methylation of [1,2-*a*]-*s*-triazine **4**.

Methylation reaction yields were very dependant on the strength of the base which was used to perform this synthesis. With a strong base as sodium ethoxide, methylation did not occur. With lithium hydride, less than 10% of the *N*-alkylated compound **46** were obtained. In these two cases, the rest of the starting *s*-triazine **4** was destroyed. When alkylation was performed in the presence of a weakly base as potassium carbonate, the reaction yield increased to 39% and the unreacted *s*-triazine **4** was recovered.

On *N*-alkylated compound **46**, which could only exist in tautomeric form A, correlations were observed. Methyl group correlated with N-9 by ^{1}H-^{15}N Heteronuclear Multiple Quantum Correlation NMR experiment. The same methyl group correlated with C-8 and C-9a by ^{1}H-^{13}C Heteronuclear Multiple Bond Correlation NMR experiment. ^{13}C-NMR spectral data for compound **46** showed C-8 and C-9a signals respectively at 170.92 and 140.74 ppm. For non-alkylated compound **4**, C-8 and C-9a appeared, for similar values of chemical shift, at 173.67 and 145.17 (or 145.39) ppm. So, these data were in agreement with the tautomeric form A.

Concerning eventual by products, contrarily to what was observed in the pyrimido[3,4-*a*]-*s*-triazine series by S. Ménager *et al*. [5], products resulting from three Mannich reactions of the aromatic amine on itself were never present in the reaction medium. Neither products resulting from triaminomethylation of the aminopyrimidinedione nucleus, nor products resulting from a single Mannich reaction of the extracyclic amine, were observed. On the other hand, 2% of a by product, compound **47**, resulting from both an iminodimethylation and an aminomethylation were observed in NMR spectra in the case of the condensation of 2-trifluoromethylaniline with 2-amino-5,5-dipropylpyrimidine-4,6-dione (Scheme 6).

Scheme 6



47

Formation of by product.

All compounds have been submitted to an automated pharmacological screening. Unfortunately, some tested compounds were not soluble in ethanol at the concentration of 2.2 mmol/L. Amongst the octahydropyrimido[1,2-*a*]-*s*-triazine tested, compound **12** exhibited an antifungal activity against *Microsporum canis* ($10^{-6}<IC_{50}<10^{-5}$ mol/L). Compound **42** showed an average affinity for serotoninergic 5-HT_{1A} and 5-HT_{2B} receptors ($10^{-8}<IC_{50}<10^{-7}$ mol/L).

EXPERIMENTAL

Melting points were determined on a Kofler hot-plate melting point apparatus and are not corrected. IR spectra were obtained on a Shimadzu IR-408 spectrometer. Absorption bands are expressed in cm^{-1} and only noteworthy absorptions are listed. ^{1}H, ^{13}C and ^{15}N-NMR spectra were recorded on a Bruker DMX 500 spectrometer working at 500 MHz (^{1}H-NMR), 125 MHz (^{13}C-NMR) and 50 MHz (^{15}N-NMR). Chemical shifts are reported in ppm downfield δ from TMS. Microanalyses are indicated only by symbols of the elements analyzed. The results obtained had a maximum deviation of 0.4% from the theoretical value.

General Procedure for Preparation of Octahydropyrimido[1,2-*a*]-*s*-triazines.

A solution of 5,5-dialkyl-2-aminopyrimidine-4,6-dione (0.01 mol), formaldehyde (0.02 mol), primary aromatic amine (0.01 mol) in ethanol was heated under reflux for one hour. After cooling, the mixture was filtered and the precipitate was then recrystallyzed in ethanol.

7-Ethyl-7-methyl-6,8-dioxo-3-phenyl-2,3,4,5,6,7,8,9-octahydropyrimido-[1,2-*a*]-*s*-triazine (**1**).

Compound **1** was obtained in 65% yield; mp 195-197°; ir: 1725, 1635 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.65 (t, 3H, CH_2CH_3), 1.43 (s, 3H, CH_3), 1.88 (q, 2H, CH_2CH_3), 5.07 (d, 1H, N-CH_2-N), 5.14 (d, 1H, N-CH_2-N), 5.20 (d, 1H, N-CH_2-N), 5.47 (d, 1H, N-CH_2-N), 6.97 (t, 1H, phenyl), 7.00 (d, 2H, phenyl), 7.24 (t, 2H, phenyl) , 10.82 (s, 1H, NH).

Anal. Calcd for $C_{15}H_{18}N_4O_2$: C, 62.94; H, 6.29; N, 19.58. Found: C, 62.70; H, 6.43; N, 19.39.

3-(2-Chlorophenyl)-7-ethyl-7-methyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**2**).

Compound **2** was obtained in 27% yield; mp 222-224°; ir: 1705, 1671, 1620 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.70 (t, 3H, CH_2CH_3), 1.45 (s, 3H, CH_3), 1.84 (q, 2H, CH_2CH_3), 4.96 (d, 1H, N-CH_2-N), 5.02 (d, 1H, N-CH_2-N), 5.14 (d, 1H, N-CH_2-N), 5.39 (d, 1H, N-CH_2-N), 7.09 (m, 3H, phenyl), 7.40 (d, 1H, phenyl), 11.20 (1H, NH).

Anal. Calcd for $C_{15}H_{17}N_4O_2Cl$: C, 56.16; H, 5.30; N, 17.47. Found: C, 56.40; H, 5.67; N, 17.72.

3-(3-Chlorophenyl)-7-ethyl-7-methyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**3**).

Compound **3** was obtained in 59% yield; mp 191-193°; ir: 1725, 1705, 1670, 1625 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.70 (t, 3H, CH_2CH_3), 1.45 (s, 3H, CH_3), 1.92 (q, 2H, CH_2CH_3), 5.06 (s, 2H, N-CH_2-N), 5.18 (d, 1H, N-CH_2-N), 5.45 (d, 1H, N-CH_2-N), 6.86 (d, 1H, phenyl), 6.90 (s, 1H, phenyl), 6.95 (d, 1H, phenyl), 7.17 (t, 1H, phenyl), 11.84 (s, 1H, NH).

