

1,2,4-TRIAZINE DERIVATIVES, PREPARATION AND USE THEREOF IN HUMAN THERAPY

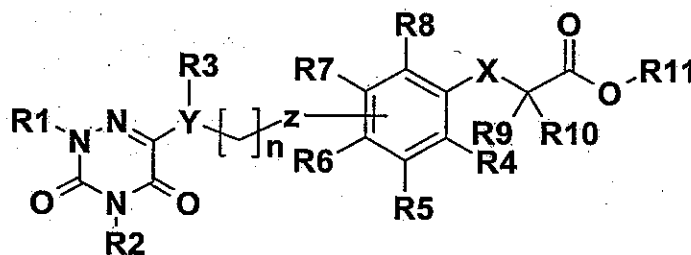
The present invention has as an aim new
5 derivatives of 3,5-dioxo-(2H,4H)-1,2,4-triazine
functionalized at 2, 4 and 6 which activate PPAR alpha
and/or gamma receptors, their preparation and their
application in human therapeutics.

Metabolic syndrome is the result of a
10 peripheral resistance to increased insulin and is
characterized by hyperinsulinemia, intolerance to
glucose, change in lipid metabolism and arterial
hypertension (Grundy, S.M.: Hypertriglyceridemia,
insulin resistance, and the metabolic syndrome. *Am. J.*
15 *Cardiol.* 1999, **83**, 25F-29F). Obesity is often
associated with these metabolic disorders, and the
conjunction of these multiple risk factors favors the
development of the atheromatosis at the origin of
arterial thrombosis, today the number one cause of
20 mortality in industrialized areas. Peroxisome
proliferator-activated receptors (PPAR) belong to the
superfamily of transcription factor nuclear receptors.
After activation, they form heterodimers with 9-cis
retinoic acid receptor (RXR); this complex (PPAR-RXR)
25 is linked specifically with DNA sequences located in
the regulatory regions of genes implicated in the
metabolism of lipids and carbohydrates (Pineda Torra,
I., Gervois, P. and Staels, B.: Peroxisome proliferator-
activated receptor alpha in metabolic disease,
30 inflammation, atherosclerosis and aging. *Curr. Opin.*
Lipidol. 1999, **10**, 151-159. Vamecq, J. and Latruffe,
N.: Medical significance of peroxisome proliferator-

activated receptors. *Lancet* 1999, 354, 141-148.). PPAR activation, on the one hand, restores certain altered metabolic pathways that predispose to atherosclerosis, and on the other reduces the inflammatory events which favor atheroma plaque development and rupture.

The compounds of the present invention are characterized by their original structure, their affinity with respect to alpha and/or gamma PPAR receptors and their pharmacological profile.

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



I

in which

-R₁ and R₂ can be identical or different and represent an alkyl or alkenyl radical, linear or branched, at C₁-C₇, an alkyl radical at C₁-C₆ substituted by groups such as trifluoromethyl, cycloalkyl at C₅-C₆, nitrile, alkoxy carbonyl vinyl at C₁-C₄, hydroxycarbonyl vinyl, alkoxy carbonyl at C₁-C₄, carboxylate, benzyloxy or phenyl (for which the core phenyl is possibly substituted by one or more groups such as alkyl at C₁-C₄, alkoxy at C₁-C₄, nitro, halogen or trifluoromethyl),

- YR₃ represents oxygen or NR₃ in which R₃ represents hydrogen, an alkyl or alkenyl radical, linear or branched at C₁-C₇, an alkyl radical at C₁-C₆ substituted by groups such as trifluoromethyl or phenyl (for which the core phenyl is possibly substituted by one or more groups such as alkyl at C₁-C₄, alkoxy at C₁-C₄, nitro, halogen or trifluoromethyl),
- 5 -Z represents an oxygen atom or a carbon atom which can be bound in ortho, meta or para position on the phenyl group of formula I, -n can range from 0 to 5 when Z=C or from 2 to 4 when Z=O,
- 10 -X represents oxygen or sulfur, -R₄, R₅, R₆, R₇ and R₈ represent hydrogen or fluorine, -R₉, R₁₀ and R₁₁ represent hydrogen or an alkyl group, linear or branched, at C₁-C₅, as well as additive salts with pharmaceutically
- 15 acceptable bases and the various enantiomers of compounds having asymmetrical carbons, as well as their mixtures in all proportions, including racemic mixtures in particular.
- 20 The invention relates, in particular, to the compounds of formula I in which:
- 25 -R₁ and R₂ represent, independently one from the other, an alkyl or alkenyl radical, linear or branched, at C₁-C₇, an alkyl radical at C₁-C₆ substituted by groups such as trifluoromethyl, cycloalkyl at C₆, nitrile,
- 30

- or phenyl (for which the core phenyl is possibly substituted by one or more groups such as alkyl at C₁-C₄, alkoxy at C₁-C₄, nitro, halogen or trifluoromethyl),
- 5 -YR₃ represents oxygen or NR₃ in which R₃ represents hydrogen, an alkyl or alkenyl radical, linear or branched, at C₁-C₇, an alkyl radical at C₁-C₆ substituted by groups such as trifluoromethyl or phenyl,
- 10 -Z represents an oxygen atom or a carbon atom which can be bound in ortho, meta or para position on the phenyl group of formula I
- n can range from 0 to 5 when Z=C or from 2 to 4 when Z=O,
- 15 -X represents oxygen or sulfur,
- R₄, R₅, R₆, R₇ and R₈ represent hydrogen or fluorine,
- R₉, R₁₀ and R₁₁ represent hydrogen or an alkyl group, linear or branched, at C₁-C₅.
- 20 The invention relates, more particularly, to the compounds of formula I in which:
- R₁ and R₂ represent independently one from the other, an alkyl or alkenyl radical, linear or branched, at C₁-C₇, an alkyl radical at C₁-C₆
- 25 substituted by groups such as trifluoromethyl or nitrile,
- YR₃ represents oxygen or NR₃ in which R₃ represents hydrogen or a linear or branched alkyl radical at C₁-C₇,

- Z represents a carbon atom which can be bound in ortho, meta or para position on the phenyl group of formula I,
- n can range from 0 to 5,
- 5 -X represents oxygen or sulfur,
- R₄, R₅, R₆, R₇ and R₈ represent hydrogen or fluorine,
- R₉, R₁₀ and R₁₁ represents hydrogen or a linear or branched alkyl group at C₁-C₅, in particular R₉ and R₁₀ represent a methyl group and R₁₁ hydrogen or an ethyl
- 10 group.

The invention relates still more particularly to the derivatives of 3,5-dioxo-(2H,4H)-1,2,4-triazine of formula I in which:

- 15 -R₁ and R₂ represent independently one from the other, an alkyl or alkenyl radical, linear or branched, at C₁-C₇, possibly substituted at the end of the chain by a trifluoromethyl group,
- YR₃ represents oxygen or NR₃ in which R₃ represents
- 20 hydrogen or a linear or branched alkyl radical at C₁-C₇,
- Z represents a carbon atom which can be bound in meta or para position on the phenyl group of formula I,
- 25 -n can range from 1 to 5,
- X represents oxygen or sulfur,
- R₄ to R₈ represent hydrogen,
- R₉ and R₁₀ represent a methyl radical
- R₁₁ represents hydrogen or an ethyl radical.

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The invention encompasses salts of the compounds of general formula I with pharmaceutically acceptable

bases, as well as the various enantiomers of compounds possessing asymmetrical carbons, as well as their mixtures in all proportions including racemic mixtures in particular.

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SYNTHESIS

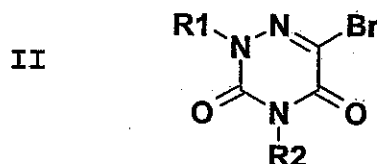
The compounds of the present invention can be synthesized by using the synthetic pathways described below or by using synthesis methods known to those skilled in the art.

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Method 1

The synthesis of compounds of general formula I is characterized (diagram 1) wherein a derivative of general formula II is condensed

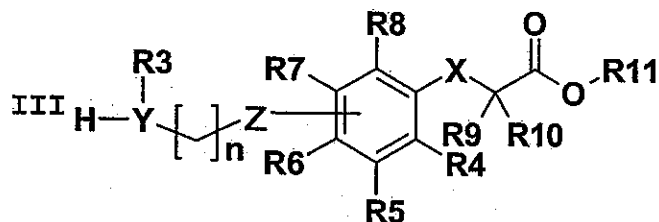
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in which R_1 and R_2 represent the groups as previously described in formula I with a derivative of general formula III

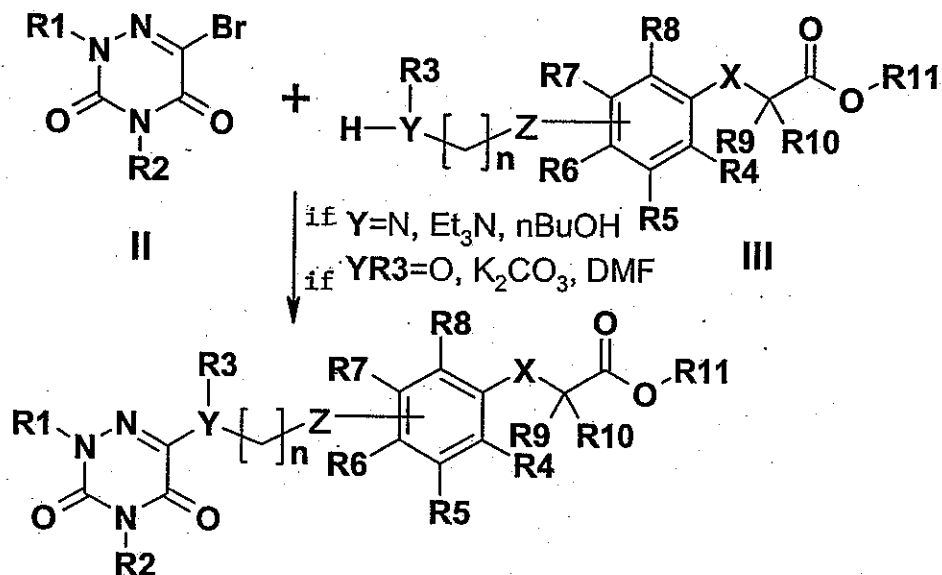
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where YR_3 , n , Z , X , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} and R_{11} are such as described previously in formula I. This reaction can be carried out in the presence of a base

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such as triethylamine in n-butanol (when $Y=N$) or potassium carbonate in dimethylformamide (when $YR_3=O$);



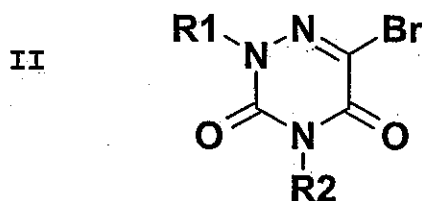
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Diagram 1

Method 2

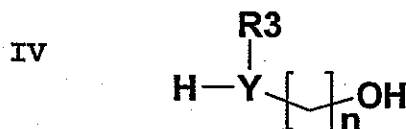
This synthesis method for compounds of general formula I for which $Z=O$ (diagram 2) is characterized wherein:

- 10 1) a derivative of general formula II is condensed



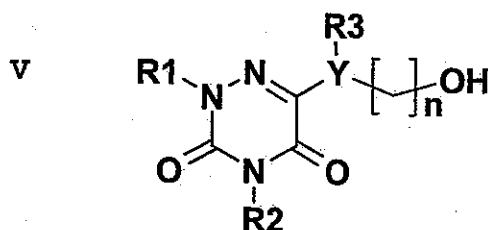
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in which R_1 and R_2 represent the groups as previously described in formula I with a derivative of general formula IV

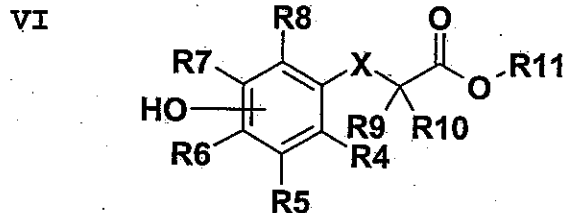


in which R_3Y can be equal to NH or O and n is such as described previously in formula I. This reaction can be carried out in the absence of solvent without adding base (in the case where $R_3Y=NH$) or in the presence of a base such as K_2CO_3 (in the case where $R_3Y=O$).

2) the derivative obtained **V** is condensed



with a compound of general formula **VI**



where X , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} and R_{11} are as described previously in formula I. This reaction can be carried out under conditions such as those of the Mitsunobu reaction in the presence of triphenylphosphine and diethylazodicarboxylate in THF.

