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(71) Applicant (for all designated States except US):  
**PIERRE FABRE MEDICAMENT** [FR/FR]; 45, place  
Abel Gance, F-92100 Boulogne-Billancourt (FR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **LEROY, Isabelle**  
[FR/FR]; 39, Hameau de Fedevieille, F-81710 Saix (FR).  
**DUPONT-PASSELAIGUE, Elisabeth** [FR/FR]; 58, rue  
de Kervenoael, F-81100 Castres (FR). **VALEILLE,**  
**Karine** [FR/FR]; 1 rue de la Libération, F-81100 Castres  
(FR). **RIVAL, Yves** [FR/FR]; 40, rue François Mitterand,  
F-81090 Lagarrigue (FR). **JUNQUERO, Didier**  
[FR/FR]; 112 Chemin des Fourches, F-81100 Castres  
(FR).

(74) Agent: **AHNER, Francis**; Cabinet REGIMBEAU, 20,  
rue de Chazelles, F-75847 Paris Cedex 17 (FR).

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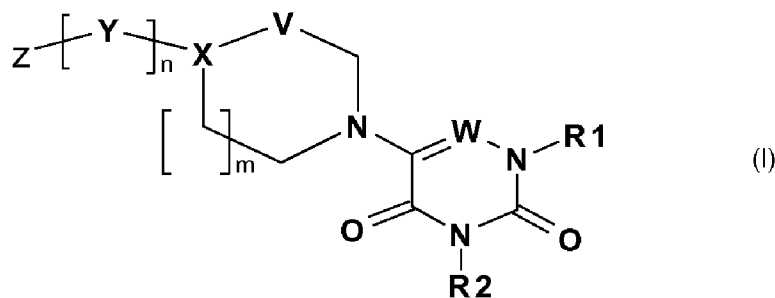
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(54) Title: DERIVATIVES OF TRIAZINES AND URACILS, THEIR PREPARATION AND THEIR APPLICATION IN HUMAN THERAPEUTICS



(57) Abstract: The present invention relates to derivatives of general formula I wherein : - W represents nitrogen, - R<sub>1</sub> represents:  
• a hydrogen or a linear or branched C<sub>1</sub>-C<sub>5</sub> alkyl radical or, • a C<sub>1</sub>-C<sub>3</sub> alkyl radical substituted with groups such as trifluoromethyl,  
nitrile, hydroxy, C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> alkoxyalkoxy, indolyl, thiophenyl, oxothiophenyl, C<sub>1</sub>-C<sub>3</sub> N-alkylcarbamoyl groups or, • a  
phenyl or pyridyl or naphthyl, or thiophenyl group optionally substituted with one or more groups such as halogen atoms, nitro,  
nitrile, trifluoromethyl, vinyl, methylsulfanyl, linear branched C<sub>1</sub>-C<sub>4</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>3</sub> alkoxy groups, • a C<sub>6</sub> 2-oxocycloalkyl radical - R<sub>2</sub> represents a methyl or heptyl, - m, n are equal to 1, - V represents CH<sub>2</sub>, - X-Y represents -N- (C=O) -, -CH-O-, - Z represents a phenyl group substituted with one or more trifluoromethyl groups, halogen atoms or linear C<sub>1</sub>-C<sub>4</sub> alkyl groups.

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DERIVATIVES OF TRIAZINES AND URACILS, THEIR PREPARATION  
AND THEIR APPLICATION IN HUMAN THERAPEUTICS

The object of the present invention is derivatives of triazines and uracils inhibiting the activity of the SCD-1 enzyme and their application in human therapeutics.

The metabolic syndrome is the result of increased peripheral resistance to insulin, and is characterized by obesity, intolerance to glucose, certain dyslipidemias which may be associated with arterial hypertension and vascular inflammation. The conjunction of these multiple risk factors promotes development of atheromatous pathology at the origin of thrombotic episodes and to the development of peripheral, coronary, cerebrovascular and arterial diseases (Grundy, S.M. Drug therapy of the metabolic syndrome: minimizing the emerging crisis in polypharmacy. *Nat Rev Drug Discov* 5, 295-309 (2006)).

Stearoyl-CoA Desaturase-1 (SCD-1), also called  $\Delta^9$ -desaturase, is an enzyme which limits the synthesis of mono-unsaturated fatty acids under the control of the transcription factor SREBP<sub>1c</sub> (Miyazaki, M., Kim, Y.C., Ntambi, J.M. A lipogenic diet in mice with a disruption of the stearoyl-CoA desaturase-1 gene reveals a stringent requirement of endogenous monounsaturated fatty acids for triglyceride synthesis. *J Lipid Res* 42, 1018-1024 (2001)).

Invalidation of the SCD-1 gene in mice makes it resistant to genetic obesity or obesity induced by diet; the peripheral effect of leptin on the increase of energy expense, weight loss and sensitivity to insulin are inversely correlated with the expression of the SCD-1 gene and with the enzymatic activity (Cohen, P., Miyazaki, M., Socci, N.D. *et al.* Role for stearoyl-CoA desaturase-1 in leptin-mediated weight loss. *Science* 297, 240-243 (2002), Ntambi, J.M., Miyazaki, M., Stoehr, J.P. *et al.* Loss of stearoyl-CoA desaturase-1 function protects mice against adiposity. *Proc Natl Acad Sci* 99, 11482-11486 (2002),

Biddinger, S.B., Miyazaki, M., Boucher, J. *et al.* Leptin suppresses stearoyl-CoA desaturase-1 by mechanisms independent of insulin and sterol regulatory element-binding protein-1c. *Diabetes* 55, 2032-2041 (2006)).

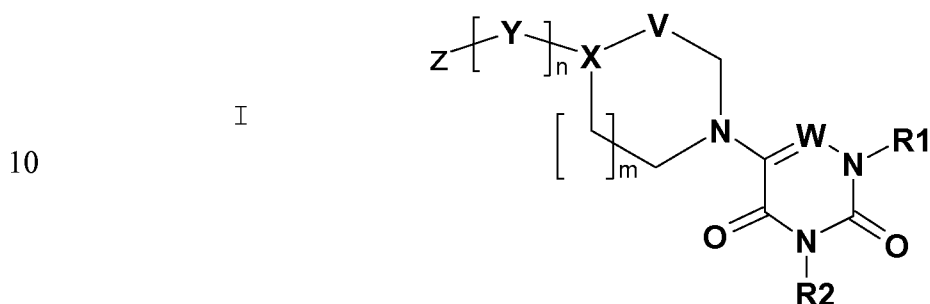
5           The involvement of SCD-1 in the pathogenesis of obesity is reinforced by the correlation between plasma concentration of palmitoleic acid and abdominal adiposity in children (Okada, T., Furuhashi, N., Kuromori, Y. *et al.* Plasma palmitoleic acid content and obesity in children. *Am J Clin Nutr* 82, 747-750 (2005)), the association of over-  
10           expression of SCD-1 in the skeletal muscle in obese adults with a bad distribution of fatty acids which causes inhibition of hepatic  $\beta$ -oxidation (Hulver, M.W., Berggren, J.R., Carper, M.J. *et al.* Elevated stearoyl-CoA desaturase-1  
15           expression in skeletal muscle contributes to abnormal fatty acid partitioning in obese humans. *Cell Metab* 2, 251-261 (2005)). The plasma ratio 18:1/18:0, also called the "desaturation index", appears as the biomarker of SCD-1 activity in humans and correlates with the plasma  
20           triglyceride level and in an inversely proportional way with the level of HDL (Attie, A.D., Krauss, R.M., Gray-Keller, M.P. *et al.* Relationship between stearoyl-CoA desaturase activity and plasma triglycerides in human and mouse hypertriglyceridemia. *J Lipid Res* 43, 1899-1907 (2002)).  
25           Accordingly, inhibition of SCD-1 appears as a therapeutic target of choice in the treatment of obesity, of type 2 diabetes and of lipid disorders related to the metabolic syndrome.

30           The compounds of the invention are characterized by their property of inhibiting the activity of the SCD-1 enzyme and by their pharmacological profile.

          The compounds of the invention correspond to the general formula I.

35           The invention relates to the derivatives of 2H-[1,2,4] triazine-3,5-dione and of H-pyrimidine-2,4-dione for

their use as inhibitors of the activity of the SCD-1 enzyme and corresponding to the general formula I:



wherein:

- W represents nitrogen or CH
- R<sub>1</sub> and R<sub>2</sub> represent independently of each other:
  - 20 • a hydrogen or
  - a linear or branched C<sub>1</sub>-C<sub>7</sub> alkyl or alkenyl radical or
  - a C<sub>1</sub>-C<sub>3</sub> alkyl radical substituted with groups such as:
    - trifluoromethyl, nitrile, hydroxy, C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> alkoxyalkoxy, indolyl, thiophenyl, oxothiophenyl, C<sub>1</sub>-
    - 25 C<sub>3</sub> N-alkyl or N-dialkylcarbamoyl or,
    - phenyl or aroyl or benzyloxy or N-arylcabamoyl (for which the phenyl ring is optionally substituted with one or more groups such as a linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, nitro group, a halogen atom),
    - 30 • a phenyl or pyridyl or naphthyl, or thiophenyl group optionally substituted with one or more groups such as a halogen, a nitro, nitrile, trifluoromethyl, vinyl, methylsulfanyl, linear branched C<sub>1</sub>-C<sub>4</sub>, alkyl, linear or branched C<sub>1</sub>-C<sub>3</sub> alkoxy, phenyl, C<sub>1</sub>-C<sub>3</sub>N-mono- or di-
    - 35 alkylcarbamoyl ou dialkylcarbamoyl, C<sub>1</sub>-C<sub>4</sub> alkylcarboxamido group,
    - a C<sub>5</sub>-C<sub>6</sub> 2-oxocycloalkyl radical optionally fused with a phenyl group,
  - m is equal to 0 or 1
  - 40 - V represents CH<sub>2</sub>, CHCH<sub>3</sub> or C=O
  - when n=1

X-Y represents -N-(C=O)-, -N-CH<sub>2</sub>-, -CH-CH<sub>2</sub>-, -CH-O-,  
-CH-(C=O)-,

Z represents a phenyl group optionally substituted  
with one or more trifluoromethyl groups,  
halogens, linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, linear  
or branched C<sub>1</sub>-C<sub>3</sub> alkoxy groups,

-when n=0

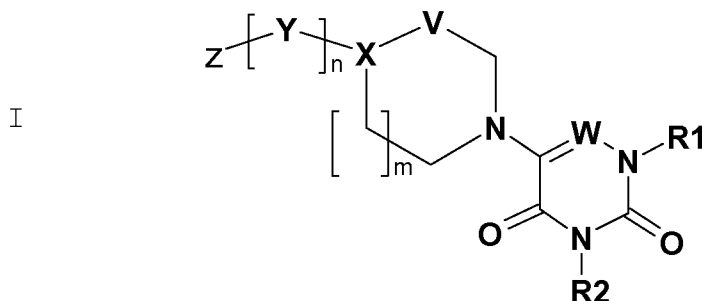
X represents N,

Z represents a phenyl or cinnamyl or  
aryloxy carbonyl or 2-phenylacetyl group (the  
position 2 of which is optionally substituted  
with a linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl) for which  
the aromatic group is optionally substituted with  
one or more trifluoromethyl groups, halogens,  
linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, linear or branched  
C<sub>1</sub>-C<sub>3</sub> alkoxy, nitro groups,

as well as addition salts with pharmaceutically acceptable  
bases and acids, and the different enantiomers of the  
compounds having asymmetrical carbons, as well as their  
mixtures in any proportions notably including the racemic  
mixtures.

The present invention also relates to novel  
derivatives of 2H-[1,2,4]triazine-3,5-dione and of H-  
pyrimidine-2,4-dione, to their preparation and to their  
application in human therapeutics.

These compounds correspond to the general formula I.



wherein:

- W represents nitrogen or CH
- R<sub>1</sub> and R<sub>2</sub> represent:
  - a hydrogen in a non-simultaneous way or a linear or  
5 branched C<sub>1</sub>-C<sub>7</sub> alkyl or alkenyl radical or,
  - a C<sub>1</sub>-C<sub>3</sub> alkyl radical substituted with groups such as:
    - trifluoromethyl, nitrile, hydroxy, C<sub>1</sub>-C<sub>3</sub>  
alkoxy, C<sub>3</sub>-C<sub>6</sub> alkoxyalkoxy, indolyl,  
10 thiophenyl, oxothiophenyl, C<sub>1</sub>-C<sub>3</sub> N-alkyl or N-  
dialkylcarbamoyl or,
    - phenyl or aroyl or benzyloxy or N-  
arylcarbamoyl (for which the phenyl ring is  
possibly substituted with one or more groups  
such as linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, nitro  
15 groups, halogen atoms),
    - a phenyl or pyridyl or naphthyl or thiophenyl group,  
possibly substituted with one or more groups such as  
halogen atoms, nitro, nitrile, trifluoromethyl, vinyl,  
methylsulfanyl, linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, linear  
20 or branched C<sub>1</sub>-C<sub>3</sub> alkoxy, phenyl, C<sub>1</sub>-C<sub>3</sub> N-mono- or di-  
alkylcarbamoyl, C<sub>1</sub>-C<sub>4</sub> alkylcarboxamido groups,
    - a C<sub>5</sub>-C<sub>6</sub> 2-oxocycloalkyl radical optionally fused with a  
phenyl group,
- m is equal to 0 or 1
- 25 - V represents CH<sub>2</sub>, CHCH<sub>3</sub> or C=O
- when n=1
  - X-Y represents -N-(C=O)-, -N-CH<sub>2</sub>-, -CH-CH<sub>2</sub>-, -CH-O-,  
-CH-(C=O)-,
  - Z represents a phenyl group substituted with one or  
30 more trifluoromethyl groups, halogen atoms,  
linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, linear or branched  
C<sub>1</sub>-C<sub>3</sub> alkoxy groups except for the compounds 6-[4-  
(4-isopropyl-benzyl)-piperazin-1-yl]-2,4-  
dimethyl-2H-[1,2,4]triazine-3,5-dione and 2,4-

dimethyl-6-[4-(3-trifluoro-methyl-benzyl)-  
piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione,

-when n=0

X represents N,

5 Z represents a phenyl or cinnamyl or  
aryloxycarbonyl or 2-phenylacetyl group (the  
position 2 of which is optionally substituted  
with a linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl) for which  
the aromatic group is substituted with one or  
10 more trifluoromethyl groups, halogen atoms,  
linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, linear or branched  
C<sub>1</sub> or C<sub>3</sub> alkoxy, nitro groups, and this except for  
the following compounds:

15 6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2,4-  
dimethyl-2H-[1,2,4]triazine-3,5-dione

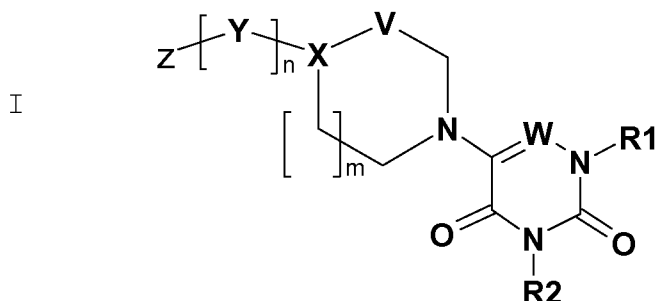
6-[4-(4-methoxy-phenyl)-piperazin-1-yl]-2,4-  
dimethyl-2H-[1,2,4]triazine-3,5-dione

6-[4-(2-chloro-phenyl)-piperazin-1-yl]-2,4-  
dimethyl-2H-[1,2,4]triazine-3,5-dione

20 as well as the addition salts with pharmaceutically  
acceptable bases and acids, and the different enantiomers  
of the compounds having asymmetrical carbons, as well as  
their mixtures in any proportions notably including racemic  
mixtures.

25 The present invention more particularly relates to  
derivatives of 2H-[1,2,4]triazine-3,5-dione and of H-  
pyrimidine-2,4-dione corresponding to the general formula I

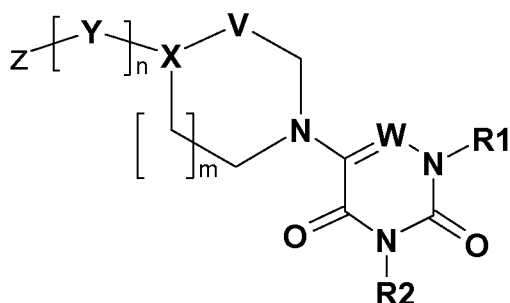
30



wherein:

- W represents nitrogen or CH
- R<sub>1</sub> and R<sub>2</sub> represent:
  - a hydrogen (in a non-simultaneous way) or a linear or branched C<sub>1</sub>-C<sub>7</sub> alkyl or alkenyl radical or, 5
  - a C<sub>1</sub>-C<sub>3</sub> alkyl radical substituted with groups such as:
    - trifluoromethyl, nitrile, hydroxy, C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> alkoxyalkoxy, indolyl, thiophenyl, oxothiophenyl, C<sub>1</sub>-C<sub>3</sub> N-alkyl or N-dialkylcarbamoyl groups or, 10
    - phenyl or aroyl or benzyloxy or N-arylcarbamoyl (for which the phenyl ring is optionally substituted with one or more groups such as a linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, nitro groups, halogen atoms),
    - a phenyl or pyridyl or naphthyl or thiophenyl group 15 optionally substituted with one or more groups such as halogen atoms, nitro, nitrile, trifluoromethyl, vinyl, methylsulfanyl, linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>3</sub> alkoxy, phenyl, C<sub>1</sub>-C<sub>3</sub> N-mono- or dialkylcarbamoyl, C<sub>1</sub>-C<sub>4</sub> alkylcarboxamido groups,
    - a C<sub>5</sub>-C<sub>6</sub> 2-oxocycloalkyl radical optionally fused with a phenyl group, 20
  - m, n are equal to 1
  - V represents CH<sub>2</sub>
  - X-Y represents -N-(C=O)-, - -CH-CH<sub>2</sub>-, -CH-O-, -CH- 25 (C=O)-,
  - Z represents a phenyl group substituted with one or more trifluoromethyl groups, halogen atoms, linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>3</sub> alkoxy groups.

30 The present invention still more particularly relates to the derivatives of 2H-[1,2,4]triazine-3,5-dione and of H-pyrimidine-2,4-dione corresponding to the general formula I



wherein:

- W represents nitrogen or CH
- R<sub>1</sub> and R<sub>2</sub> represent:
  - 5 • a hydrogen (in a non-simultaneous way) or a linear or branched C<sub>1</sub>-C<sub>7</sub> alkyl radical or,
  - a C<sub>1</sub>-C<sub>3</sub> alkyl radical substituted with groups such as: trifluoromethyl, nitrile, hydroxy, C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> alkoxyalkoxy, indolyl, oxothiophenyl, C<sub>1</sub>-C<sub>3</sub> N-alkyl or
  - 10 • a phenyl or pyridyl or naphthyl or thiophenyl group optionally substituted with one or more groups such as halogen atoms, nitro, nitrile, trifluoromethyl, vinyl, methylsulfanyl, linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>1</sub>-C<sub>3</sub> N-mono- or
  - 15 • a C<sub>5</sub>-C<sub>6</sub> 2-oxocycloalkyl radical optionally fused with a phenyl group,
- m, n are equal to 1
- 20 - V represents CH<sub>2</sub>
- X-Y represents -N-(C=O)-, -CH-O-,
- Z represents a phenyl group substituted with one or more trifluoromethyl groups, halogen atoms, linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl groups,
- 25 The present invention particularly relates to the derivatives of 2H-[1,2,4]triazine-3,5-dione corresponding to the general formula I wherein:
  - W represents nitrogen,
  - R<sub>1</sub> represents:

- a hydrogen or a linear or branched C<sub>1</sub>-C<sub>5</sub> alkyl radical or,
  - a C<sub>1</sub>-C<sub>3</sub> alkyl radical substituted with groups such as trifluoromethyl, nitrile, hydroxy, C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> alkoxyalkoxy, indolyl, oxothiophenyl, C<sub>1</sub>-C<sub>3</sub> N-alkylcarbamoyl groups,
  - a phenyl or pyridyl or naphthyl or thiophenyl group optionally substituted with one or more groups such as halogen atoms, nitro, nitrile, trifluoromethyl, vinyl, methylsulfanyl, linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>3</sub> alkoxy, phenyl, C<sub>1</sub>-C<sub>3</sub> N-mono- or di-alkylcarbamoyl, C<sub>1</sub>-C<sub>4</sub> alkylcarboxamido groups,
  - a C<sub>5</sub>-C<sub>6</sub> 2-oxocycloalkyl radical,
- R<sub>2</sub> represents: a linear or branched C<sub>1</sub>-C<sub>7</sub> alkyl radical, and preferably a methyl,  
- m, n are equal to 1,  
- V represents CH<sub>2</sub>,  
- X-Y represents -N-(C=O)-, -CH-O-,  
- Z represents a phenyl group substituted with one or more trifluoromethyl groups, halogen atoms, or linear C<sub>1</sub>-C<sub>4</sub> alkyl groups.

The present invention still more particularly relates to the derivatives of 2H-[1,2,4]triazine-3,5-dione corresponding to the general formula I wherein:

- W represents nitrogen,  
- R<sub>1</sub> represents:
- a hydrogen or a linear or branched C<sub>1</sub>-C<sub>5</sub> alkyl radical or,
  - a C<sub>1</sub>-C<sub>3</sub> alkyl radical substituted with groups such as trifluoromethyl, nitrile, hydroxy, C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> alkoxyalkoxy, indolyl, oxothiophenyl, C<sub>1</sub>-C<sub>3</sub> N-alkylcarbamoyl groups,
  - a phenyl or pyridyl or thiophenyl group possibly substituted with one or more groups such as halogen

atoms, nitrile, linear or branched C<sub>1</sub>-C<sub>4</sub> alky, linear or branched C<sub>1</sub>-C<sub>3</sub> alkoxy groups,

- a C<sub>6</sub> 2-oxocycloalkyl radical,
- R<sub>2</sub> represents a methyl or heptyl,
- 5 - m, n are equal to 1,
- V represents CH<sub>2</sub>,
- X-Y represents -N-(C=O)-, -CH-O-,
- Z represents a phenyl group substituted with one or more trifluoromethyl groups, halogen atoms or
- 10 linear C<sub>1</sub>-C<sub>4</sub> alkyl groups.

The present invention relates to the compounds of the general formula I characterized in that they are selected from:

- 4-heptyl-2-methyl-6-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 15 ▪ 2-methyl-6-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 4-methyl-2-(4,4,4-trifluoro-butyl)-6-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-
- 20 [1,2,4]triazine-3,5-dione
- 4-methyl-6-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 2,4-dimethyl-6-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 25 ▪ 2,4-dimethyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 3-{4-heptyl-3,5-dioxo-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-4,5-dihydro-3H-[1,2,4]triazin-2-yl}-propionitrile
- 30 ▪ 2-butyl-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- N-methyl-2-{4-methyl-3,5-dioxo-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-4,5-dihydro-3H-[1,2,4]triazin-2-yl}-acetamide

- 2-(2-ethoxy-ethyl)-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 2-[2-(1H-indol-3-yl)-ethyl]-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-  
5 [1,2,4]triazine-3,5-dione
- 4-methyl-2-(4-oxo-4-thiophen-2-yl-butyl)-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 3-{6-[4-(2-chloro-phenoxy)-piperidin-1-yl]-4-methyl-3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl}-propionitrile  
10
- 6-[4-(2-chloro-phenoxy)-piperidin-1-yl]-4-methyl-2-(4,4,4-trifluoro-butyl)-2H-[1,2,4]triazine-3,5-dione
- 6-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione
- 15
- 6-[4-(2-fluoro-phenoxy)-piperidin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione
- 6-[4-(2-chloro-5-trifluoromethyl-phenoxy)-piperidin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione
- 6-[4-(2-chloro-5-fluoro-phenoxy)-piperidin-1-yl]-2,4-  
20 dimethyl-2H-[1,2,4]triazine-3,5-dione
- 2,4-dimethyl-6-(4-o-tolyloxy-piperidin-1-yl)-2H-[1,2,4]triazine-3,5-dione
- 6-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione
- 25
- 6-[4-(5-fluoro-2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione
- 6-[4-(5-fluoro-2-trifluoromethyl-benzoyl)-piperazin-1-yl]-4-methyl-2-(4,4,4-trifluoro-butyl)-2H-[1,2,4]triazine-3,5-dione
- 30
- 6-[4-(5-fluoro-2-trifluoromethyl-benzoyl)-piperazin-1-yl]-4-methyl-2-(3-methyl-butyl)-2H-[1,2,4]triazine-3,5-dione
- 2,4-dimethyl-6-[4-(2-trifluoromethyl-benzyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione

- 4-methyl-2-(4,4,4-trifluoro-butyl)-6-[4-(2-trifluoromethyl-benzyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 5   ▪ 4-methyl-6-[4-(2-trifluoromethyl-benzyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 6-[4-(5-fluoro-2-trifluoromethyl-benzoyl)-piperazin-1-yl]-4-methyl-2H-[1,2,4]triazine-3,5-dione
- 6-[4-(4-fluoro-2-trifluoromethyl-benzoyl)-piperazin-1-yl]-4-methyl-2H-[1,2,4]triazine-3,5-dione
- 10   ▪ 6-[4-(4-fluoro-2-trifluoromethyl-benzyl)-piperazin-1-yl]-4-methyl-2H-[1,2,4]triazine-3,5-dione
- 2-butyl-4-methyl-6-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 6-[4-(2-chloro-phenoxy)-piperidin-1-yl]-4-heptyl-2H-[1,2,4]triazine-3,5-dione
- 15   ▪ 4-methyl-2-o-tolyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 2-(4-fluoro-phenyl)-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 20   ▪ 4-methyl-2-pyridin-3-yl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 4-methyl-2-thiophen-3-yl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 25   ▪ 4-{4-methyl-3,5-dioxo-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-4,5-dihydro-3H-[1,2,4]triazin-2-yl}-benzotrile
- 2-(2-methoxy-phenyl)-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 30   ▪ 4-methyl-2-(2-oxo-cyclohexyl)-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 2-[2-(2-ethoxy-ethoxy)-ethyl]-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 35

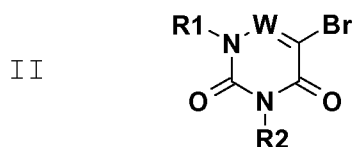
▪ 2-(2-hydroxy-ethyl)-4-methyl-6-[4-(2-trifluoromethyl-  
phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione

SYNTHESIS

The compounds of the present invention may be  
5 synthesized by using the synthesis routes described below  
or by using synthesis methods known to one skilled in the  
art.