Anal. Calcd for $C_{15}H_{17}N_4O_2Cl$: C, 56.16; H, 5.30; N, 17.47. Found: C, 55.97; H, 5.37; N, 17.39.

3-(4-Chlorophenyl)-7-ethyl-7-methyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**4**).

Compound **4** was obtained in 75% yield; mp 209-211°; ir: 1730, 1630 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.63 (t, 3H, CH_2CH_3), 1.39 (s, 3H, CH_3), 1.85 (q, 2H, CH_2CH_3), 4.99 (AB pattern, 2H, N-CH_2-N), 5.15 (d, 1H, N-CH_2-N), 5.38 (d, 1H, N-CH_2-N), 6.88 (d, 2H, phenyl), 7.18 (d, 2H, phenyl), 11.77 (s, 1H, NH); ^{13}C-NMR (deuteriochloroform): δ 9.87 (CH_3), 23.66 (CH_2CH_3), 33.01 (CH_2CH_3), 53.20 (C-7), 59.45 (C-2), 62.69 (C-4), 119.66 (2 x CH-Phenyl), 127.96 (C-Phenyl), 129.86 (2 x CH-Phenyl), 145.17 (C-9a or C-Phenyl), 145.39 (C-9a or C-Phenyl), 171.87 (C-6), 173.67 (C-8).

Anal. Calcd for $C_{15}H_{17}N_4O_2Cl$: C, 56.16; H, 5.30; N, 17.47. Found: C, 56.06; H, 5.46; N, 17.38.

3-(2,3-Dichlorophenyl)-7-ethyl-7-methyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**5**).

Compound **5** was obtained in 41% yield; mp 209-211°; ir: 1670, 1615 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.68 (t, 3H, CH_2CH_3), 1.43 (s, 3H, CH_3), 1.90 (q, 2H, CH_2CH_3), 4.97 (s, 2H, N-CH_2-N), 5.13 (d, 1H, N-CH_2-N), 5.37 (d, 1H, N-CH_2-N), 7.01 (d, 1H, phenyl), 7.10 (t, 1H, phenyl), 7.24 (d, 1H, phenyl), 10.68 (s, 1H, NH).

Anal. Calcd for $C_{15}H_{16}N_4O_2Cl_2$: C, 50.70; H, 4.51; N, 15.77. Found: C, 50.53; H, 4.66; N, 15.59.

3-(2,4-Dichlorophenyl)-7-ethyl-7-methyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**6**).

Compound **6** was obtained in 36% yield; mp 210-212°; ir: 1735, 1680, 1625 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.69 (t, 3H, CH_2CH_3), 1.44 (s, 3H, CH_3), 1.90 (q, 2H, CH_2CH_3), 4.94 (AB pattern, 2H, N-CH_2-N), 5.13 (d, 1H, N-CH_2-N), 5.36 (d, 1H, N-CH_2-N), 7.01 (d, 1H, phenyl), 7.10 (d, 1H, phenyl), 7.40 (s, 1H, phenyl), 11.40 (s, 1H, NH).

Anal. Calcd for $C_{15}H_{16}N_4O_2Cl_2$: C, 50.70; H, 4.51; N, 15.77. Found: C, 50.67; H, 4.63; N, 15.72.

3-(3,4-Dichlorophenyl)-7-ethyl-7-methyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**7**).

Compound **7** was obtained in 21% yield; mp 219-221°; ir: 1730, 1705, 1670, 1625 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.73 (t, 3H, CH_2CH_3), 1.46 (s, 3H, CH_3), 1.94 (q, 2H, CH_2CH_3), 5.02 (AB pattern, 2H, N-CH_2-N), 5.18 (d, 1H, N-CH_2-N), 5.43 (d, 1H, N-CH_2-N), 6.85 (d, 1H, phenyl), 7.06 (s, 1H, phenyl), 7.30 (d, 1H, phenyl), 11.42 (s, 1H, NH).

Anal. Calcd for $C_{15}H_{16}N_4O_2Cl_2$: C, 50.70; H, 4.51; N, 15.77. Found: C, 50.63; H, 4.62; N, 15.64.

7-Ethyl-7-methyl-6,8-dioxo-3-(2-trifluoromethylphenyl)-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**8**).

Compound **8** was obtained in 61% yield; mp 208-210°; ir: 1680, 1620 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.76 (t, 3H, CH_2CH_3), 1.48 (s, 3H, CH_3), 1.92 (q, 2H, CH_2CH_3), 4.89 (AB pattern, 2H, N-CH_2-N), 5.00 (d, 1H, N-CH_2-N), 5.17 (d, 1H, N-CH_2-N), 7.27 (t, 2H, phenyl), 7.46 (d, 1H, phenyl), 7.68 (d, 1H, phenyl), 11.65 (s, 1H, NH).

Anal. Calcd for $C_{16}H_{17}N_4O_2F_3$: C, 54.24; H, 4.80; N, 15.82. Found: C, 54.09; H, 4.99; N, 15.71.

7-Ethyl-7-methyl-6,8-dioxo-3-(3-trifluoromethylphenyl)-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**9**).

Compound **9** was obtained in 45% yield; mp 186-188°; ir: 1720, 1675, 1620 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.61 (t, 3H, CH_2CH_3), 1.44 (s, 3H, CH_3), 1.90 (q, 2H, CH_2CH_3), 5.11 (AB pattern, 2H, N-CH_2-N), 5.24 (d, 1H, N-CH_2-N), 5.50 (d, 1H, N-CH_2-N), 7.21 (m, 3H, phenyl), 7.35 (t, 1H, phenyl), 11.80 (s, 1H, NH).

Anal. Calcd for $C_{16}H_{17}N_4O_2F_3$: C, 54.24; H, 4.80; N, 15.82. Found: C, 53.90; H, 5.18; N, 15.79.

7-Ethyl-7-methyl-6,8-dioxo-3-(4-trifluoromethylphenyl)-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**10**).