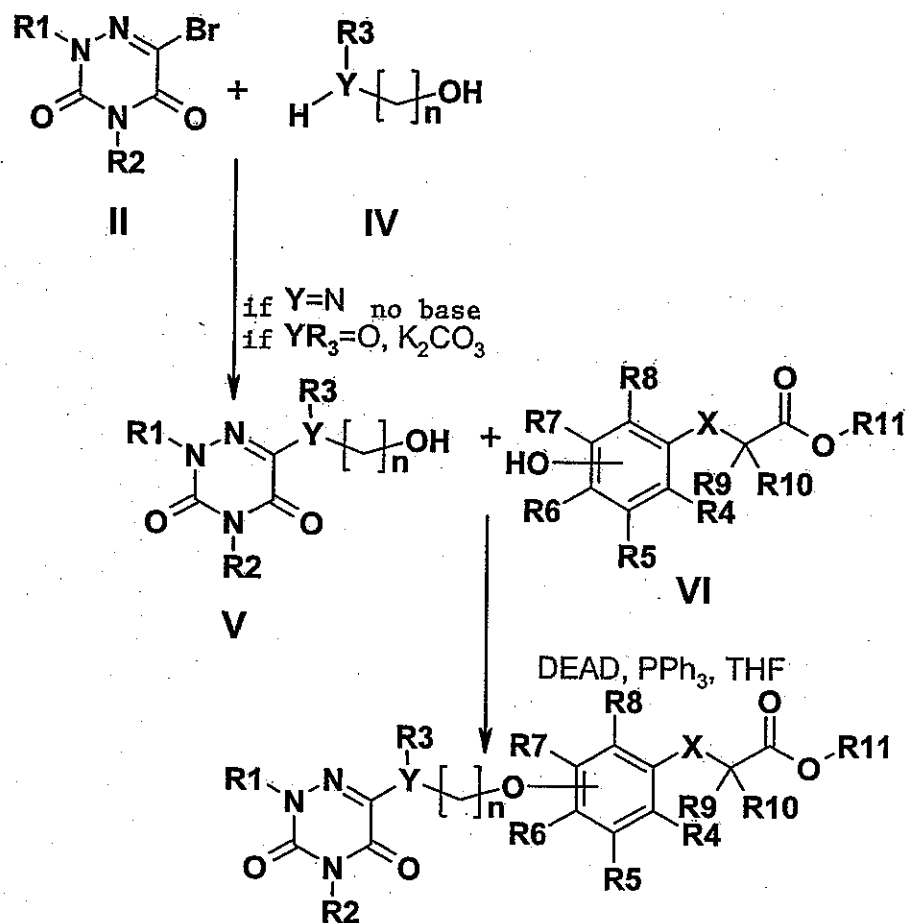


Diagram 2

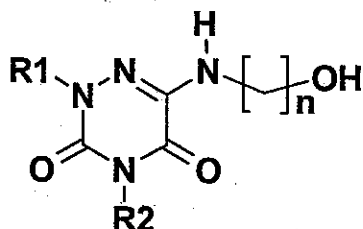
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Method 3

This synthesis method for compounds of general formula I for which Z=O (diagram 3) is characterized wherein:

- 1) the alcohol function of a derivative of general formula VII is protected

VII



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2) the nitrogen of compound VIII previously
20 obtained is alkylated by a halogenated derivative R_3Hal
in which the Hal group represents a halogen such as Cl,
Br or I and R_3 is as described previously in formula I,
under operating conditions such as NaH or tBuOK in DMF.



35 3) the compound IX thus obtained is deprotected under operating conditions such as tetrabutylammonium fluoride in THF.

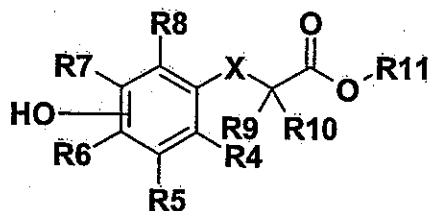
4) the derivative obtained **X** is condensed



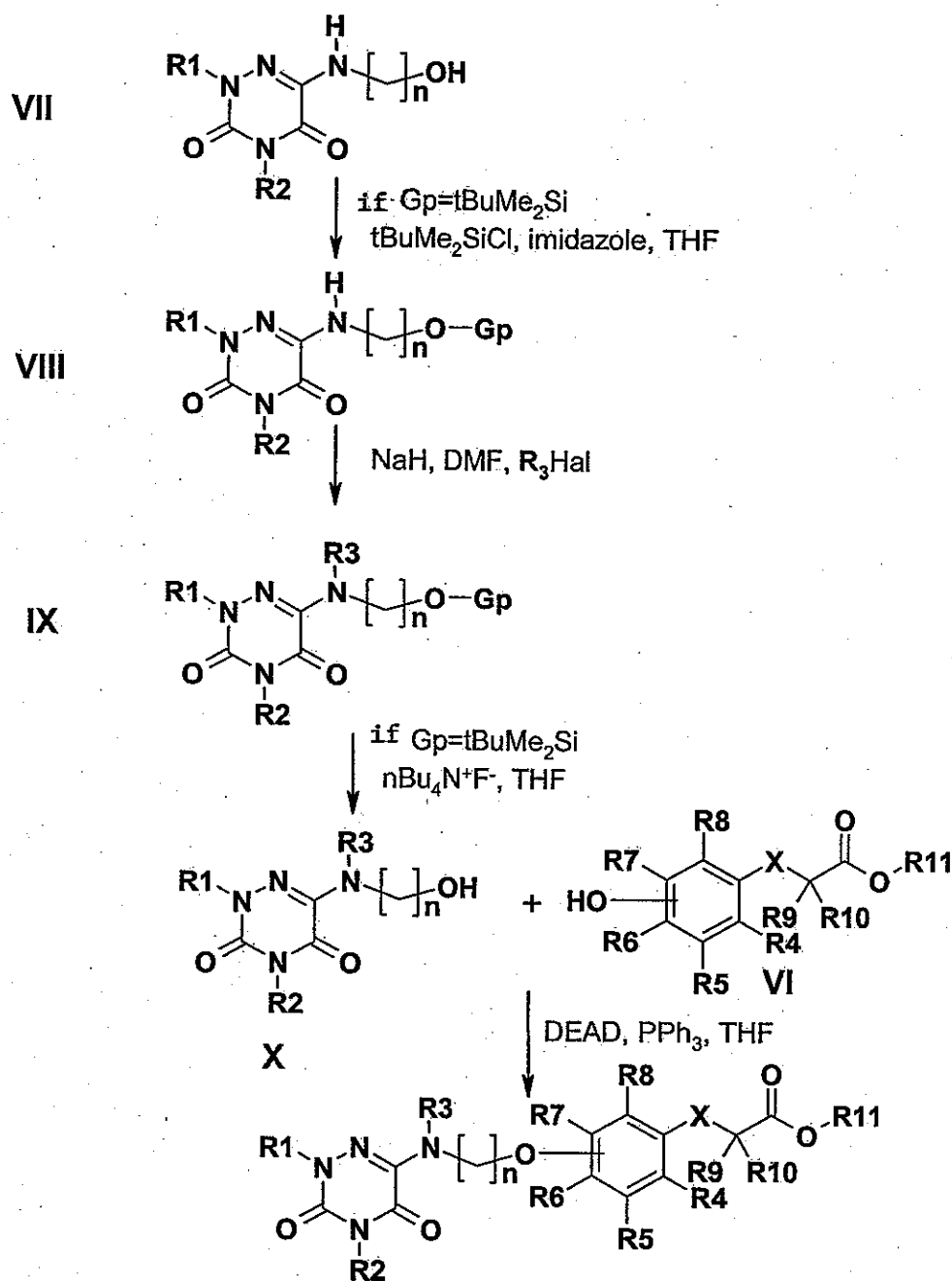
with a compound of general formula VI

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VI

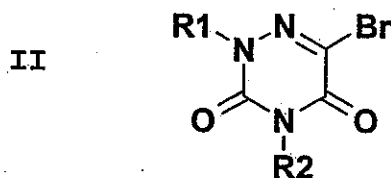


where X, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀ and R₁₁ are as described previously in formula I. This reaction can be carried out under conditions such as those of the Mitsunobu reaction in the presence of triphenylphosphine and diethylazodicarboxylate in THF.

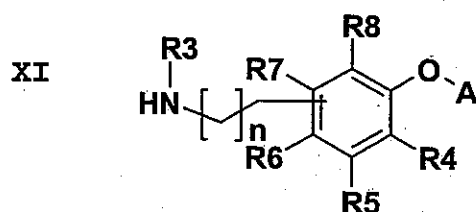
Diagram 35 Method 4

This method is implemented when Y=N and Z=C and it is characterized (diagram 4) wherein:

1) a derivative of general formula II is condensed

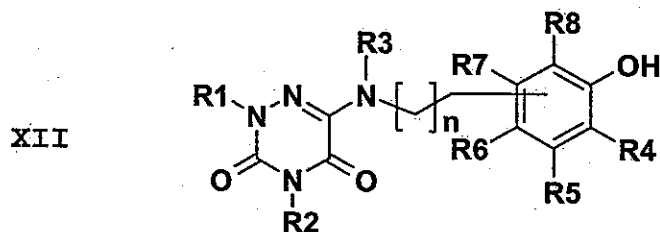


in which R_1 and R_2 represent the groups as previously described in formula I with a derivative of general formula XI

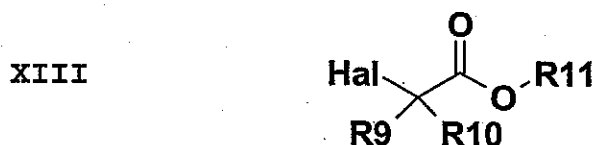


in which n , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are as described previously in formula I and A can be hydrogen or a methyl group. This reaction can be carried out in the presence of a base such as triethylamine in n-butanol.

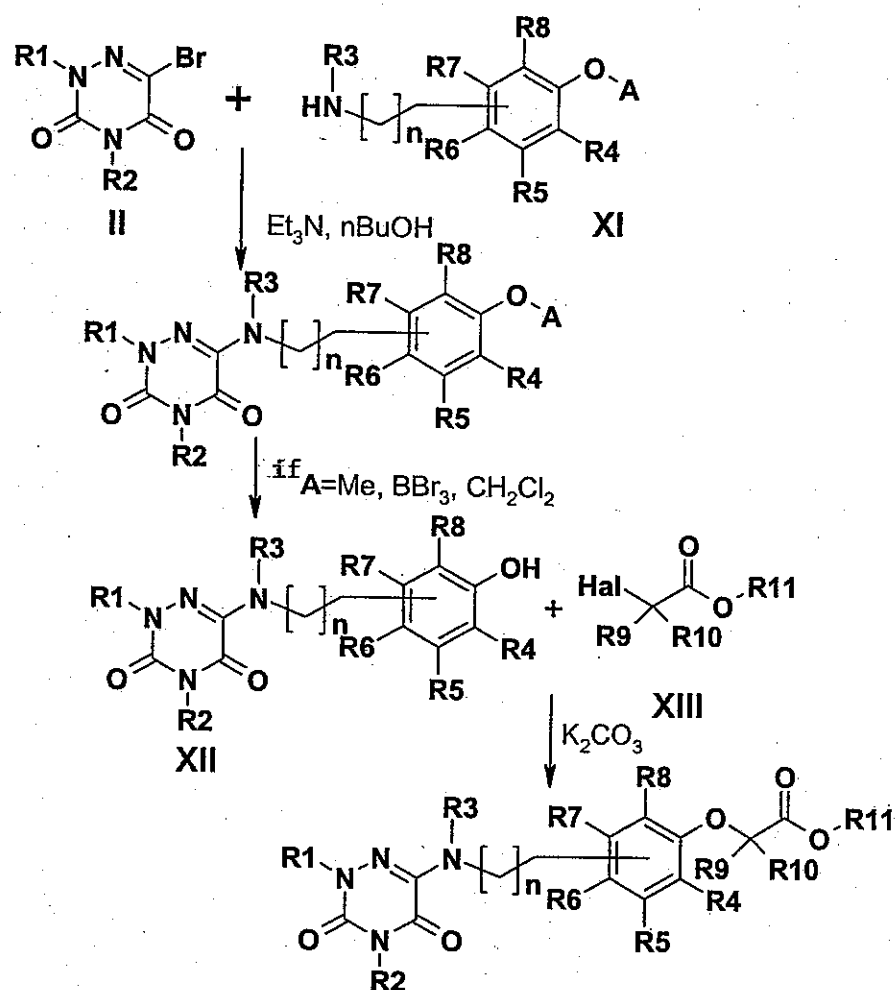
2) after demethylation (if $A=Me$, under conditions such as BBr_3 in dichloromethane), the phenol function of derivative XII is alkylated



by a halogenated derivative of general formula XIII (used as a solvent in the presence of a base such as potassium carbonate)



in which the Hal group represents a halogen such as Cl, Br or I, and R₉, R₁₀ and R₁₁ are as previously described in general formula I.



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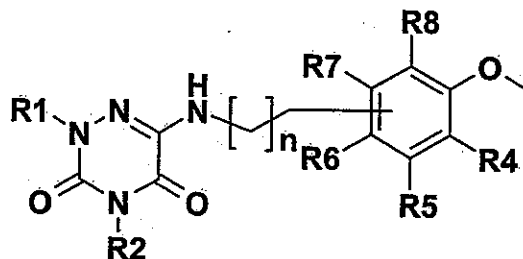
Diagram 4

Method 5

This method is implemented when Y=N and Z=C and it is characterized (diagram 5) wherein:

- 1) a derivative of general formula **XIV** is alkylated

XIV

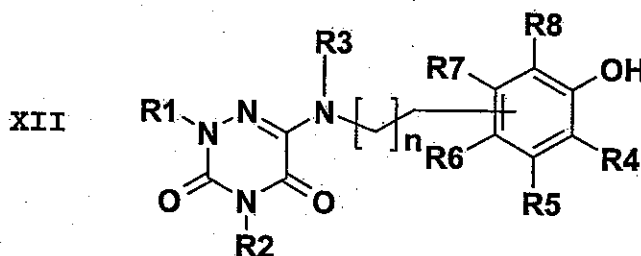


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in which R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 et n are as described previously in formula I with a derivative of formula $R_3\text{Hal}$ in which the Hal group represents a halogen such as Cl, Br or I and R_3 is as described previously in formula I, under operating conditions such as NaH or tBuOK in DMF.

2) after demethylation under conditions such as BBR_3 in dichloromethane, the phenol function of the derivative XII thus obtained is alkylated

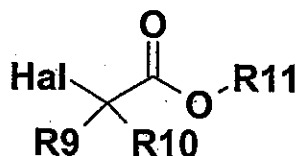
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by a halogenated derivative of general formula XIII (used as a solvent in the presence of a base such as potassium carbonate)

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XIII



in which the Hal group represents a halogen such as Cl, Br or I, and R_9 , R_{10} and R_{11} are as previously described in general formula I.