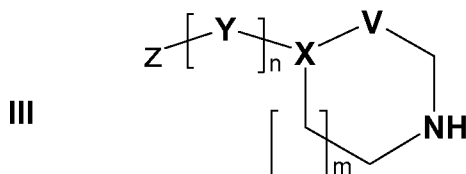
Method 1

The synthesis of compounds of general formula I is  
10 characterized (Scheme 1) in that a derivative of general  
formula II



15

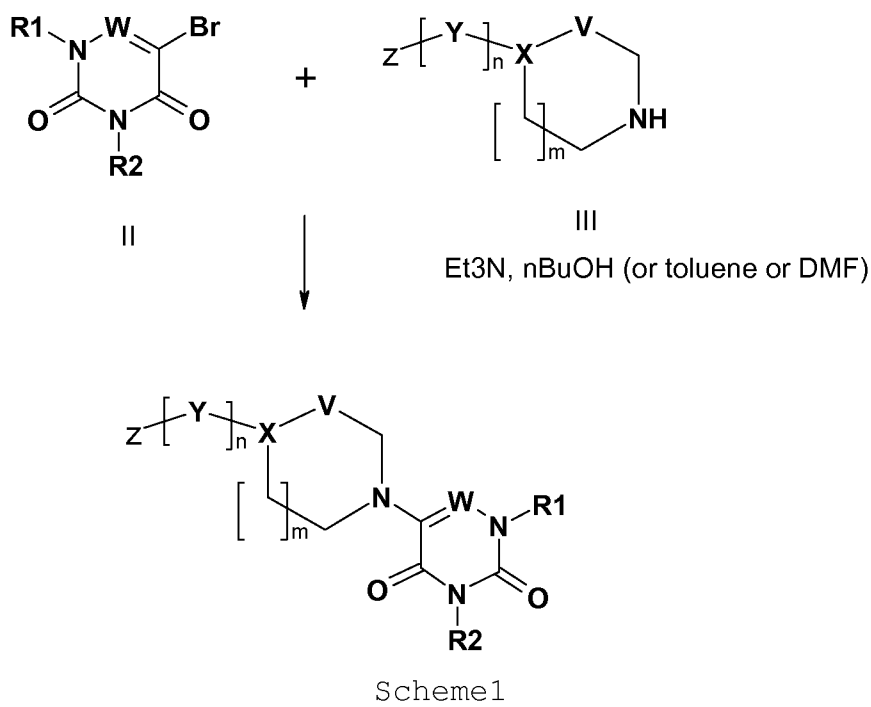
wherein W, R<sub>1</sub> and R<sub>2</sub> represent the groups as described  
earlier in formula I is fused with a derivative of general  
20 formula III



20

wherein m, n, X, Y, V, and Z are as described earlier in  
30 formula I. This reaction may be conducted in the presence  
of a base such as triethylamine in n-butanol or toluene or  
dimethylformamide;

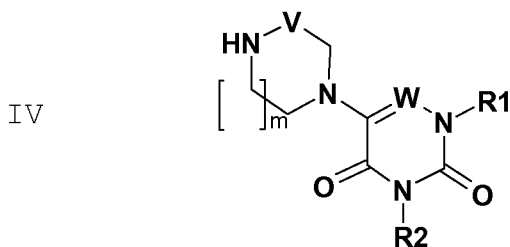
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Method 2

This synthesis method for compounds of general formula I (Scheme 2) for which X represents a nitrogen, is characterized in that a derivative of general formula IV

10



wherein m, V, W, R<sub>1</sub> and R<sub>2</sub> are as described earlier in formula I, is fused with a compound of general formula V

20



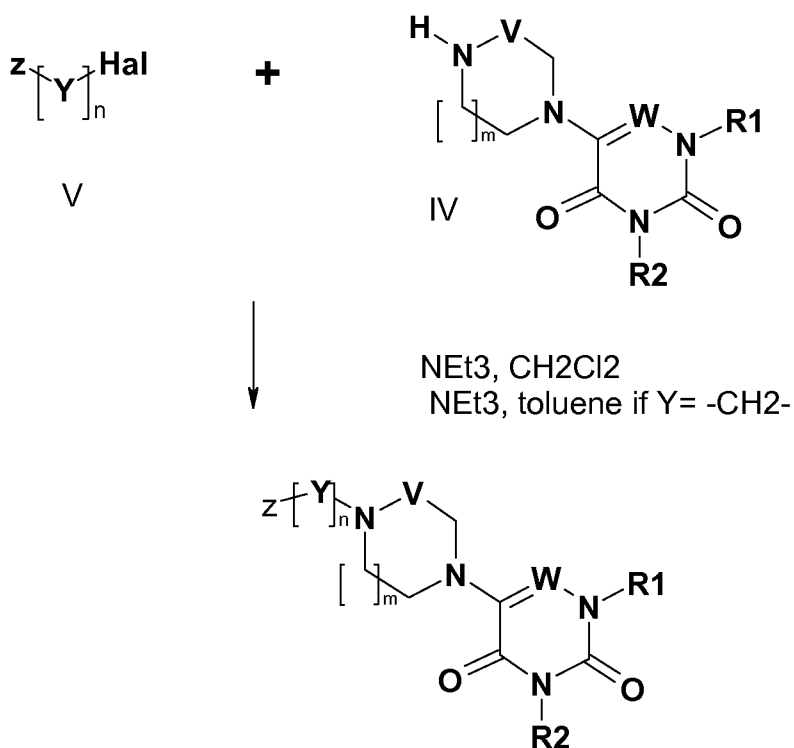
wherein Hal represents a halogen such as Cl, Br or I, when n=1, Y represents -(C=O)-, -CH<sub>2</sub>- and Z is as described earlier in formula I,

30

and when  $n=0$ , Z represents a cinnamyl or aryloxy carbonyl or 2-phenylethyl group (the position 2 of which is optionally substituted with a linear or branched  $C_1-C_4$  alkyl) for which the aromatic group is substituted with one or more trifluoromethyl groups, halogen atoms, linear or branched  $C_1-C_4$  alkyl, linear or branched  $C_1-C_3$  alkoxy, nitro groups.

This reaction may be carried out in the presence of triethylamine in dichloromethane or in toluene (when Y is  $-CH_2-$ ).

10

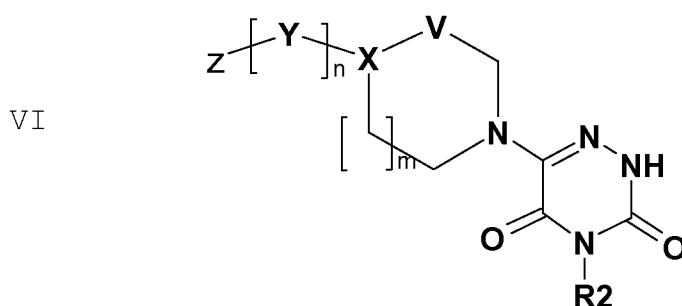


Scheme 2

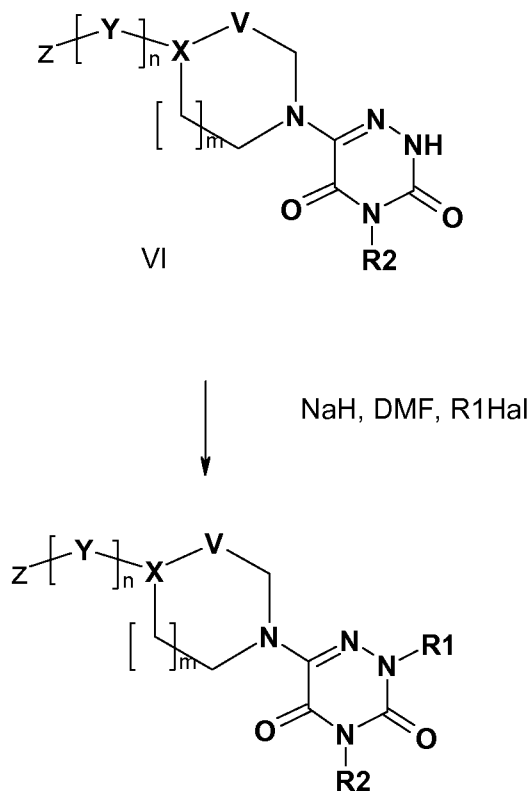
Method 3

This synthesis method of the compounds of general formula I for which W represents a nitrogen (Scheme 3) is characterized in that the nitrogen is alkylated in the position 2 of the compound VI, obtained according to the synthesis method 1 (for  $R_1$  representing a hydrogen)

20



wherein X, Y, V, Z, m, n and R<sub>2</sub> are as described earlier in formula I, by a halogenated derivative of general formula R<sub>1</sub>Hal, wherein Hal represents a halogen such as Cl, Br or I and R<sub>1</sub> is as described earlier in general formula I, under operating conditions such as NaH or tBuOK in dimethylformamide.



Scheme 3

The intermediate and final compounds may if desired be purified according to one or several purification methods selected from extraction, filtration, silica gel chromatography, preparative normal or reverse phase HPLC, crystallization.

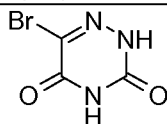
The raw materials used in the methods described earlier are commercial or easily accessible to one skilled in the art according to methods described in the literature.

The following Examples illustrate the invention without limiting the scope thereof.

Elementary analyses and mass and NMR spectra confirm the structures of the compounds.

Intermediates 1:

a) 6-bromo-2H-[1,2,4]triazine-3,5-dione (1a)



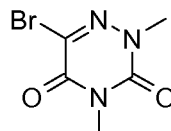
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2H-[1,2,4]triazin-3,5-dione (20 g, 177 mmol) is placed in the presence of pyridinium perbromide in 200 mL of water at 90°C for 4 h. The reaction medium is then extracted with ethyl acetate and the organic phases are dried on MgSO<sub>4</sub>. After filtration and dry concentration, 1a is isolated as a white solid (27 g, yield=80%).  
TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 90-10, R<sub>f</sub> = 0.32.

10

b) 6-bromo-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione (1b)

15



20

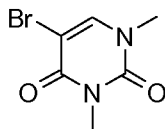
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30

11,8g (295mmol) of NaH (at 60% in paraffin) are placed in suspension at 0°C in 250mL of DMF under nitrogen. 25.80g (135mmol) of intermediate 1a diluted in 150mL of DMF are poured dropwise. This solution is then placed at room temperature, and then 18.4mL (296mmol) of methyl iodide are poured dropwise. After one night of stirring and dry concentration of the reaction medium, the obtained residue is taken up with water and extracted with ethyl acetate. The organic phases are washed with brine, dried on magnesium sulfate and then dry concentrated. The obtained residue, taken up with ether, crystallizes and a first fraction of crystals is isolated. The filtrate is dry concentrated and then purified by flash chromatography on silica (heptane-AcOEt: 50-50). 24g of intermediate 1b as a solid are thereby isolated (yield 81%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 80-20, R<sub>f</sub> = 0.59.

c) 5-bromo-1,3-dimethyl-1H-pyrimidine-2,4-dione  
(1c)

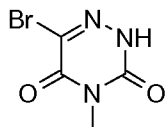


5

Synthesis of the intermediate 1c is achieved from 5-bromo-1H-pyrimidine-2,4-dione according to the operating procedure described for the synthesis of 1b (solid, yield 82%).

10 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 90-10, R<sub>f</sub>=0.8.  
Intermediates 2:

a) 6-bromo-4-methyl-2H-[1,2,4]triazine-3,5-dione  
(2a)

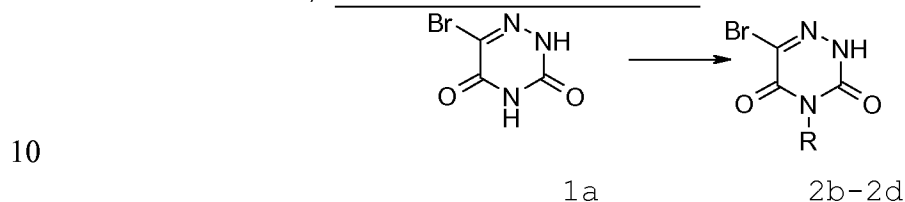


15 20.3 g (105.7mmol) of triazine 1a are placed in 150mL of acetic anhydride under reflux for 4.5 h. After dry concentration of the reaction medium, a precipitate is isolated and then recrystallized from ether: 24.3 g of crystals are isolated (yield=98%). 4.5 g (114.2 mmol) of  
20 NaH (60% in paraffin) are placed in 50mL of DMF under nitrogen. A solution of 24.3 g (103.8 mmol) of crystals isolated earlier, in 150mL of DMF is poured dropwise. The reaction medium is stirred for 45 min at room temperature and then 7 mL (114.2 mmol) of methyl iodide are added, and  
25 stirring then continues for 21 h at room temperature. After dry concentration, the obtained residue is taken up with H<sub>2</sub>O and extracted with ethyl acetate. After drying on MgSO<sub>4</sub>, the organic phases are evaporated and the obtained clear oil is purified by flash chromatography on silica  
30 (CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 90-10). 22.9 g of crystals (yield=89%) are isolated, which are placed in 300 mL of ethanol in the

presence of 0.6 g of paratoluene-sulfonic acid. This mixture is heated with reflux for 4.5h and then dry concentrated. The residue is taken up with H<sub>2</sub>O and then extracted with ethyl acetate. After drying and evaporation of the organic phases, 17 g of intermediate 2a are isolated as a solid (yield=89%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 90-10, R<sub>f</sub> = 0.29.

b) Intermediates 2b-2d



The synthesis of the 2b-2d intermediates is achieved from 1a according to the operating procedure described for the synthesis of 2a by using various alkylation agents RX.

15 Table 1 intermediates 2b-2d

RX	Total yield	TLC	state	Intermediates 2b-2d
	76%	CH <sub>2</sub> Cl <sub>2</sub> -AcOEt: 90-10 R <sub>f</sub> =0.45	solid	2b: 6-bromo-4-(4,4,4-trifluorobutyl)-2H-[1,2,4] triazine-3,5-dione
	84%	EP-AcOEt: 70-30 R <sub>f</sub> =0.73	solid	2c: 6-bromo-4-heptyl-2H-[1,2,4]triazine-3,5-dione
	81%	EP-AcOEt: 50-50 R <sub>f</sub> =0.61	solid	2d: 4-benzyloxymethyl-6-bromo-2H-[1,2,4]triazine-3,5-dione

TLC: silica gel 60 F 254 Merck, EP=petroleum ether

c) 6-bromo-2-methyl-2H-[1,2,4]triazine-3,5-dione (2e)



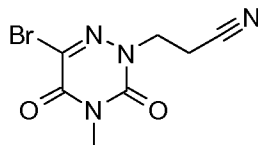
20 10 g (88mmol) of 2H-[1,2,4]triazine-3,5-dione are placed in 177 mL of hexamethyldisilazane at room temperature. 17.7mL (132mmol) of trimethylsilyl chloride are added. The mixture is heated to 125°C for 2.5 h and then placed at 60°C and 55mL (880mmol) of methyl iodide are

added. The medium is stirred at 60°C for 15h. After cooling to 0°C, 400mL of acetic acid are slowly added. The mixture is left under stirring for 30 min. After dry concentration of the reaction medium, the obtained residue is purified by  
5 flash chromatography on silica (CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 95-5). 4.7 g of crystals (yield=43%) are isolated. 4.7g (37.2 mmol) of the obtained solid are placed in 50mL of water in the presence of 7.6mL of bromine (148.8mmol). The medium is heated to 60°C for 14h. The reaction medium is then slowly  
10 poured onto a Na<sub>2</sub>SO<sub>3</sub> 10% solution cooled to 0°C, up to a pH=7. It is then extracted with ethyl acetate and the organic phases are dried on MgSO<sub>4</sub>. After filtration and dry concentration, 2e is isolated as a white powder (6,6g, yield=85%).  
15 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 90-10, Rf = 0.75.

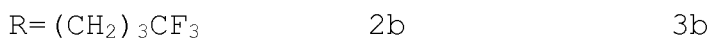
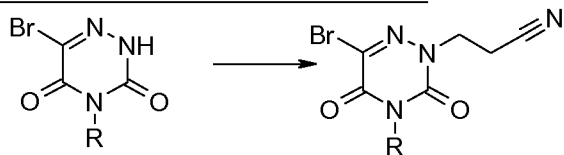
Intermediates 3:

a) 3-(6-bromo-4-methyl-3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-propionitrile (3a)

20



2.4 g (11.6mmol) of the triazine 2a and 7mL (106mmol) of acrylonitrile are placed in 24mL of a solution of pyridine and water (1/1) under reflux for 3h. After concentration,  
25 the reaction medium is extracted with AcOEt and then after drying on MgSO<sub>4</sub>, the organic phases are dry concentrated. After washing the obtained solid with ether, 2.8 g of intermediate 3a are obtained (yield=93%).  
TLC silica gel 60 F 254 Merck, petroleum ether-AcOEt: 70-  
30 30, Rf=0.18.

b) Intermediates 3b and 3c:

The synthesis of the intermediates 3b and 3c is achieved from the intermediates 2b and 2c respectively according to the operating procedure described for the synthesis of 3a.

Table 2 intermediates 3b and 3c

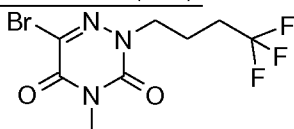
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Starting synthons	Yield	TLC	State	Intermediates 3b-3c
2b	91%	EP-AcOEt: 70-30 Rf=0.34	solid	3b: 3-[6-bromo-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-4,5-dihydro-3H-[1,2,4]triazin-2-yl]-propionitrile
2c	95%	CH <sub>2</sub> Cl <sub>2</sub> -AcOEt: 70-30 Rf=0.51	solid	3c: 3-(6-bromo-4-heptyl-3,5-dioxo-4,5-dihydro-3H-[1,2,4] triazin-2-yl)-propionitrile

TLC: silica gel 60 F 254 Merck, EP=petroleum ether

Intermediates 4:

a) 6-bromo-4-methyl-2-(4,4,4-trifluoro-butyl)-2H-[1,2,4]triazine-3,5-dione (4a)



15

0.85 g (21.3 mmol) of NaH (at 60% in paraffin) are placed in 10 mL of DMF under nitrogen. A solution of 4 g (19.4mmol) of intermediate 2a in 40mL of DMF is poured dropwise. The reaction medium is stirred for 1h at room temperature and then 5g (21.3 mmol) of 1,1,1-trifluoro-4-iodo-butane are added dropwise, and stirring is then continued for 3h at room temperature. After dry concentration, the obtained residue is taken up with H<sub>2</sub>O and extracted with ethyl acetate. After drying on MgSO<sub>4</sub>, the organic phases are evaporated and the obtained oil is purified by flash chromatography on silica (petroleum

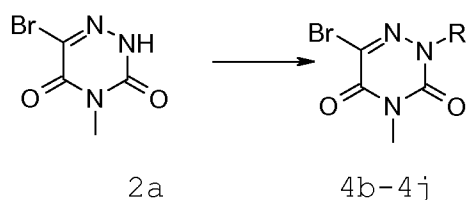
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ether-AcOEt: 80-20). 5.3 g of crystals corresponding to the compound 4a (yield=87%) are isolated.

TLC silica gel 60 F 254 Merck, petroleum ether-AcOEt: 70-30, Rf=0.58.

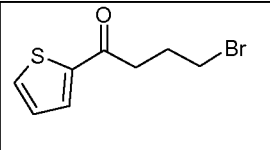
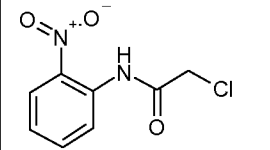
5 b) Intermediates 4b-4j



10 The synthesis of the intermediates 4b-4j is achieved from 2a according to the operating procedure described for the synthesis of 4a by using various alkylation agents RX.

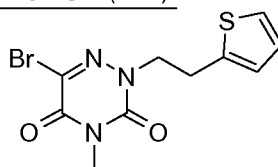
Table 3 intermediates 4b-4j

RX	Total yield	TLC	state	Intermediates 4b-4j
	88%	EP-AcOEt: 50-50 Rf=0.37	solid	4b: 2-(6-bromo-4-methyl-3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-ylmethyl)-isoindole-1,3-dione
	90%	CH <sub>2</sub> Cl <sub>2</sub> -MeOH: 95-5 Rf=0.82	solid	4c: 6-bromo-2-butyl-4-methyl-2H-[1,2,4]triazine-3,5-dione
	65%	CH <sub>2</sub> Cl <sub>2</sub> -MeOH: 90-10 Rf=0.49	solid	4d: 2-(6-bromo-4-methyl-3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-N-methylacetamide
	80%	CH <sub>2</sub> Cl <sub>2</sub> -MeOH: 95-5 Rf=0.76	oil	4e: 6-bromo-2-(2-ethoxy-ethyl)-4-methyl-2H-[1,2,4]triazine-3,5-dione
	54%	CH <sub>2</sub> Cl <sub>2</sub> -AcOEt: 95-5 Rf=0.72	solid	4f: 6-bromo-2-[2-(1H-indol-3-yl)-ethyl]-4-methyl-2H-[1,2,4]triazine-3,5-dione
	86%	CH <sub>2</sub> Cl <sub>2</sub> -AcOEt: 95-5 Rf=0.79	oil	4g: 6-bromo-4-methyl-2-(3-methyl-butyl)-2H-[1,2,4]triazine-3,5-dione
	42%	CH <sub>2</sub> Cl <sub>2</sub> -AcOEt: 95-5 Rf=0.61	solid	4h: 6-bromo-4-methyl-2-[2-(2-nitro-phenyl)-2-oxo-ethyl]-2H-[1,2,4]triazine-3,5-dione

	43%	CH <sub>2</sub> Cl <sub>2</sub> -AcOEt: 95-5 Rf=0.49	solid	4i: 6-bromo-4-methyl-2-(4-oxo-4-thiophen-2-yl-butyl)-2H-[1,2,4]triazine-3,5-dione
	79%	CH <sub>2</sub> Cl <sub>2</sub> -MeOH: 95-5 Rf=0.58	solid	4j: 2-(6-bromo-4-methyl-3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-N-(2-nitrophenyl)-acetamide

TLC: silica gel 60 F 254 Merck, EP=petroleum ether

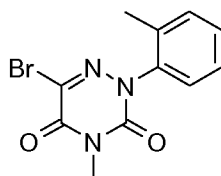
c) 6-bromo-4-methyl-2-(2-thiophen-2-yl-ethyl)-2H-[1,2,4]triazine-3,5-dione (4k)



10

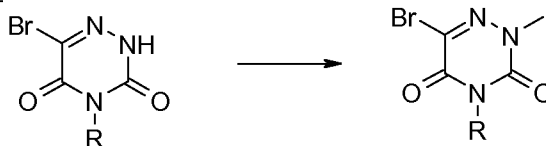
0.4g (1.94 mmol) of intermediate 2a are placed in the presence of 0.24 mL (2.14mmol) of 2-thiophen-2-yl-ethanol, 15 0.61g (2.33mmol) of triphenylphosphine in 4 mL of THF. At 0°C, 0.54 mL (2.33mmol) of DEAD in solution in toluene are added dropwise. The reaction medium is heated for 7h at 70°C. After concentration, the obtained residue is taken up with ethyl acetate and washed with water. After drying on 20 MgSO<sub>4</sub>, the organic phase is dry concentrated. The obtained residue is purified by flash chromatography on silica (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, gradient 100/0 to 97/3 over 30 min). 0.48g of crystals corresponding to the compound 4k are obtained (yield: 79%).

25 d) 6-bromo-4-methyl-2-o-tolyl-2H-[1,2,4]triazine-3,5-dione (4l)



0.5g (2.43mmol) of intermediate 2a are placed in the presence of 0.4 mL (4.85 mmol) of pyridine, 0.66g 30 (4.85mmol) of o-tolyl boronic acid, 0.66g (3.64mmol) of copper acetate in 50 mL of CH<sub>2</sub>Cl<sub>2</sub>. The reaction medium is



Intermediates 5

	R= (CH <sub>2</sub> ) <sub>3</sub> CF <sub>3</sub>	2b	5a
	R= (CH <sub>2</sub> ) <sub>6</sub> CH <sub>3</sub>	2c	5b
5	R= CH <sub>2</sub> OCH <sub>2</sub> Ph	2d	5c

The synthesis of the intermediates 5a-5c is achieved from 2b-2d respectively according to the operating procedure described for the synthesis of 4a by using iodomethane as an alkylation agent.