Compound **10** was obtained in 61% yield; mp 208-210°; ir: 1680, 1620 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.67 (t, 3H, CH_2CH_3), 1.46 (s, 3H, CH_3), 1.92 (q, 2H, CH_2CH_3), 5.12 (s, 2H, N-CH_2-N), 5.27 (d, 1H, N-CH_2-N), 5.52 (d, 1H, N-CH_2-N), 7.06 (d, 2H, phenyl), 7.50 (d, 2H, phenyl), 11.40 (s, 1H, NH).

Anal. Calcd for $C_{16}H_{17}N_4O_2F_3$: C, 54.24; H, 4.80; N, 15.82. Found: C, 54.12; H, 4.88; N, 15.78.

7,7-Diethyl-6,8-dioxo-3-phenyl-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**11**).

Compound **11** was obtained in 72% yield; mp 207-209°; ir: 1720, 1670, 1625 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.69 (t, 6H, 2 x CH_2CH_3), 1.94 (q, 4H, 2 x CH_2CH_3), 5.13 (s, 2H, N-CH_2-N), 5.43 (s, 2H, N-CH_2-N), 6.98 (t, 1H, phenyl), 7.03 (d, 2H, phenyl), 7.26 (t, 2H, phenyl), 12.02 (s, 1H, NH).

Anal. Calcd for $C_{16}H_{20}N_4O_2$: C, 64.00; H, 6.67; N, 18.67. Found: C, 63.79; H, 6.73; N, 18.65.

3-(2-Chlorophenyl)-7,7-diethyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**12**).

Compound **12** was obtained in 53% yield; mp 190-192°; ir: 1720, 1670, 1640 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.66 (t, 6H, 2 x CH_2CH_3), 1.88 (q, 4H, 2 x CH_2CH_3), 5.00 (s, 2H, N-CH_2-N), 5.32 (s, 2H, N-CH_2-N), 7.05 (m, 3H, phenyl), 7.37 (d, 1H, phenyl), 11.84 (s, 1H, NH).

Anal. Calcd for $C_{16}H_{19}N_4O_2Cl$: C, 57.40; H, 5.68; N, 16.74. Found: C, 57.45; H, 5.79; N, 16.68.

3-(3-Chlorophenyl)-7,7-diethyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**13**).

Compound **13** was obtained in 76% yield; mp 206-208°; ir: 1710, 1670, 1625 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.68 (t, 6H, 2 x CH_2CH_3), 1.93 (q, 4H, 2 x CH_2CH_3), 5.08 (s, 2H, N-CH_2-N), 5.36 (s, 2H, N-CH_2-N), 6.91 (d, 2H, phenyl), 6.98 (s, 1H, phenyl), 7.17 (t, 1H, phenyl), 11.96 (s, 1H, NH).

Anal. Calcd for $C_{16}H_{19}N_4O_2Cl$: C, 57.40; H, 5.68; N, 16.74. Found: C, 57.21; H, 5.85; N, 16.65.

3-(4-Chlorophenyl)-7,7-diethyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**14**).

Compound **14** was obtained in 70% yield; mp 213-215°; ir: 1720, 1670, 1625 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.65 (t, 6H, 2 x CH_2CH_3), 1.90 (q, 4H, 2 x CH_2CH_3), 5.05 (s, 2H, N-CH_2-N), 5.31 (s, 2H, N-CH_2-N), 6.93 (d, 2H, phenyl), 7.17 (d, 2H, phenyl), 12.05 (s, 1H, NH)

Anal. Calcd for $C_{16}H_{19}N_4O_2Cl$: C, 57.40; H, 5.68; N, 16.74. Found: C, 57.08; H, 5.93; N, 16.74.

3-(2,3-Dichlorophenyl)-7,7-diethyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**15**).

Compound **15** was obtained in 38% yield; mp 191-193°; ir: 1710, 1670, 1630 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.66 (t, 6H, 2 x CH_2CH_3), 1.88 (q, 4H, 2 x CH_2CH_3), 5.00 (s, 2H, N-CH_2-N), 5.32 (s, 2H, N-CH_2-N), 7.02 (d, 1H, phenyl), 7.28 (t, 1H, phenyl), 7.35 (d, 1H, phenyl), 10.98 (s, 1H, NH).

Anal. Calcd for $C_{16}H_{18}N_4O_2Cl_2$: C, 52.03; H, 4.88; N, 15.18. Found: C, 52.04; H, 4.91; N, 15.14.

3-(2,4-Dichlorophenyl)-7,7-diethyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**16**).

Compound **16** was obtained in 18% yield; mp 215-217°; ir: 1720, 1670, 1625 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.68 (t, 6H, 2 x CH_2CH_3), 1.90 (q, 4H, 2 x CH_2CH_3), 4.98 (s, 2H, N-CH_2-N), 5.29 (s, 2H, N-CH_2-N), 6.98 (d, 1H, phenyl), 7.09 (d, 1H, phenyl), 7.44 (s, 1H, phenyl), 11.23 (s, 1H, NH).

Anal. Calcd for $C_{16}H_{18}N_4O_2Cl_2$: C, 52.03, H, 4.88, N, 15.18. Found: C, 52.01, H, 5.08, N, 15.11.

3-(3,4-Dichlorophenyl)-7,7-diethyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**17**).

Compound **17** was obtained in 38% yield; mp 187-189°; ir: 1720, 1675, 1625 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.68 (t, 6H, 2 x CH_2CH_3), 1.91 (q, 4H, 2 x CH_2CH_3), 5.02 (s, 2H, N-CH_2-N), 5.31 (s, 2H, N-CH_2-N), 6.84 (d, 1H, phenyl), 7.04 (s, 1H, phenyl), 7.25 (d, 1H, phenyl), 11.95 (s, 1H, NH).

Anal. Calcd for $C_{16}H_{18}N_4O_2Cl_2$: C, 52.03; H, 4.88; N, 15.18. Found: C, 52.08; H, 4.99; N, 15.30.

7,7-Diethyl-6,8-dioxo-3-(2-trifluoromethylphenyl)-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**18**).