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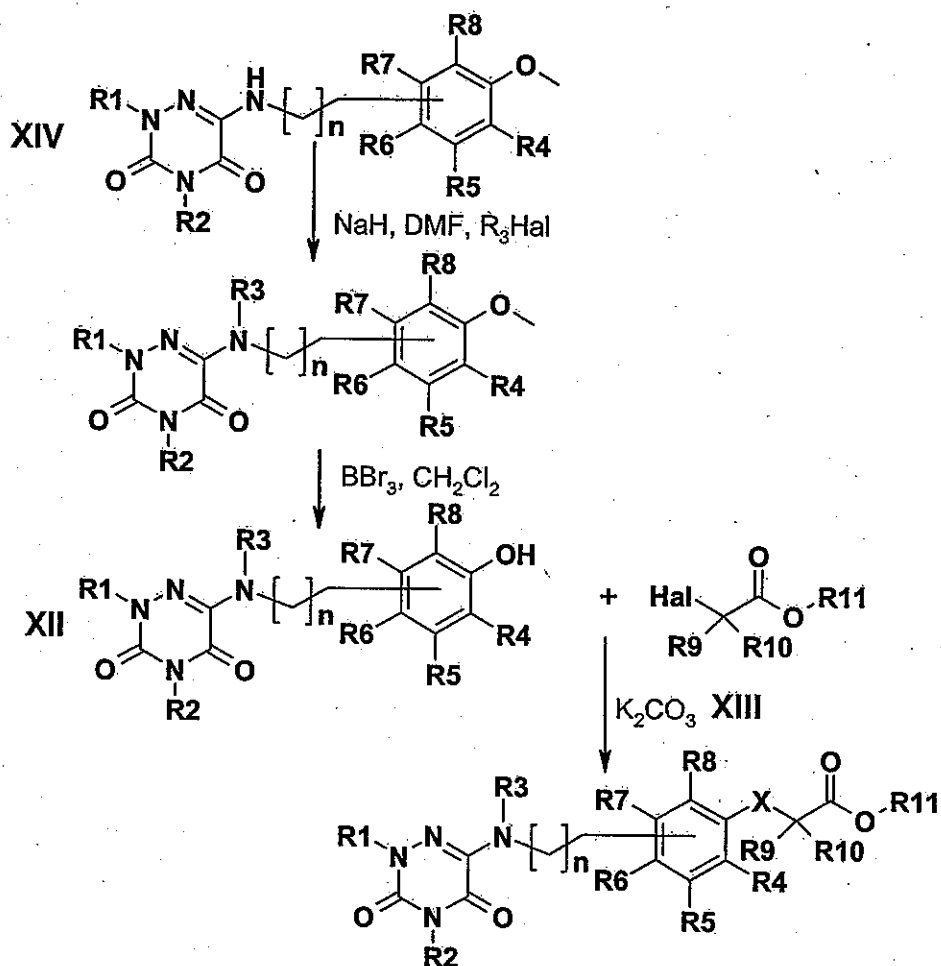


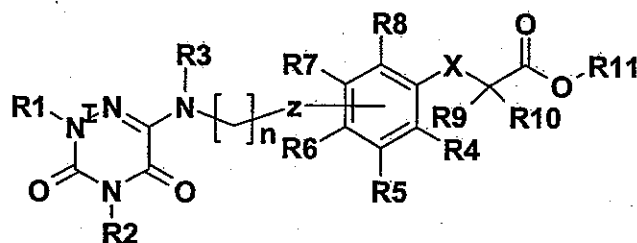
Diagram 5

Method 6

5 This method is characterized (diagram 6) wherein:

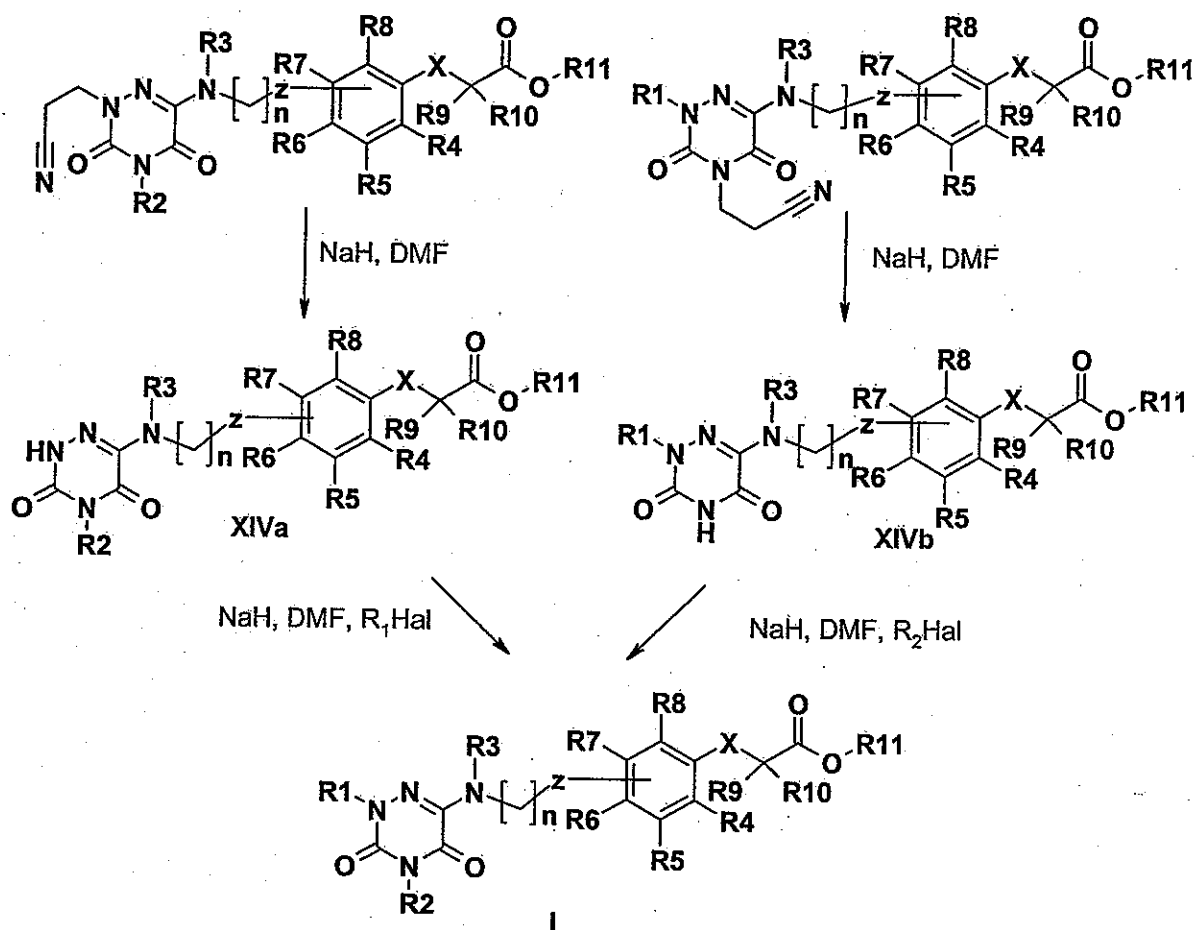
1) a derivative of general formula XIV is placed

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XIVb

by a halogenated derivative of general formula R_1Hal in the case of the intermediate **XIVa** and of general formula R_2Hal in the case of the intermediate **XIVb** in which the **Hal** group represents a halogen such as Cl, Br or I and R_1 and R_2 are as described previously in formula I, under operating conditions such as NaH or tBuOK in DMF.

**Diagram 6**

If desired, the intermediate and final compounds can be purified according to one or more purification methods chosen among extraction, filtration, silica gel chromatography, normal or reverse phase preparative HPLC and crystallization.

The raw materials used in the methods described previously are commercially available or easily accessible to those skilled in the art according to methods described in the literature.

The following examples illustrate the invention without limiting its scope.

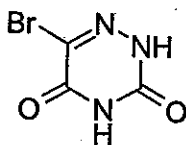
Elementary analyses and IR and NMR spectra confirm the compounds' structures.

INTERMEDIATES

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Intermediate 1:

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

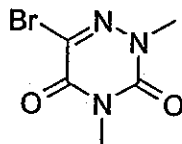


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2H-[1,2,4]triazine-3,5-dione (50 g, 442 mmol) is placed in the presence of 60 ml of bromine in 800 ml of water at 60°C for 10 h. The reaction medium is then slowly added to an ammonia solution until pH=5. It is then extracted in ethyl acetate and the organic phases are dried on MgSO₄. After filtration and dry concentration, **1a** is isolated in the form of a white solid (79.2 g, yield=93%). TLC silica gel 60 F 254 Merck, CH₂Cl₂:MeOH 90:10, R_f = 0.32.

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

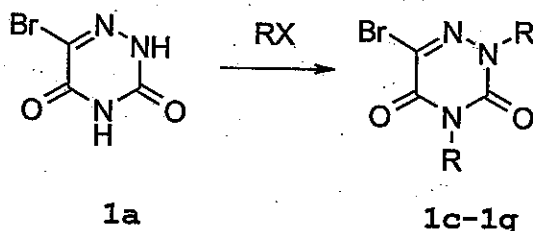


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11.8 g (295 mmol) of NaH (60% in paraffin) is placed in suspension at 0 °C in 250 ml of DMF under nitrogen. 25.80 g (135 mmol) of intermediate **1a** diluted

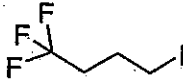
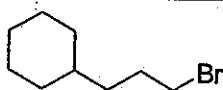
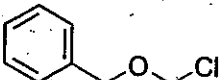
in 150 ml of DMF is added drop by drop. This solution is then placed at ambient temperature and 18.4 ml (296 mmol) of methyl iodide is added dropwise. After a night of stirring and after dry concentration of the reaction medium, the residue obtained is taken up in water and extracted with ethyl acetate. The organic phases are washed with brine, dried on magnesium sulfate then dry concentrated. The residue obtained, taken up in ether, crystallizes and a first crystal fraction is isolated. The filtrate is dry concentrated the purified by plash chromatograph on silica (heptane:AcOEt 50:50). 24 g of intermediate **1b** are thus isolated (81% yield). TLC silica gel 60 F 254 Merck, CH₂Cl₂:AcOEt 80:20, R_f = 0.59.

c) Intermediates (1c)-(1g)

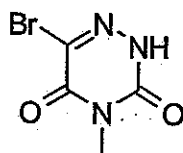


The synthesis of intermediates **1c-1g** is carried out starting from **1a** according to the procedure described for the synthesis of **1b** by using various alkylation agents **RX**.

Table 1: intermediates 1c-1g

RX	Yield	TLC	State	Intermediates 1c-1g
	80%	PE:AcOEt 80:20 Rf=0.42	oil	1c : 6-Bromo-2,4-dibutyl-2H-[1,2,4]triazine-3,5-dione
	95%	PE:AcOEt 80:20 Rf=0.75	solid	1d : 6-Bromo-2,4-bis-(4,4,4-trifluorobutyl)-2H-[1,2,4]triazine-3,5-dione
	95%	PE:AcOEt 90:10 Rf=0.81	oil	1e : 6-Bromo-2,4-diheptyl-2H-[1,2,4]triazine-3,5-dione
	92%	PE:AcOEt 90:10 Rf=0.82	oil	1f : 6-Bromo-2,4-bis-(3-cyclohexylpropyl)-2H-[1,2,4]triazine-3,5-dione
	98%	PE:AcOEt 70:30 Rf=0.62	oil	1g : 2,4-Bis-benzyloxymethyl-6-bromo-2H-[1,2,4]triazine-3,5-dione

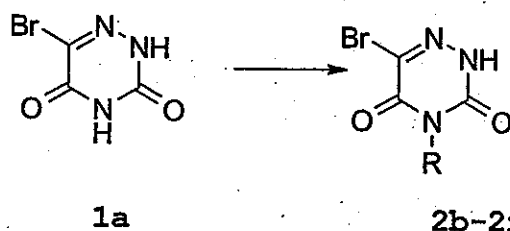
TLC: silica gel 60 F 254 Merck, PE=petroleum ether

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

- 5 20.3 g (105.7 mmol) of triazine **1a** are placed in 150 ml of acetic anhydride at reflux for 4.5 h. After dry concentration of the reaction medium, a precipitate is isolated then recrystallized in ether: 24.3 g of crystals are isolated (yield=98%).
- 10 4.5 g (114.2 mmol) of NaH (60% in paraffin) are placed in 50 ml of DMF under nitrogen. A solution of 24.3 g (103.8 mmol) of crystals isolated previously in 150 ml of DMF is added dropwise. The reaction medium is stirred for 45 mn at ambient temperature and then 7 ml (114.2 mmol) of
- 15 methyl iodide are added; stirring is then continued for 21 h at ambient temperature. After dry concentration, the residue obtained is taken up in H₂O and extracted with ethyl acetate. After drying on MgSO₄, the organic phases are evaporated and the clear oil obtained is
- 20 purified by flash chromatography on silica (CH₂Cl₂:AcOEt 90:10). 22.9 g of crystals (yield=89%) are isolated and are placed in 300 ml of ethanol in the presence of 0.6 g of p-toluene sulfonic acid. This mixture is heated at reflux for 4.5 h and then dry
- 25 concentrated. The residue is taken up in H₂O and extracted with ethyl acetate. After drying and evaporation of the organic phases, 17 g of intermediate **2a** is isolated in the form of a solid (yield=89%). TLC

silica gel 60 F 254 Merck, CH_2Cl_2 :AcOEt 90:10, R_f = 0.29.

b) Intermediates (2b)-(2f)



The synthesis of intermediates **2b-2f** is carried out starting from **1a** according to the procedure described for the synthesis of **2a** by using various alkylation agents **RX**.

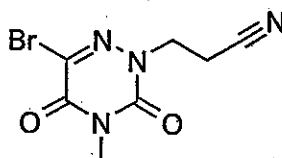
Table 2: intermediates **2b-2f**

RX	Total yield	TLC	State	Intermediates 2b-2f
	73%	PE:AcOEt 80:20 R_f =0.28	solid	2b : 6-Bromo-4-butyl-2H-[1,2,4]triazine-3,5-dione
	60%	PE:AcOEt 80:20 R_f =0.26	solid	2c : 6-Bromo-4-(3-methyl-but-2-enyl)-2H-[1,2,4]triazine-3,5-dione
	76%	CH_2Cl_2 :AcOEt 90:10 R_f =0.45	solid	2d : 6-Bromo-4-(4,4,4-trifluoro-butyl)-2H-[1,2,4]triazine-3,5-dione
	84%	PE:AcOEt 70:30 R_f =0.73	solid	2e : 6-Bromo-4-heptyl-2H-[1,2,4]triazine-3,5-dione
	82%	PE:AcOEt 70:30 R_f =0.25	solid	2f : 4-Benzyl-6-bromo-2H-[1,2,4]triazine-3,5-dione

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

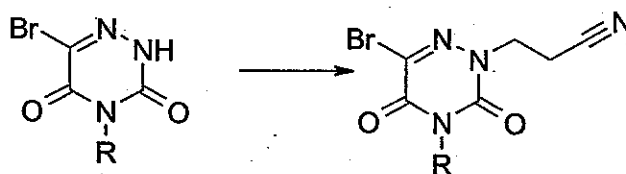
Intermediate 3:

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



2.4 g (11.6 mmol) of triazine **2a** and 7 ml (106 mmol) of acrylonitrile are placed in 24 ml of a solution of pyridine and water (1:1) at reflux for 3 h. After concentration the reaction medium is extracted by AcOEt, and after drying on MgSO₄ the organic phases are dry concentrated. 2.8 g of solid **3a** are isolated and then washed with ether (yield=93%). TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, R_f=0.18.

b) Intermediates 3b and 3c



R=(CH₂)₃CF₃

2d

3b

R=(CH₂)₆CH₃

2e

3c

The synthesis of intermediates **3b** and **3c** is carried out starting from intermediates **2d** and **2e**, respectively,

following the procedure described for the synthesis of 3a.