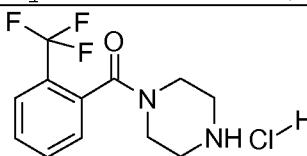
10 Table 5: intermediates 5a-5c

Starting synthons	Yield	TLC	State	Intermediates 5a-5b
2b	91%	EP-AcOEt: 70-30 Rf=0.61	solid	5a: 6-bromo-2-methyl-4-(4,4,4-trifluoro-butyl)-2H-[1,2,4]triazine-3,5-dione
2c	92%	CH <sub>2</sub> Cl <sub>2</sub> -MeOH: 95-5 Rf=0.65	oil	5b: 6-bromo-4-heptyl-2-methyl-2H-[1,2,4]triazine-3,5-dione
2d	87%	EP-AcOEt: 80-20 Rf=0.49	solid	5c: 4-benzyloxymethyl-6-bromo-2-methyl-2H-[1,2,4]triazine-3,5-dione

TLC: silica gel 60 F 254 Merck, EP=petroleum ether

Intermediates 6

a) piperazin-1-yl-(2-trifluoromethyl-phenyl)-methanone hydrochloride (6a)



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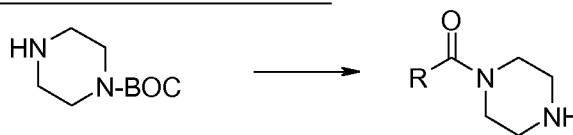
23.44g (125mmol) of BOC-piperazine are placed in the presence of 26mL (186mmol) of triethylamine in 250mL de dichloromethane at 0°C. 25g (119.8 mmol) of 2-trifluoromethyl-benzoyl chloride are added dropwise, the reaction medium is stirred for 30min at 0°C, and then left with stirring at room temperature for 1h30min. After concentration, the obtained residue is taken up with AcOEt, washed with water, and then with water saturated with NaCl.

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After drying on  $\text{MgSO}_4$ , the organic phases are dry concentrated. After washing the obtained residue with petroleum ether, 40.5 g of a beige solid are isolated (yield=94%). *TLC silica gel 60 F 254 Merck, petroleum ether- AcOEt: 50-50 Rf=0.4*. The obtained solid is placed in 100mL of dichloromethane in the presence of 65mL (877 mmol) of trifluoroacetic acid at room temperature for 1h. After concentration, the obtained residue is taken up with water and then brought to pH 7 by adding  $\text{NaHCO}_3$ . The medium is extracted with AcOEt and then with dichloromethane. After drying on  $\text{MgSO}_4$ , the organic phases are dry concentrated. The obtained residue is taken up with EtOH, salified by adding a 2.3N HCl solution in isopropanol. The medium is saturated by adding ether, the formed crystals are filtered. 29.45 g of intermediate 4a are thereby isolated as a white powder (yield 88%).

*TLC silica gel 60 F 254 Merck,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  85/15, Rf=0.43.*

b) intermediates 6b-6d



6b-6d

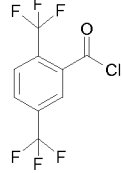
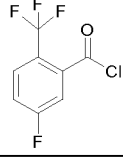
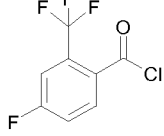
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The synthesis of the intermediates 6b-6d is achieved from BOC-piperazine according to the operating procedure described for the synthesis of 6a by using various acid chlorides  $\text{RCOCl}$ , but without carrying out the final step for salifying the amine.

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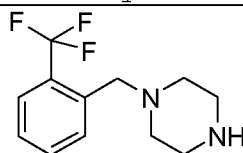
Table 6: intermediates 6b-6d

RCOCl	Yield	TLC	State	Intermediates 6b-6d
	91%	CH <sub>2</sub> Cl <sub>2</sub> -AcOEt: 95-5 Rf=0.02	oil	6b: (2,5-Bis-trifluoromethyl-phenyl)-piperazin-1-yl-methanone
	77%	CH <sub>2</sub> Cl <sub>2</sub> -AcOEt: 95-5 Rf=0.02	oil	6c: (5-fluoro-2-trifluoromethyl-phenyl)-piperazin-1-yl-methanone
	41%	CH <sub>2</sub> Cl <sub>2</sub> -MeOH: 95-5 Rf=0.07	oil	6d: (4-fluoro-2-trifluoromethyl-phenyl)-piperazin-1-yl-methanone

TLC: silica gel 60 F 254 Merck.

### Intermediates 7

#### a) 1-(2-trifluoromethyl-benzyl)-piperazine (7a)



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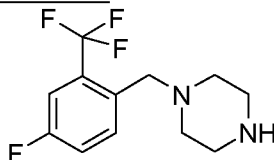
1.08g (12.5mmol) of piperazine are placed in the presence of 1g (4.2 mmol) of 1-bromomethyl-2-trifluoromethyl-benzene and 0.64mL (4.6mmol) of triethylamine in 10 mL of toluene. The reaction medium is stirred for 30min at room temperature and then heated to 110°C for 6h. After dry concentration, the obtained residue is taken up with AcOEt and washed with water. After drying on MgSO<sub>4</sub>, the organic phases are dry concentrated, the obtained residue is purified by flash chromatography on silica (CH<sub>2</sub>Cl<sub>2</sub>-MeOH-NH<sub>4</sub>OH: 90-9-1). 0.7 g of intermediate 7a are thereby isolated as a clear oil (yield 68%).

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TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH-NH<sub>4</sub>OH: 90-9-1, Rf=0.27.

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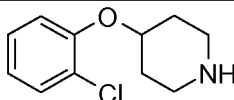
b) 1-(4-fluoro-2-trifluoromethyl-benzyl)-  
piperazine (7b)



The synthesis of intermediate 7b is achieved from 1-  
5 bromomethyl-4-fluoro-2-trifluoromethyl-benzene according to  
the operating procedure described for synthesis of 4a  
(clear oil, yield 70%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 95-5, R<sub>f</sub>=0.15.  
Intermediates 8

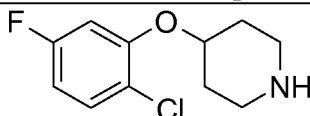
10 a) 4-(2-chloro-phenoxy)-piperidine (8a)



10g (49.68mmol) of BOC-4-hydroxy-piperidine are placed in  
the presence of 5.5mL (54.65mmol) of 2-chlorophenol, 15.6g  
(59.62mmol) of triphenylphosphine in 160 mL of THF. At 0°C,  
15 20mL (59.62mmol) of DEAD (55% solution in toluene) are  
added dropwise. The reaction medium is heated for 8h at  
65°C, and then stirred for 16h at room temperature. After  
concentration, the obtained residue is taken up with ether,  
washed with a soda (1N) solution and then with a NaCl  
20 saturated solution. After drying on MgSO<sub>4</sub>, the organic  
phases are dry concentrated, and then taken up with a  
petroleum ether-Et<sub>2</sub>O mixture: 65-35 in order to remove  
triphenylphosphine oxide. After filtration, the filtrate is  
25 concentrated, the obtained residue is purified by flash  
chromatography on silica (petroleum ether-Et<sub>2</sub>O, gradient  
100-0 to 65-35 over 30 min). 9.1 g of clear oil are  
obtained (yield 59%). TLC silica gel 60 F 254 Merck,  
CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 90-10, R<sub>f</sub>=0.75. This oil is placed in 80mL of  
30 dichloromethane in the presence of 8.67mL (116.7mmol) of  
TFA, and this solution is then stirred for 24h at room  
temperature. The medium is concentrated, the obtained

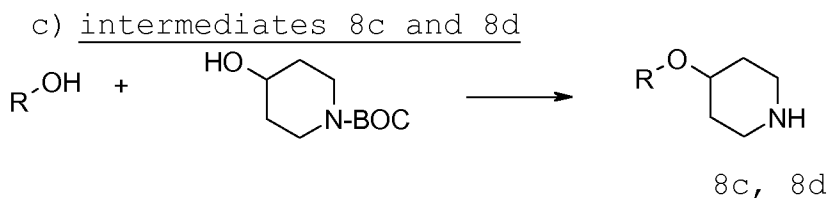
residue is taken up with AcOEt, washed with a soda (1N) solution and then with NaCl saturated water. After drying on MgSO<sub>4</sub>, the organic phases are dry concentrated. 6.5 g of intermediate 8a are thus isolated as a clear oil (quantitative yield). TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH-NH<sub>4</sub>OH: 90-9-1, Rf=0.24.

b) 4-(2-chloro-5-fluoro-phenoxy)-piperidine (8b)



9g (44.7mmol) of BOC-4-hydroxy-piperidine are placed in 30mL of dichloromethane at 0°C. 3.5 mL (44.7mmol) of mesyl chloride and 8mL (58.1mmol) of triethylamine are slowly added. The reaction medium is stirred for 3h at 0°C, and then filtered on a frit. The filtrate is washed with water. After drying on MgSO<sub>4</sub>, the organic phase is concentrated. 12.48g of oil are obtained (quantitative yield). TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 95-5, Rf=0.60. 1.34 g (4.78mmol) of this oil is placed in the presence of 0.50 mL (2.48 mmol) of 2-chloro-5-fluorophenol and of 3g (4.78mmol) of cesium carbonate in 5mL of DMF. This solution is stirred for 24h at 70°C. After concentration of the reaction medium, the obtained residue is purified by flash chromatography (petroleum ether-AcOEt, gradient 100-0 to 85-15 over 60 min). 0.84g of clear oil is obtained (yield: 53%). TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, Rf=0.72. This oil is placed in 5mL of CH<sub>2</sub>Cl<sub>2</sub> in the presence of 0.76 mL (10.2mmol) of TFA. The solution is stirred for 6h at room temperature. After concentration of the reaction medium, the residue is taken up with AcOEt, washed with a soda (1N) solution and then with NaCl saturated water. After drying the organic phase on MgSO<sub>4</sub>, 0.4g of intermediate 8b is obtained as a clear oil (yield 69%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 95-5, Rf=0.19.



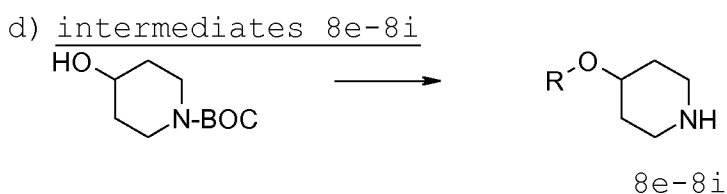
The synthesis of the intermediates 8c and 8d is achieved according to the operating procedure described for synthesis of 8a by using various phenols R-OH.

Table 7: intermediates 8c-8d

ROH	Yield	TLC	State	intermediates 8c-8d
	65%	CH <sub>2</sub> Cl <sub>2</sub> -MeOH-NH <sub>4</sub> OH: 90-9-1 Rf=0.24	solid	8c: 4-(2-trifluoromethyl-phenoxy)-piperidine
	71%	CH <sub>2</sub> Cl <sub>2</sub> -MeOH-NH <sub>4</sub> OH: 90-9-1 Rf=0.22	solid	8d: 4-(4-fluoro-phenoxy)-piperidine

TLC: silica gel 60 F 254 Merck.

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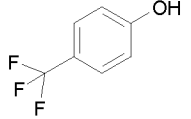
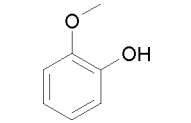


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The synthesis of the intermediates 8e-8i is achieved according to the operating procedure described for the synthesis of 8b by using various phenols R-OH.

Table 8: intermediates 8e-8i

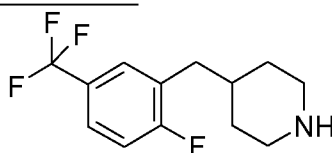
ROH	Yield	TLC	State	Intermediates 8e-8i
	48%	CH <sub>2</sub> Cl <sub>2</sub> -AcOEt: 90-10 Rf=0.14	oil	8e: 4-(2-fluoro-phenoxy)-piperidine
	38%	CH <sub>2</sub> Cl <sub>2</sub> -AcOEt: 90-10 Rf=0.18	oil	8f: 4-(2-chloro-5-trifluoromethyl-phenoxy)-piperidine
	30%	CH <sub>2</sub> Cl <sub>2</sub> -MeOH: 95-5 Rf=0.17	oil	8g: 4-o-Tolyloxy-piperidine

	43%	CH <sub>2</sub> Cl <sub>2</sub> -MeOH: 95-5 Rf=0.34	oil	8h: 4-(4-trifluoromethylphenoxy)-piperidine
	32%	CH <sub>2</sub> Cl <sub>2</sub> -MeOH: 95-5 Rf=0.11	oil	8i: 4-(2-methoxyphenoxy)-piperidine

TLC: silica gel 60 F 254 Merck.

Intermediates 9:

a) 4-(2-fluoro-5-trifluoromethyl-benzyl)-piperidine (9a)



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0.8g (3.1mmol) of 2-bromomethyl-1-fluoro-4-trifluoromethylbenzene is placed in the presence of 0.9mL (5.36mmol) of triethylphosphite at 150°C for 24h. The reaction medium is purified by flash chromatography on silica (CH<sub>2</sub>Cl<sub>2</sub>-MeOH, gradient 100-0 to 95-5 over 45 min). 0.96 g of a clear oil is obtained (quantitative yield). TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 95-5, Rf=0.75. This oil is placed in the presence of few drops of 15-crown-5 crown ether in 10mL of THF at 0°C and 0.15g (3.98mmol) of NaH (60% in paraffin) are added. The reaction medium is stirred for 30min at 0°C and then 0.55mL (3.06mmol) of benzyl-piperidin-4-one are added at 0°C. The mixture is then stirred at room temperature for 24h, and then poured into water at 0°C and extracted with AcOEt. The organic phase is washed with a saturated NaHCO<sub>3</sub> solution, and then with a saturated NaCl solution. After drying on MgSO<sub>4</sub>, the organic phases are dry concentrated. The obtained residue is purified by flash chromatography on silica (petroleum ether-AcOEt, gradient 100-0 to 90-10 over 45min). 0.64g of a clear oil is obtained (yield 60%). TLC silica gel 60 F 254 Merck petroleum ether-AcOEt: 90-10, Rf: 0,32. This oil is placed in 5mL of MeOH in the presence of 0.12g of palladium on

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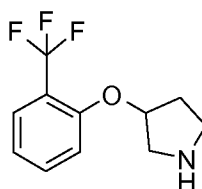
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then the residue is taken up with 2mL of 1,2-dichloroethane. This solution is added to a mixture of 0.90g (6.72 mmol) of  $\text{AlCl}_3$  and 1.29mL (13.73 mmol) of fluorobenzene in 1mL of 1,2-dichloroethane. The reaction  
5 medium is heated to  $80^\circ\text{C}$  for 3h. After the solution has returned to room temperature, it is poured on ice water, then the medium is extracted with dichloromethane. After drying on  $\text{MgSO}_4$ , the organic phases are dry concentrated, the obtained residue is purified by flash chromatography on  
10 silica ( $\text{CH}_2\text{Cl}_2$ -MeOH: 95-5). 0.44 g of an oil are isolated (60%). *TLC silica gel 60 F 254 Merck,  $\text{CH}_2\text{Cl}_2$ -MeOH: 95-5,  $R_f=0.38$ .* The obtained oil is placed in 6mL of 6N hydrochloric acid and the mixture is heated to  $100^\circ\text{C}$  for 18h. The medium is neutralized by adding a concentrated  
15 soda solution and extracted with ethyl acetate. After drying on  $\text{MgSO}_4$ , the organic phases are dry concentrated. 0.23 g of intermediate 10 are obtained as an oil (62%). *TLC silica gel 60 F 254 Merck,  $\text{CH}_2\text{Cl}_2$ -MeOH: 95-5,  $R_f=0.13$ .*

Intermediates 11

20 a) 3-(2-trifluoromethyl-phenoxy)-pyrrolidine  
(11a)

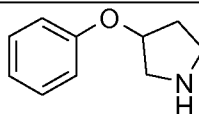


0.67mL (4mmol) of 1-benzyl-pyrrolidin-3-ol are placed in the presence of 0.71g (4.4mmol) of 2-trifluoromethyl-phenol  
25 and of 1.26 g (4.8mmol) of triphenylphosphine in 10 mL of THF. At  $0^\circ\text{C}$ , 2mL (4.8mmol) of DEAD (a 40% solution in toluene), are added dropwise. The reaction medium is heated for 6h at  $65^\circ\text{C}$ , and then stirred for 16h at room temperature. After concentration, the obtained residue is  
30 taken up with ether, washed with a soda (1N) solution and then with a NaCl solution. After drying on  $\text{MgSO}_4$ , the organic phases are dry concentrated, and then the residue

is taken up with a petroleum ether-Et<sub>2</sub>O 65-35 mixture for removing triphenylphosphine oxide. After filtration, the filtrate is concentrated, the obtained residue is purified by flash chromatography on silica (petroleum ether-Et<sub>2</sub>O, gradient 100-0 to 60-40 over 45 min). 1.06 g of clear oil are obtained (yield 82%). *TLC silica gel 60 F 254 Merck, petroleum ether-Et<sub>2</sub>O 65-35, R<sub>f</sub>=0.18.* This oil is placed in 10mL of a ethanol/THF 50/50 mixture in the presence of palladium on charcoal and under a pressure of 5bars of hydrogen at room temperature for 18h. The reaction medium is filtered on celite, the filtrate is dry concentrated. The obtained residue is purified by flash chromatography on silica (CH<sub>2</sub>Cl<sub>2</sub>-MeOH-NH<sub>4</sub>OH, 90-9-1). 0.51 g of intermediate 11a are obtained as a clear oil (yield 83%).

15 *TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10, R<sub>f</sub>=0.13.*

b) 3-phenoxy-pyrrolidine (11b)

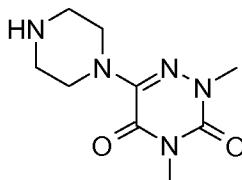


The synthesis of intermediate 11b is achieved from phenol according to the operating procedure described for the synthesis of 11a (solid, yield 24%).

20 *TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 90-10, R<sub>f</sub>=0.21.*

Intermediates 12

a) 2,4-dimethyl-6-piperazin-1-yl-2H-[1,2,4]triazine-3,5-dione (12a)



4.75g (55.15mmol) of piperazine are placed in the presence of 4.05g (18.4mmol) of intermediate 1b in toluene at room temperature for 30min. 2.8mL (20.1mmol) of triethylamine are added and the mixture is heated for 18h at 110°C. After concentration of the reaction medium, the obtained residue

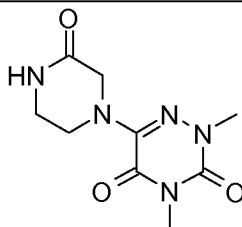
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is taken up with dichloromethane and washed with water. After drying on  $MgSO_4$ , the organic phase is dry concentrated. The obtained residue is purified by flash chromatography ( $CH_2Cl_2$ -MeOH: 60-40). 3.3g of intermediate 5 12a is obtained as a white powder (yield: 79%).

TLC silica gel 60 F 254 Merck,  $CH_2Cl_2$ -MeOH: 50-50,  $R_f=0.4$ .

b) 2,4-dimethyl-6-(3-oxo-piperazin-1-yl)-2H-[1,2,4]triazine-3,5-dione (12b)

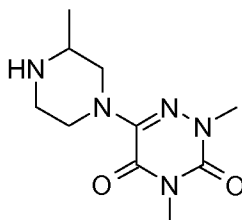


10 The synthesis of the intermediate 12b is achieved from piperazin-2-one according to the operating procedure described in the synthesis of 12a, in n-butanol at  $120^\circ C$  for 24h (solid, yield 55%).

TLC silica gel 60 F 254 Merck,  $CH_2Cl_2$ -MeOH: 90-10,  $R_f=0.44$ .

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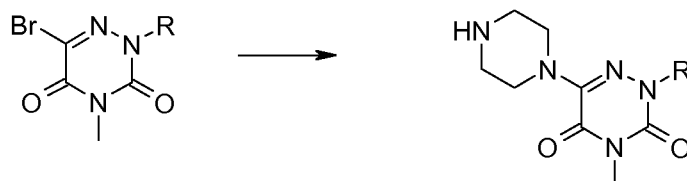
c) 2,4-dimethyl-6-(3-methyl-piperazin-1-yl)-2H-[1,2,4]triazine-3,5-dione (12c)



20 The synthesis of the intermediate 12c is achieved from 2-methyl-piperazine according to the operating procedure described for the synthesis of 12a (solid, yield: 58%).

TLC silica gel 60 F 254 Merck,  $CH_2Cl_2$ -MeOH: 90-10,  $R_f=0.19$ .

d) Intermediates 12d-12f



R= (CH <sub>2</sub> ) <sub>3</sub> CF <sub>3</sub>	4a	12d
R= (CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	4c	12e
R= (CH <sub>2</sub> ) <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	4g	12f

The synthesis of the intermediates 12d-12f is achieved from the intermediates 4a, 4c and 4g respectively according to the operating procedure described for the synthesis of 12a.

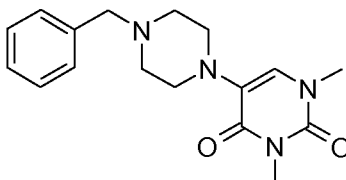
Table 9: intermediates 12d-12f

Starting synthons	Yield	TLC	State	Intermediates 12d-12f
4a	64%	CH <sub>2</sub> Cl <sub>2</sub> -MeOH: 90-10 Rf=0.28	solid	12d: 4-methyl-6-piperazin-1-yl-2-(4,4,4-trifluoro-butyl)-2H-[1,2,4]triazine-3,5-dione
4c	88%	CH <sub>2</sub> Cl <sub>2</sub> -MeOH: 90-10 Rf=0.18	solid	12e: 2-butyl-4-methyl-6-piperazin-1-yl-2H[1,2,4]triazine-3,5-dione
4g	53%	CH <sub>2</sub> Cl <sub>2</sub> -MeOH: 90-10 Rf=0.27	oil	12f: 4-methyl-2-(3-methyl-butyl)-6-piperazin-1-yl-2H[1,2,4]triazine-3,5-dione

TLC: silica gel 60 F 254 Merck

## 10 Intermediates 13

### a) 5-(4-benzyl-piperazin-1-yl)-1,3-dimethyl-1H-pyrimidine-2,4-dione (13a)

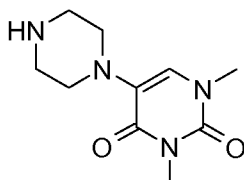


9.6g (33.53mmol) of 5-(4-benzyl-piperazin-1-yl)-1H-pyrimidine-2,4-dione are placed at 0°C in 10mL of dimethylformamide. 2.95g (73.56mmol) of sodium hydride (at 60% in paraffin) are added portion wise. The mixture is stirred for 40min at 0°C. 5mL (80.5mmol) of methyl iodide are added, the medium is stirred at room temperature for 7h. After concentration of the reaction medium, the obtained residue is taken up with AcOEt and washed with water. After drying on MgSO<sub>4</sub>, the organic phase is concentrated. The obtained residue is triturated with ether, and then a precipitate is isolated by filtration. 4g

of intermediate 13a are obtained as a beige powder (yield: 38%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH-NH<sub>4</sub>OH: 90-9-1, R<sub>f</sub>=0.64.

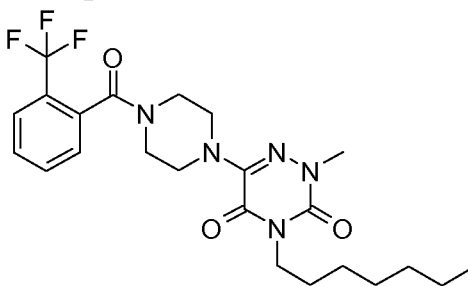
5            b) 1,3-dimethyl-5-piperazin-1-yl-1H-pyrimidine-2,4-dione (13b)



2.6g (8.26mmol) of compound 13a are placed in the presence of 1.3g of palladium and of 130mL of formic acid in 300mL of acetic acid at room temperature for 4h. The mixture is heated to 100°C° for 2h30min. After neutralization with a 10% soda solution, the reaction medium is extracted with CHCl<sub>3</sub>. The organic phase is washed with water and then with a saturated NaCl solution. After drying on MgSO<sub>4</sub>, the organic phase is concentrated. The obtained residue is purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>-MeOH-NH<sub>4</sub>OH, gradient 90-10-0 to 90-9-1 over 30min). 1.05g of intermediate 13b is obtained as a beige solid (yield: 56%). TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH-NH<sub>4</sub>OH: 90-9-1, R<sub>f</sub>=0.07.

EXAMPLES

Example 1: 4-heptyl-2-methyl-6-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (1)



25 The compound 1 is prepared according to the synthesis method 1: 0.33 g (1.12mmol) of derivative 6a and 0.41g (1.35mmol) of the triazine 5b are placed in 10mL of

butanol-1 in the presence of 0.55mL (3.93mmol) of  $\text{NEt}_3$ . This mixture is stirred at  $120^\circ\text{C}$  for 24 h. After dry concentration of the reaction medium, the obtained residue is taken up with AcOEt and washed with water and with an

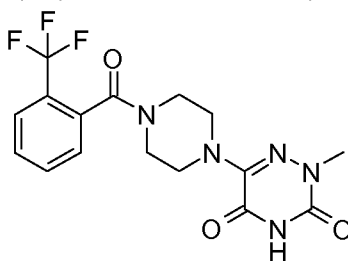
5 NaCl saturated solution. After drying on  $\text{MgSO}_4$ , the organic phase is concentrated. The obtained residue is purified by flash chromatography on silica (petroleum ether-AcOEt: 60-40). 0.53g of a clear oil are isolated (yield: 98%).