Compound **18** was obtained in 15% yield; mp 205-207°; ir: 1705, 1675, 1620 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.73 (t, 6H, 2 x CH_2CH_3), 1.88 (q, 4H, 2 x CH_2CH_3), 4.89 (s, 2H, N-CH_2-N), 5.10 (s, 2H, N-CH_2-N), 7.25 (t, 2H, phenyl), 7.42 (d, 1H, phenyl), 7.64 (d, 1H, phenyl), 11.88 (s, 1H, NH).

Anal. Calcd for $C_{17}H_{19}N_4O_2F_3$: C, 55.43; H, 5.16; N, 15.22. Found: C, 55.30; H, 5.33; N, 15.12.

7,7-Diethyl-6,8-dioxo-3-(3-trifluoromethylphenyl)-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**19**).

Compound **19** was obtained in 20% yield; mp 174-176°; ir: 1710, 1675, 1620 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.65 (t, 6H, 2 x CH_2CH_3), 1.92 (q, 4H, 2 x CH_2CH_3), 5.18 (s, 2H, N-CH_2-N), 5.41 (s, 2H, N-CH_2-N), 7.22 (m, 3H, phenyl), 7.35 (t, 1H, phenyl), 11.94 (s, 1H, NH).

Anal. Calcd for $C_{17}H_{19}N_4O_2F_3$: C, 55.43; H, 5.16; N, 15.22. Found: C, 55.24; H, 5.26; N, 15.07.

7,7-Diethyl-6,8-dioxo-3-(4-trifluoromethylphenyl)-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**20**).

Compound **20** was obtained in 33% yield; mp 201-203°; ir: 1705, 1675, 1620 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.66 (t, 6H, 2 x CH_2CH_3), 1.94 (q, 4H, 2 x CH_2CH_3), 5.12 (s, 2H, N-CH_2-N), 5.40 (s, 2H, N-CH_2-N), 7.05 (d, 2H, phenyl), 7.46 (d, 2H, phenyl), 12.08 (s, 1H, NH).

Anal. Calcd for $C_{17}H_{19}N_4O_2F_3$: C, 55.43; H, 5.16; N, 15.22. Found: C, 55.32; H, 5.27; N, 15.11.

3-(4-Chloro-3-trifluoromethylphenyl)-7,7-diethyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**21**).

Compound **21** was obtained in 77% yield; mp 201-203°; ir: 1735, 1715, 1675, 1620 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.68 (t, 6H, 2 x CH_2CH_3), 1.94 (q, 4H, 2 x CH_2CH_3), 5.08 (s, 2H, N-CH_2-N), 5.38 (s, 2H, N-CH_2-N), 7.11 (d, 1H, phenyl), 7.28 (s, 1H, phenyl), 7.38 (d, 1H, phenyl).

Anal. Calcd for $C_{17}H_{18}N_4O_2F_3Cl$: C, 50.68; H, 4.47; N, 13.91. Found: C, 50.77; H, 4.68; N, 13.81.

7-Ethyl-6,8-dioxo-3-phenyl-7-propyl-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**22**).

Compound **22** was obtained in 30% yield; mp 165-167°; ir: 1725, 1665, 1615 cm^{-1}; ^{1}H-NMR (deuteriochloroform):δ 0.67 (t, 3H, $(CH_2)_2CH_3$), 0.73 (t, 3H, CH_2CH_3), 1.05 (m, 2H, $(CH_2)_2CH_3$), 1.82 (m, 4H, CH_2CH_3, $(CH_2)_2CH_3$), 5.08 (s, 2H, N-CH_2-N), 5.35 (s, 2H, N-CH_2-N), 6.97 (m, 3H, phenyl), 7.18 (t, 2H, phenyl).

Anal. Calcd for $C_{17}H_{22}N_4O_2$: C, 64.97; H, 7.01; N, 17.83. Found: C, 64.85; H, 7.18; N, 17.64.

3-(2-Chlorophenyl)-7-ethyl-6,8-dioxo-7-propyl-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**23**).

Compound **23** was obtained in 36% yield; mp 221-223°; ir: 1715, 1675, 1625, 1610 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.65 (t, 3H, $(CH_2)_2CH_3$), 0.75 (t, 3H, CH_2CH_3), 1.06 (m, 2H, $(CH_2)_2CH_3$), 1.80 (m, 4H, CH_2CH_3, $(CH_2)_2CH_3$), 5.00 (s, 2H, N-CH_2-N), 5.30 (AB pattern, 2H, N-CH_2-N), 7.08 (m, 3H, phenyl), 7.40 (d, 1H, phenyl).

Anal. Calcd for $C_{17}H_{21}N_4O_2Cl$: C, 58.54; H, 6.03; N, 16.07. Found: C, 58.68; H, 6.19; N, 15.98.

3-(3-Chlorophenyl)-7-ethyl-6,8-dioxo-7-propyl-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**24**).

Compound **24** was obtained in 36% yield; mp 221-223°; ir: 1715, 1675, 1635, 1610 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.67 (t, 3H, $(CH_2)_2CH_3$), 0.71 (t, 3H, CH_2CH_3), 1.06 (m, 2H, $(CH_2)_2CH_3$), 1.83 (m, 4H, CH_2CH_3, $(CH_2)_2CH_3$), 5.05 (s, 2H, N-CH_2-N), 5.31 (AB pattern, 2H, N-CH_2-N), 6.93 (m, 3H, phenyl), 7.14 (t, 1H, phenyl).

Anal. Calcd for $C_{17}H_{21}N_4O_2Cl$: C, 58.54; H, 6.03; N, 16.07. Found: C, 58.61; H, 6.20; N, 15.98.

3-(4-Chlorophenyl)-7-ethyl-6,8-dioxo-7-propyl-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**25**).

Compound **25** was obtained in 36% yield; mp 167-169°; ir: 1725, 1665, 1615 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.66 (t, 3H, $(CH_2)_2CH_3$), 0.76 (t, 3H, CH_2CH_3), 1.02 (m, 2H, $(CH_2)_2CH_3$), 1.88 (m, 4H, CH_2CH_3, $(CH_2)_2CH_3$), 5.05 (s, 2H, N-CH_2-N), 5.33 (AB pattern, 2H, N-CH_2-N), 6.93 (d, 2H, phenyl), 7.18 (d, 2H, phenyl), 11.82 (s, 1H, NH).