Table 3: intermediates 3b and 3c

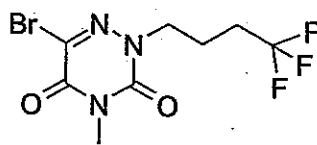
Starting molecule	Yield	TLC	State	Intermediates 3b-3c
2d	91%	PE:AcOEt 70:30 Rf=0.34	solid	3b: 3-[6-Bromo-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-4,5-dihydro-3H-[1,2,4]triazin-2-yl]-propionitrile
2e	95%	CH ₂ Cl ₂ :AcOEt 70:30 Rf=0.51	solid	3c: 3-(6-Bromo-4-heptyl-3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-propionitrile

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

Intermediate 4:

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

10

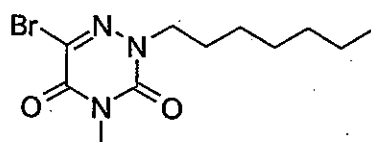


0.85 g (21.3 mmol) of NaH (60% in paraffin) is placed in 10 ml of DMF under nitrogen. A solution of 4 g (19.4 mmol) of intermediate 2a in 40 ml of DMF is added dropwise. The reaction medium is stirred for 1 h at ambient temperature and then 5 g (21.3 mmol) of 1,1,1-trifluoro-4-iodo-butane are added; stirring is then continued for 3 h at ambient temperature. After dry concentration, the residue obtained is taken up in H₂O

15

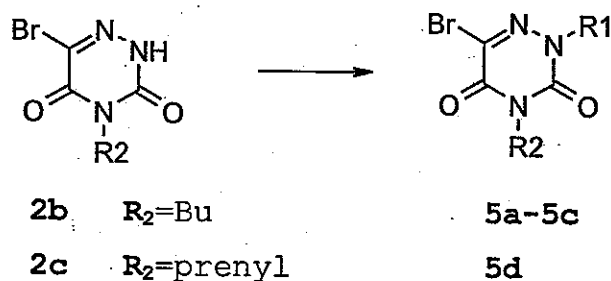
and extracted with ethyl acetate. After drying on MgSO_4 , the organic phases are evaporated and the oil obtained is purified by flash chromatography on silica (petroleum ether:AcOEt 80:20). 5.3 g of crystals
 5 corresponding to compound **4a** are isolated (yield=87%).
 TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, $R_f=0.58$.

d) 6-Bromo-2-heptyl-4-methyl-2H-
 10 [1,2,4]triazine-3,5-dione (4b)



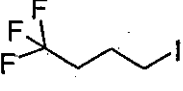
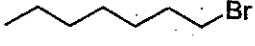
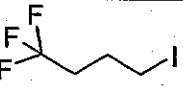
The synthesis of intermediate **4b** is carried out starting from **2a** according to the procedure described for the synthesis of **4a** by using 1-bromoheptane for the
 15 alkylation step (yield=91%). TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, $R_f=0.76$.

Intermediate 5:

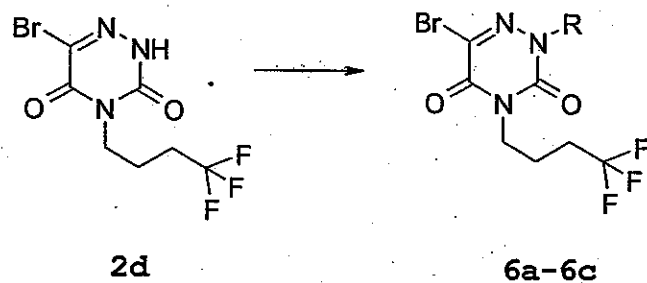


The synthesis of intermediates **5a-5d** is carried out starting from intermediates **2b** and **2c** according to the
 25 procedure described for the synthesis of **4a** by using various halogenated derivatives R_1X .

Table 4: intermediates 5a-5d

R_1X	Yield	TLC	State	Intermediates 5a-5c
—I	64%	CH ₂ Cl ₂ :AcOEt 95:5 R _f =0.75	solid	5a : 6-Bromo-4-butyl-2-methyl-2H-[1,2,4]triazine-3,5-dione
	95%	PE:AcOEt 80:20 R _f =0.61	oil	5b : 6-Bromo-4-butyl-2-(4,4,4-trifluorobutyl)-2H-[1,2,4]triazine-3,5-dione
	72%	PE:AcOEt 80:20 R _f =0.75	oil	5c : 6-Bromo-4-butyl-2-heptyl-2H-[1,2,4]triazine-3,5-dione
	90%	PE:AcOEt 80:20 R _f =0.58	oil	5d : 6-Bromo-4-(3-methylbut-2-enyl)-2-(4,4,4-trifluorobutyl)-2H-[1,2,4]triazine-3,5-dione

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

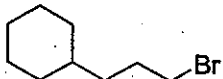
Intermediate 6:

5

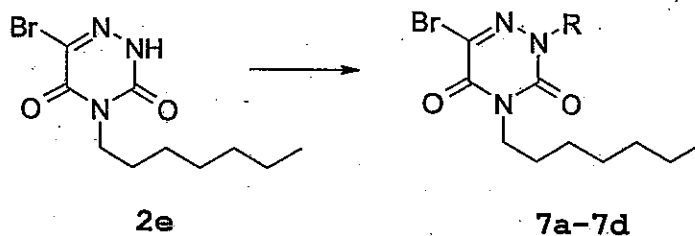
The synthesis of intermediates **6a-6c** is carried out starting from intermediate **2d** according to the procedure described for the synthesis of **4a** by using

10 various halogenated derivatives **RX**.

Table 5: intermediates 6a-6c

RX	Yield	TLC	State	Intermediates 6a-6b
—I	91%	PE:AcOEt 70:30 Rf=0.61	solid	6a : 6-Bromo-2-methyl-4-(4,4,4-trifluorobutyl)-2H-[1,2,4]triazine-3,5-dione
 Br	88%	PE:AcOEt 60:40 Rf=0.53	oil	6b : 6-Bromo-2-heptyl-4-(4,4,4-trifluorobutyl)-2H-[1,2,4]triazine-3,5-dione
 Br	80%	PE:AcOEt 60:40 Rf=0.43	oil	6c : 6-Bromo-2-(3-cyclohexyl-propyl)-4-(4,4,4-trifluorobutyl)-2H-[1,2,4]triazine-3,5-dione

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

Intermediate 7:

5

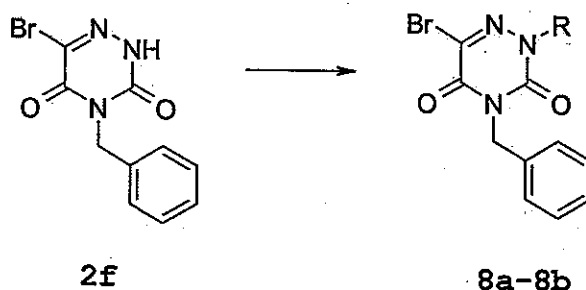
The synthesis of intermediates **7a-7d** is carried out starting from intermediate **2e** according to the procedure described for the synthesis of **4a** by using various halogenated derivatives **RX**.

10

Table 6: intermediates 7a-7d

RX	Yield	TLC	State	Intermediates 7a-7d
	92%	CH ₂ Cl ₂ :MeOH 95:5 R _f =0.65	oil	7a : 6-Bromo-4-heptyl-2-methyl-2H-[1,2,4]triazine-3,5-dione
	98%	PE:AcOEt 70:30 R _f =0.81	oil	7b : 6-Bromo-4-heptyl-2-(4,4,4-trifluorobutyl)-2H-[1,2,4]triazine-3,5-dione
	80%	PE:AcOEt 80:20 R _f =0.60	oil	7c : 2-Benzyl-6-bromo-4-heptyl-2H-[1,2,4]triazine-3,5-dione
	78%	PE:AcOEt 80:20 R _f =0.59	oil	7d : 6-Bromo-2-cyclohexylmethyl-4-heptyl-2H-[1,2,4]triazine-3,5-dione

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

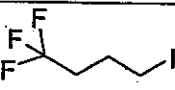
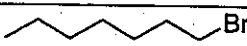
Intermediate 8:

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The synthesis of intermediates **8a-8b** is carried out starting from intermediate **2f** according to the procedure described for the synthesis of **4a** by using various halogenated derivatives **RX**.

10

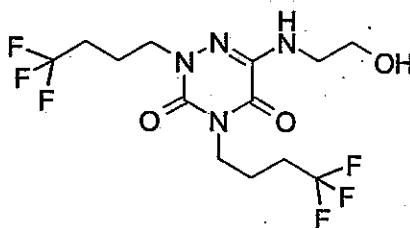
Table 7: intermediates 8a-8b

RX	Yield	TLC	State	Intermediates 8a-8b
	93%	PE:AcOEt 80:20 Rf=0.46	oil	8a: 4-Benzyl-6-bromo-2-(4,4,4-trifluoro-butyl)-2H-[1,2,4]triazine-3,5-dione
	98%	PE:AcOEt 80:20 Rf=0.66	oil	8b: 4-Benzyl-6-bromo-2-heptyl-2H-[1,2,4]triazine-3,5-dione

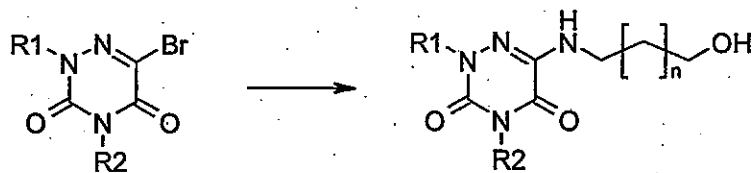
TLC: silica gel 60 F 254 Merck, PE=petroleum ether

Intermediate 9:

- 5 a) 6-(2-Hydroxy-ethylamino)-2,4-bis-(4,4,4-trifluoro-butyl)-2H-[1,2,4]triazine-3,5-dione (9a)



- 3 g (7.3 mmol) of triazine **1d** are placed in 1.3 ml of ethanolamine at 130 °C for 5 h. After cooling, 50 ml of water are added to the reaction medium which is then extracted with AcOEt. After drying on MgSO₄, the organic phases are dry concentrated and the residue obtained is purified by flash chromatography on silica (petroleum ether:AcOEt 70:30). 1.9 g of oil corresponding to intermediate **9a** is thus isolated (66% yield). TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, Rf=0.28.

b) Intermediates 9b-9l

9b-9d n=0

9e-9j n=1

9k-9l n=2

5

The synthesis of intermediates **9b-9l** is carried out from the starting compounds listed in table 8 following the procedure described for the synthesis of **9a**.

Table 8: intermediates **9b-9l**

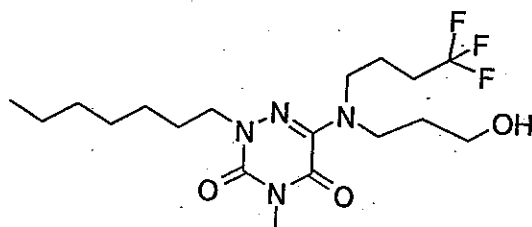
Starting molecule	Amino alcohol	Yield	TLC	State	Intermediates 9b-9k
4b	Ethanol - amine	77%	CH ₂ Cl ₂ :AcOEt 60:40 R _f =0.28	solid	9b : 2-Heptyl-6-(2-hydroxy-ethylamino)-4-methyl-2H-[1,2,4]triazine-3,5-dione
1e	Ethanol - amine	67%	PE:AcOEt 70:30 R _f =0.56	oil	9c : 2,4-Diheptyl-6-(2-hydroxy ethylamino)-2H-[1,2,4]triazine-3,5-dione
1f	Ethanol - amine	56%	PE:AcOEt 80:20 R _f =0.18	oil	9d : 2,4-Bis-(3-cyclohexyl-propyl)-6-(2-hydroxy-ethyl-amino)-2H-[1,2,4]triazine-3,5-dione
1b	Amino-propanol	18%	AcOEt R _f =0.42	oil	9e : 6-(3-Hydroxy-propyl-amino)-2,4-dimethyl-2H-[1,2,4]triazine-3,5-

					dione
4a	Amino-propano 1	44%	PE:AcOEt 70:30 Rf=0.13	solid	9f: 6-(3-Hydroxy-propylamino)-4-methyl-2-(4,4,4-trifluoro-butyl)-2H-[1,2,4]triazine-3,5-dione
4b	Amino-propano 1	67%	CH ₂ Cl ₂ :AcOEt 60:40 Rf=0.32	solid	9g: 2-Heptyl-6-(3-hydroxy-propylamino)-4-methyl-2H-[1,2,4]triazine-3,5-dione
6a	Amino-propano 1	45%	PE:AcOEt 80:20 Rf=0.05	solid	9h: 6-(3-Hydroxy-propyl-amino)-2-methyl-4-(4,4,4-trifluoro-butyl)-2H-[1,2,4]triazine-3,5-dione
7a	Amino-propano 1	34%	CH ₂ Cl ₂ :MeOH 90:10 Rf=0.47	solid	9i: 4-Heptyl-6-(3-hydroxy-propylamino)-2-methyl-2H-[1,2,4]triazine-3,5-dione
7b	Amino-propano 1	64%	PE:AcOEt 70:30 Rf=0.30	solid	9j: 4-Heptyl-6-(3-hydroxy-propylamino)-2-(4,4,4-trifluoro-butyl)-2H-[1,2,4]triazine-3,5-dione
1b	Amino-butanol	50%	AcOEt Rf=0.35	solid	9k: 6-(4-Hydroxy-butyl-amino)-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione

7a	Amino- butanol	21%	CH ₂ Cl ₂ :MeOH 90:10 Rf=0.45	solid	91: 4-Heptyl-6-(4- hydroxy-butylamino)- 2-methyl-2H- [1,2,4]triazine-3,5- dione
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TLC: silica gel 60 F 254 Merck, PE=petroleum ether

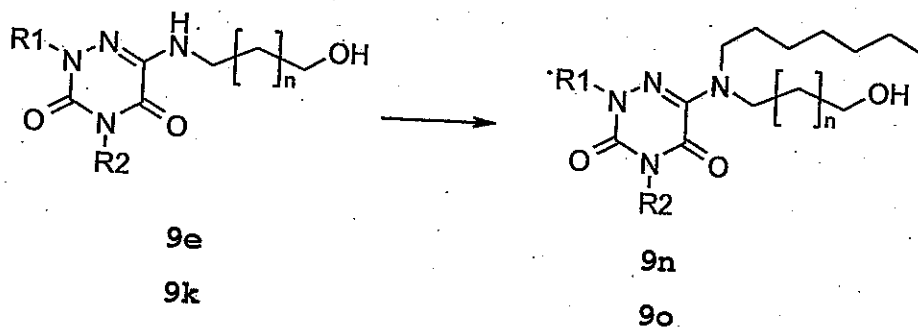
c) 2-heptyl-6-[(3-hydroxy-propyl)-(4,4,4-trifluoro-butyl)-amino]-4-methyl-2H-[1,2,4]triazine-3,5-dione (9m)



7.3 g (24.2 mmol) of triazine **9g** are placed in the presence of tert-butyl-chloro-dimethyl-silane (4 g, 26.5 mmol) in 50 ml of dichloromethane at ambient temperature overnight. The reaction medium is then washed with water followed with brine. After drying on MgSO₄, the organic phase is dry concentrated and the residue obtained is purified by flash chromatography on silica (CH₂Cl₂:AcOEt 95:5). 10 g of oil are isolated (quantitative yield). 4.1g (10 mmol) of this compound are placed in 40 ml of DMF at 0 °C under nitrogen, and then 0.4g (10 mmol) of NaH (60% in paraffin) is added by fractions; this mixture is then stirred for 10 mn. 2.4 g (10 mmol) of 1,1,1-trifluoro-4-iodo-butane are added and the solution is stirred at ambient temperature for 3 h. 0.5 equivalent of NaH as well as 1,1,1-trifluoro-4-iodo-butane are again added and stirring is continued for 2 h. After dry concentration,

the residue is taken up in H_2O then extracted with AcOEt. After drying on $MgSO_4$, the organic phases are dry concentrated and the oil obtained is purified by flash chromatography on silica (petroleum ether:AcOEt 90:10). 2 g of compound (yield=40%) are isolated and then diluted in 30 ml of THF; 7.4 ml of a tetrabutylammonium fluoride solution (1 M in THF) is then added dropwise. This mixture is stirred for 2 h at ambient temperature and then 50 ml of water are added and the medium is extracted with AcOEt. After drying on $MgSO_4$, the organic phases are dry concentrated and the oil obtained is purified by flash chromatography on silica (petroleum ether:AcOEt 70:30). 1.5 g of triazine **9m** is this isolated in the form of oil (quantitative yield). TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 90:10, $R_f=0.38$.

d) Intermediates 9n-9o



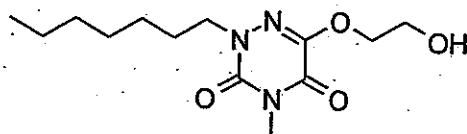
The synthesis of intermediates **9n** and **9o** is carried out starting from intermediates **9e** and **9k**, respectively, following the procedure described for the synthesis of **9m** using bromoheptane.

Table 9: intermediates 9n-9o

Starting molecule	Yield	TLC	State	Intermediates 9n-9o
9e	59%	heptane:AcOEt 50:50 Rf=0.16	oil	9n: 6-[Heptyl-(3-hydroxy-propyl)-amino]-2,4-dimethyl-2H-[1,2,4]triazine-3, 5-dione
9k	59%	heptane:AcOEt 50:50 Rf=0.24	oil	9o: 6-[Heptyl-(4-hydroxy-butyl)-amino]-2,4-dimethyl-2H-[1,2,4]triazine-3,5-dione

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

e) 2-heptyl-6-(2-hydroxy-ethoxy)-4-methyl-2H-[1,2,4]triazine-3,5-dione (9p)



1.5 g (4.9 mmol) of triazine 4b and 0.8 g (5.8 mmol) of K₂CO₃ are placed in 1.5 ml of ethyleneglycol at 130 °C for 0.5 h. 50 ml of water are added to the reaction medium which is then extracted with AcOEt. After drying on MgSO₄, the organic phases are dry concentrated and the residue obtained is purified by flash chromatography on silica (CH₂Cl₂:AcOEt 70:30). 0.5 g of oil corresponding to intermediate 9p is thus isolated (39% yield). TLC silica gel 60 F 254 Merck, heptane:AcOEt 50:50, Rf=0.08.

10



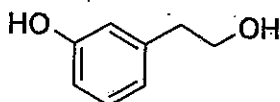
9q, 9r n=1

9s n=2

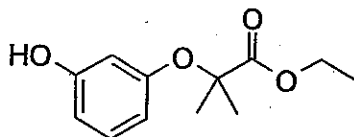
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Table 10: intermediates 9q-9s

TLC: silica gel 60 F 254 Merck

Intermediate 10:**a) 3-(2-Hydroxy-ethyl)-phenol (10a)**

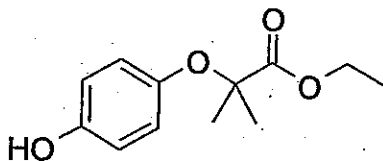
5 11.3 g of (3-hydroxy-phenyl)-acetic acid (74.2 mmol) are placed in 100 ml of THF at 0°C under nitrogen. 100 ml of a solution of LiAlH₄ (1 M in THF) is added dropwise at this temperature. The mixture is
 10 then placed at 60 °C for 2 h. It is then neutralized slowly with a 6 N HCl solution then extracted with diethyl ether. The organic phases are washed with water, dried on MgSO₄, then dry concentrated. The
 15 residue obtained is purified by flash chromatography on silica (CH₂Cl₂:AcOEt 70:30). 9 g of oil corresponding to intermediate **10a** are thus isolated (88% yield). TLC silica gel 60 F 254 Merck, CH₂Cl₂:AcOEt 70:30, R_f=0.18.

b) Ethyl 2-(3-hydroxy-phenoxy)-2-methyl-propionate (10b)

20 15 g of resorcinol (136 mmol) are added to
 25 120 ml of a solution of sodium (6.3 g, 274 mmol) in ethanol. The mixture is placed at reflux for 1 h then a solution of ethyl bromoisobutyrate (13.2 ml, 90 mmol) in 30 ml of ethanol is added dropwise. Heating is

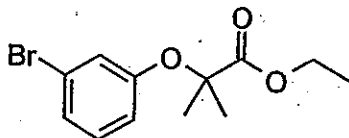
maintained for 3 h then the reaction medium is dry concentrated. The residue obtained is taken up in a solution of water and acetic acid then extracted with AcOEt. The organic phases are washed with water, dried on MgSO_4 , then dry concentrated. The residue obtained is purified by flash chromatography on silica (CH_2Cl_2 :AcOEt 90:10). 14.4 g of oil corresponding to intermediate **10b** are thus isolated (72% yield). TLC silica gel 60 F 254 Merck, CH_2Cl_2 :AcOEt 70:30, R_f =0.66.

c) Ethyl 2-(4-hydroxy-phenoxy)-2-methyl-propionate (10c)



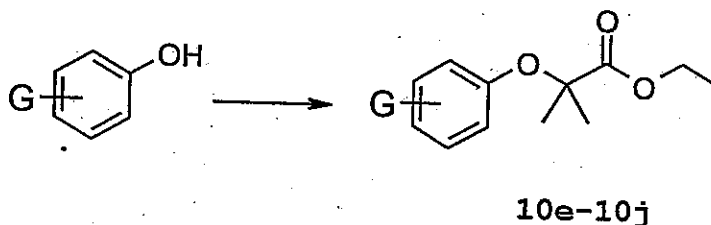
11 g of hydroquinone (100 mmol) in 100 ml of DMF is placed at 80 °C for 2 h. This mixture is cooled at ambient temperature then a solution of ethyl bromoisobutyrate (14.7 ml, 100 mmol) in 30 ml of DMF is added dropwise. The mixture is stirred for 3 h then the reaction medium is dry concentrated. The residue obtained is taken up in a 1 N HCl solution then extracted with AcOEt. The organic phases are washed with water, dried on MgSO_4 , then dry concentrated. The residue obtained is purified by flash chromatography on silica (petroleum ether:AcOEt 80:20). 9 g of oil corresponding to intermediate **10c** are thus isolated (40% yield). TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, R_f =0.50.

d) Ethyl 2-(3-bromo-phenoxy)-2-methyl-
propionate (10d)



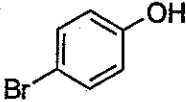
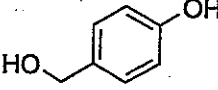
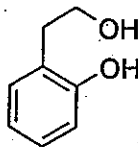
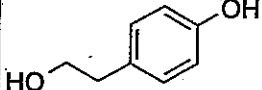
25 g (144.5 mmol) of 3-bromophenol are placed
5 in the presence of K_2CO_3 (21 g, 152 mmol) in 75 ml of
ethyl 2-bromoisobutyrate and heated to reflux for 7 h.
After elimination of K_2CO_3 by filtration, the reaction
medium is dry concentrated. After purification by flash
chromatography on silica (petroleum ether:AcOEt 90:10),
10 37 g of intermediate **10d** are collected in the form of
clear oil (yield=89%). TLC silica gel 60 F 254 Merck,
petroleum ether:AcOEt 90:10, R_f = 0.40.

d) Intermediates 10e-10j

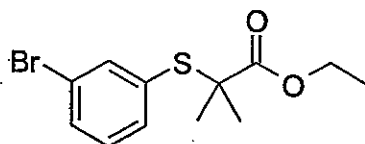


15 The synthesis of intermediates **10e-10j** is carried out
from the variously substituted phenols listed in table
20 **8** following the procedure described for the synthesis
of **10d**.

Table 11: intermediates 10e-10j

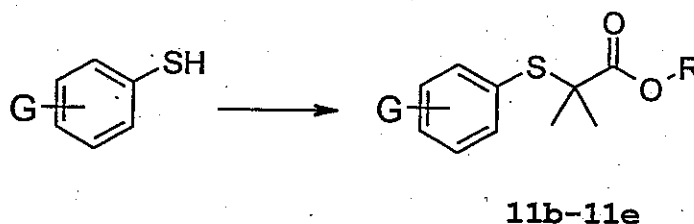
Starting phenol	Yield	TLC	State	Intermediates 10e-10j
	98%	PE:AcOEt 90:10 Rf=0.52	oil	10e: Ethyl 2-(4-bromophenoxy)-2-methylpropionate
	52%	CH ₂ Cl ₂ :AcOEt 80:20 Rf=0.36	oil	10f: Ethyl 2-(4-hydroxymethylphenoxy)-2-methylpropionate
	19%	CH ₂ Cl ₂ :AcOEt 90:10 Rf=0.50	oil	10g: Ethyl 2-[2-(2-hydroxy-ethyl)-phenoxy]-2-methylpropionate
10a	9%	CH ₂ Cl ₂ :AcOEt 70:30 Rf=0.68	oil	10h: Ethyl 2-[3-(2-hydroxy-ethyl)-phenoxy]-2-methylpropionate
	61%	CH ₂ Cl ₂ :AcOEt 90:10 Rf=0.21	oil	10j: Ethyl 2-[4-(2-hydroxy-ethyl)-phenoxy]-2-methylpropionate

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

5. Intermediate 11:a) Ethyl 2-(3-bromo-phenylsulfanyl)-2-methylpropionate (11a)

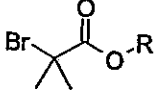
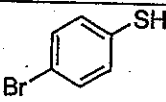
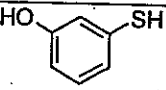
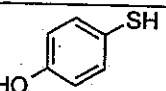
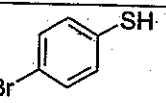
10 g (52.9 mmol) of 3-bromothiophenol are placed in the presence of 9.4 ml (63.5 mmol) of ethyl bromoisobutyrate and 8 g (57.9 mmol) of K_2CO_3 in 100 ml of EtOH. This mixture is stirred at reflux for 4 h and then dry concentrated. The residue is taken up in water. After extraction in AcOEt and then drying on $MgSO_4$, the organic phases are dry concentrated. The oil obtained is purified by flash chromatography on silica (petroleum ether:AcOEt 90:10) and **11a** is isolated in the form of clear oil (16.8 g, quantitative yield). TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 90:10, $R_f=0.72$.

c) Intermediates 11b-11e



The synthesis of intermediates **11b-11e** is carried out starting from variously substituted thiophenols (G) listed in table 12 following the procedure described for the synthesis of **11a** using ethyl or tert-butyl bromoisobutyrate.