TLC silica gel 60 F 254 Merck, petroleum ether-AcOEt: 50-10  
50,  $R_f=0.43$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) ppm: 0.87 (t, 3H,  $J=6.57\text{Hz}$ ) 1.21-1.38 (m, 8H), 1.57-1.66 (m, 2H), 3.23-3.34 (m, 4H), 3.40-3.47 (m, 1H), 3.46-3.57 (m, 4H), 3.82-3.95 (m, 3H), 3.98-4.05 (m, 1H), 7.35 (d, 1H,  $J=7.83\text{Hz}$ ), 7.54 (t, 1H,  $J=8.08\text{Hz}$ ) 7.62  
15 (t, 1H,  $J=7.07\text{Hz}$ ), 7.72 (d, 1H,  $J=7.33\text{Hz}$ ).

MS (+ESI) m/z 482 (MH+)

Example 2: 2-methyl-6-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (2)



20

The compound 2 (yellow powder) is prepared from the triazine 2e and from the intermediate 6a according to the synthesis method 1 in toluene (yield: 25%).

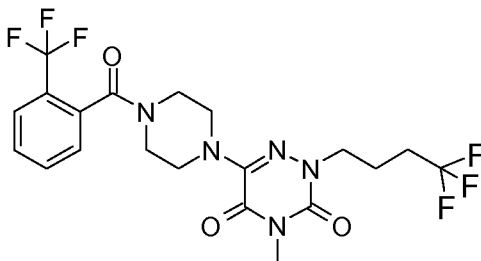
TLC silica gel 60 F 254 Merck, petroleum ether-AcOEt: 80-25  
20,  $R_f=0.2$ .

MP=  $146^\circ\text{C}$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) ppm: 3.24-3.42 (m, 4H), 3.42-3.52 (m, 4H), 3.52-3.61 (m, 1H), 3.80-3.89 (m, 1H), 4.06-3.97 (m, 1H), 7.35 (d, 1H,  $J=7.32\text{Hz}$ ), 7,54 (t, 1H,  $J=7.57\text{Hz}$ ) 7.61 (t, 1H,  
30  $J=7.57\text{Hz}$ ), 7.72 (d, 1H,  $J=7.83\text{Hz}$ ), 8.58 (s, 1H).

MS (+ESI) m/z 384 (MH+)

Example 3: 4-methyl-2-(4,4,4-trifluoro-butyl)-6-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (3)

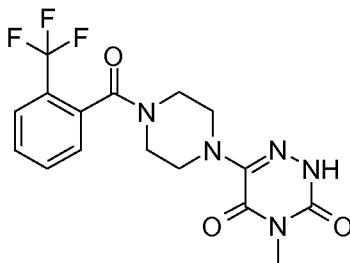


5 The compound 3 (oil) is prepared from the triazine 4a and from the intermediate 6a according to the synthesis method 1 in n-butanol (yield: 19%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.28.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.95-2.05 (m, 2H), 2.08-2.22, (m, 2H),  
 10 3.26-3.32 (m, 4H), 3.35 (s, 3H), 3.41-3.50 (m, 1H), 3.50-3.58 (m, 1H), 3.82-3.90 (m, 1H), 3.95 (t, 2H, J=6.82Hz), 3.98-4.08 (m, 1H), 7.35 (d, 1H, J=7.83Hz), 7.55 (t, 1H, J=7.83Hz), 7.62 (t, 1H, J=7.83Hz), 7.73 (d, 1H, J=7.32Hz).  
 MS (+APCI) m/z 494 (MH<sup>+</sup>)

15 Example 4: 4-methyl-6-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (4)



The compound 4 (solid) is prepared from the triazine 2a and the intermediate 6a according to the synthesis method 1 in  
 20 toluene (yield: 27%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 70-30, R<sub>f</sub>=0.26.

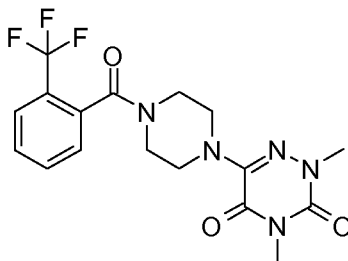
MP= 235°C

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 2.28-3.34 (m, 4H), 3.34 (s, 3H), 3.39-  
 25 3.48 (m, 1H), 3.48-3.57 (m, 1H), 3.80-3.91 (m, 1H), 3.96-4.07 (m, 1H), 7.35 (d, 1H, J=7.58Hz), 7.54 (t, 1H,

J=7.83Hz) 7.62 (t, 1H, J=7.58Hz), 7.72 (d, 1H, J=7.58Hz), 8.77 (s, 1H).

MS (+ESI) m/z 384 (MH<sup>+</sup>)

Example 5: 2,4-dimethyl-6-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (5)



The compound 5 (solid) is prepared from the triazine 1b and the intermediate 6a according to the synthesis method 1 in toluene (yield: 55%).

10 TLC silica gel 60 F 254 Merck, AcOEt: 100, R<sub>f</sub>=0.37.

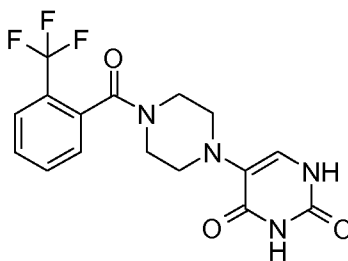
MP= 76°C

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 3.26-3.33 (m, 4H), 3.34 (s, 3H), 3.40-3.49 (m, 1H), 3.49-3.58 (m, 3H), 3.81-3.90 (m, 1H), 3.97-4.06 (m, 1H), 7.35 (d, 1H, J=7.07Hz), 7.54 (t, 1H, J=7.83Hz) 7.61 (t, 1H, J=7.83Hz), 7.73 (d, 1H, J=8.08Hz).

15

MS (+ESI) m/z 398 (MH<sup>+</sup>)

Example 6: 5-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-1H-pyrimidine-2,4-dione (6)



20 The compound 6 (solid) is prepared from 5-bromo-1H-pyrimidine-2,4-dione and from the intermediate 6a according to the synthesis method 1 in dimethylformamide (yield: 47%).

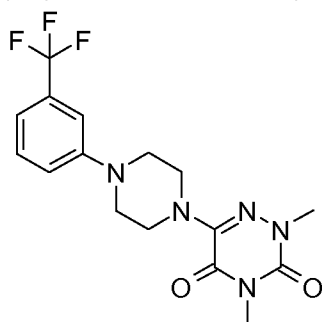
TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 90-10, R<sub>f</sub>=0.3.

25 MP= 285°C

<sup>1</sup>H NMR (DMSO) ppm: 2.59-2.69 (m, 1H), 2.72-2.87 (m, 2H), 2.88-2.98 (m, 1H), 3.05-3.16 (m, 1H), 3.16-3.25 (m, 1H), 3.63-3.79 (m, 2H), 6.79 (s, 1H), 7.49 (d, 1H, J=7.07Hz), 7.66 (t, 1H, J=7.83Hz) 7.76 (t, 1H, J=7.58Hz), 7.82 (d, 1H, J=7.58Hz), 10.53 (s, 1H), 11.10 (s, 1H).

MS (+APCI) m/z 369 (MH<sup>+</sup>)

Example 7: 2,4-dimethyl-6-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (7)



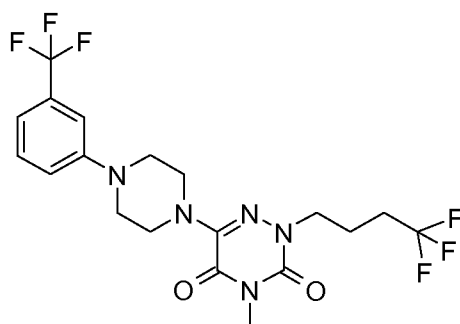
10 The compound 7 (solid) is prepared from the triazine 1b and from 1-(3-trifluoromethyl-phenyl)-piperazine according to the synthesis method 1 in n-butanol (yield: 63%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 95-5, R<sub>f</sub>=0.78.

MP= 163°C

15 MS (+ESI) m/z 370 (MH<sup>+</sup>)

Example 8: 4-methyl-2-(4,4,4-trifluoro-butyl)-6-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (8)

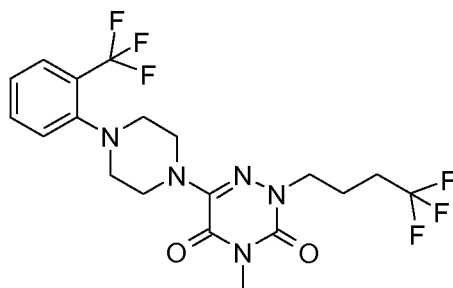


20 The compound 8 (oil) is prepared from the triazine 4a and from 1-(3-trifluoromethyl-phenyl)-piperazine according to the synthesis method 1 in n-butanol (yield: 76%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 90-10, Rf=0.59.

MS (+ESI) m/z 466 (MH<sup>+</sup>)

Example 9: 4-methyl-2-(4,4,4-trifluoro-butyl)-6-[4-(2-trifluoromethyl-phenyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (9)

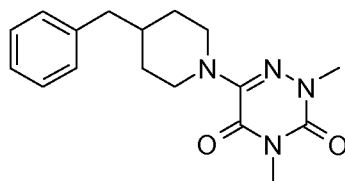


The compound 9 (solid) is prepared from the triazine 4a and from 1-(2-trifluoromethyl-phenyl)-piperazine according to the synthesis method 1 in n-butanol (yield: 82%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 90-10, Rf=0.54.

MS (+ESI) m/z 466 (MH<sup>+</sup>)

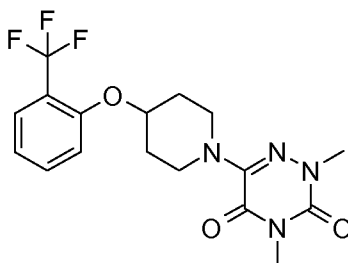
Example 10: 6-(4-benzyl-piperidin-1-yl)-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione (10)



The compound 10 (oil) is prepared from the triazine 1b and from 4-benzyl-piperidine according to the synthesis method 1 in n-butanol (yield: 93%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, Rf=0.28.  
MS (+ESI) m/z 315 (MH<sup>+</sup>)

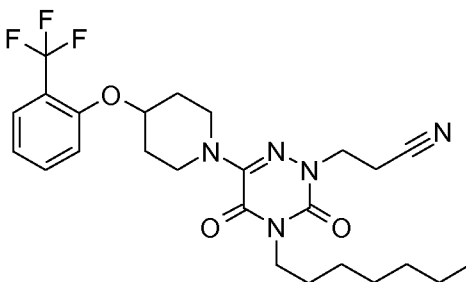
Example 11: 2,4-dimethyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione (11)



The compound 11 (oil) is prepared from the triazine 1b and from the intermediate 8c according to the synthesis method 1 in n-butanol (yield: 56%).

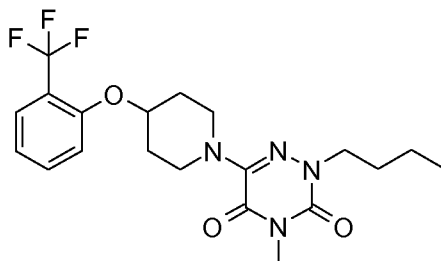
- 5 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.27.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.95-2.11 (m, 4H), 3.36 (s, 3H), 3.49-3.57 (m, 7H), 4.70 (m, 1H), 6.99 (t, 1H, J=7.07Hz) 7.00 (d, 1H, J=7.07Hz), 7.47 (t, 1H, J=8.08Hz), 7.58 (d, 1H, J=7.58Hz).
- 10 MS (+ESI) m/z 385 (MH<sup>+</sup>)

Example 12: 3-{4-heptyl-3,5-dioxo-6-[4-(2-trifluoromethylphenoxy)-piperidin-1-yl]-4,5-dihydro-3H-[1,2,4]triazin-2-yl}-propionitrile (12)



- 15 The compound 12 (oil) is prepared from the triazine 3c and from the intermediate 8c according to the synthesis method 1 in n-butanol (yield: 46%).  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 0.87 (t, 3H, J=6.31Hz), 1.24-1.36 (m, 8H), 1.58-1.67 (m, 2H), 1.97-2.10 (m, 4H), 2.80 (t, 2H, J=7.83Hz), 3.48-3.56 (m, 2H), 3.59-3.65 (m, 2H), 3.91 (t, 2H, J=7.07Hz), 4.18 (t, 2H, J=6.57Hz), 4.72 (m, 1H), 6.97-7.02 (m, 2H), 7.47 (t, 1H, J=7.83Hz), 7.58 (d, 1H, J=7.07Hz).
- 20 MS (+ESI) m/z 508 (MH<sup>+</sup>)

Example 13: 2-butyl-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione (13)

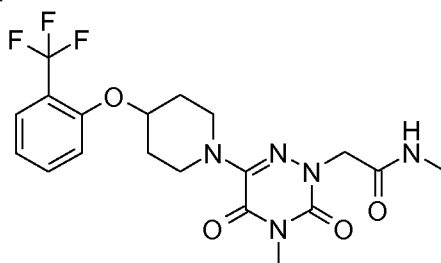


The compound 13 (oil) is prepared from the triazine 4c and  
5 from the intermediate 8c according to the synthesis method  
1 in n-butanol (yield: 44%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 0.95 (t, 3H, J=7.58Hz), 1.31-1.41 (m,  
2H), 1.66-1.75 (m, 2H), 1.96-2.10 (m, 4H), 3.35 (s, 3H),  
3.47-3.55 (m, 4H), 3.89 (t, 2H, J=7.58Hz), 4.70 (m, 1H),  
10 6.99 (t, 1H, J=7.58Hz), 7.00 (d, 1H, J=7.32Hz), 7.47 (t,  
1H, J=8.08Hz), 7.58 (d, 1H, J=7.32Hz).

MS (+ESI) m/z 427 (MH<sup>+</sup>)

Example 14: N-methyl-2-{4-methyl-3,5-dioxo-6-[4-(2-  
trifluoromethyl-phenoxy)-piperidin-1-yl]-4,5-dihydro-3H-  
15 [1,2,4]triazin-2-yl}-acetamide (14)

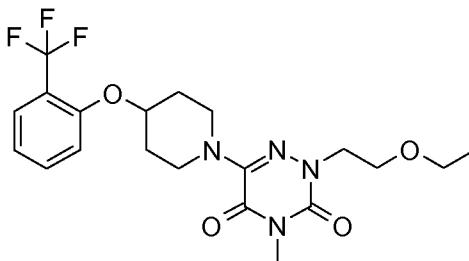


The compound 14 (oil) is prepared from the triazine 4d and  
from the intermediate 8c according to the synthesis method  
1 in n-butanol (yield: 52%).

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.94-2.09 (m, 4H), 2.85 (d, 3H,  
J=5.05Hz), 3.36 (s, 3H), 3.48-3.63 (m, 4H), 4.51 (s, 2H),  
4.70 (m, 1H), 5.90 (m, 1H), 6.99 (d, 1H, J=7.32Hz), 7.00  
(t, 1H, J=6.82Hz), 7.47 (t, 1H, J=7.83Hz), 7.58 (d, 1H,  
J=7.83Hz).

25 MS (+ESI) m/z 442 (MH<sup>+</sup>)

Example 15: 2-(2-ethoxy-ethyl)-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione (15)

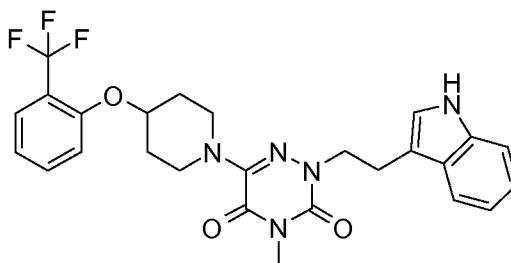


5 The compound 15 (oil) is prepared from the triazine 4e and from the intermediate 8c according to the synthesis method 1 in n-butanol (yield: 47%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.18 (t, 3H, J=7.07Hz), 1.95-2.10 (m, 4H), 3.35 (s, 3H), 3.47-3.58 (m, 6H), 3.74 (t, 2H, J=5.81Hz), 4.08 (t, 2H, J=5.81Hz), 4.71 (m, 1H), 6.99 (t, 1H, J=7.07Hz), 7.00 (d, 1H, J=7.83Hz), 7.47 (t, 1H, J=7.58Hz), 7.58 (d, 1H, J=7.07Hz).

MS (+ESI) m/z 443 (MH<sup>+</sup>)

Example 16: 2-[2-(1H-Indol-3-yl)-ethyl]-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione (16)

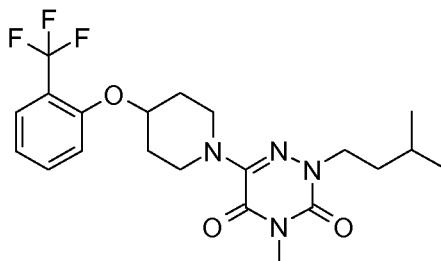


20 The compound 16 (oil) is prepared from the triazine 4f and from the intermediate 8c according to the synthesis method 1 in n-butanol (yield: 20%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.84-2.00 (m, 4H), 3.21 (t, 2H, J=7.32Hz), 3.34 (s, 3H), 3.36-3.46 (m, 4H), 4.22 (t, 2H, J=7.32Hz), 4.63 (m, 1H), 6.99 (d, 1H, J=8.34Hz), 7.00 (t, 1H, J=8.34Hz), 7.06 (s br, 1H), 7.10 (t, 3H, J=7.83Hz), 7.17 (t, 1H, J=7.32Hz), 7.34 (d, 1H, J=8.08Hz), 7.48 (t, 1H, J=7.83Hz), 7.57-7.65 (m, 2H), 7.99 (s br, 1H).

MS (+ESI) m/z 514 (MH<sup>+</sup>)

Example 17: 4-methyl-2-(3-methyl-butyl)-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione (17)

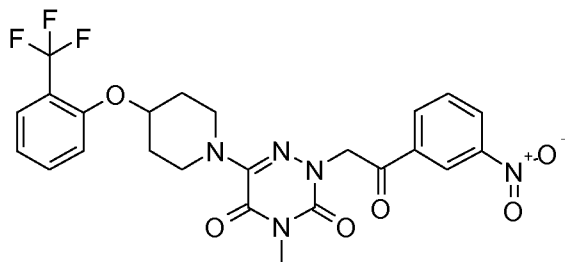


5

The compound 17 (oil) is prepared from the triazine 4g and from the intermediate 8c according to the synthesis method 1 in n-butanol (yield: 42%).

MS (+ESI) m/z 441 (MH<sup>+</sup>)

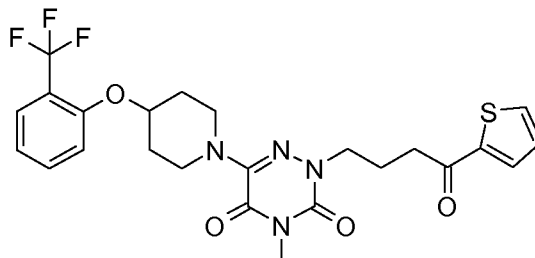
10 Example 18: 4-methyl-2-[2-(3-nitro-phenyl)-2-oxo-ethyl]-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione (18)



15 The compound 18 (oil) is prepared from the triazine 4h and of the intermediate 8c according to the synthesis method 1 in n-butanol (yield: 32%).

MS (+ESI) m/z 534 (MH<sup>+</sup>)

20 Example 19: 4-methyl-2-(4-oxo-4-thiophen-2-yl-butyl)-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione (19)

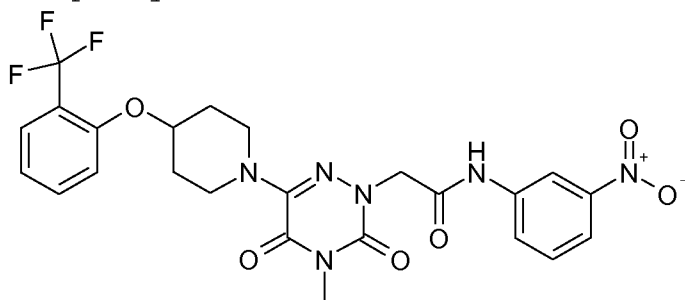


The compound 19 (oil) is prepared from the triazine 4i and from the intermediate 8c according to the synthesis method 1 in n-butanol (yield: 51%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.91-2.07 (m, 4H), 2.21 (m, 2H, J=6.82Hz), 3.00 (t, 2H, J=7.32Hz), 3.31 (s, 3H), 3.42-3.54 (m, 4H), 4.01 (t, 2H, J=6.31Hz), 4.67 (m, 1H), 6.98 (d, 1H, J=8.08Hz), 6.99 (t, 1H, J=7.59Hz), 7.11 (m, 1H), 7.47 (t, 1H, J=7.83Hz), 7.58 (d, 1H, J=7.83Hz), 7.61 (d, 1H, J=5.30Hz), 7.69 (m, 1H).

10 MS (+ESI) m/z 523 (MH<sup>+</sup>)

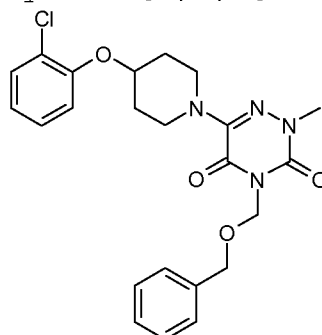
Example 20: 2-{4-methyl-3,5-dioxo-6-[4-(2-trifluoromethylphenoxy)-piperidin-1-yl]-4,5-dihydro-3H-[1,2,4]triazin-2-yl}-N-(3-nitro-phenyl)-acetamide (20)



15 The compound 20 (oil) is prepared from the triazine 4j and from the intermediate 8c according to the synthesis method 1 in n-butanol (yield: 67%).

MS (+ESI) m/z 549 (MH<sup>+</sup>)

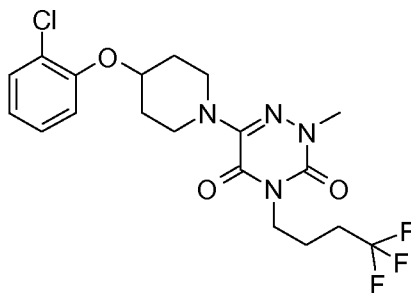
Example 21: 4-benzyloxymethyl-6-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-methyl-2H-[1,2,4]triazine-3,5-dione (21)



The compound 21 (oil) is prepared from the triazine 5c and from the intermediate 8a according to the synthesis method 1 in n-butanol (yield: 60%).

MS (+ESI) m/z 457 (MH+)

- 5 Example 22: 6-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-methyl-4-(4,4,4-trifluoro-butyl)-2H-[1,2,4]triazine-3,5-dione (22)

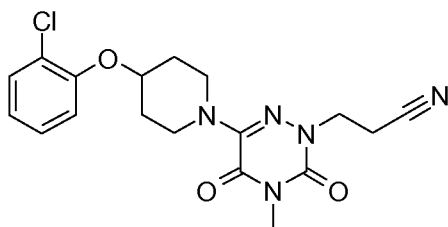


- 10 The compound 22 (oil) is prepared from the triazine 5a and from the intermediate 8a according to the synthesis method 1 in n-butanol (yield: 39%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.71.

MS (+APCI) m/z 447 (MH+)

- 15 Example 23: 3-{6-[4-(2-chloro-phenoxy)-piperidin-1-yl]-4-methyl-3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl}-propionitrile (23)



- 20 The compound 23 (oil) is prepared from the triazine 3a and from the intermediate 8a according to the synthesis method 1 in n-butanol (yield: 58%).

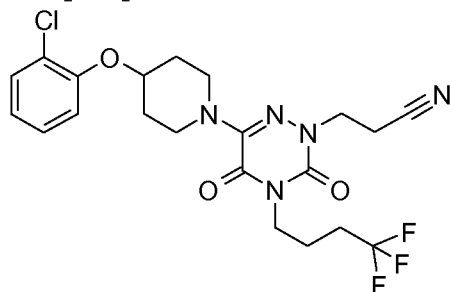
TLC silica gel 60 F 254 Merck, petroleum ether-AcOEt: 80-20, R<sub>f</sub>=0.36.

- 25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.94-2.11 (m, 4H), 2.81 (t, 2H, J=6.57Hz), 3.36 (s, 3H), 3.49-3.58 (m, 2H), 3.64-3.73 (m, 2H), 4.19 (t, 2H, J=7.07Hz), 4.56-4.63 (m, 1H), 6.92 (t,

1H, J=7.07Hz), 6.97 (d, 1H, J=8.33Hz), 7.20 (t, 1H, J=8.34Hz), 7.38 (d, 1H, J=7.32Hz),

MS (+APCI) m/z 390 (MH+)

5 Example 24: 3-[6-[4-(2-chloro-phenoxy)-piperidin-1-yl]-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-4,5-dihydro-3H-[1,2,4]triazin-2-yl]-propionitrile (24)

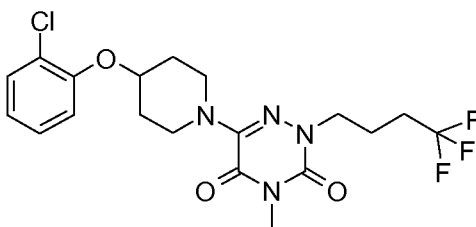


10 The compound 24 (oil) is prepared from the triazine 3b and from the intermediate 8a according to the synthesis method 1 in n-butanol (yield: 76%).

TLC silica gel 60 F 254 Merck, petroleum ether-AcOEt: 80-20, Rf=0.11.

MS (+APCI) m/z 486 (MH+)

15 Example 25: 6-[4-(2-chloro-phenoxy)-piperidin-1-yl]-4-methyl-2-(4,4,4-trifluoro-butyl)-2H-[1,2,4]triazine-3,5-dione (25)



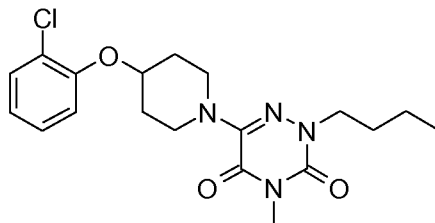
20 The compound 25 (oil) is prepared from the triazine 4a and the intermediate 8a according to the synthesis method 1 in n-butanol (yield: 77%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, Rf=0.69.