Anal. Calcd for $C_{17}H_{21}N_4O_2Cl$: C, 58.54; H, 6.03; N, 16.07. Found: C, 58.35; H, 6.24; N, 16.01.

3-(2,3-Dichlorophenyl)-7-ethyl-6,8-dioxo-7-propyl-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**26**).

Compound **26** was obtained in 33% yield; mp 183-185°; ir: 1725, 1675, 1620 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.68 (t, 3H, $(CH_2)_2CH_3$), 0.77 (t, 3H, CH_2CH_3), 1.10 (m, 2H, $(CH_2)_2CH_3$), 1.83 (m, 4H, CH_2CH_3, $(CH_2)_2CH_3$), 4.98 (s, 2H, N-CH_2-N), 5.29 (s, 2H, N-CH_2-N), 6.99 (d, 1H, phenyl), 7.06 (t, 1H, phenyl), 7.23 (d, 1H, phenyl).

Anal. Calcd for $C_{17}H_{20}N_4O_2Cl_2$: C, 53.26; H, 5.22; N, 14.62. Found: C, 53.19; H, 5.31; N, 14.59.

3-(2,4-Dichlorophenyl)-7-ethyl-6,8-dioxo-7-propyl-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**27**).

Compound **27** was obtained in 6% yield; mp 179-181°; ir: 1725, 1675, 1620 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.68 (t, 3H, $(CH_2)_2CH_3$), 0.76 (t, 3H, CH_2CH_3), 1.08 (m, 2H, $(CH_2)_2CH_3$), 1.82 (m, 4H, CH_2CH_3, $(CH_2)_2CH_3$), 4.98 (s, 2H, N-CH_2-N), 5.29 (AB pattern, 2H, N-CH_2-N), 6.96 (d, 1H, phenyl), 7.06 (d, 1H, phenyl), 7.38 (s, 1H, phenyl), 11.60 (s, 1H, NH).

Anal. Calcd for $C_{17}H_{20}N_4O_2Cl_2$: C, 53.26; H, 5.22; N, 14.62. Found: C, 53.21; H, 5.37; N, 14.57.

3-(3,4-Dichlorophenyl)-7-ethyl-6,8-dioxo-7-propyl-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**28**).

Compound **28** was obtained in 59% yield; mp 199-201°; ir: 1725, 1650 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.70 (t, 3H, $(CH_2)_2CH_3$), 0.78 (t, 3H, CH_2CH_3), 1.07 (m, 2H, $(CH_2)_2CH_3$), 1.84 (m, 4H, CH_2CH_3, $(CH_2)_2CH_3$), 5.04 (s,

2H, N-CH_2-N), 5.32 (AB pattern, 2H, N-CH_2-N), 6.86 (d, 1H, phenyl), 7.06 (s, 1H, phenyl), 7.28 (d, 1H, phenyl), 11.70 (s, 1H, NH).

Anal. Calcd for $C_{17}H_{20}N_4O_2Cl_2$: C, 53.26; H, 5.22; N, 14.62. Found: C, 53.27; H, 5.26; N, 14.54.

7-Ethyl-6,8-dioxo-7-propyl-3-(2-trifluoromethylphenyl)-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**29**).

Compound **29** was obtained in 32% yield; mp 209-211°; ir: 1710, 1670, 1630 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.70 (t, 3H, $(CH_2)_2CH_3$), 0.78 (t, 3H, CH_2CH_3), 1.07 (m, 2H, $(CH_2)_2CH_3$), 1.85 (m, 4H, CH_2CH_3, $(CH_2)_2CH_3$), 4.90 (s, 2H, N-CH_2-N), 5.10 (s, 2H, N-CH_2-N), 7.28 (t, 2H, phenyl), 7.44 (d, 1H, phenyl), 7.65 (d, 1H, phenyl), 11.89 (s, 1H, NH).

Anal. Calcd for $C_{18}H_{21}N_4O_2F_3$: C, 56.54; H, 5.50; N, 14.66. Found: C, 56.33; H, 5.53; N, 14.50.

7-Ethyl-6,8-dioxo-7-propyl-3-(3-trifluoromethylphenyl)-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**30**).

Compound **30** was obtained in 54% yield; mp 195-197°; ir: 1710, 1675, 1630 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.65 (t, 3H, $(CH_2)_2CH_3$), 0.75 (t, 3H, CH_2CH_3), 1.05 (m, 2H, $(CH_2)_2CH_3$), 1.92 (m, 4H, CH_2CH_3, $(CH_2)_2CH_3$), 5.10 (s, 2H, N-CH_2-N), 5.40 (AB pattern, 2H, N-CH_2-N), 7.25 (t, 2H, phenyl), 7.40 (d, 1H, phenyl), 7.67 (d, 1H, phenyl), 11.55 (s, 1H, NH).

Anal. Calcd for $C_{18}H_{21}N_4O_2F_3$: C, 56.54; H, 5.50; N, 14.66. Found: C, 56.14; H, 5.63; N, 14.07.

7-Ethyl-6,8-dioxo-7-propyl-3-(4-trifluoromethylphenyl)-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**31**).

Compound **31** was obtained in 42% yield; mp 201-203°; ir: 1705, 1675, 1625 cm^{-1}. ^{1}H-NMR (deuteriochloroform): δ 0.66 (t, 3H, $(CH_2)_2CH_3$), 0.75 (t, 3H, CH_2CH_3), 1.02 (m, 2H, $(CH_2)_2CH_3$), 1.90 (m, 4H, CH_2CH_3, $(CH_2)_2CH_3$), 5.12 (s, 2H, N-CH_2-N), 5.43 (AB pattern, 2H, N-CH_2-N), 7.08 (d, 2H, phenyl), 7.47 (d, 2H, phenyl).