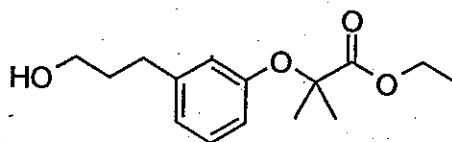
Table 12: intermediates 11b-11e

Starting thiophenol		Yield	TLC	State	Intermediates 11b-11e
	ethyl bromoisobutyrate	87%	PE:AcOEt 90:10 Rf=0.70	oil	11b: Ethyl 2-(4-bromo-phenylsulfanyl)-2-methyl-propionate
	ethyl bromoisobutyrate	74%	Heptane:AcOEt 80:20 Rf=0.50	oil	11c: Ethyl 2-(3-hydroxy-phenylsulfanyl)-2-methyl-propionate
	ethyl bromoisobutyrate	64%	Heptane:AcOEt 80:20 Rf=0.20	oil	11d: Ethyl 2-(4-hydroxy-phenylsulfanyl)-2-methyl-propionate
	tert-butyl bromoisobutyrate	98%	PE:AcOEt 90:10 Rf=0.70	solid	11e: Tert-butyl 2-(4-bromo-phenyl-sulfanyl)-2-methyl-propionate

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

Intermediate 12:

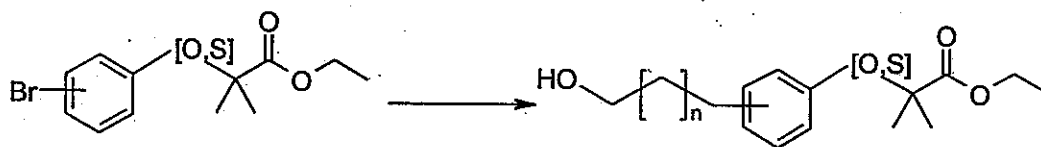
- 5 a) Ethyl 2-[3-(3-hydroxy-propyl)-phenoxy]-2-methyl-propionate (12a)



10 **10d** (50 g, 175 mmol) is placed in the presence of 2-propynol (12 ml, 210 mmol) in 400 ml of diisopropylamine, under nitrogen. Pd(PPh₃)₂Cl₂ (3.5 g) and CuI (500 mg) are added and the reaction medium is stirred at reflux for 5 h. The precipitate formed in

the course of the reaction is filtered on celite and the reaction medium is dry concentrated. The oil obtained is purified by flash chromatography on silica (petroleum ether:AcOEt 80:20). It is then placed in a solution of 250 ml of THF and 150 ml of EtOH in the presence of Pd/C under hydrogen at 6 bar. This mixture is stirred for 24 h. at ambient temperature. After filtration on celite, the reaction medium is dry concentrated and **12a** is isolated in the form of a clear oil (32 g, yield=69%). TLC silica gel 60 F 254 Merck, heptane:AcOEt 80:20, R_f=0.56.

b) Intermediates 12b-12e



15

10d

12b n=3

10e, 11a

12c, 12e n=1

10e

12d n=2

The synthesis of intermediates **12b-12e** is carried out from the starting bromine compounds listed in table 13 following the procedure described for the synthesis of **12a** using various alkynols. Note: in the case of a sulfur derivative, a Wilkinson catalyst is used for the hydrogenation step

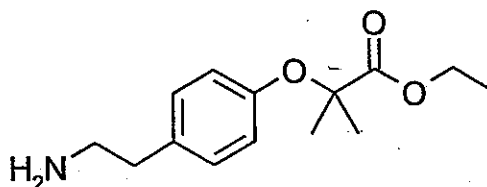
Table 13: intermediates 12b-12e

Starting molecule	alkynol	Yield	TLC	State	Intermediates 12b-12d
10d		76%	Heptane:AcOEt 60-40 Rf=0.37	oil	12b: Ethyl 2-[3-(5-hydroxy-pentyl)-phenoxy]-2-methyl-propionate
10e		5%	Heptane:AcOEt 60-40 Rf=0.33	oil	12c: Ethyl 2-[4-(3-hydroxy-propyl)-phenoxy]-2-methyl-propionate
10e		55%	PE:AcOEt 80:20 Rf=0.14	oil	12d: Ethyl 2-[4-(4-hydroxy-butyl)-phenoxy]-2-methyl-propionate
11a		73%	PE:AcOEt 70:30 Rf=0.26	oil	12e: Ethyl 2-[3-(3-hydroxy-propyl)-phenylsulfanyl]-2-methyl-propionate

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

Intermediate 13:

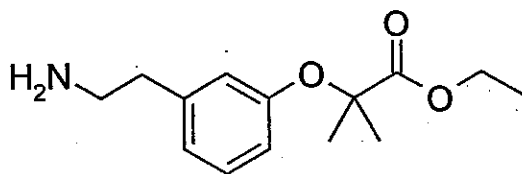
- 5 a) Ethyl 2-[4-(2-amino-ethyl)-phenoxy]-2-methyl-propionate (13a)



10.1 g (73.6 mmol) of tyramine is placed in the presence of sodium bicarbonate (6.1 g, 72.6 mmol) in a mixture of 100 ml of water and 50 ml of acetone at 0 °C. 11.6 ml (81.2 mmol) of benzyl chloroformate is added dropwise at this temperature then the reaction

medium is stirred 4 h at ambient temperature. After dry concentration, the residue obtained is taken up in water then extracted with AcOEt. After drying on MgSO_4 , the organic phases are dry concentrated and the solid obtained is recrystallized in diethyl ether: 17.2 g of solid is thus obtained (86% yield). They are then placed in 37 ml of ethyl bromoisobutyrate in the presence of 8.8 g (63.7 mmol) of potassium carbonate at 130 °C for 5 h. After filtration, the reaction medium is dry concentrated and the residue obtained is purified by flash chromatography on silica (petroleum ether:AcOEt 70:30). 22.7 g of clear oil are obtained (yield=93%). This oil is then placed in 200 ml of EtOH in the presence of palladium on carbon under hydrogen at 3 bar and then this solution is stirred for 3 h at ambient temperature. After filtration on celite, the reaction medium is dry concentrated and 14.7 g of intermediate **13a** is thus isolated in the form of an oil (quantitative yield). TLC silica gel 60 F 254 Merck, CH_2Cl_2 :MeOH 90:10, R_f =0.11.

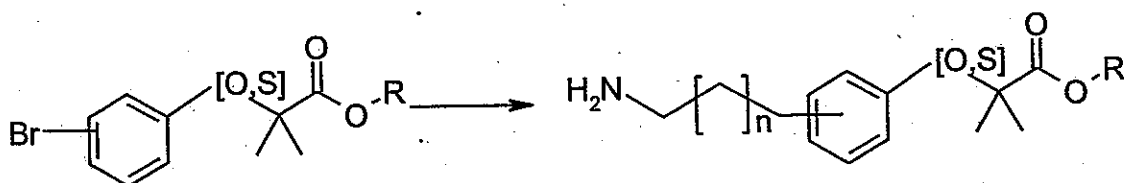
b) Ethyl 2-[3-(2-amino-ethyl)-phenoxy]-2-methyl-propionate (13b)



10d (14 g, 49 mmol) is placed in the presence of N-vinylphthalimide (11 g, 63 mmol) and 27 ml (194 mmol) of triethylamine in 160 ml of DMF. $\text{Pd}(\text{OAc})_2$ (0.3 g) and $\text{P}(\text{oTol})_3$ (0.4g) are added and the reaction medium is stirred for 10 h at 110 °C. The reaction

medium is dry concentrated and the residue obtained is taken up in water and extracted with AcOEt. After drying on MgSO_4 , the organic phases are dry concentrated and the oil isolated is purified by flash chromatography on silica (heptane:AcOEt 90:10). 11.5 g of oil is obtained (62% yield) then placed in a solution of 70 ml of THF and 70 ml of EtOH in the presence of Pd/C under hydrogen at 6 bar. This mixture is stirred for 72 h at ambient temperature. After filtration on celite, the reaction medium is dry concentrated and the residue obtained is purified by flash chromatography on silica (petroleum ether:AcOEt 80:20). 10.9 g of clear oil are obtained (yield=94%). This oil is then placed in 140 ml of EtOH in the presence of 3.5 ml of hydrazine hydrate then this solution is heated at reflux for 4 h. After filtration of the insolubles, the reaction medium is dry concentrated and then the residue obtained is purified by flash chromatography on silica (CH_2Cl_2 :MeOH: NH_4OH 90:9:1). 5.7 g of intermediate **13b** are thus isolated in the form of an oil (yield=80%). TLC silica gel 60 F 254 Merck, CH_2Cl_2 :MeOH: NH_4OH 90:9:1, R_f =0.28.

c) Intermediates 13c-13i



25

13d, 13g, 13i	$n=0$
13c, 13e, 13h	$n=1$
13f	$n=3$

The synthesis of intermediates **13c-13i** is carried out from the starting bromine compounds listed in table **14** following the procedure described for the synthesis of **13b** using variously N-alkylated phthalimides. (Note: in the case of a sulfur derivative, a Wilkinson catalyst is used for the hydrogenation step

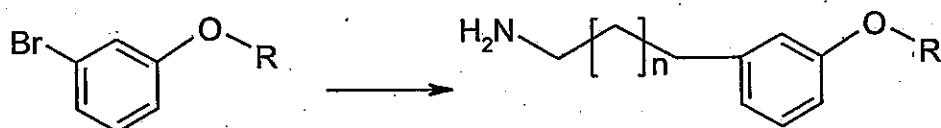
Table 14: intermediates **13b-13i**

Starting molecule	N-substituted phthalimide	Total yield	TLC Form	State	Intermediates 13c-13h
10d	N-allylphthalimide	80%	CH ₂ Cl ₂ :MeOH 90:10 Rf=0.12	oil	13c : Ethyl 2-[3-(3-amino-propyl)-phenoxy]-2-methyl-propionate
11a	N-vinylphthalimide	66%	CH ₂ Cl ₂ :MeOH:NH ₄ OH 90:9:1 Rf=0.20	oil	13d : Ethyl 2-[3-(2-amino-ethyl)-phenyl-sulfanyl]-2-methyl-propionate
11a	N-allylphthalimide	70%	CH ₂ Cl ₂ :MeOH:NH ₄ OH 90:9:1 Rf=0.30	oil	13e : Ethyl 2-[3-(3-amino-propyl)-phenylsulfanyl]-2-methyl-propionate
11a	N-but-3-enyl-phthalimide	38%	CH ₂ Cl ₂ :MeOH:NH ₄ OH 90:9:1 Rf=0.27	oil	13f : Ethyl 2-[3-(4-amino-butyl)-phenyl-sulfanyl]-2-methyl-propionate
11b	N-vinylphthalimide	41%	CH ₂ Cl ₂ :MeOH:NH ₄ OH 90:9:1 Rf=0.28	oil	13g : Ethyl 2-[4-(2-amino-ethyl)-phenyl-sulfanyl]-2-methyl-propionate
11b	N-allylphthalimide	38%	CH ₂ Cl ₂ :MeOH:NH ₄ OH 90:9:1	oil	13h : Ethyl 2-[4-(3-amino-propyl)-

	ide		Rf=0.23		phenylsulfanyl]-2-methyl-propionate
11e	N-vinylphthalimide	63%	CH ₂ Cl ₂ :MeOH 90:10 Rf=0.18	oil	13i : Tert-butyl 2-[4-(2-amino-ethyl)-phenylsulfanyl]-2-methyl-propionate

TLC: silica gel 60 F 254 Merck

b) Intermediates 13j-13n



5

13j, 13l n=1

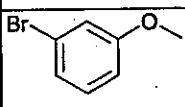
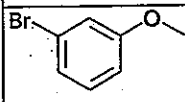
13k, 13m n=2

13n n=3

The synthesis of intermediates **13j-13n** is carried out from the starting bromine compounds listed in table 15 following the procedures described for the synthesis of **13b** using variously N-alkylated phthalimides.

Table 15: intermediates 13j-13n

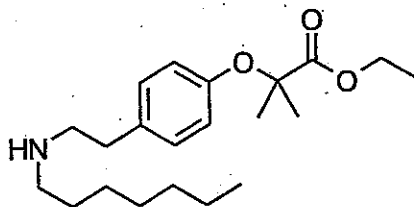
Starting molecule	N-substituted phthalimide	Yield	TLC	State	Intermediates 13i-13n
	N-allylphthalimide	47%	CH ₂ Cl ₂ :MeOH:NH ₄ OH 80:18:2 Rf=0.25	solid	13j : 3-(3-Amino-propyl)-phenol
	N-but-3-enylphthalimide	49%	CH ₂ Cl ₂ :MeOH:NH ₄ OH 80:18:2 Rf=0.24	oil	13k : 3-(4-Amino-butyl)-phenol
	N-allylphthalimide	59%	CH ₂ Cl ₂ :MeOH:NH ₄ OH 80:18:2	oil	13l : 3-(3-Methoxy-

	ide		Rf=0.20		phenyl)-propylamine
	N-but-3-enylphthalimide	77%	CH ₂ Cl ₂ :MeOH:NH ₄ OH 80:18:2 Rf=0.28	oil	13m: 4-(3-Methoxyphenyl)-butylamine
	N-pent-4-enylphthalimide	24%	CH ₂ Cl ₂ :MeOH:NH ₄ OH 90:9:1 Rf=0.45	oil	13n: 5-(3-Methoxyphenyl)-pentylamine

TLC: silica gel 60 F 254 Merck

Intermediate 14:

- 5 a) Ethyl 2-[4-(2-heptylamino-ethyl)-phenoxy]-2-methyl-propionate (14a)

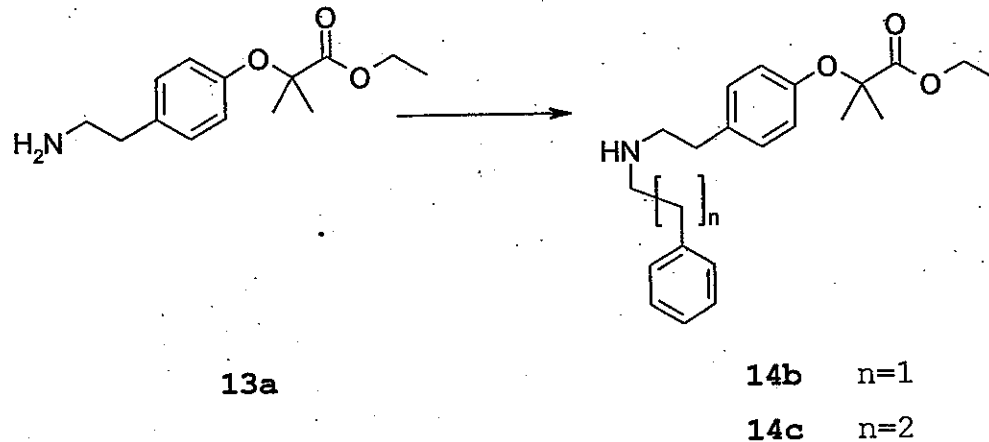


- 10 13a (4.1 g, 5 mmol) is placed in the presence of heptanoic acid (2.3 ml, 16.5 mmol) in 42 ml of dichloromethane. 2.3 ml (16.5 mmol) of triethylamine is added followed by 2.8 ml (18.2 mmol) of diethylcyanophosphonate. This mixture is stirred for 24 h at ambient temperature then the reaction medium is dry concentrated. The residue is taken up in H₂O and
- 15 extracted with ethyl acetate. After drying on MgSO₄, the organic phases are dry concentrated and the oil isolated is purified by flash chromatography on silica (CH₂Cl₂:MeOH 90:10). 4.7 g of oil are obtained (yield=78%). 13 ml of a BH₃/THF solution (1 M) is

placed at 0 °C under nitrogen then the oil previously obtained, diluted in 20 ml of THF, is added dropwise. This mixture is placed at reflux for 2 h then neutralized by 10 ml of EtOH/HCl (1.5 N). The solution
 5 is again placed at reflux for 1 h then dry concentrated. The residue obtained is taken up in a saturated sodium bicarbonate solution then extracted with dichloromethane. After drying on MgSO₄, the organic phases are dry concentrated and the oil
 10 isolated is purified by flash chromatography on silica (CH₂Cl₂:MeOH 90:10). 1.6 g of intermediate **14a** is thus isolated in the form of an oil (yield=73%). TLC silica gel 60 F 254 Merck, CH₂Cl₂:MeOH:NH₄OH 90:9:1, R_f=0.50.