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.95-2.10 (m, 6H), 2.10-2.24 (m, 2H), 3.36 (s, 3H), 3.43-3.51 (m, 2H), 3.60-3.69 (m, 2H), 3.96 (t, 2H, J=7.32Hz), 4.56-4.62 (m, 1H), 6.92 (t, 1H, J=7.58Hz), 6.97 (d, 1H, J=8.33Hz), 7.20 (t, 1H, J=8.33Hz), 7.38 (d, 1H, 7.83Hz).

MS (+APCI) m/z 447 (MH<sup>+</sup>)

Example 26: 2-butyl-6-[4-(2-chloro-phenoxy)-piperidin-1-yl]-4-methyl-2H-[1,2,4]triazine-3,5-dione (26)

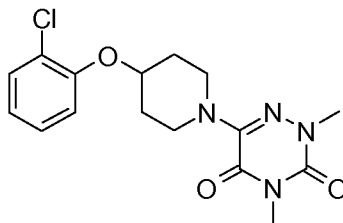


5 The compound 26 (oil) is prepared from the triazine 4c and from the intermediate 8a according to the synthesis method 1 in n-butanol (yield: 44%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.62.

MS (+APCI) m/z 393 (MH<sup>+</sup>)

10 Example 27: 6-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione (27)



The compound 27 (solid) is prepared from the triazine 1b and from the intermediate 8a according to the synthesis method 1 in n-butanol (yield: 60%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.51.

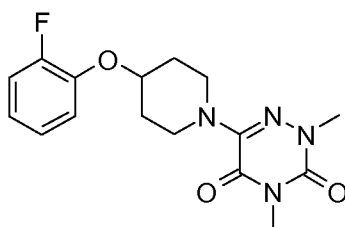
F= 109°C

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.96-2.08 (m, 4H), 3.35 (s, 3H), 3.35-3.46 (m, 2H), 3.54 (s, 3H), 3.61-3.64 (m, 2H), 4.58 (m, 1H), 6.92 (t, 1H, J=7.6Hz), 6.97 (d, 1H, J=8.2Hz), 7.2 (t, 1H, J=7.8Hz), 7.37 (d, 1H, J=7.88Hz).

MS (+ESI) m/z 351 (MH<sup>+</sup>)

Example 28: 6-[4-(2-fluoro-phenoxy)-piperidin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione (28)

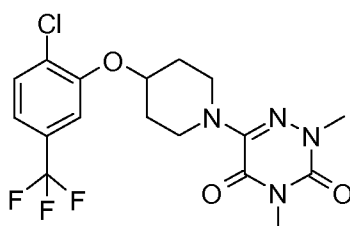
51



The compound 28 (oil) is prepared from the triazine 1b and from the intermediate 8e according to the synthesis method 1 in n-butanol (yield: 63%).

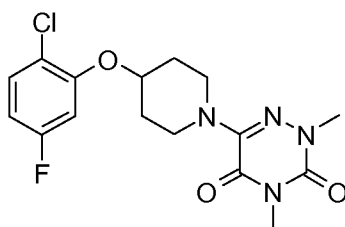
- 5 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.29.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.94-1.99 (m, 2H), 2.02-2.09 (m, 2H), 3.26-3.38 (m, 2H), 3.35 (s, 3H), 3.54 (s, 3H), 3.67-3.74 (m, 2H), 4.48 (m, 1H), 6.92-6.97 (m, 1H), 6.99-7.12 (m, 3H).
- 10 MS (+ESI) m/z 335 (MH<sup>+</sup>)

Example 29: 6-[4-(2-chloro-5-trifluoromethyl-phenoxy)-piperidin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione (29)



- 15 The compound 29 (solid) is prepared from the triazine 1b and from the intermediate 8f according to the synthesis method 1 in n-butanol (yield: 58%).  
 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.44.  
 MP= 160°C
- 20 <sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.98-2.03 (m, 2H), 2.05-2.12 (m, 2H), 3.36 (s, 3H), 3.43-3.51 (m, 2H), 3.54 (s, 3H), 3.58-3.65 (m, 2H), 4.65 (m, 1H), 7.16-7.19 (m, 2H), 7.49 (d, 1H, J=8.08Hz).
- MS (+ESI) m/z 419 (MH<sup>+</sup>)
- 25 Example 30: 6-[4-(2-chloro-5-fluoro-phenoxy)-piperidin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione (30)

52



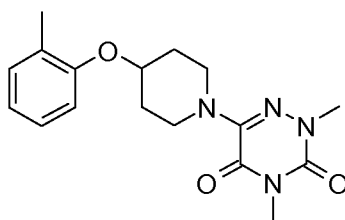
The compound 30 (solid) is prepared from the triazine 1b and from the intermediate 8b according to the synthesis method 1 in n-butanol (yield: 77%).

5 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.55.  
MP= 168°C

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.99-2.11 (m, 4H), 3.36 (s, 3H), 3.42-3.49 (m, 2H), 3.54 (s, 3H), 3.61-3.3,67 (m, 2H), 4.55 (m, 1H), 6.62-6.72 (m, 2H), 7.29-7.34 (m, 1H).

10 MS (+ESI) m/z 369(MH<sup>+</sup>)

Example 31: 2,4-dimethyl-6-(4-o-tolyloxy-piperidin-1-yl)-2H-[1,2,4]triazine-3,5-dione (31)



The compound 31 (solid) is prepared from the triazine 1b and from the intermediate 8g according to the synthesis method 1 in n-butanol (yield: 56%).

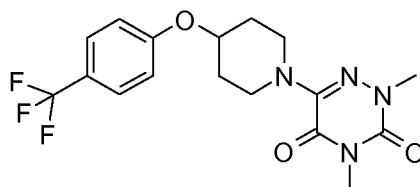
15 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.67.  
MP= 102°C

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.93-1.98 (m, 2H), 2.03-2.09 (m, 2H), 2.24 (s, 3H), 3.36 (s, 3H), 3.36-3.44 (m, 2H), 3.54 (s, 3H), 3.55-3.64 (m, 2H), 4.54 (m, 1H), 6.84-6.89 (m, 2H), 7.12-7.17 (m, 2H).

MS (+ESI) m/z 331(MH<sup>+</sup>)

25 Example 32: 2,4-dimethyl-6-[4-(4-trifluoromethyl-phenoxy)-piperidin-1-yl]2H-[1,2,4]triazine-3,5-dione (32)

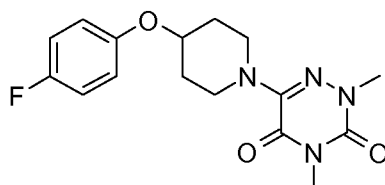
53



The compound 32 (oil) is prepared from the triazine 1b and from the intermediate 8h according to the synthesis method 1 in n-butanol (yield: 51%).

- 5 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.49.  
MS (+ESI) m/z 385 (MH<sup>+</sup>)

Example 33: 6-[4-(4-fluorophenoxy)-piperidin-1-yl]-2,4-dimethyl-1,2,4-triazine-3,5-dione (33)



- 10 The compound 33 (solid) is prepared from the triazine 1b and from the intermediate 8d according to the synthesis method 1 in n-butanol (yield: 35%).

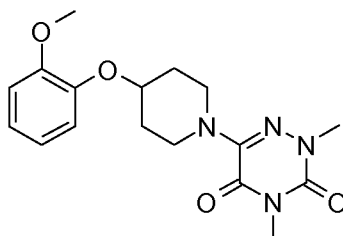
TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 90-10, R<sub>f</sub>=0.35.

- 15 MP= 70°C

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.83-1.94 (m, 2H), 1.99-2.09 (m, 2H), 3.26-3.34 (m, 2H), 3.36 (s, 3H), 3.54 (s, 3H), 3.63-3.73 (m, 2H), 4.37-4.44 (m, 1H), 6.83-6.90 (m, 2H), 6.98 (t, 2H, J=8.08Hz).

- 20 MS (+ESI) m/z 335 (MH<sup>+</sup>)

Example 34: 6-[4-(2-methoxyphenoxy)-piperidin-1-yl]-2,4-dimethyl-1,2,4-triazine-3,5-dione (34)



The compound 34 (solid) is prepared from the triazine 1b and from the intermediate 8i according to the synthesis method 1 in n-butanol (yield: 77%).

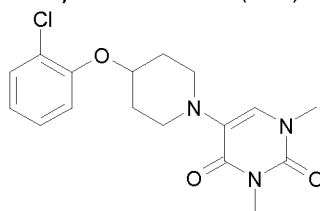
TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.45.

5 MP= 78°C

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.90-1.98 (m, 2H), 2.02-2.09 (m, 2H), 3.20-3.27 (m, 2H), 3.35 (s, 3H), 3.53 (s, 3H), 3.76-3.83 (m, 2H), 3.85 (s, 3H), 4.41-4.44 (m, 1H), 6.87-6.91 (m, 2H), 6.93-7.01 (m, 2H) .

10 MS (+ESI) m/z 347 (MH<sup>+</sup>)

Example 35: 5-[4-(2-chloro-phenoxy)-piperidin-1-yl]-1,3-dimethyl-1H-pyrimidine-2,4-dione (35)

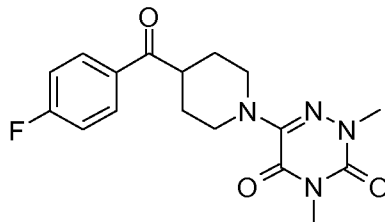


15 The compound 35 (oil) is prepared from the uracil 1c and from the intermediate 8a according to the synthesis method 1 in n-butanol (yield: 17%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH-NH<sub>4</sub>OH: 90-9-1, R<sub>f</sub>=0.25.

MS (+ESI) m/z 350 (MH<sup>+</sup>)

20 Example 36: 6-[4-(4-fluoro-benzoyl)-piperidin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione (36)



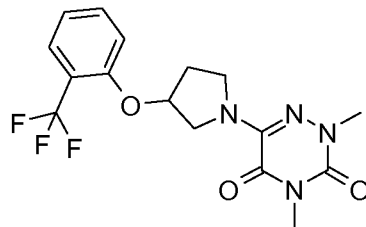
25 The compound 36 (solid) is prepared from the triazine 1b and from the intermediate 10 according to the synthesis method 1 in n-butanol (yield: 50%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 90-10, R<sub>f</sub>=0.78.

MP= 129°C

MS (+ESI) m/z 347 (MH<sup>+</sup>)

Example 37: 2,4-dimethyl-6-[3-(2-trifluoromethyl-phenoxy)-pyrrolidin-1-yl]-2H-[1,2,4]triazine-3,5-dione (37)

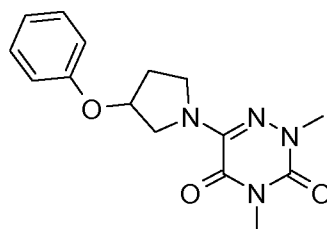


The compound 37 (solid) is prepared from the triazine 1b  
5 and from the intermediate 11a according to the synthesis  
method 1 in n-butanol (yield: 60%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 90-10, R<sub>f</sub>=0.4.  
MP= 84°C

MS (+ESI) m/z 371 (MH<sup>+</sup>)

10 Example 38: 2,4-dimethyl-6-(3-phenoxy-pyrrolidin-1-yl)-2H-[1,2,4]triazine-3,5-dione (38)

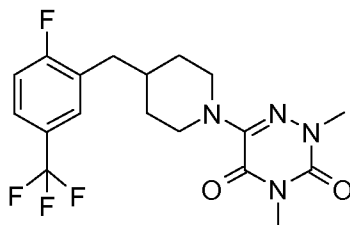


The compound 38 (solid) is prepared from the triazine 1b  
15 and from the intermediate 11b according to the synthesis  
method 1 in n-butanol (yield: 72%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 90-10, R<sub>f</sub>=0.4.  
MP= 80°C

MS (+ESI) m/z 303 (MH<sup>+</sup>)

20 Example 39: 6-[4-(2-fluoro-5-trifluoromethyl-benzyl)-piperidin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione (39)



The compound 39 (oil) is prepared from the triazine 1b and from the intermediate 9 according to the synthesis method 1 in n-butanol (yield: 78%).

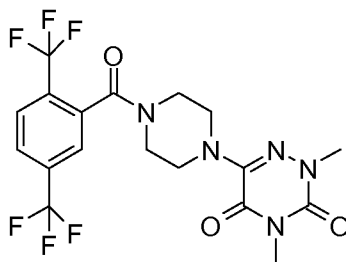
TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.46.

5 MP= 116°C

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.39-1.47 (m, 2H), 1.66-1,71 (m, 2H), 1.74-1.80 (m, 1H), 2.59-2.68 (m, 4H), 3.34 (s, 3H), 3.52 (s, 3H), 4.05 (d, 2H, J= 12.76Hz), 7.13 (t, 1H, J= 8.90Hz), 7.43 (d, 1H, J= 6.48Hz), 7.45-7.48 (m, 1H).

10 MS (+ESI) m/z 401(MH<sup>+</sup>)

Example 40: 6-[4-(2,5-Bis-trifluoromethyl-benzoyl)-piperazin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione (40)



15 The compound 40 is prepared according to the synthesis method 2: 0.16 g (0.72 mmol) of derivative 12a is placed in 1mL of dichloromethane in the presence of 0.15mL (1.08 mmol) of NEt<sub>3</sub> at 0°C. 0.2g (0.72 mmol) of 2,5-bis-trifluoromethyl-benzoyl chloride is added. This mixture is stirred for 15min at 0°C, and then for 1h at room temperature. The medium is taken up with water and extracted with CH<sub>2</sub>Cl<sub>2</sub>. After drying on MgSO<sub>4</sub>, the organic phase is concentrated. The obtained residue is purified by flash chromatography on silica (CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 90-10). 0.24g

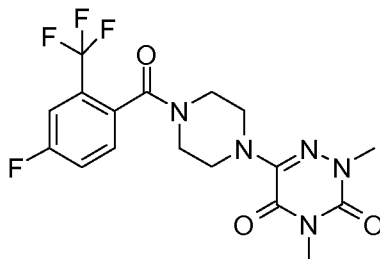
20 of white crystals are isolated (yield: 71%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.19.

MP= 90°C

MS (+ESI) m/z 466 (MH<sup>+</sup>)

Example 41: 6-[4-(4-fluoro-2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione (41)



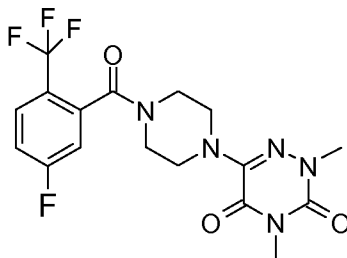
5 The compound 41 (solid) is prepared from 4-fluoro-2-trifluoromethyl-benzoyl chloride and from the intermediate 12a according to the synthesis method 2 under the operating conditions described for Example 40 (yield: 61%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.23.

10 MP= 128°C

MS (+ESI) m/z 416 (MH<sup>+</sup>)

Example 42: 6-[4-(5-fluoro-2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione (42)



15

The compound 42 (solid) is prepared from 5-fluoro-2-trifluoromethyl-benzoyl chloride and from the intermediate 12a according to the synthesis method 2 under the operating conditions described for Example 40 (yield: 86%).

20 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.10.

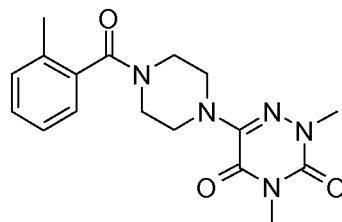
MP= 87°C

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 3.32 (s br, 4H), 3.35 (s, 3H), 3.41-3.49 (m, 1H), 3.49-3.57 (m, 4H), 3.81-3.89 (m, 1H), 3.95-4.02 (m, 1H), 7.07 (d, 1H, J=8.08Hz), 7.23 (t, 1H, J=8.34Hz), 7.74 (dd, 1H, J=8.59Hz and J=5.30Hz).

25

MS (+ESI) m/z 416 (MH<sup>+</sup>)

Example 43: 2,4-dimethyl-6-[4-(2-methyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (43)

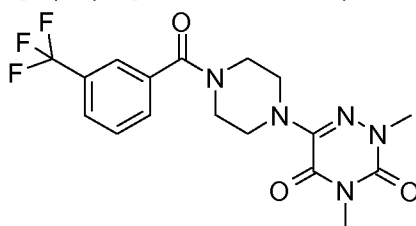


The compound 43 (solid) is prepared from 2-methyl-benzoyl chloride and from the intermediate 12a according to the synthesis method 2 under the operating conditions described for Example 40 (yield: 70%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 70-30, R<sub>f</sub>=0.30. MP= 60°C

10 MS (+ESI) m/z 344 (MH<sup>+</sup>)

Example 44: 2,4-dimethyl-6-[4-(3-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (44)

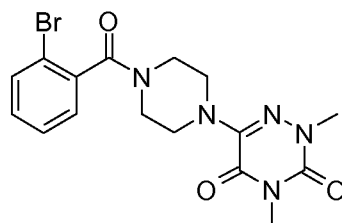


The compound 44 (solid) is prepared from 3-trifluoromethyl-benzoyl chloride and from the intermediate 12a according to the synthesis method 2 under the operating conditions described for Example 40 (yield: 75%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 70-30, R<sub>f</sub>=0.30. MP= 92°C

20 MS (+APCI) m/z 398 (MH<sup>+</sup>)

Example 45: 6-[4-(2-bromo-benzoyl)-piperazin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione (45)

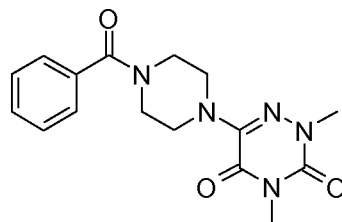


The compound 45 (solid) is prepared from 2-bromo-benzoyl chloride and from the intermediate 12a according to the synthesis method 2 under the operating conditions described for Example 40 (yield: 87%).

5 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 70-30, R<sub>f</sub>=0.30.  
MP= 119°C

MS (+APCI) m/z 408 (MH<sup>+</sup>)

Example 46: 6-(4-benzoyl-piperazin-1-yl)-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione (46)



10

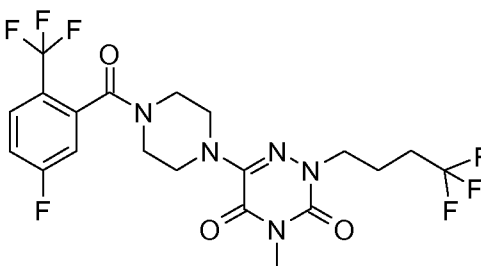
The compound 46 (solid) is prepared from benzoyl chloride and from the intermediate 12a according to the synthesis method 2 under the operating conditions described for Example 40 (quantitative yield).

15 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 70-30, R<sub>f</sub>=0.26.  
MP= 132°C

MS (+APCI) m/z 330 (MH<sup>+</sup>)

Example 47: 6-[4-(5-fluoro-2-trifluoromethyl-benzoyl)-piperazin-1-yl]-4-methyl-2-(4,4,4-trifluoro-butyl)-2H-

20 [1,2,4]triazine-3,5-dione (47)



The compound 47 (solid) is prepared from 5-fluoro-2-trifluoromethyl-benzoyl chloride and from the intermediate 12d according to the synthesis method 2 under the operating conditions described for Example 40 (yield: 91%).

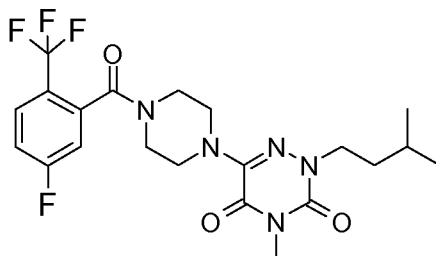
25

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 90-10, R<sub>f</sub>=0.78.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.95-2.07 (m, 2H), 2.07-2.22 (m, 2H), 3.28-3.34 (m, 4H), 3.34 (s, 3H), 3.43-3.59 (m, 2H), 3.81-3.91 (m, 1H), 3.91-4.03 (m, 3H), 7.07 (d, 1H, J=7.58Hz), 7.23 (t, 1H, J=8.83Hz), 7.74 (dd, 1H, J=8.84Hz and J=5.05Hz).

MS (+ESI) m/z 512 (MH<sup>+</sup>)

Example 48: 6-[4-(5-fluoro-2-trifluoromethyl-benzoyl)-piperazin-1-yl]-4-methyl-2-(3-methyl-butyl)-2H-[1,2,4]triazine-3,5-dione (48)



10

The compound 48 (oil) is prepared from 5-fluoro-2-trifluoromethyl-benzoyl chloride and from the intermediate 12f according to the synthesis method 2 under the operating conditions described for Example 40 (yield: 58%).

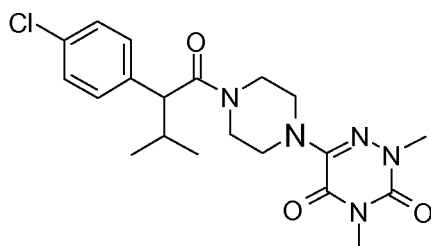
15 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 90-10, R<sub>f</sub>=0.28.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 0.93-0.97 (m, 6H), 1.56-1.63 (m, 3H), 3.29-3.33 (m, 4H), 3.35 (s, 3H), 3.43-3.56 (m, 2H), 3.82-3.93 (m, 3H), 4.02-3.93 (m, 1H), 7.07 (d, 1H, J=7.83 Hz), 7.23 (t, 1H, J=8.34Hz), 7.73 (dd, 1H, J=8.33Hz and J=5.05Hz)

20

MS (+ESI) m/z 472 (MH<sup>+</sup>)

Example 49: 6-{4-[2-(4-chloro-phenyl)-3-methyl-butyryl]-piperazin-1-yl}-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione (49)



25

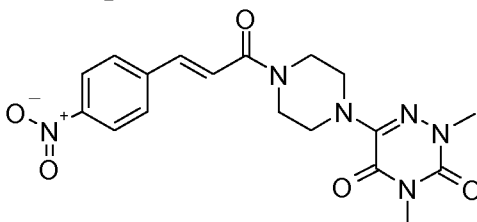
The compound 49 (solid) is prepared from 2-(4-chlorophenyl)-3-methyl-butryl chloride and from the intermediate 12a according to the synthesis method 2 under the operating conditions described for Example 40 (yield: 90%).

5 TLC silica gel 60 F 254 Merck, petroleum ether-AcOEt: 60-40, Rf=0.36.

MP= 58°C

MS (+APCI) m/z 420 (MH+)

Example 50: 2,4-dimethyl-6-{4-[(E)-3-(4-nitro-phenyl)-  
10 acryloyl]-piperazin-1-yl}-2H-[1,2,4]triazine-3,5-dione (50)



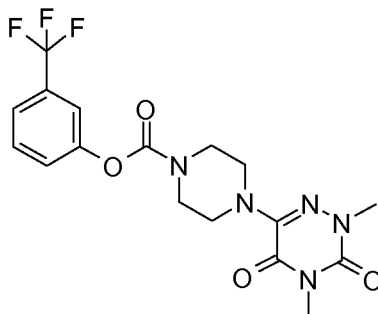
The compound 50 (solid) is prepared from (E)-3-(4-nitrophenyl)-acryloyl chloride and from the intermediate 12a according to the synthesis method 2 under the operating  
15 conditions described for Example 40 (yield: 8%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 80-20, Rf=0.19.

MP= 198°C

MS (+ESI) m/z 401 (MH+)

Example 51: 4-(2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-  
20 [1,2,4]triazin-6-yl)-piperazine-1-carboxylic acid 3-trifluoromethyl-phenyl ester (51)



The compound 51 (solid) is prepared from 3-trifluoromethyl-phenylchloroformate and from the intermediate 12a according

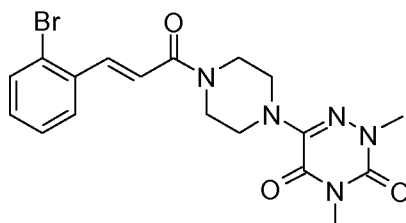
to the synthesis method 2 under the operating conditions described for Example 40 (yield: 27%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH-NH<sub>4</sub>OH: 90-9-1, R<sub>f</sub>=0.9.

5 MP= 93°C

MS (+ESI) m/z 414 (MH<sup>+</sup>)

Example 52: 6-{4-[(E)-3-(2-bromo-phenyl)-acryloyl]-piperazin-1-yl}-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione (52)



10

The compound 52 ( glassy solid) is prepared from the acrylic acid of (E)-3-(2-bromo-phenyl) converted into an acid chloride (SOCl<sub>2</sub>, toluene, 100°C, 3h), and from the intermediate 12a according to the synthesis method 2 under the operating conditions described for Example 40 (yield: 90%).

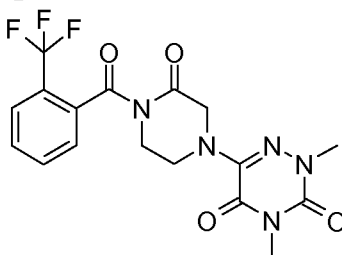
15

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 80-20, R<sub>f</sub>=0.7.

MS (+ESI) m/z 546 (MH<sup>+</sup>)

Example 53: 2,4-dimethyl-6-[3-oxo-4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (53)

20



The compound 53 (solid) is prepared from 2-trifluoromethyl-benzoyl chloride and from the intermediate 12b according to the synthesis method 2 under the operating conditions described for Example 40 (yield: 77%).