Anal. Calcd for $C_{18}H_{21}N_4O_2F_3$: C, 56.54; H, 5.50; N, 14.66. Found: C, 56.59; H, 5.58; N, 14.57.

3-(4-Chloro-3-trifluoromethylphenyl)-7-ethyl-6,8-dioxo-7-propyl-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**32**).

Compound **32** was obtained in 60% yield; mp 225-227°; ir: 1725, 1630 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.65 (t, 3H, $(CH_2)_2CH_3$), 0.78 (t, 3H, CH_2CH_3), 1.03 (m, 2H, $(CH_2)_2CH_3$), 1.87 (m, 4H, CH_2CH_3, $(CH_2)_2CH_3$), 5.07 (s, 2H, N-CH_2-N), 5.36 (AB pattern, 2H, N-CH_2-N), 7.11 (d, 1H, phenyl), 7.27 (s, 1H, phenyl), 7.35 (d, 1H, phenyl).

Anal. Calcd for $C_{18}H_{20}N_4O_2F_3Cl$: C, 51.86; H, 4.80; N, 13.45. Found: C, 51.69; H, 4.97; N, 13.29.

7-Butyl-7-ethyl-6,8-dioxo-3-phenyl-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**33**).

Compound **33** was obtained in 69% yield; mp 187-189°; ir: 1730, 1705, 1680, 1640 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.64 (t, 3H, $(CH_2)_3CH_3$), 0.73 (t, 3H, CH_2CH_3), 1.18 (m, 4H, $(CH_2)_3CH_3$), 1.90 (m, 4H, CH_2CH_3, $(CH_2)_3CH_3$), 5.10 (s, 2H, N-CH_2-N), 5.38 (AB pattern, 2H, N-CH_2-N), 7.01 (m, 3H, phenyl), 7.21 (t, 2H, phenyl), 11.90 (s, 1H, NH).

Anal. Calcd for $C_{18}H_{24}N_4O_2$: C, 65.85; H, 7.32; N, 17.07. Found: C, 65.70; H, 7.42; N, 17.02.

7-Butyl-3-(2-chlorophenyl)-7-ethyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**34**).

Compound **34** was obtained in 28% yield; mp 139-141°; ir: 1725, 1620 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.69 (t, 3H, $(CH_2)_3CH_3$), 0.74 (t, 3H, CH_2CH_3), 1.18 (m, 4H, $(CH_2)_3CH_3$), 1.88 (m, 4H, CH_2CH_3, $(CH_2)_3CH_3$), 5.01 (s, 2H, N-CH_2-N), 5.35 (AB pattern, 2H, N-CH_2-N), 7.18 (m, 3H, phenyl), 7.40 (d, 1H, phenyl).

Anal. Calcd for $C_{18}H_{23}N_4O_2Cl$: C, 59.59; H, 6.34; N, 15.45. Found: C, 60.05; H, 6.51; N, 15.44.

7-Butyl-3-(3-chlorophenyl)-7-ethyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**35**).

Compound **35** was obtained in 53% yield; mp 171-173°; ir: 1710, 1670, 1635, 1610 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.69 (t, 3H, $(CH_2)_3CH_3$), 0.76 (t, 3H, CH_2CH_3), 1.15 (m, 4H, $(CH_2)_3CH_3$), 1.89 (m, 4H, CH_2CH_3, $(CH_2)_3CH_3$), 5.05 (s, 2H, N-CH_2-N), 5.35 (AB pattern, 2H, N-CH_2-N), 6.90 (d, 2H, phenyl), 6.97 (s, 1H, phenyl), 7.15 (t, 1H, phenyl), 11.98 (s, 1H, NH).

Anal. Calcd for $C_{18}H_{23}N_4O_2Cl$: C, 59.59; H, 6.34; N, 15.45. Found: C, 59.41; H, 6.39; N, 15.43.

7-Butyl-3-(4-chlorophenyl)-7-ethyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**36**).

Compound **36** was obtained in 41% yield; mp 209-211°; ir: 1730, 1710, 1665, 1630 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.65 (t, 3H, $(CH_2)_3CH_3$), 0.77 (t, 3H, CH_2CH_3), 1.01 (m, 4H, $(CH_2)_3CH_3$), 1.81 (m, 4H, CH_2CH_3, $(CH_2)_3CH_3$), 5.04 (s, 2H, N-CH_2-N), 5.32 (s, 2H, N-CH_2-N), 6.93 (d, 2H, phenyl), 7.17 (d, 2H, phenyl), 11.26 (s, 1H, NH).

Anal. Calcd for $C_{18}H_{23}N_4O_2Cl$: C, 59.59; H, 6.34; N, 15.45. Found: C, 59.44; H, 6.51; N, 15.36.

7-Butyl-3-(2,3-dichlorophenyl)-7-ethyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**37**).

Compound **37** was obtained in 38% yield; mp 145-147°; ir: 1705, 1670, 1615 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.70 (t, 3H, $(CH_2)_3CH_3$), 0.75 (t, 3H, CH_2CH_3), 1.15 (m, 4H, $(CH_2)_3CH_3$), 1.88 (m, 4H, CH_2CH_3, $(CH_2)_3CH_3$), 5.07 (s, 2H, N-CH_2-N), 5.35 (AB pattern, 2H, N-CH_2-N), 6.85 (d, 1H, phenyl), 7.08 (t, 1H, phenyl), 7.28 (d, 1H, phenyl).

Anal. Calcd for $C_{18}H_{22}N_4O_2Cl_2$: C, 54.41; H, 5.54; N, 14.11. Found: C, 54.30; H, 5.63; N, 13.97.

7-Butyl-3-(2,4-dichlorophenyl)-7-ethyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**38**).

Compound **38** was obtained in 15% yield; mp 175-177°; ir: 1730, 1710, 1665, 1630 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.68 (t, 3H, $(CH_2)_3CH_3$), 0.75 (t, 3H, CH_2CH_3), 1.15 (m, 4H, $(CH_2)_3CH_3$), 1.88 (m, 4H, CH_2CH_3, $(CH_2)_3CH_3$), 4.98 (s, 2H, N-CH_2-N), 5.28 (AB pattern, 2H, N-CH_2-N), 7.00 (d, 1H, phenyl), 7.07 (d, 1H, phenyl), 7.40 (s, 1H, phenyl), 10.92 (s, 1H, NH).