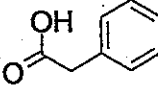
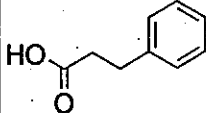
15

b) Intermediates 14b-14c



The synthesis of intermediates **14b-14c** is carried out starting from intermediate **13a** according to the
 20 procedure described for the synthesis of **14a** using various carboxylic acids.

Table 16: intermediates 14b-14c

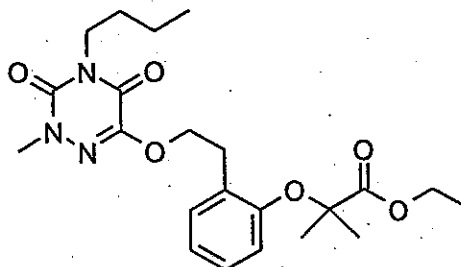
Carboxylic acid	Total yield	Eluent	Form	Intermediates 14b-14c
	78%	CH ₂ Cl ₂ :MeOH 90:10 Rf=0.37	oil	14b : Ethyl 2-methyl-2-[4-(2-phenethylamino-ethyl)-phenoxy]-propionate
	65%	CH ₂ Cl ₂ :MeOH 90:10 Rf=0.44	oil	14c : Ethyl 2-methyl-2-{4-[2-(3-phenyl-propylamino)-ethyl]-phenoxy}-propionate

TLC: silica gel 60 F 254 Merck

EXAMPLES

5

Example 1: Ethyl 2-{2-[2-(4-butyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-ethyl]-phenoxy}-2-methyl-propionate (1)

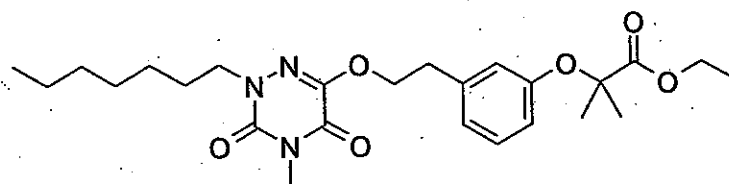


10 Compound 1 is prepared according to synthesis method 1:
 1 g (4 mmol) of derivative 10g and 1 g (3.8 mmol) of triazine 5a are placed in 3 ml of DMF in the presence of 0.5 g (3.7 mmol) of K₂CO₃. This mixture is stirred at 120 °C for 7 h. After filtration and dry
 15 concentration of the reaction medium, the residue obtained is purified by flash chromatography on silica (CH₂Cl₂:AcOEt 98:2). 1.2 g of white crystals are isolated (yield=74%).

TLC silica gel 60 F 254 Merck, CH_2Cl_2 :AcOEt 95:5,
 $R_f=0.40$. $F=76^\circ\text{C}$

RMN ^1H (CDCl_3): 0.94 ppm (t, 3H, $J=7.4$ Hz), 1.20 ppm
 (t, 3H, $J=7.2$ Hz), 1.39 ppm (m, 2H, $J=7.5$ ppm),
 5 1.63 ppm (m, 8H), 3.16 ppm (t, 2H, $J=7.6$ Hz), 3.50 ppm
 (s, 3H), 3.95 ppm (t, 2H, $J=7.6$ Hz), 4.22 ppm (q, 2H,
 $J=7.0$ Hz), 4.37 ppm (t, 2H, $J=7.6$ Hz), 7.00 ppm (m,
 4H).

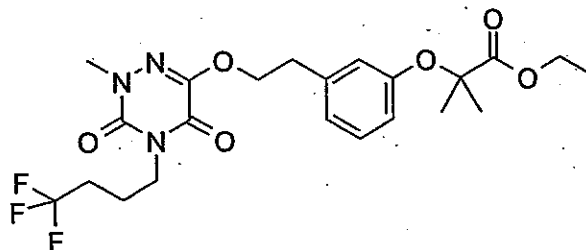
10 **Example 2:** Ethyl 2-{3-[2-(2-heptyl-4-methyl-3,5-dioxo-
 2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-ethyl]-
 phenoxy}-2-methyl-propionate (2)



Compound 2 (oil) is prepared from triazine **4b** and from
 15 intermediate **10h** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, CH_2Cl_2 :AcOEt 90:10,
 $R_f=0.62$.

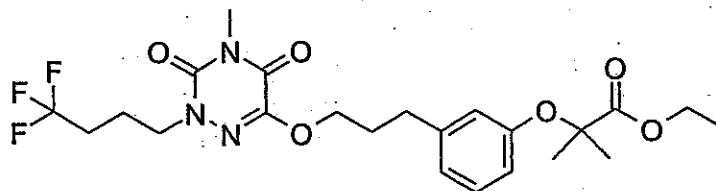
20 **Example 3:** Ethyl 2-methyl-2-(3-{2-[2-methyl-3,5-dioxo-
 4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-
 [1,2,4]triazin-6-yloxy]-ethyl}-phenoxy)-propionate (3)



Compound 3 (oil) is prepared from triazine **6a** and from
 intermediate **10h** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, CH₂Cl₂:AcOEt 90:10, R_f=0.57.

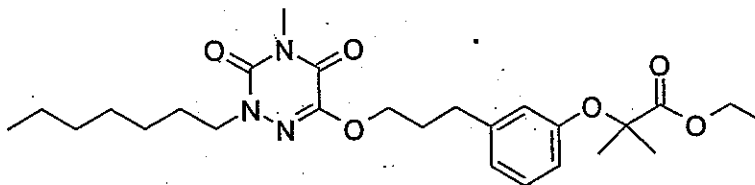
Example 4: Ethyl 2-methyl-2-(3-{3-[4-methyl-3,5-dioxo-
2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-
[1,2,4]triazin-6-yloxy]-propyl}-phenoxy)-propionate (4)



Compound 4 (oil) is prepared from triazine 4a and from intermediate 12a according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, R_f=0.30.

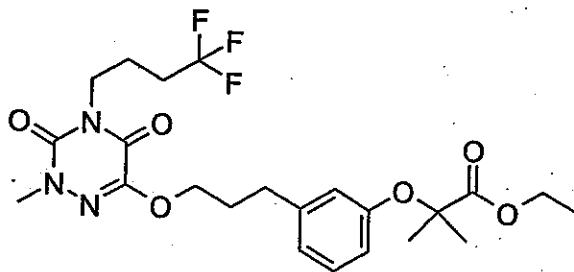
Example 5: Ethyl 2-{3-[3-(2-heptyl-4-methyl-3,5-dioxo-
2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-propyl]-
phenoxy}-2-methyl-propionate (5)



Compound 5 (oil) is prepared from triazine 4b and from intermediate 12a according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, R_f=0.52.

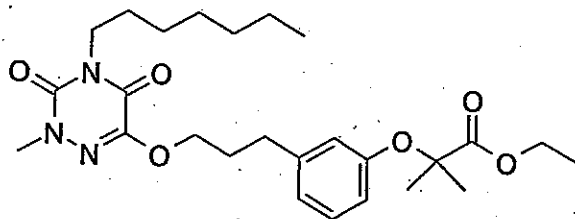
Example 6: Ethyl 2-methyl-2-(3-{3-[2-methyl-3,5-dioxo-
4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-
[1,2,4]triazin-6-yloxy]-propyl}-phenoxy)-propionate (6)



Compound **6** (oil) is prepared from triazine **6a** and from intermediate **12a** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, $R_f=0.46$.

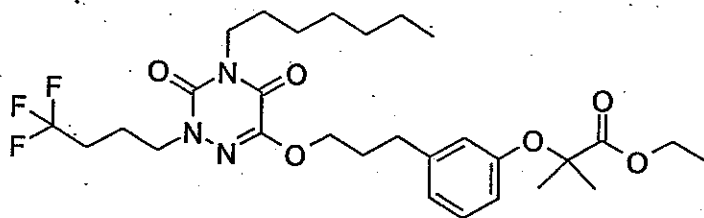
Example 7: Ethyl 2-{3-[3-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-propyl]-phenoxy}-2-methyl-propionate (**7**)



Compound **7** (oil) is prepared from triazine **7a** and from intermediate **12a** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, $R_f=0.61$.

Example 8: Ethyl 2-(3-{3-[4-heptyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-propyl}-phenoxy)-2-methyl-propionate (**8**)

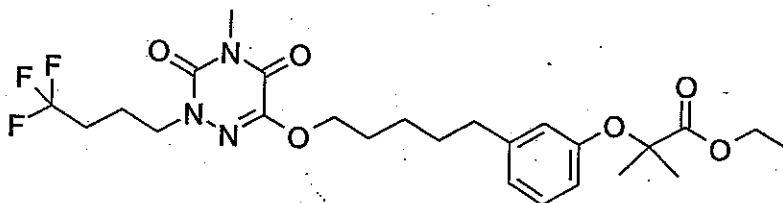


Compound **8** (oil) is prepared from triazine **7b** and from intermediate **12a** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, R_f=0.53.

5

Example 9: Ethyl 2-methyl-2-(3-{5-[4-methyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-pentyl}-phenoxy)-propionate (**9**)



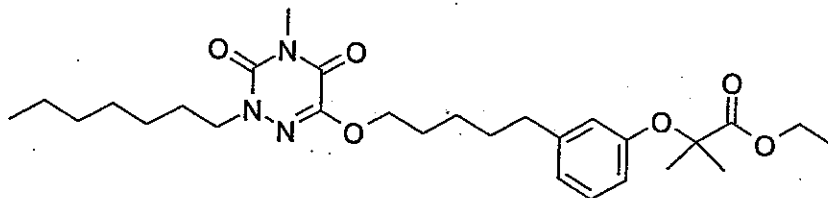
10

Compound **9** (oil) is prepared from triazine **4a** and from intermediate **12b** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, R_f=0.34.

15

Example 10: Ethyl 2-{3-[5-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-pentyl]-phenoxy}-2-methyl-propionate (**10**)

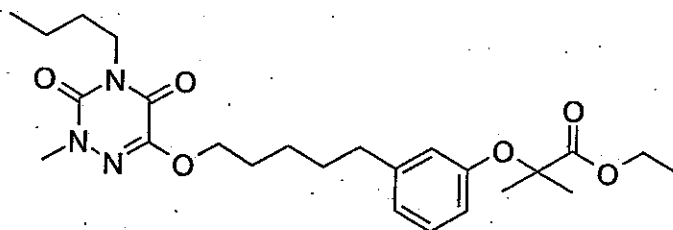


20

Compound **10** (oil) is prepared from triazine **4b** and from intermediate **12b** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, R_f=0.54.

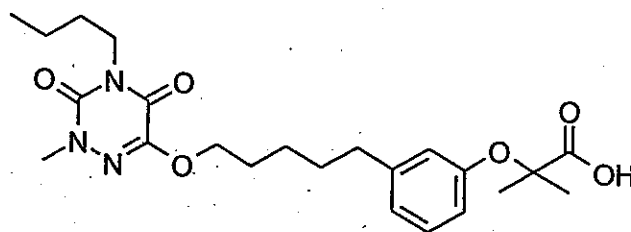
Example 11: Ethyl 2-{3-[5-(4-butyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-pentyl]-phenoxy}-2-methyl-propionate (11)



Compound **11** (oil) is prepared from triazine **5a** and from intermediate **12b** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, R_f=0.29.

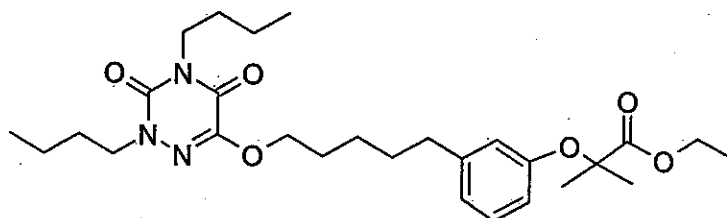
Example 12: 2-{3-[5-(4-Butyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-pentyl]-phenoxy}-2-methyl-propionic acid (12)



Compound **12** (oil) is prepared by hydrolysis of compound **11** (HCl 12 N, reflux, 16 h, 62%).

TLC silica gel 60 F 254 Merck, CH₂Cl₂:MeOH 90:10, R_f=0.43.