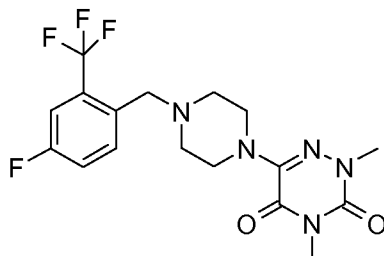
25

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 90-10, R<sub>f</sub>=0.83.

MP= 90°C

MS (+ESI) m/z 412 (MH+)

Example 54: 6-[4-(4-fluoro-2-trifluoromethyl-benzyl)-piperazin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione (54)



5

The compound 54 is prepared according to the synthesis method 2: 0.26g (1.17 mmol) of derivative 12a is placed in 3mL of toluene in the presence of 0.24mL (1.75mmol) of  $\text{NEt}_3$  and of 0.3g (1.17mmol) of 1-bromomethyl-4-fluoro-2-trifluoromethyl-benzene. This mixture is stirred 2h at 110°C. The medium is taken up with water and extracted with AcOEt. After drying on  $\text{MgSO}_4$ , the organic phase is dry concentrated. The obtained residue is purified by flash chromatography on silica ( $\text{CH}_2\text{Cl}_2$ -AcOEt: 95-5). 0.37g of a yellow oil are isolated (yield: 79%).

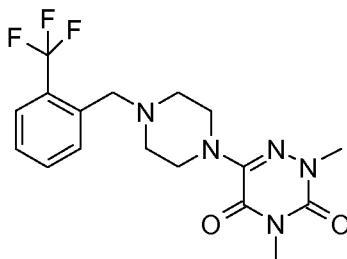
10

15

TLC silica gel 60 F 254 Merck,  $\text{CH}_2\text{Cl}_2$ -AcOEt: 95-5,  $R_f=0.29$ .

MS (+ESI) m/z 402 (MH+)

Example 55: 2,4-dimethyl-6-[4-(2-trifluoromethyl-benzyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (55)



20

The compound 55 (solid) is prepared from 1-bromomethyl-2-trifluoromethyl-benzene and from the intermediate 12a according to the synthesis method 2 under the operating conditions described for Example 54 (yield: 92%).

25

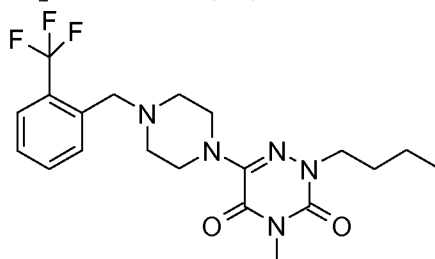
TLC silica gel 60 F 254 Merck, petroleum ether-AcOEt: 80-20,  $R_f=0.25$ .

MP= 92°C

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 2.56-2.64 (m, 4H), 3.34 (s, 3H), 3.39-3.47 (m, 4H), 3.53 (s, 3H), 3.70 (s, 2H), 7.34 (t, 1H, J=7.58Hz), 7.52 (t, 1H, J=7.83Hz) 7.63 (d, 1H, J=7.83Hz),  
5 7.80 (d, 1H, J=7.58Hz)

MS (+APCI) m/z 384 (MH<sup>+</sup>)

Example 56: 2-butyl-4-methyl-6-[4-(2-trifluoromethyl-benzyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (56)

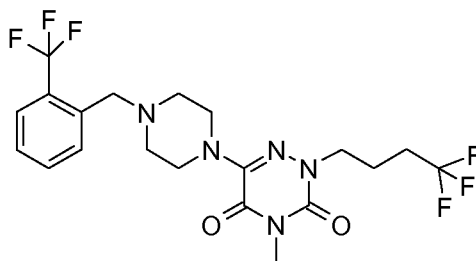


10 The compound 56 (oil) is prepared from 1-bromomethyl-2-trifluoromethyl-benzene and from the intermediate 12e according to the synthesis method 2 under the operating conditions described for Example 54 (yield: 84%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.36.

15 MS (+ESI) m/z 426 (MH<sup>+</sup>)

Example 57: 4-methyl-2-(4,4,4-trifluoro-butyl)-6-[4-(2-trifluoromethyl-benzyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (57)



20 The compound 57 (solid) is prepared from 1-bromomethyl-2-trifluoromethyl-benzene and from the intermediate 12d according to the synthesis method 2 under the operating conditions described for Example 54 (yield: 66%).

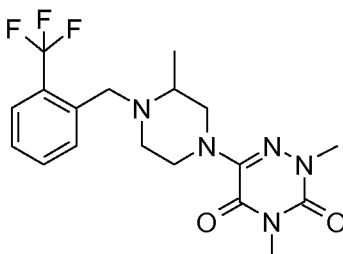
TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 90-10, R<sub>f</sub>=0.65.

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.95-2.06 (m, 2H), 2.09-2.23 (m, 2H), 2.56-2.63 (m, 4H), 3.34 (s, 3H), 3.42-3.48 (m, 4H), 3.70

(s, 2H), 3.95 (t, 2H, J=6.57Hz), 7.35 (t, 1H, J=7.58Hz), 7.52 (t, 1H, J=7.58Hz), 7.62 (d, 1H, J=7.58Hz), 7.79 (d, 1H, J=8.08Hz).

MS (+ESI) m/z 480 (MH+)

- 5 Example 58: 2,4-dimethyl-6-[3-methyl-4-(2-trifluoromethyl-benzyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (58)

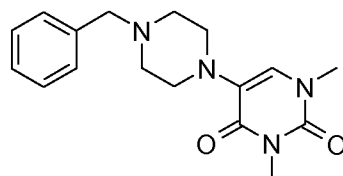


- The compound 58 (oil) is prepared from 1-bromomethyl-2-trifluoromethyl-benzene and from the intermediate 12c according to the synthesis method 2 under the operating conditions described for Example 54 (yield: 76%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.40.

MS (+ESI) m/z 398 (MH+)

- 15 Example 59: 5-(4-benzyl-piperazin-1-yl)-1,3-dimethyl-1H-pyrimidine-2,4-dione (59)



The compound 59 (solid) is prepared according to the synthesis method described in the intermediate paragraph 13a (yield: 54%).

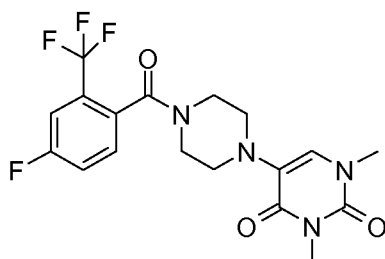
- 20 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH-NH<sub>4</sub>OH: 90-9-1, R<sub>f</sub>=0.64.

MP= 162°C

MS (+ESI) m/z 315 (MH+)

- 25 Example 60: 5-[4-(4-fluoro-2-trifluoromethyl-benzoyl)-piperazin-1-yl]-1,3-dimethyl-1H-pyrimidine-2,4-dione (60)

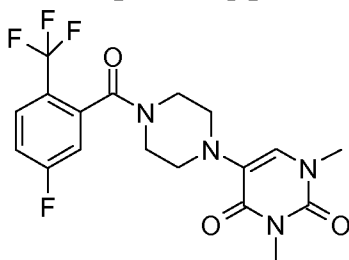
66



The compound 60 (solid) is prepared from 4-fluoro-2-trifluoromethyl-benzoyl chloride and from the intermediate 13b according to the synthesis method 2 under the operating conditions described for Example 40 (yield: 65%).  
 5  
 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH-NH<sub>4</sub>OH: 90-9-1, R<sub>f</sub>=0.57.

MS (+ESI) m/z 415 (MH<sup>+</sup>)

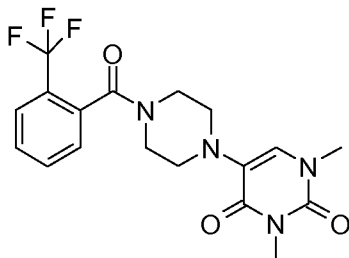
Example 61: 5-[4-(5-fluoro-2-trifluoromethyl-benzoyl)-  
 10 piperazin-1-yl]-1,3-dimethyl-1H-pyrimidine-2,4-dione (61)



The compound 61 (solid) is prepared from 5-fluoro-2-trifluoromethyl-benzoyl chloride and from the intermediate 13b according to the synthesis method 2 under the operating conditions described for Example 40 (yield: 80%).  
 15  
 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH-NH<sub>4</sub>OH: 90-9-1, R<sub>f</sub>=0.60.

MS (+ESI) m/z 415 (MH<sup>+</sup>)

Example 62: 1,3-dimethyl-5-[4-(2-trifluoromethyl-benzoyl)-  
 20 piperazin-1-yl]-1H-pyrimidine-2,4-dione (62)

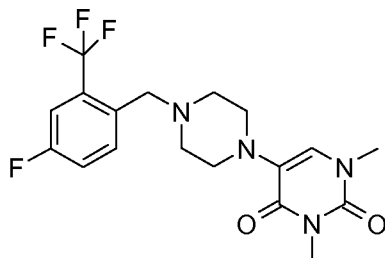


The compound 62 (solid) is prepared from 2-trifluoromethyl-benzoyl chloride and from the intermediate 13b according to the synthesis method 2 under the operating conditions described for Example 40 (yield: 59%).

5 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 98-2, R<sub>f</sub>=0.2.  
MP= 163°C

MS (+APCI) m/z 397 (MH<sup>+</sup>)

Example 63: 5-[4-(4-fluoro-2-trifluoromethyl-benzyl)-piperazin-1-yl]-1,3-dimethyl-1H-pyrimidine-2,4-dione (63)

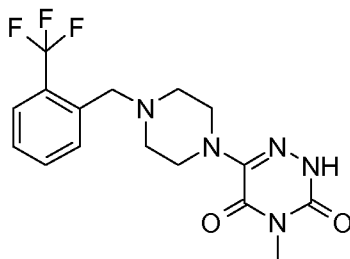


10

The compound 63 (oil) is prepared from 1-bromomethyl-4-fluoro-2-trifluoromethyl-benzene and from the intermediate 13b according to the synthesis method 2 under the operating conditions described for Example 54 (yield: 67%).

15 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 90-10, R<sub>f</sub>=0.60.  
MS (+ESI) m/z 401 (MH<sup>+</sup>)

Example 64: 4-methyl-6-[4-(2-trifluoromethyl-benzyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (64)



20 The compound 64 is prepared from the triazine 4b and from the intermediate 7a according to the synthesis method 1 in n-butanol. After deprotection of the nitrogen in position 2 (NH<sub>2</sub>NH<sub>2</sub>.H<sub>2</sub>O, EtOH, 78°C, 3h), the compound 64 is obtained as a solid (yield: 64%).

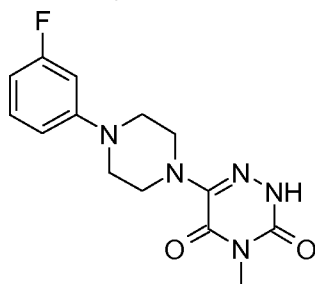
25 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 90-10, R<sub>f</sub>=0.15.

MP= 205°C

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 2.56-2.63 (m, 4H), 3.34 (s, 3H), 3.39-3.47 (m, 4H), 3.70 (s, 2H), 7.34 (t, 1H, J=7.58Hz), 7.52 (t, 1H, J=7.58Hz), 7.63 (d, 1H, J=7.58Hz), 7.79 (d, 1H, J=8.08Hz), 8.65 (s, 1H).

MS (+ESI) m/z 370 (MH<sup>+</sup>)

Example 65: 6-[4-(3-fluoro-phenyl)-piperazin-1-yl]-4-methyl-2H-[1,2,4]triazine-3,5-dione (65)

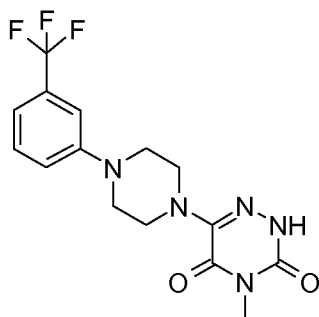


10 The compound 65 is prepared from the triazine 4b and from 1-(3-fluoro-phenyl)-piperazine according to the synthesis method 1 in n-butanol. After deprotection of the nitrogen in position 2 (NH<sub>2</sub>NH<sub>2</sub>.H<sub>2</sub>O, EtOH, 78°C, 3h), the compound 65 is obtained as a solid (yield: 17%).

15 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 90-10, R<sub>f</sub>=0.14.

MS (+ESI) m/z 306 (MH<sup>+</sup>)

Example 66: 4-methyl-6-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (66)



20

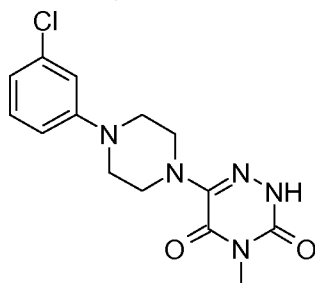
The compound 66 is prepared from the triazine 4b and from 1-(3-trifluoromethyl-phenyl)-piperazine according to the synthesis method 1 in n-butanol. After deprotection of the

nitrogen in position 2 ( $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ , EtOH,  $78^\circ\text{C}$ , 3h), the compound 66 is obtained as a solid (yield: 73%).

TLC silica gel 60 F 254 Merck,  $\text{CH}_2\text{Cl}_2$ -MeOH: 95-5,  $R_f=0.55$ .

MS (+ESI) m/z 356 (MH+)

- 5 Example 67: 6-[4-(3-chloro-phenyl)-piperazin-1-yl]-4-methyl-2H-[1,2,4]triazine-3,5-dione (67)



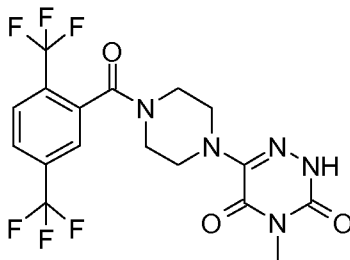
The compound 67 is prepared from the triazine 4b and from 1-(3-chloro-phenyl)-piperazine according to the synthesis method 1 in n-butanol. After deprotection of the nitrogen in position 2 ( $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ , EtOH,  $78^\circ\text{C}$ , 3h), the compound 67 is obtained as a solid (yield: 77%).

10

TLC silica gel 60 F 254 Merck,  $\text{CH}_2\text{Cl}_2$ -MeOH: 95-5,  $R_f=0.53$ .

MS (+ESI) m/z 322 (MH+)

- 15 Example 68: 6-[4-(2,5-Bis-trifluoromethyl-benzoyl)-piperazin-1-yl]-4-methyl-2H-[1,2,4]triazine-3,5-dione (68)



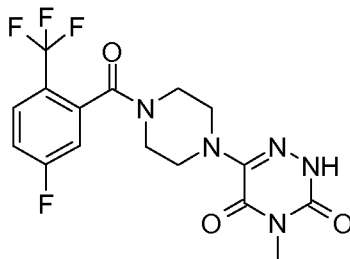
The compound 68 is prepared from the triazine 4b and from the intermediate 6a according to the synthesis method 1 in n-butanol. After deprotection of the nitrogen in position 2 ( $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ , EtOH,  $78^\circ\text{C}$ , 3h), the compound 68 is obtained as a solid (yield: 86%).

20

TLC silica gel 60 F 254 Merck,  $\text{CH}_2\text{Cl}_2$ -MeOH: 95-5,  $R_f=0.62$ .

MS (+ESI) m/z 452 (MH+)

Example 69: 6-[4-(5-fluoro-2-trifluoromethyl-benzoyl)-piperazin-1-yl]-4-methyl-2H-[1,2,4]triazine-3,5-dione (69)



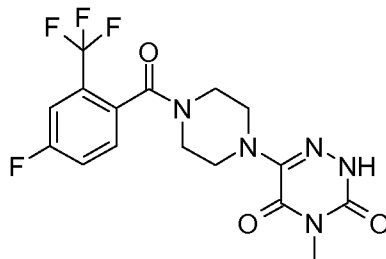
The compound 69 is prepared from the triazine 4b and from the intermediate 6c according to the synthesis method 1 in n-butanol. After deprotection of the nitrogen in position 2 (NH<sub>2</sub>NH<sub>2</sub>.H<sub>2</sub>O, EtOH, 78°C, 3h), the compound 69 is obtained as a solid (yield: 63%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 95-5, R<sub>f</sub>=0.17.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 3.30-3.32 (m, 4H), 3.34 (s, 3H), 3.40-3.48 (m, 1H), 3.47-3.55 (m, 1H), 3.81-3.88 (m, 1H), 3.95-4.02 (m, 1H), 7.07 (dd, 1H, J=2.05Hz and J=8.34Hz), 7.20-7.26 (m, 1H), 7.74 (dd, 1H, J=5.05Hz and J=8.84Hz), 8.62 (s, br, 1H).

MS (+ESI) m/z 402 (MH<sup>+</sup>)

Example 70: 6-[4-(4-fluoro-2-trifluoromethyl-benzoyl)-piperazin-1-yl]-4-methyl-2H-[1,2,4]triazine-3,5-dione (70)



The compound 70 is prepared from the triazine 4b and from the intermediate 6d according to the synthesis method 1 in n-butanol. After deprotection of the nitrogen in position 2 (NH<sub>2</sub>NH<sub>2</sub>.H<sub>2</sub>O, EtOH, 78°C, 3h), the compound 70 is obtained as a solid (yield: 66%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 95-5, R<sub>f</sub>=0.36.

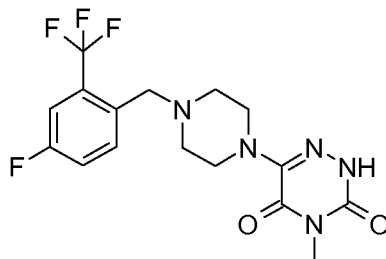
<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 3.28-3.31 (m, 4H), 3.34 (s, 3H), 3.38-3.46 (m, 1H), 3.49-3.56 (m, 1H), 3.79-3.86 (m, 1H), 3.97-

71

4.04 (m, 1H), 7.29-7.38 (m, 2H), 7.44 (dd, 1H, J=2.52Hz and J=8.84Hz), 8.62 (s, br, 1H).

MS (+APCI) m/z 402 (MH+)

Example 71: 6-[4-(4-fluoro-2-trifluoromethyl-benzyl)-piperazin-1-yl]-4-methyl-2H-[1,2,4]triazine-3,5-dione (71)



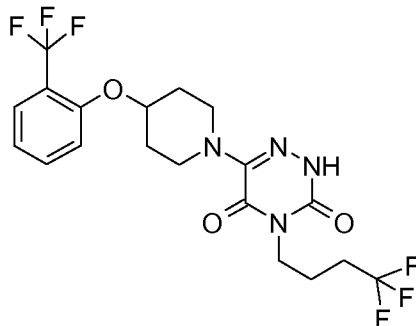
The compound 71 is prepared from the triazine 4b and from the intermediate 7b according to the synthesis method 1 in n-butanol. After deprotection of the nitrogen in position 2 (NH<sub>2</sub>NH<sub>2</sub>.H<sub>2</sub>O, EtOH, 78°C, 3h), the compound 71 is obtained as a solid (yield: 34%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 95-5, R<sub>f</sub>=0.64.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 2.56-2.62 (m, 4H), 3.33 (s, 3H), 3.39-3.42 (m, 4H), 3.65 (s, 2H), 7.22 (m, 1H), 7.34 (d, 1H, J=8.96Hz), 7.78 (t, 1H, J=6.56Hz), 8.60 (s, br, 1H).

MS (+ESI) m/z 388 (MH+)

Example 72: 4-(4,4,4-trifluoro-butyl)-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione (72)



20

The compound 72 is prepared from the triazine 3b and from the intermediate 8c according to the synthesis method 1 in n-butanol. After deprotection of the nitrogen in position 2

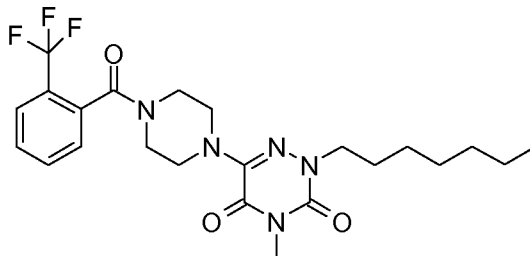
(Na, EtOH, 80°C, 5h), the compound 72 is obtained as a solid (yield: 38%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 90-10, R<sub>f</sub>=0.5.

MP=102°C

5 MS (+ESI) m/z 467 (MH<sup>+</sup>)

Example 73: 2-heptyl-4-methyl-6-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (73)

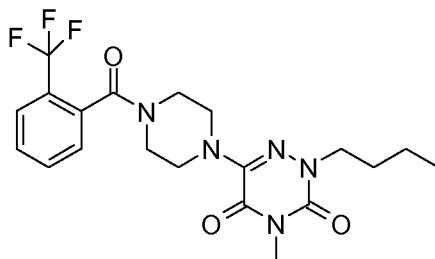


The compound 73 is prepared according to the synthesis  
 10 method 3: 0.20g (0.52 mmol) of the compound described for  
 Example 4 is placed in 2 mL of dimethylformamide at 0°C.  
 0.023g (0.57 mmol) of NaH are added. The mixture is stirred  
 for 30min at room temperature. 0.12g (0.57 mmol) of 1-  
 bromo-heptane in 1mL of dimethylformamide are added. This  
 15 mixture is stirred for 4h30min at room temperature. After  
 concentration, the residue is taken up with water and  
 extracted with AcOEt. After drying on MgSO<sub>4</sub>, the organic  
 phase is concentrated. The obtained residue is purified by  
 flash chromatography on silica (CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 90-10). 0.21g  
 20 of a yellow oil are isolated (yield: 84%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 95-5, R<sub>f</sub>=0.5.

MS (+ESI) m/z 482 (MH<sup>+</sup>)

Example 74: 2-butyl-4-methyl-6-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (74)



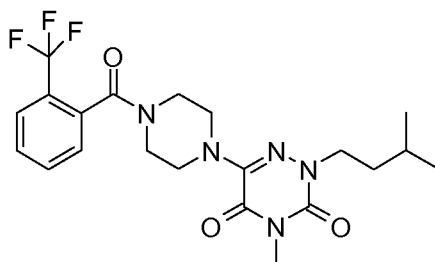
The compound 74 (oil) is prepared from 1-bromo-butane and from the compound described for Example 4 according to the synthesis method 3 (yield: 70%).

5 TLC silica gel 60 F 254 Merck, petroleum ether-AcOEt: 50-50, Rf=0.35.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 0.93-0.96 (t, 3H, J=7.6Hz) 1.29-1.40 (m, 2H), 1.64-1.73 (m, 2H), 3.26-3.32 (m, 4H), 3.34 (s, 3H), 3.40-3.60 (m, 2H), 3.82-3.91 (m, 3H), 3.97-4.06 (m, 1H), 7.35 (d, 1H, J=7.83Hz), 7.54 (t, 1H, J=7.83Hz) 7.62 (t, 1H, J=7.07Hz), 7.72 (d, 1H, J=8.08Hz)

MS (+ESI) m/z 440 (MH+)

Example 75: 4-methyl-2-(3-methyl-butyl)-6-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione (75)



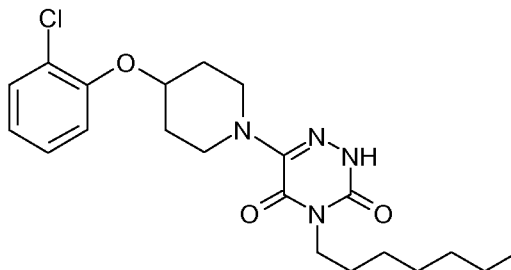
15

The compound 75 (oil) is prepared from 1-bromo-3-methyl-butane and from the compound described for Example 4 according to the synthesis method 3 (yield: 79%).

20 TLC silica gel 60 F 254 Merck, petroleum ether-AcOEt: 50-50, Rf=0.35.

MS (+ESI) m/z 454 (MH+)

Example 76: 6-[4-(2-chloro-phenoxy)-piperidin-1-yl]-4-heptyl-2H-[1,2,4]triazine-3,5-dione (76)



25 The compound 76 is prepared from the triazine 3c and from the intermediate 8a according to the synthesis method 1 in

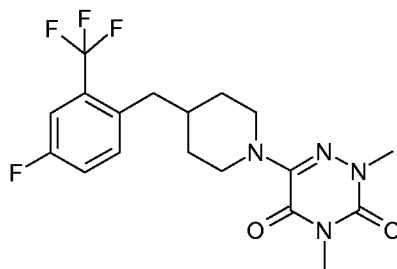
n-butanol. After deprotection of the nitrogen in position 2 (NaH, DMF, 20°C, 3h), the compound 76 is obtained as a solid (yield: 67%).

5 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 90-10, R<sub>f</sub>=0.55.

MP=95°C

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 0.88 (t, 3H, J=6.82Hz), 1.22-1.38 (m, 8H), 1.60-1.69 (m, 2H), 1.94-2.09 (m, 4H), 3.38-3.46 (m, 2H). 3.57-3.65 (m, 2H), 3.91 (t, 2H, J=6.56Hz), 4.58 (m, 10 1H), 6.91 (t, 1H, J=7.32Hz), 7.00 (d, 1H, J=8.59Hz), 7.20 (t, 1H, J=8.08Hz), 7.37 (d, 1H, J=8.08Hz), 8.72 (s br, 1H). MS (+ESI) m/z 421 (MH+)

Example 77: 6-[4-(4-fluoro-2-trifluoromethyl-benzyl)-piperidin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione (77)



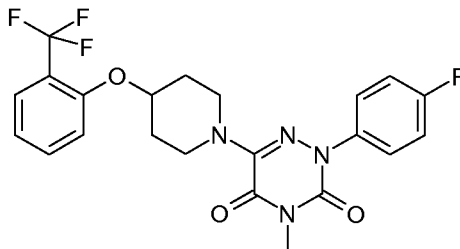
The compound 77 (oil) is prepared from the triazine 1b and from the intermediate 9b according to the synthesis method 1 in n-butanol (yield: 43%).