Anal. Calcd for $C_{18}H_{22}N_4O_2Cl_2$: C, 54.41; H, 5.54; N, 14.11. Found: C, 54.21; H, 5.38; N, 14.06.

7-Butyl-3-(3,4-dichlorophenyl)-7-ethyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**39**).

Compound **39** was obtained in 61% yield; mp 197-199°; ir: 1710, 1680, 1640 cm^{-1}. ^{1}H-NMR (deuteriochloroform): δ 0.70 (t, 3H, $(CH_2)_3CH_3$), 0.74 (t, 3H, CH_2CH_3), 1.15 (m, 4H, $(CH_2)_3CH_3$), 1.90 (m, 4H, CH_2CH_3, $(CH_2)_3CH_3$), 5.05 (s, 2H,

N-CH_2-N), 5.32 (AB pattern, 2H, N-CH_2-N), 6.85 (d, 1H, phenyl), 7.05 (s, 1H, phenyl), 7.28 (d, 1H, phenyl).

Anal. Calcd for $C_{18}H_{22}N_4O_2Cl_2$: C, 54.41; H, 5.54; N, 14.11. Found: C, 54.28; H, 5.41; N, 14.08.

7-Butyl-7-ethyl-6,8-dioxo-3-(2-trifluoromethylphenyl)-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**40**).

Compound **40** was obtained in 54% yield; mp 175-177°; ir: 1720, 1670, 1640 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.74 (t, 3H, $(CH_2)_3CH_3$), 0.78 (t, 3H, CH_2CH_3), 1.16 (m, 4H, $(CH_2)_3CH_3$), 1.88 (m, 4H, CH_2CH_3, $(CH_2)_3CH_3$), 4.90 (s, 2H, N-CH_2-N), 5.12 (AB pattern, 2H, N-CH_2-N), 7.28 (m, 2H, phenyl), 7.43 (t, 1H, phenyl), 7.68 (d, 1H, phenyl), 10.80 (s, 1H, NH).

Anal. Calcd for $C_{19}H_{23}N_4O_2F_3$: C, 57.58; H, 5.81; N, 14.14. Found: C, 57.41; H, 5.96; N, 14.03.

7-Butyl-7-ethyl-6,8-dioxo-3-(3-trifluoromethylphenyl)-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**41**).

Compound **41** was obtained in 20% yield; mp 173-175°; ir: 1710, 1675, 1635 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.65 (t, 3H, $(CH_2)_3CH_3$), 0.70 (t, 3H, CH_2CH_3), 1.14 (m, 4H, $(CH_2)_3CH_3$), 1.87 (m, 4H, CH_2CH_3, $(CH_2)_3CH_3$), 5.10 (s, 2H, N-CH_2-N), 5.40 (AB pattern, 2H, N-CH_2-N), 7.20 (m, 3H, phenyl), 7.32 (t, 1H, phenyl), 11.27 (s, 1H, NH).

Anal. Calcd for $C_{19}H_{23}N_4O_2F_3$: C, 57.58; H, 5.81; N, 14.14. Found: C, 57.46; H, 5.94; N, 14.09.

7-Butyl-7-ethyl-6,8-dioxo-3-(4-trifluoromethylphenyl)-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**42**).

Compound **42** was obtained in 15% yield; mp 197-199°; ir: 1710, 1680, 1640 cm^{-1}. ^{1}H-NMR (deuteriochloroform): δ 0.66 (t, 3H, $(CH_2)_3CH_3$), 0.77 (t, 3H, CH_2CH_3), 1.01 (m, 4H, $(CH_2)_3CH_3$), 1.83 (m, 4H, CH_2CH_3, $(CH_2)_3CH_3$), 5.11 (s, 2H, N-CH_2-N), 5.39 (AB pattern, 2H, N-CH_2-N), 7.07 (d, 2H, phenyl), 7.45 (d, 2H, phenyl), 11.74 (s, 1H, NH).

Anal. Calcd for $C_{19}H_{23}N_4O_2F_3$: C, 57.58; H, 5.81; N, 14.14. Found: C, 57.44; H, 5.97; N, 13.96.

7-Butyl-3-(4-chloro-3-trifluoromethylphenyl)-7-ethyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**43**).

Compound **43** was obtained in 71% yield; mp 214-216°; ir: 1720, 1685, 1635 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.66 (t, 3H, $(CH_2)_3CH_3$), 0.73 (t, 3H, CH_2CH_3), 1.17 (m, 4H, $(CH_2)_3CH_3$), 1.90 (m, 4H, CH_2CH_3, $(CH_2)_3CH_3$), 5.05 (s, 2H, N-CH_2-N), 5.35 (AB pattern, 2H, N-CH_2-N), 7.10 (d, 1H, phenyl), 7.30 (s, 1H, phenyl), 7.35 (d, 1H, phenyl).

Anal. Calcd for $C_{19}H_{22}N_4O_2F_3Cl$: C, 52.96; H, 5.11; N, 13.01. Found: C, 52.81; H, 5.22; N, 13.01.

7,7-Diethyl-3-(4-nitrophenyl)-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**44**).

Compound **44** was obtained in 21% yield; mp 217-219°; ir: 1710, 1675, 1600 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.75 (t, 6H, 2 x CH_2CH_3), 1.97 (q, 4H, 2 x CH_2CH_3), 5.03 (s, 2H, N-CH_2-N), 5.38 (s, 2H, N-CH_2-N), 6.89 (d, 2H, phenyl), 7.18 (d, 2H, phenyl), 12.05 (s, 1H, NH).

Anal. Calcd for $C_{16}H_{19}N_5O_4$: C, 55.65; H, 5.51; N, 20.29. Found: C, 55.30; H, 5.76; N, 20.49.

7,7-Diethyl-3-(4-methylphenyl)-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**45**).