20 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.48. <sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.38-1.50 (m, 2H), 1.64-1.79 (m, 3H), 2.60 (t, 2H, J=12.6Hz), 2.72 (d, 2H, J=6.82Hz), 3.34 (s, 3H), 3.52 (s, 3H), 4.05 (d, 2H, J=12.3Hz), 7.17 (t, 1H, J=8.33Hz), 7.25-7.30 (m, 1H), 7.32-7.38 (m, 1H). MS (+ESI) m/z 401 (MH+)

Example 78: 4-methyl-2-(2-thiophen-2-yl-ethyl)-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione (78)



Example 80: 2-(4-fluoro-phenyl)-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione (80)



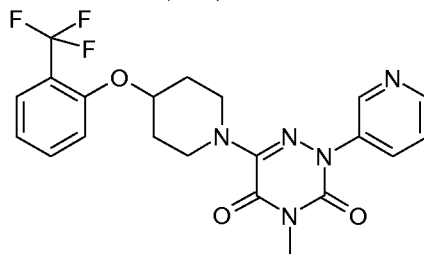
5 The compound 80 (solid) is prepared from the triazine 4m and from the intermediate 8c according to the synthesis method 1 in n-butanol (yield: 48%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.64.  
MP=111°C

10 <sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.99-2.12 (m, 4H), 3.42 (s, 3H), 3.51-3.60 (m, 2H), 3.60-3.69 (m, 2H), 4.72 (m, 1H), 6.97-7.02 (m, 2H), 7.11 (t, 2H, J=8.21Hz), 7.47 (t, 1H, J=7.32Hz), 7.53-7.60 (m, 3H).

MS (+ESI) m/z 465 (MH<sup>+</sup>)

15 Example 81: 4-methyl-2-pyridin-3-yl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione (81)



20 The compound 81 (solid) is prepared from the triazine 4n and from the intermediate 8c according to the synthesis method 1 in n-butanol (yield: 56%).

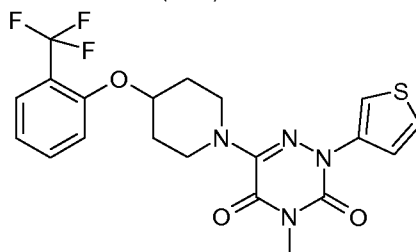
TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 90-10, R<sub>f</sub>=0.62.  
MP=63°C

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.99-2.13 (m, 4H), 3.44 (s, 3H), 3.56-3.64 (m, 2H), 3.67-3.74 (m, 2H), 4.74 (m, 1H), 6.97-7.02 (m, 2H), 7.37 (ddd, 1H, J=0.6Hz and J=4.67Hz and J=8.21Hz),

7.48 (dt, 1H, J=1.40Hz and J=7.20Hz), 7.59 (dd, 1H, J=1.40Hz and J=8.08Hz), 8.01 (ddd, 1H, J=1.51Hz and J=2.65Hz and J=7.96Hz), 8.53 (dd, 1H, J=1.51Hz and J=4.92Hz), 8.93 (d, 1H, J=2.65Hz).

5 MS (+ESI) m/z 448 (MH+)

Example 82: 4-methyl-2-thiophen-3-yl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione (82)



10 The compound 82 (solid) is prepared from the triazine 4o and from the intermediate 8c according to the synthesis method 1 in n-butanol (yield: 57%).

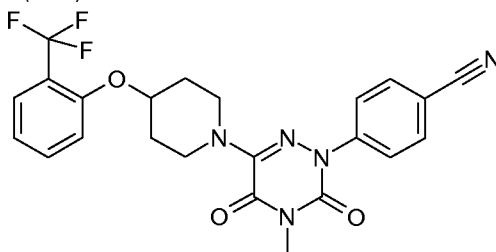
TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>- AcOEt: 95-5, R<sub>f</sub>=0.72.

15 MP=85°C

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 2.00-2.14 (m, 4H), 3.43 (s, 3H), 3.56-3.64 (m, 2H), 3.67-3.73 (m, 2H), 4.74 (m, 1H), 7.00 (t, 1H, J=6.69Hz), 7.01 (d, 1H, J=8.46Hz), 7.29 (dd, 1H, J=3.28Hz and J=5.30Hz), 7.48 (dt, 1H, J=1.64Hz and J=7.83Hz), 7.52 (dd, 1H, J=1.40Hz and J=5.43Hz), 7.59 (dd, 1H, J=1.51Hz and J=8.08Hz), 7.69 (dd, 1H, J=1.51Hz and J=3.28Hz).

MS (+ESI) m/z 453 (MH+)

Example 83: 4-{4-methyl-3,5-dioxo-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-4,5-dihydro-3H-[1,2,4]triazin-2-yl}-benzonitrile (83)



The compound 83 (solid) is prepared from the triazine 4p and from the intermediate 8c according to the synthesis method 1 in n-butanol (yield: 60%).

5 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>- AcOEt: 95-5, R<sub>f</sub>=0.18.

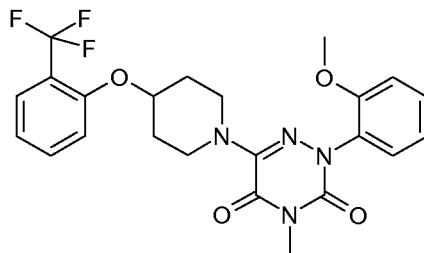
MP=72°C

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 2.04-2.10 (m, 4H), 3.43 (s, 3H), 3.54-3.62 (m, 2H), 3.70-3.77 (m, 2H), 4.75 (m, 1H), 7.00 (d, 1H, J=7.58Hz), 7.01 (t, 1H, J=6.06Hz), 7.48 (t, 1H, J=7.70Hz),  
10 7.59 (d, 1H, J=7.95Hz), 7.71 (d, 2H, J=8.84Hz), 7.86 (d, 2H, J=8.84Hz).

MS (+ESI) m/z 472 (MH<sup>+</sup>)

Example 84: 2-(2-methoxy-phenyl)-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-

15 [1,2,4]triazine-3,5-dione (84)



The compound 84 (solid) is prepared from the triazine 4q and from the intermediate 8c according to the synthesis method 1 in n-butanol (yield: 74%).

20 TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>- AcOEt: 95-5, R<sub>f</sub>=0.32.

MP=128°C

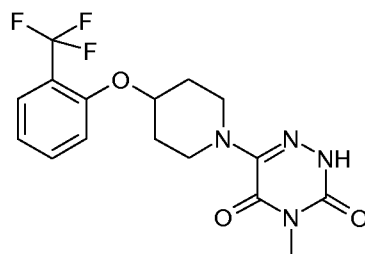
<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.94-2.10 (m, 4H), 3.41 (s, 3H), 3.45-3.59 (m, 4H), 3.84 (s, 3H), 4.67 (m, 1H), 6.95-7.05 (m, 4H), 7.31 (dd, 1H, J=1.64Hz and J=7.58Hz), 7.39 (td, 1H, J=1.89Hz and J=7.70Hz), 7.45 (td, 1H, J=1.64Hz and J=7.96Hz), 7.57 (dd, 1H, J=1.26Hz and J=7.95Hz).

25 MS (+ESI) m/z 477 (MH<sup>+</sup>)

Example 85: 4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione (85)

30

79



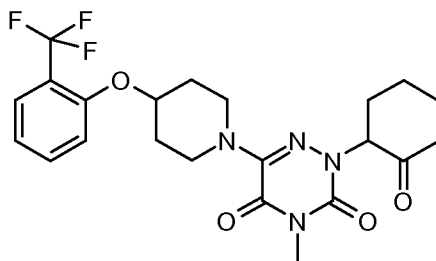
The compound 85 is prepared from the triazine 3a and from the intermediate 8c according to the synthesis method 1 in n-butanol. After deprotection of the nitrogen in position 2 (NaH, DMF, 20°C, 20h), the compound 85 is obtained as a solid (yield: 77%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-AcOEt: 95-5, R<sub>f</sub>=0.16.  
MP=150°C

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.96-2.09 (m, 4H), 3.35 (s, 3H), 3.46-3.57 (m, 4H), 4.71 (m, 1H), 6.99 (t, 1H, J=7.32Hz), 7.00 (d, 1H, J=8.59Hz), 7.47 (t, 1H, J=7.56Hz), 7.58 (d, 1H, J=8.08Hz), 8.99 (s br, 1H).

MS (+ESI) m/z 371 (MH<sup>+</sup>)

Example 86: 4-methyl-2-(2-oxo-cyclohexyl)-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione (86)



The compound 86 (solid) is prepared from 2-chloro-cyclohexanone and from the compound described for Example 85 according to the synthesis method 3 (yield: 31%).

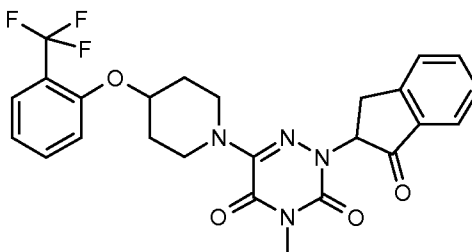
TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 95-5, R<sub>f</sub>=0.63.  
MP=65°C

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.64-1.90 (m, 2H), 1.93-2.18 (m, 6H), 2.19-2.49 (m, 3H), 2.54-2.62 (m, 1H), 3.34 (s, 3H), 3.46 (t, 2H, J=6.95Hz), 3.48-3.61 (m, 2H), 4.68 (m, 1H), 5.14

(dd, 1H, J=5.93Hz and J=12.88Hz), 6.97-7.01 (m, 2H), 7.46 (t, 1H, J=7.32Hz), 7.58 (d, 1H, J=8.46Hz).

MS (+ESI) m/z 467 (MH<sup>+</sup>)

Example 87: 4-methyl-2-(1-oxo-indan-2-yl)-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione (87)



The compound 87 (solid) is prepared from 2-bromo-indan-1-one and from the compound described for Example 85 according to the synthesis method 3 (yield: 38%).

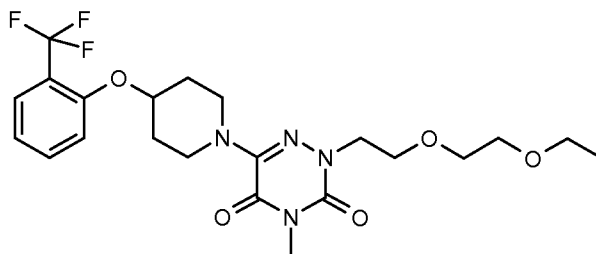
TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 95-5, R<sub>f</sub>=0.63.

MP=110°C

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.86-2.04 (m, 4H), 3.37 (s, 3H), 3.38-3.51 (m, 4H), 3.55-3.65 (m, 2H), 4.64 (m, 1H), 5.37 (m, 1H), 6.93-7.00 (m, 2H), 7.41-7.47 (m, 2H), 7.51 (d, 1H, J=8.21Hz), 7.56 (d, 1H, J=7.96Hz), 7.66 (td, 1H, J=1.40Hz and J=7.58Hz), 7.82 (d, 1H, J=7.70Hz).

MS (+ESI) m/z 501 (MH<sup>+</sup>)

Example 88: 2-[2-(2-ethoxy-ethoxy)-ethyl]-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione (88)



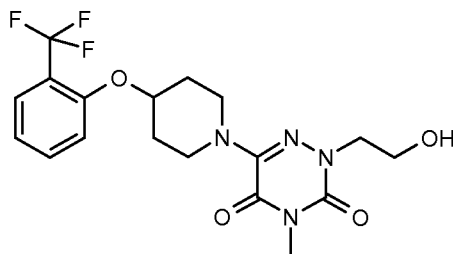
The compound 88 (solid) is prepared from 1-bromo-2-(2-ethoxy-ethoxy)-ethane and from the compound described for Example 85 according to the synthesis method 3 (yield: 77%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 95-5, R<sub>f</sub>=0.85.  
MP=44°C

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.19 (t, 3H, J=7.07Hz), 1.95-2.01 (m, 4H), 3.34 (s, 3H), 3.46-3.58 (m, 8H), 3.63-3.67 (m, 2H),  
5 3.82 (t, 2H, J=5.81Hz), 4.10 (t, 2H, J=5.81Hz), 4.70 (m, 1H), 6.99 (t, 1H, J=7.20Hz), 7.00 (d, 1H, J=7.07Hz), 7.47 (t, 1H, J=7.96Hz), 7.58 (d, 1H, J=7.83Hz).

MS (+ESI) m/z 487 (MH<sup>+</sup>)

Example 89: 2-(2-hydroxy-ethyl)-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-  
10 [1,2,4]triazine-3,5-dione (89)



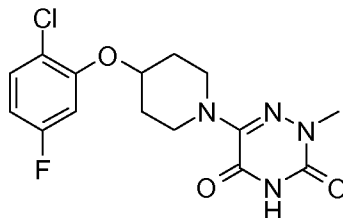
The compound 89 (solid) is prepared from 2-bromo-ethyl acetate and from the compound described for Example 85  
15 according to the synthesis method 3 (yield: 68%).

TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 95-5, R<sub>f</sub>=0.85.  
MP=112°C

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.97-2.10 (m, 4H), 2.41 (m, 1H), 3.36 (s, 3H), 3.46-3.54 (m, 2H), 3.54-3.62 (m, 2H), 3.94-3.99  
20 (m, 2H), 4.11 (t, 2H, J=4.56Hz), 4.71 (m, 1H), 7.00 (d, 1H, J=8.58Hz), 7.00 (t, 1H, J=7.56Hz), 7.48 (t, 1H, J=8.08Hz), 7.59 (d, 1H, J=7.96Hz).

MS (+ESI) m/z 415 (MH<sup>+</sup>)

Example 90: 6-(4-(2-chloro-5-fluorophenoxy)piperidin-1-yl)-  
25 2-methyl-1,2,4-triazine-3,5(2H,4H)-dione (90)



The compound 90 (white powder) is prepared from the triazine 2e and from the intermediate 8b according to the synthesis method 1 in toluene.

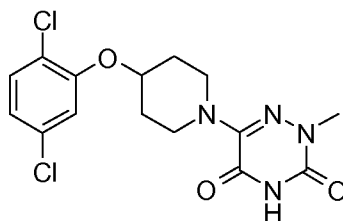
TLC silica gel 60 F 254 Merck, CH<sub>2</sub>Cl<sub>2</sub>-MeOH: 95-5, R<sub>f</sub>=0.66.

5 MP= 172°C

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.95-2.00 (m, 2H), 2.02-2.08 (m, 2H), 3.54 (s, 3H) 3.50-3.55 (m, 2H), 3.60-3.67 (m, 2H), 4.56 (m, 1H), 6.64 (m, 1H), 6.7 (dd, 1H), 7.32 (dd, 1H), 8.91 (s, 1H).

10 MS (+ESI) m/z 355 (MH<sup>+</sup>)

Example 91: 6-(4-(2,5-dichlorophenoxy)piperidin-1-yl)-2-methyl-1,2,4-triazine-3,5(2H,4H)-dione (91)

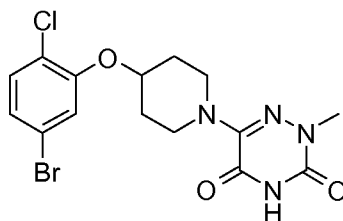


15 The compound 91 (white solid) is prepared from the triazine 2e and from 4-(2,5-dichlorophenoxy)piperidine (obtained as under the preparative methods of intermediate 8a) according to the synthesis method 1 in toluene.

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.95-2.08 (m, 4H), 3.50 (s, 3H), 3.50-3.53 (m, 2H), 3.61-3.67 (m, 2H), 4.57 (s, 1H), 6.90 (d, 1H, J=8.4Hz), 6.94 (s, 1H), 7.29 (d, 1H, J=8.4Hz), 8.75 (s, 1H).

MS (+ESI) m/z 371 (MH<sup>+</sup>)

Example 92: 6-(4-(5-bromo-2-chlorophenoxy)piperidin-1-yl)-2-methyl-1,2,4-triazine-3,5(2H,4H)-dione (92)



25

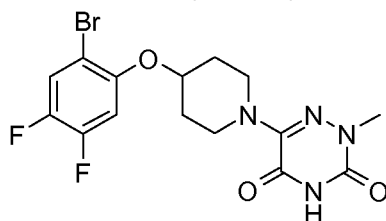
The compound 92 (yellow powder) is prepared from the triazine 2e and from 4-(5-bromo-2-chlorophenoxy)piperidine (obtained as under the preparative conditions of

intermediate 8a) according to the synthesis method 1 in toluene.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.95-2.08 (m, 4H), 3.50 (s, 3H), 3.50-3.53 (m, 2H), 3.59-3.62 (m, 2H), 4.57 (s, 1H), 7.05 (d, 1H, J=8.8Hz), 7.09 (s, 1H), 7.22-7.26 (m, 1H), 8.52 (s, 1H).

MS (+ESI) m/z 416 (MH<sup>+</sup>)

Example 93: 6-(4-(2-bromo-4,5-difluorophenoxy)piperidin-1-yl)-2-methyl-1,2,4-triazine-3,5(2H,4H)-dione (93)



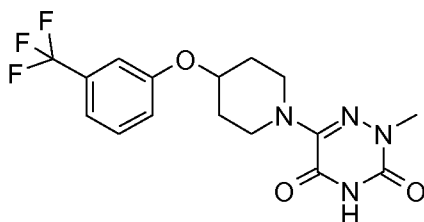
10 The compound 93 (white solid) is prepared from the triazine 2e and from 4-(2-bromo-4,5-difluorophenoxy)piperidine (obtained as under the preparative conditions of intermediate 8a) according to the synthesis method 1 in toluene.

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.94-2.09 (m, 4H), 3.51 (s, 3H), 3.51-3.58 (m, 2H), 3.61-3.67 (m, 2H), 4.48-4.52 (m, 1H), 6.78-6.83 (m, 1H), 7.39-7.44 (m, 1H), 8.22-8.29 (m, 1H).

MS (+ESI) m/z 418 (MH<sup>+</sup>)

Example 94: 2-methyl-6-(4-(3-

20 (trifluoromethyl)phenoxy)piperidin-1-yl)-1,2,4-triazine-3,5(2H,4H)-dione (94)



The compound 94 (white solid) is prepared from the triazine 2e and from 4-(3-(trifluoromethyl)phenoxy)piperidine (obtained as under the preparative conditions of intermediate 8a) according to the synthesis method 1 in toluene.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm: 1.88-1.98 (m, 2H), 2.03-2.13 (m, 2H), 3.39-3.45 (m, 2H), 3.51 (s, 3H), 3.68-3.73 (m, 2H), 4.57-4.59 (m, 1H), 7.09 (d, 1H, J=8.4Hz), 7.22 (d, 1H, J=7.2Hz), 7.41 (t, 1H, J=8Hz), 8.34-8.37 (m, 1H).

5 MS (+ESI) m/z 371 (MH<sup>+</sup>)

#### PHARMACOLOGICAL EVALUATION

In vitro: Human SCD-1 enzymatic activity from microsomes of HepG2 cells after treatment with inhibitory compounds (inhibition %).

- 10 Human hepatocarcinoma HepG2 cells (ATCC, HB-8065) are grown to confluence and then trypsinized. The cell pellet is taken up in 10 mM Tris buffer (pH 7.4), saccharose (250 mM) DTT (1 mM) and then the cells are lysed by sonication. The microsomes are obtained after centrifugation at 10,000 g
- 15 for 20 minutes à 4°C followed by centrifugation of the supernatant at 100,000 g for 60 minutes à 4°C. The pellet is taken up in 10 mM Tris buffer (pH 7.4) saccharose (250 mM) at 4°C and the microsomal proteins are assayed and stored at -196°C (liquid nitrogen).
- 20 The enzymatic reaction measures the conversion of stearic acid (a C18:0 fatty acid) into oleic acid (C18:1 fatty acid) by SCD-1. The enzymatic reaction is started by adding 125 µg of microsomal fraction of HepG2 cells to tubes (total reaction volume of 500 µl) containing 62 µM of
- 25 stearic acid (45 µM of stearic acid and 17 µM of [<sup>14</sup>C] stearic acid) in a phosphate buffer at 100 mM (pH 7.16) with 7.2 mM of ATP, 0.54 mM of CoA, 6 mM of MgCl<sub>2</sub>, 0.8 mM of NADH and the inhibitory compound or the carrier (0.1% DMSO). The tubes are incubated for 20 minutes at 37°C and
- 30 the enzymatic reaction is then stopped by adding KOH (12%) and saponification for 30 minutes at 80°C. After acidification (3N HCl), the fatty acids are extracted twice with ethyl ether, evaporated under nitrogen before being taken up with a methanol/dichloromethane (3:1) mixture. The
- 35 product of the reaction (C18:1) is separated from the

substrate of the reaction (C18:0) by HPLC (Perkin Elmer, C18 reverse phase column) coupled to a on-line radioactivity detector (FlowOne). Enzymatic activity is calculated in picomoles of stearic acid converted into oleic acid per minute and per mg of protein. For each inhibitory compound, an inhibition % is determined relatively to the reference enzymatic activity (carrier 0.1% DMSO). Sterculic acid is the reference inhibitory compound (Gomez F.E., Bauman D.E., Ntambi J.M., Fox B.G. Effects of sterculic acid on stearyl-CoA desaturase in differentiating 3T3-L1 adipocytes. *Biochem Biophys Res Commun.* 300 316-326 (2003)).

Table 10: Human SCD-1 enzymatic activity inhibition % at 10  $\mu$ M).

Example	HSCD-1 (HEPG2) % inh. (10 $\mu$ M)
Sterculic acid	100
1	11
2	63
3	90
4	77
5	43
6	73
11	92
12	71
13	75
14	74
15	74
16	57
19	57
23	73
25	70
27	82
28	50
29	71
30	86
31	73
33	48
42	80
47	84
48	64

Example	HSCD-1 (HEPG2) % inh. (10 $\mu$ M)
55	65
57	71
64	57
69	84
70	66
71	50
74	60
76	62
79	54
80	87
81	98
82	100
83	79
84	53
85	95
86	90
88	48
89	100

The invention also relates to the compounds of general formula (I) for their use as drugs intended for treating diseases requiring inhibitors of SCD-1 enzyme activity.

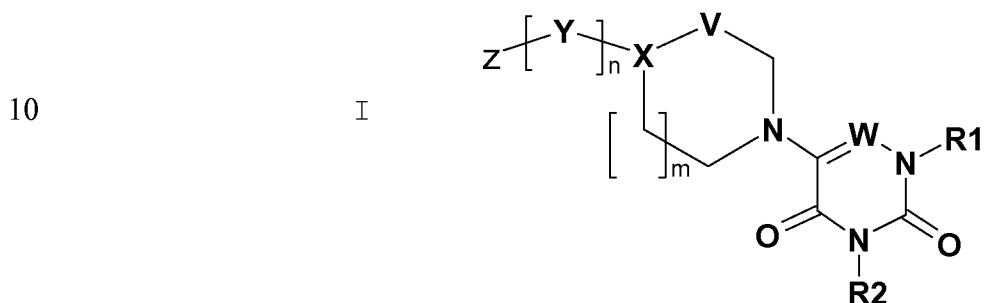
The invention also relates to compounds of general formula (I) for their use as drugs intended for treating diseases such as obesity, diabetic dyslipidemia, hypertriglyceridemia, hypercholesterolemia, the metabolic syndrome, atherosclerosis, hepatic steatosis, cardiovascular risks.

The invention also extends to compounds of general formula (I) for their use as drugs intended for treating pathologies related to lipid disorders of the skin.

The invention also relates to compounds of general formula (I) for their use as drugs intended for treating diseases such as acne, psoriasis, hirsutism.

REVENDICATIONS

1) Derivatives of 2H-[1,2,4]triazine-3,5-dione and of H-pyrimidine-2,4-dione for their use as SCD-1 enzyme activity inhibitors corresponding to the general formula I



wherein:

- 20 - W represents nitrogen or CH
- R<sub>1</sub> and R<sub>2</sub> represent independently of each other:
- a hydrogen or a linear or branched C<sub>1</sub>-C<sub>7</sub> alkyl or alkenyl radical or
  - a C<sub>1</sub>-C<sub>3</sub> alkyl radical substituted with groups such as:
 

25 - trifluoromethyl, nitrile, hydroxy, C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> alkoxyalkoxy, indolyl, thiophenyl, oxothiophenyl, C<sub>1</sub>-C<sub>3</sub> N-alkyl or N-dialkylcarbamoyl groups or,

- phenyl or aroyl or benzyloxy or N-arylcarbamoyl groups (for which the phenyl ring is optionally substituted with one or more groups such as linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, nitro groups, halogen atoms),

30 • a phenyl or pyridyl or naphthyl, or thiophenyl group optionally substituted with one or more groups such as

35 halogen atoms, nitro, nitrile, trifluoromethyl, vinyl, methylsulfanyl, linear branched C<sub>1</sub>-C<sub>4</sub>, alkyl, linear or branched C<sub>1</sub>-C<sub>3</sub> alkoxy, phenyl, C<sub>1</sub>-C<sub>3</sub>N-mono- or dialkylcarbamoyl ou dialkylcarbamoyl, C<sub>1</sub>-C<sub>4</sub> alkylcarboxamido groups,

40 • a C<sub>5</sub>-C<sub>6</sub> 2-oxocycloalkyl radical optionally fused with a phenyl group,
- m is equal to 0 or 1

- V represents  $\text{CH}_2$ ,  $\text{CHCH}_3$  or  $\text{C=O}$

-when  $n=1$

X-Y represents  $-\text{N}-(\text{C=O})-$ ,  $-\text{N}-\text{CH}_2-$ ,  $-\text{CH}-\text{CH}_2-$ ,  $-\text{CH}-\text{O}-$ ,  
 $-\text{CH}-(\text{C=O})-$ ,

5 Z represents a phenyl group optionally substituted with one or more trifluoromethyl groups, halogen atoms, linear or branched  $\text{C}_1$ - $\text{C}_4$  alkyl, linear or branched  $\text{C}_1$ - $\text{C}_3$  alkoxy groups,

-when  $n=0$

10 X represents N,

Z represents a phenyl or cinnamyl or aryloxy carbonyl or 2-phenylacetyl (the position 2 of which is optionally substituted with a linear or branched  $\text{C}_1$ - $\text{C}_4$  alkyl) group for which the aromatic group is optionally substituted with one or more trifluoromethyl groups, halogen atoms, linear or branched  $\text{C}_1$ - $\text{C}_4$  alkyl, linear or branched  $\text{C}_1$ - $\text{C}_3$  alkoxy, nitro, groups,

15 as well as addition salts with pharmaceutically acceptable  
 20 bases and acids, and the different enantiomers of the compounds having asymmetrical carbons, as well as their mixtures in any proportions notably including the racemic mixtures.

25 2) The derivatives of 2H-[1,2,4]triazine-3,5-dione and of H-pyrimidine-2,4-dione corresponding to the general formula I as defined in claim 1, wherein:

wherein:

- W represents nitrogen or CH

-  $\text{R}_1$  and  $\text{R}_2$  represent:

- 30
- a hydrogen (in a non-simultaneous way) or a linear or branched  $\text{C}_1$ - $\text{C}_7$  alkyl or alkenyl radical or,
  - a  $\text{C}_1$ - $\text{C}_3$  alkyl radical substituted with groups such as:
    - trifluoromethyl, nitrile, hydroxy,  $\text{C}_1$ - $\text{C}_3$  alkoxy,  $\text{C}_3$ - $\text{C}_6$  alkoxyalkoxy, indolyl, thiophenyl, oxothiophenyl,
    - 35  $\text{C}_1$ - $\text{C}_3$  N-alkyl or N-dialkylcarbamoyl groups or,

- phenyl or aroyl or benzyloxy or N-arylcabamoylr (for which the phenyl ring is possibly substituted with one or more groups such as linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, nitro, groups, halogen atoms),
- 5 • a phenyl or pyridyl or naphthyl or thiophenyl group, possibly substituted with one or more groups such as halogen atoms, a nitro, nitrile, trifluoromethyl, vinyl, methylsulfanyl, linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, linear or branched C<sub>1</sub>C<sub>3</sub> alkoxy, phenyl, C<sub>1</sub>-C<sub>3</sub> N-mono- or di-
- 10 alkylcarbamoyl, C<sub>1</sub>-C<sub>4</sub> alkylcarboxamido groups,
  - a C<sub>5</sub>-C<sub>6</sub> 2-oxocycloalkyl radical optionally fused with a phenyl group,
- m is equal to 0 or 1
- V represents CH<sub>2</sub>, CHCH<sub>3</sub> or C=O
- 15 -when n=1
  - X-Y represents -N-(C=O)-, -N-CH<sub>2</sub>-, -CH-CH<sub>2</sub>-, -CH-O-, -CH-(C=O)-,
  - Z represents a phenyl group substituted with one or more trifluoromethyl groups, halogen atoms,
  - 20 linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>3</sub> alkoxy groups except for the compound 6-[4-(4-isopropyl-benzyl)-piperazin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione and 2,4-dimethyl-6-[4-(3-trifluoro-methyl-benzyl)-
  - 25 piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione,
- when n=0
  - X represents N,
  - Z represents a phenyl or cinnamyl or aryloxy-carbonyl or 2-phenylacetyl group (the
  - 30 position 2 of which is optionally substituted with a linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl for which the aromatic group is substituted with one or more trifluoromethyl groups, halogens atoms, linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, linear or branched

C<sub>1</sub> or C<sub>3</sub> alkoxy, nitro, groups, and this except for the following compounds:

6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione

5 6-[4-(4-methoxy-phenyl)-piperazin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione

6-[4-(2-chloro-phenyl)-piperazin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione

10 as well as the addition salts with pharmaceutically acceptable bases and acids, and the different enantiomers of the compounds having asymmetrical carbons, as well as their mixtures in any proportions notably including racemic mixtures.

15 3) The derivatives of 2H-[1,2,4]triazine-3,5-dione and of H-pyrimidine-2,4-dione according to claim 2) corresponding to the general formula I wherein:

- W represents nitrogen or CH

- R<sub>1</sub> and R<sub>2</sub> represent:

20 • a hydrogen (in a non-simultaneous way) or a linear or branched C<sub>1</sub>-C<sub>7</sub> alkyl or alkenyl radical or,

• a C<sub>1</sub>-C<sub>3</sub> alkyl radical substituted with groups such as:

- trifluoromethyl, nitrile, hydroxy, C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> alkoxyalkoxy, indolyl, thiophenyl, oxothiophenyl, C<sub>1</sub>-C<sub>3</sub> N-alkyl or N-dialkylcarbamoyl groups or,

25 - phenyl or aroyl or benzyloxy or N-arylcarbamoyl groups (for which the phenyl ring is optionally substituted with one or more groups such as linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, nitro groups, halogen atoms),

30 • a phenyl or pyridyl or naphthyl or thiophenyl group optionally substituted with one or more groups such as halogen atoms, nitro, nitrile, trifluoromethyl, vinyl, methylsulfanyl, linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>3</sub> alkoxy, phenyl, C<sub>1</sub>-C<sub>3</sub> N-mono- or di-alkylcarbamoyl, C<sub>1</sub>-C<sub>4</sub> alkylcarboxamido groups,

- a C<sub>5</sub>-C<sub>6</sub> 2-oxocycloalkyl radical optionally fused with a phenyl group,
  - m, n are equal to 1
  - V represents CH<sub>2</sub>
  - 5 - X-Y represents -N-(C=O)-, -CH-CH<sub>2</sub>-, -CH-O-, -CH-(C=O)-,
  - Z represents a phenyl group substituted with one or more trifluoromethyl groups, halogen atoms, linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, linear or branched
  - 10 C<sub>1</sub>-C<sub>3</sub> alkoxy groups.
- 4) The derivatives of 2H-[1,2,4]triazine-3,5-dione and of H-pyrimidine-2,4-dione according to claim 2) corresponding to the general formula I wherein:
- W represents nitrogen or CH
  - 15 - R<sub>1</sub> and R<sub>2</sub> represent:
    - a hydrogen (in a non-simultaneous way) or a linear or branched C<sub>1</sub>-C<sub>7</sub> alkyl radical or,
    - a C<sub>1</sub>-C<sub>3</sub> alkyl radical substituted with groups such as: trifluoromethyl, nitrile, hydroxy, C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub>
    - 20 alkoxyalkoxy, indolyl, oxothiophenyl, C<sub>1</sub>-C<sub>3</sub> N-alkyl or N-dialkylcarbamoyl groups,
    - a phenyl or pyridyl or naphthyl or thiophenyl group optionally substituted with one or more groups such as halogen atoms, nitro, nitrile, trifluoromethyl, vinyl,
    - 25 methylsulfanyl, linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>1</sub>-C<sub>3</sub> N-mono- or dialkylcarbamoyl, C<sub>1</sub>-C<sub>4</sub> alkylcarboxamido groups,
    - a C<sub>5</sub>-C<sub>6</sub> 2-oxocycloalkyl radical optionally fused with a phenyl group,
  - 30 - m, n are equal to 1
  - V represents CH<sub>2</sub>
  - X-Y represents -N-(C=O)-, -CH-O-,
  - Z represents a phenyl group substituted with one or more trifluoromethyl groups, halogen atoms,
  - 35 linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl groups.

5) The derivatives of 2H-[1,2,4]triazine-3,5-dione according to claim 2) corresponding to the general formula I wherein:

- W represents nitrogen,
- 5 - R<sub>1</sub> represents:
  - a hydrogen or linear or branched C<sub>1</sub>-C<sub>5</sub> alkyl radical or,
  - a C<sub>1</sub>-C<sub>3</sub> alkyl radical substituted with groups such as trifluoromethyl, nitrile, hydroxy, C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> alkoxyalkoxy, indolyl, oxothiophenyl, C<sub>1</sub>-C<sub>3</sub> N-alkylcarbamoyl groups,
  - 10 • a phenyl or pyridyl or naphthyl or thiophenyl group optionally substituted with one or more groups such as halogen atoms, nitro, nitrile, trifluoromethyl, vinyl, methylsulfanyl, linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>3</sub> alkoxy, phenyl, C<sub>1</sub>-C<sub>3</sub> N-mono- or di-alkylcarbamoyl, C<sub>1</sub>-C<sub>4</sub> alkylcarboxamido groups,
  - 15 • a C<sub>5</sub>-C<sub>6</sub> 2-oxocycloalkyl radical,
- R<sub>2</sub> represents: a linear or branched C<sub>1</sub>-C<sub>7</sub> alkyl radical, and preferably a methyl,
- 20 - m,n are equal to 1,
- V represents CH<sub>2</sub>,
- X-Y represents -N-(C=O)-, -CH-O-,
- Z represents a phenyl group substituted with one or more trifluoromethyl groups, halogen atoms, or linear C<sub>1</sub>-C<sub>4</sub> alkyl groups.
- 25

6) The derivatives of 2H-[1,2,4]triazine-3,5-dione according to claim 2) corresponding to the general formula I wherein:

- W represents nitrogen,
- 30 - R<sub>1</sub> represents:
  - a hydrogen or a linear or branched C<sub>1</sub>-C<sub>5</sub> alkyl radical or,

- a C<sub>1</sub>-C<sub>3</sub> alkyl radical substituted with groups such as trifluoromethyl, nitrile, hydroxy, C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> alkoxyalkoxy, indolyl, oxothiophenyl, C<sub>1</sub>-C<sub>3</sub> N-alkylcarbamoyl groups,
- 5 • a phenyl or pyridyl or thiophenyl group possibly substituted with one or more groups such as halogen atoms, nitrile, linear or branched C<sub>1</sub>-C<sub>4</sub> alky, linear or branched C<sub>1</sub>-C<sub>3</sub> alkoxygroups,
- a C<sub>6</sub> 2-oxocycloalkyl radical,
- 10 - R<sub>2</sub> represents a methyl or heptyl,
- m, n are equal to 1,
- V represents CH<sub>2</sub>,
- X-Y represents -N-(C=O)-, -CH-O-,
- Z represents a phenyl group substituted with one or
- 15 more trifluoromethyl groups, halogen atoms or linear C<sub>1</sub>-C<sub>4</sub> alkyl groups.

7) The derivatives of general formula I according to claim 2) characterized in that they are selected from:

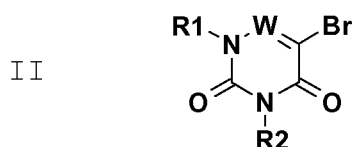
- 20 ▪ 4-heptyl-2-methyl-6-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 2-methyl-6-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 4-methyl-2-(4,4,4-trifluoro-butyl)-6-[4-(2-
- 25 trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 4-methyl-6-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 2,4-dimethyl-6-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-
- 30 yl]-2H-[1,2,4]triazine-3,5-dione
- 2,4-dimethyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 3-{4-heptyl-3,5-dioxo-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-4,5-dihydro-3H-[1,2,4]triazin-2-yl}-
- 35 propionitrile

- 2-butyl-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- N-methyl-2-{4-methyl-3,5-dioxo-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-4,5-dihydro-3H-[1,2,4]triazin-2-yl}-acetamide
- 5
- 2-(2-ethoxy-ethyl)-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 2-[2-(1H-Indol-3-yl)-ethyl]-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-
- 10 [1,2,4]triazine-3,5-dione
- 4-methyl-2-(4-oxo-4-thiophen-2-yl-butyl)-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 3-{6-[4-(2-chloro-phenoxy)-piperidin-1-yl]-4-methyl-3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl}-propionitrile
- 15
- 6-[4-(2-chloro-phenoxy)-piperidin-1-yl]-4-methyl-2-(4,4,4-trifluoro-butyl)-2H-[1,2,4]triazine-3,5-dione
- 6-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione
- 20
- 6-[4-(2-fluoro-phenoxy)-piperidin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione
- 6-[4-(2-chloro-5-trifluoromethyl-phenoxy)-piperidin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione
- 6-[4-(2-chloro-5-fluoro-phenoxy)-piperidin-1-yl]-2,4-
- 25 dimethyl-2H-[1,2,4]triazine-3,5-dione
- 2,4-dimethyl-6-(4-o-tolyloxy-piperidin-1-yl)-2H-[1,2,4]triazine-3,5-dione
- 6-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione
- 30
- 6-[4-(5-fluoro-2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione
- 6-[4-(5-fluoro-2-trifluoromethyl-benzoyl)-piperazin-1-yl]-4-methyl-2-(4,4,4-trifluoro-butyl)-2H-[1,2,4]triazine-3,5-dione

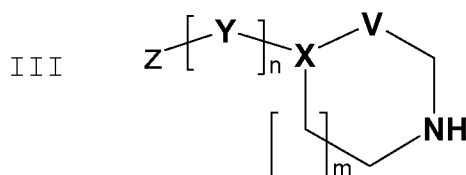
- 6-[4-(5-fluoro-2-trifluoromethyl-benzoyl)-piperazin-1-yl]-4-methyl-2-(3-methyl-butyl)-2H-[1,2,4]triazine-3,5-dione
- 2,4-dimethyl-6-[4-(2-trifluoromethyl-benzyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 5 ▪ 4-methyl-2-(4,4,4-trifluoro-butyl)-6-[4-(2-trifluoromethyl-benzyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 4-methyl-6-[4-(2-trifluoromethyl-benzyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 10 ▪ 6-[4-(5-fluoro-2-trifluoromethyl-benzoyl)-piperazin-1-yl]-4-methyl-2H-[1,2,4]triazine-3,5-dione
- 6-[4-(4-fluoro-2-trifluoromethyl-benzoyl)-piperazin-1-yl]-4-methyl-2H-[1,2,4]triazine-3,5-dione
- 6-[4-(4-fluoro-2-trifluoromethyl-benzyl)-piperazin-1-yl]-4-methyl-2H-[1,2,4]triazine-3,5-dione
- 15 ▪ 2-butyl-4-methyl-6-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 6-[4-(2-chloro-phenoxy)-piperidin-1-yl]-4-heptyl-2H-[1,2,4]triazine-3,5-dione
- 20 ▪ 4-methyl-2-o-tolyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 2-(4-fluoro-phenyl)-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 4-methyl-2-pyridin-3-yl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 25 ▪ 4-methyl-2-thiophen-3-yl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 4-{4-methyl-3,5-dioxo-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-4,5-dihydro-3H-[1,2,4]triazin-2-yl}-benzotrile
- 30 ▪ 2-(2-methoxy-phenyl)-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione

- 4-methyl-2-(2-oxo-cyclohexyl)-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 2-[2-(2-ethoxy-ethoxy)-ethyl]-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione
- 5 [1,2,4]triazine-3,5-dione
- 2-(2-hydroxy-ethyl)-4-methyl-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-2H-[1,2,4]triazine-3,5-dione

8) A method for preparing chemical compounds according to any of claims 2) to 7) characterized (Scheme 1) in that a derivative of general formula II



15 wherein W, R<sub>1</sub> and R<sub>2</sub> represent the groups as described earlier in formula I, is fused with a derivative of general formula III



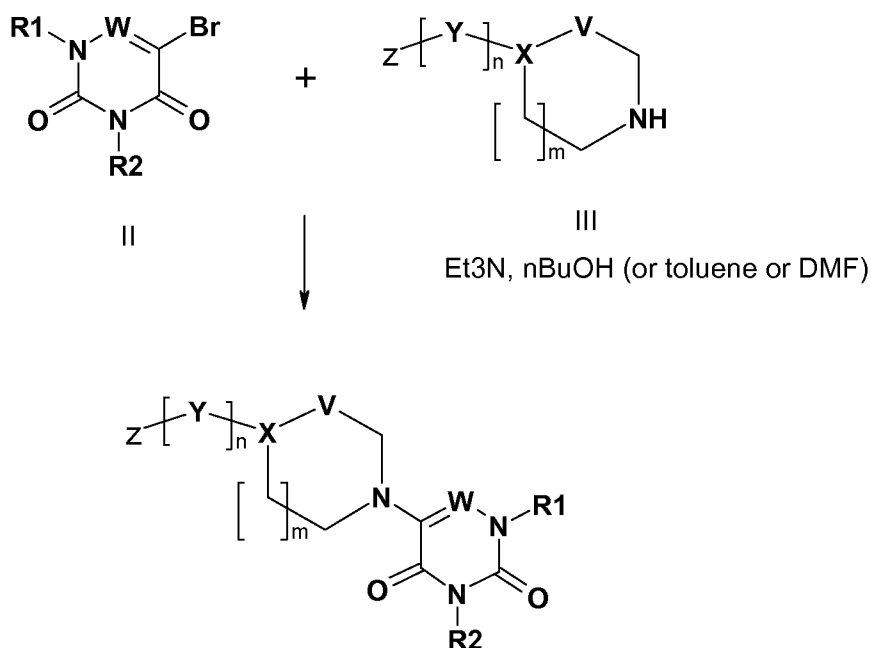
25

for which m, n, X, Y, V, and Z, are as described earlier in formula I, this reaction being preferably conducted in the presence of a base such as triethylamine in n-butanol or toluene or dimethylformamide;

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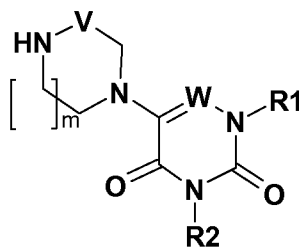


Scheme 1

9) A method for preparing chemical compounds according to any of claims 2) to 7) of general formula I for which X represents a nitrogen, (Scheme 2) characterized in that a derivative of general formula IV

10

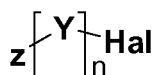
IV



wherein m, V, W, R<sub>1</sub> and R<sub>2</sub> are as described earlier in formula I, is fused with a compound of general formula V

25

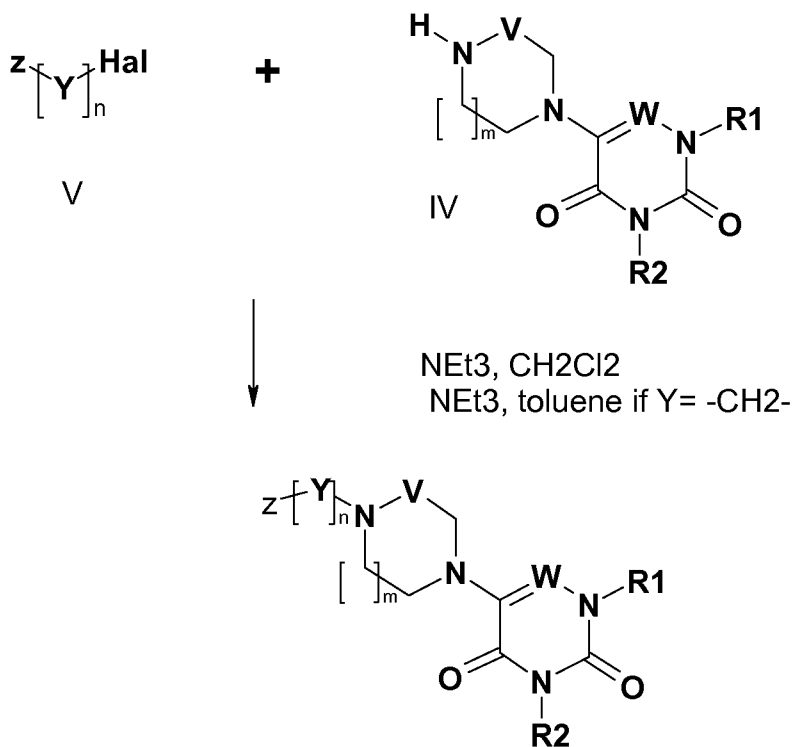
V



Wherein Hal represents a halogen such as Cl, Br or I, when n= 1, Y represents  $-(C=O)-$ ,  $-CH_2-$ ,  $-O-(C=O)-$ , and when n= 0, Y represents  $-CH=CH-(C=O)-$ ,  $-C-(CH(CH_3)_2)-$   $(C=O)-$

30

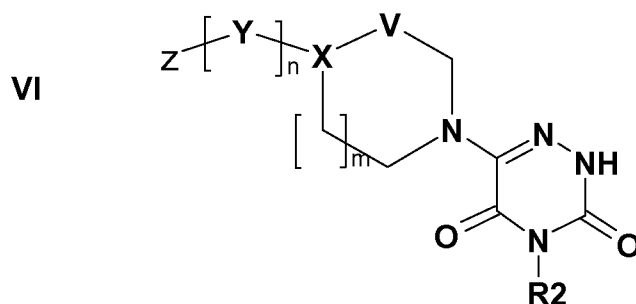
and Z is as described earlier in formula I,  
 this reaction being preferably conducted in the presence of  
 triethylamine in dichloromethane or in toluene (when Y is -  
 CH<sub>2</sub>-).



5

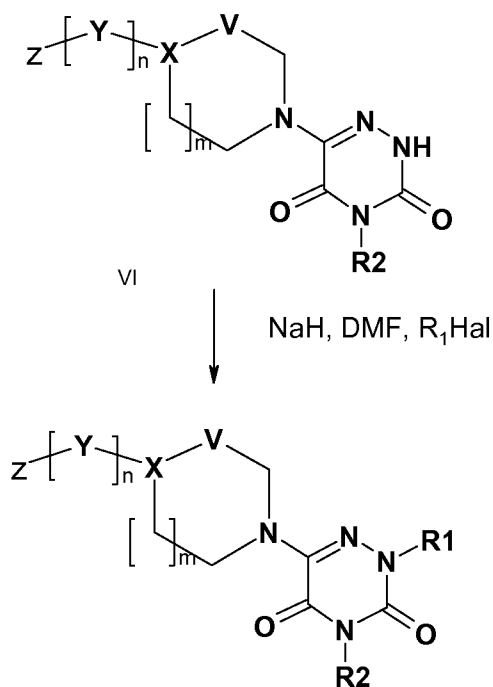
### Scheme 2

10) A method for preparing chemical compounds  
 according to any of claims 2) to 7) of general formula I  
 when W represents a nitrogen characterized in that the  
 nitrogen of the compound VI obtained according to claim 8)  
 (synthesis 1) for R<sub>1</sub> representing a hydrogen



20

wherein X, Y, V, Z, m, n and R<sub>2</sub> are as described earlier in formula I, is alkylated by a halogenated derivative of general formula R<sub>1</sub>Hal, wherein Hal represents a halogen such as Cl, Br or I and R<sub>1</sub> is as described earlier in general formula I, under operating conditions such as NaH or tBuOK in dimethylformamide



Scheme 3

10                    11) The compounds of general formula (I) as defined according to any of claims 1) to 7) for their use as a drug intended for treating diseases requiring inhibitors of SCD-1 enzyme activity.

15                    12) The compounds of general formula (I) as defined according to any of claims 1) to 7) for their use as a drug intended for treating diseases such as obesity, diabetic dyslipidemias, hypertriglyceridemia, hypercholesterolemia, metabolic syndrome, atherosclerosis, hepatic steatosis, cardiovascular risks.

20                    13) The compounds of general formula (I) as defined according to any of claims 1) to 7) for their use

as a drug intended for treating pathologies related to lipid disorders of the skin.

14) The compounds of general formula (I) as defined according to any of claims 1) to 7) for their use  
5 as a drug intended for treating diseases such as acne, psoriasis, hirsutism.

15) A pharmaceutical composition characterized in that it contains as an active ingredient a compound of general formula (I) as defined according to any of claims  
10 1) to 7).

16) A pharmaceutical composition characterized in that it contains a compound of general formula (I) as defined according to any of claims 1) to 7) in association with any suitable excipient.

15

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2009/058609

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>				
INV. C07D401/04	C07D401/14	C07D403/04	C07D403/14	C07D409/14
A61K31/506	A61K31/53	A61P3/00	A61P17/00	

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMCATS CHEMICAL ABSTRACT SERVICE, COLUMBUS, OHIO, US; retrieved from STN XP002518360 order numbers: ken-501123; kcd-781851; ken-419980; ken-011338; ken-010990; ken-018040; ken-019518; ken-040370; kend-0071441; kend-0056367; kcheb-108319 abstract &amp; AURORA SCREENING LIBRARY: 13 June 2008 (2008-06-13), AURORA FINE CHEMICALS LLC, SAN DIEGO, CA, USA ----- -/--</p>	1-6, 15, 16

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

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- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

2 September 2009

Date of mailing of the international search report

09/09/2009

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040,  
Fax: (+31-70) 340-3016

Authorized officer

Bourghida, E

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2009/058609

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOERGENSEN, PER TROLLE ET AL: "A surprising ring opening mechanism in the formation of .alpha.-D-arabinofuranosyl nucleosides from 5-substituted uracils" SYNTHESIS, (12), 1299-306 CODEN: SYNTBF; ISSN: 0039-7881, 1992, XP002518359 page 1299; compound 5D -----	1-6, 15, 16
X	WO 2005/080354 A (PF MEDICAMENT [FR]; DUPONT-PASSELAIGUE ELISABETH [FR]; LEROY ISABELLE) 1 September 2005 (2005-09-01) page 56; claims 11,13; example 8 -----	1-16

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No  
PCT/EP2009/058609

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005080354 A	01-09-2005	AR 047748 A1 FR 2866339 A1	15-02-2006 19-08-2005
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