Compound **45** was obtained in 62% yield; mp 171-173°; ir: 1720, 1670, 1625 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.64 (t, 6H, 2 x CH_2CH_3), 1.91 (q, 4H, 2 x CH_2CH_3), 2.22 (s, 3H, CH_3), 5.07 (s, 2H, N-CH_2-N), 5.33 (s, 2H, N-CH_2-N), 7.02 (d, 2H, phenyl), 7.18 (d, 2H, phenyl), 11.57 (s, 1H, NH).

Anal. Calcd for $C_{17}H_{22}N_4O_2$: C, 64.97; H, 7.01; N, 17.83. Found: C, 64.61; H, 7.20; N, 17.76.

6,8-Dioxo-7,7-dipropyl-3-(2-trifluoromethylphenyl)-9-[(2-trifluoromethylphenyl)aminomethyl]-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**47**).

Compound **47** was not isolated, but it was observed in NMR spectra; ^{1}H-NMR (deuteriochloroform): δ 0.73 (t, 6H, 2 x $CH_2CH_2CH_3$), 0.88 (m, 4H, 2 x $CH_2CH_2CH_3$), 1.81 (t, 4H, 2 x $CH_2CH_2CH_3$), 3.82 (s, 2H, N-CH_2-NH), 5.08 (s, 2H, N-CH_2-N), 5.36 (s, 2H, N-CH_2-N), 5.88 (d, 2H, N-CH_2-N), 6.13 (t, 1H, NH), 7.01-7,33 (m, 8H, 2 x phenyl).

3-(4-Chlorophenyl)-7-ethyl-7,9-dimethyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine (**46**).

A solution of 3-(4-chlorophenyl)-7-ethyl-7-methyl-6,8-dioxo-2,3,4,5,6,7,8,9-octahydropyrimido[1,2-*a*]-*s*-triazine **4** (6.7 mmol), potassium carbonate (15.6 mmol) in dimethylformamide was stirred at room temperature for three days. Methyl iodide (26.9 mmol) was then added, and the solution was stirred for three days at room temperature. The solvent was evaporated under reduced pressure. The residue was diluted in water (100 mL), extracted with chloroform (3 x 100 mL), and dried with sodium sulfate. The solvent was evaporated under reduced pressure and the residue was chromatographed (SiO_2/ethyl acetate/cyclohexane, 3/1, v/v).

Compound **46** was obtained in 39% yield; mp 98-100°; ir: 1725, 1661cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.53 (t, 3H, CH_2CH_3), 1.36 (s, 3H, CH_3), 1.82 (q, 2H, CH_2CH_3), 3.20 (s, 3H, N-CH_3), 4.99 (AB pattern, 2H, N-CH_2-N), 5.08 (AB pattern, 1H, N-CH_2-N), 5.42 (AB pattern, 1H, N-CH_2-N), 6.85 (d, 2H, phenyl), 7.16 (d, 2H, phenyl); ^{13}C-NMR (deuteriochloroform): δ 9.67 (CH_3), 23.48 (CH_2CH_3), 28.83 (N-CH_3), 33.46 (CH_2CH_3), 52.52 (C-7), 59.35 (C-2), 65.34 (C-4), 119.94 (2 x CH-Phenyl), 127.74 (C-Phenyl), 129.77 (2 x CH-Phenyl), 140.74 (C-9a), 145.77 (C-Phenyl), 170.00 (C-6), 170.92 (C-8).

Anal. Calcd for $C_{16}H_{19}N_4O_2Cl$: C, 57.40; H, 5.68; N, 16.74. Found: C, 57.24; H, 5.42; N, 16.57.

Acknowledgments.

We thank Janssen laboratory for the automated pharmacological screening.

REFERENCES AND NOTES

* Author to whom correspondence should be addressed; e-mail adress: Olivier.Lafont@univ-rouen.fr.

[1] P. Tsita, E. Antoniadou-Vyza, S. J. Hamodrakas, E. E. Eliopoulos, A. Tsantili-Kakoulidou, E. Lada-Hytiroglou, C. Roussakis, I. Chinou, A. Hempel, N. Camerman, F. P. Ottensmeyer and D. A. Vanden Berghe, *Eur. J. Med. Chem.*, **28**, 149 (1993).

[2] M. F. G. Stevens, E. A. Bliss, *Eur. J. Med. Chem. — Chim. Ther.*, **19**, 375 (1984).

[3] L. M. Werbel, E. F. Elslager, C. Hess and M. P. Hutt, *J. Med. Chem.*, **30**, 1943 (1987).

[4] I. T. Kay, *Ger. Offen.*, **2**, 452, 893 (1975); *Chem. Abstr.*, **83**, 97363v (1975).

[5] S. Ménager, C. Loire, O. Lafont, B. Champeyrol, C. Delabos, J. Garnier and C. Combet Farnoux, *Eur. J. Med. Chem.*, **26**, 79 (1991).

[6] S. Ménager, C. Loire, T. Petrakian, C. Combet Farnoux, C. Delabos, J. Garnier and O. Lafont, *Ann. Pharm. Fr.*, **53**, 29 (1995).

[7] M.-G. Karmouta, O. Lafont, C. Combet Farnoux, M. Miocque, M.-C. Rigothier, B. Louchon and P. Gayral, *Eur. J. Med. Chem. — Chim. Ther.*, **15**, 341 (1980).

[8] W. R. Greco and M. T. Hakala, *J. Pharmacol. Exp. Ther.*, **212**, 39 (1980).

[9] A. Ducarme, M. Neuwels, S. Goldstein, and R. Massingham, *Eur. J. Med. Chem.*, **33**, 215 (1998).

[10] C. Dias Selassie, C. Hansh, T. A. Khwaja, C. B. Dias and S. Pentecost, *J. Med. Chem.*, **27**, 347 (1984).

[11] M. Tramontini and L. Angiolini, *Tetrahedron*, **46**, 1791 (1990).

[12] M. G. Karmouta, O. Lafont, C. Combet Farnoux and M. Miocque, *C. R. Acad. Sci. Sér. C.*, **285**, 25 (1977).