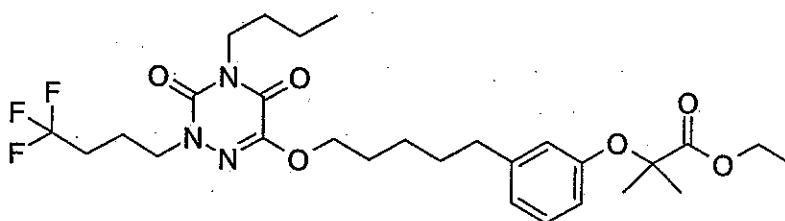
Example 13: Ethyl 2-{3-[5-(2,4-dibutyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-pentyl]-phenoxy}-2-methyl-propionate (13)



Compound 13 (oil) is prepared from triazine 1c and from intermediate 12b according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.63.

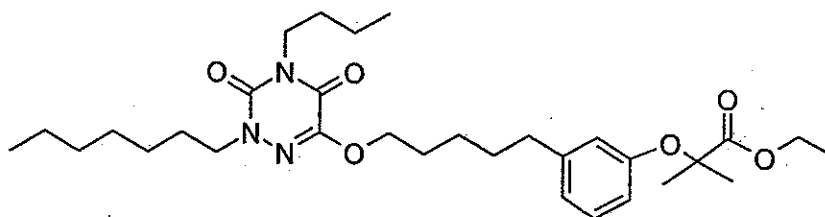
Example 14: Ethyl 2-(3-{5-[4-Butyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-pentyl}-phenoxy)-2-methyl-propionate (14)



Compound 14 (oil) is prepared from triazine 5b and from intermediate 12b according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.35.

Example 15: Ethyl 2-{3-[5-(4-butyl-2-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-pentyl]-phenoxy}-2-methyl-propionate (15)

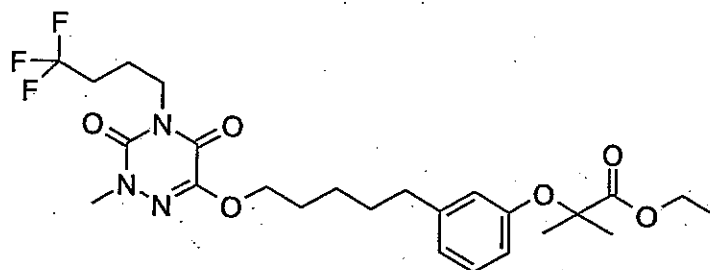


Compound **15** (oil) is prepared from triazine **5c** and from intermediate **12b** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, R_f=0.53.

5

Example 16: Ethyl 2-methyl-2-(3-{5-[2-methyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-pentyl}-phenoxy)-propionate (16)



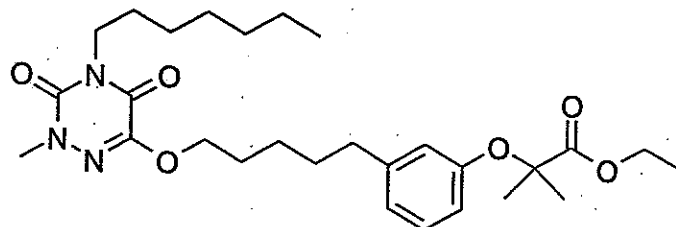
10

Compound **16** (oil) is prepared from triazine **6a** and from intermediate **12b** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, R_f=0.33.

15

Example 17: Ethyl 2-{3-[5-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-pentyl]-phenoxy}-2-methyl-propionate (17)

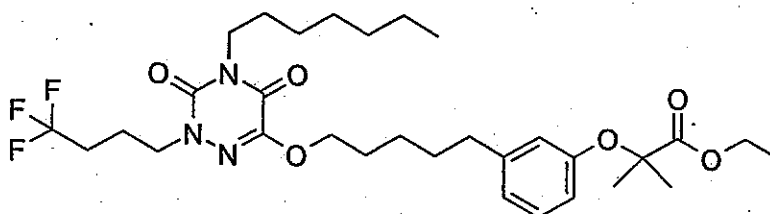


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Compound **17** (oil) is prepared from triazine **7a** and from intermediate **12b** according to synthesis method 1.

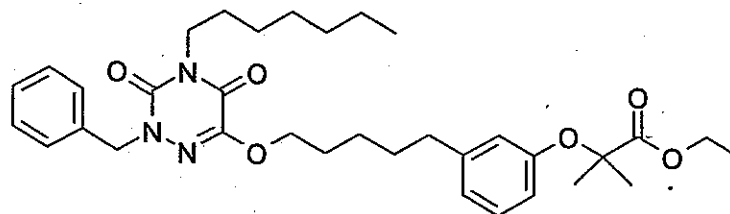
TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.36.

- 5 **Example 18:** Ethyl 2-(3-{5-[4-heptyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-pentyl}-phenoxy)-2-methyl-propionate (18)



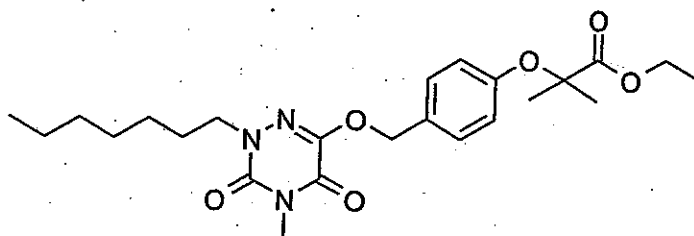
- 10 Compound 18 (oil) is prepared from triazine 7b and from intermediate 12b according to synthesis method 1.
TLC silica gel 60 F 254 Merck, heptane:AcOEt 70:30, Rf=0.35.

- 15 **Example 19:** Ethyl 2-(3-[5-(2-benzyl-4-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-pentyl]-phenoxy)-2-methyl-propionate (19)



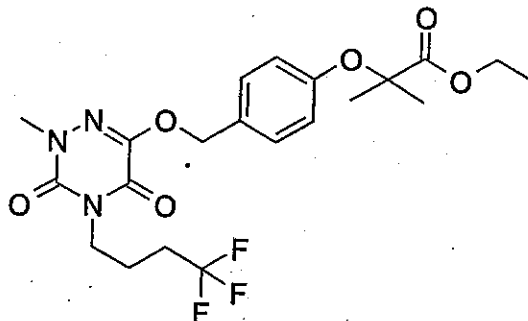
- Compound 19 (oil) is prepared from triazine 7c and from intermediate 12b according to synthesis method 1.
20 TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.51.

Example 20: Ethyl 2-[4-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxymethyl)-phenoxy]-2-methyl-propionate (20)



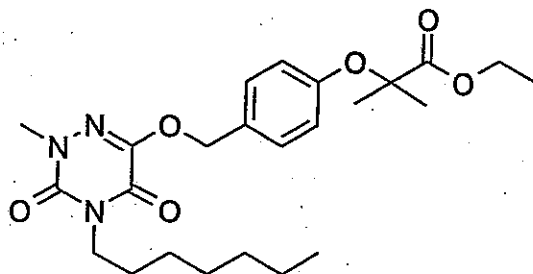
5 Compound 20 (oil) is prepared from triazine 4b and from intermediate 10f according to synthesis method 1.
TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.28.

10 **Example 21:** Ethyl 2-methyl-2-{4-[2-methyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxymethyl]-phenoxy}-propionate (21)



15 Compound 21 (oil) is prepared from triazine 6a and from intermediate 10f according to synthesis method 1.
TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 60:40, Rf=0.46.

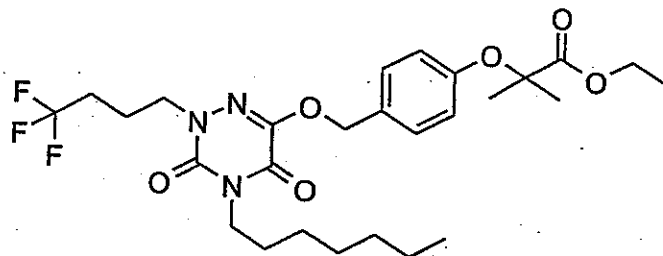
20 **Example 22:** Ethyl 2-[4-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxymethyl)-phenoxy]-2-methyl-propionate (22)



Compound 22 (oil) is prepared from triazine 7a and from intermediate 10f according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.34.

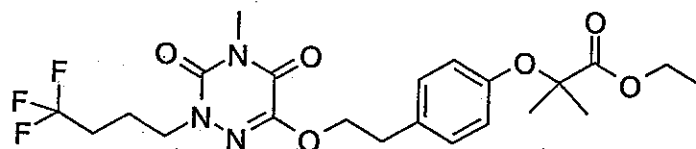
Example 23: Ethyl 2-{4-[4-heptyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxymethyl]-phenoxy}-2-methyl-propionate (23)



Compound 23 (oil) is prepared from triazine 7b and from intermediate 10f according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 90:10, Rf=0.61.

Example 24: Ethyl 2-methyl-2-(4-{2-[4-methyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-ethyl}-phenoxy)-propionate (24)

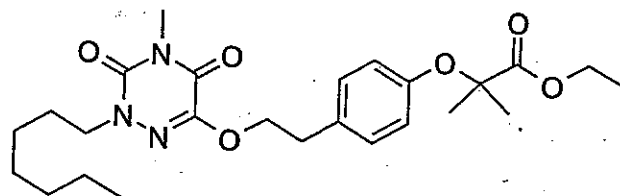


Compound **24** (oil) is prepared from triazine **4a** and from intermediate **10j** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, $\text{CH}_2\text{Cl}_2:\text{AcOEt}$ 90:10, $R_f=0.45$.

5

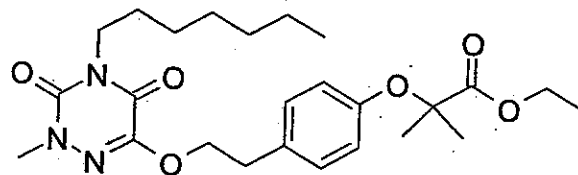
Example 25: Ethyl 2-{4-[2-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-ethyl]-phenoxy}-2-methyl-propionate (**25**)



10 Compound **25** (oil) is prepared from triazine **4b** and from intermediate **10j** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, $R_f=0.45$.

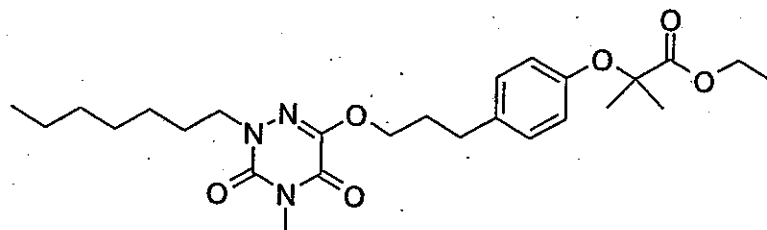
15 **Example 26:** Ethyl 2-{4-[2-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-ethyl]-phenoxy}-2-methyl-propionate (**26**)



20 Compound **26** (oil) is prepared from triazine **7a** and from intermediate **10j** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, $R_f=0.46$.

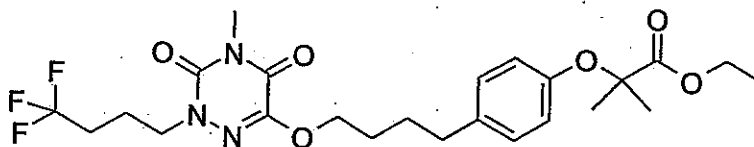
Example 27: Ethyl 2-{4-[3-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-propyl]-phenoxy}-2-methyl-propionate (27)



5 Compound 27 (oil) is prepared from triazine 4b and from intermediate 12c according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, Rf=0.33.

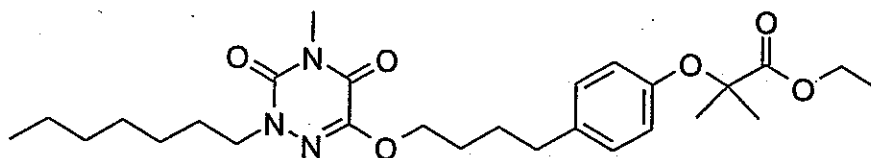
10 **Example 28:** Ethyl 2-methyl-2-(4-{4-[4-methyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-butyl}-phenoxy)-propionate (28)



15 Compound 28 (oil) is prepared from triazine 4a and from intermediate 12d according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, Rf=0.31.

20 **Example 29:** Ethyl 2-{4-[4-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-butyl]-phenoxy}-2-methyl-propionate (29)

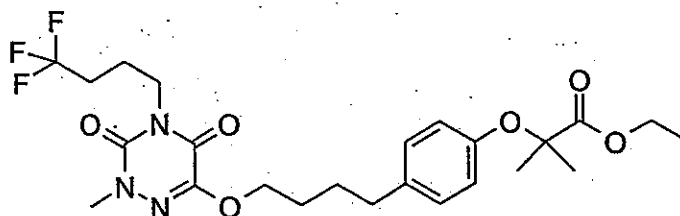


Compound **29** (oil) is prepared from triazine **4b** and from intermediate **12d** according to synthesis method **1**.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, Rf=0.49.

5

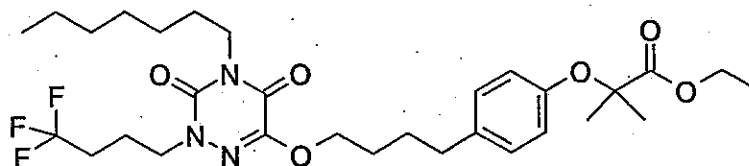
Example 30: Ethyl 2-methyl-2-(4-{4-[2-methyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-butyl}-phenoxy)-propionate (**30**)



10 Compound **30** (oil) is prepared from triazine **6a** and from intermediate **12d** according to synthesis method **1**.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, Rf=0.35.

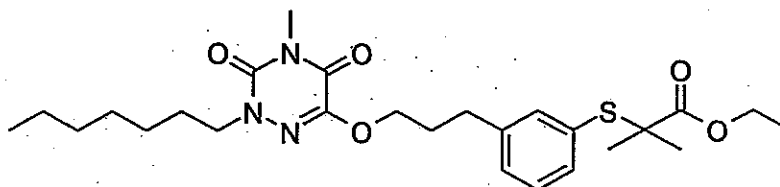
15 **Example 31:** Ethyl 2-(4-{4-[4-heptyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-butyl}-phenoxy)-2-methyl-propionate (**31**)



20 Compound **31** (oil) is prepared from triazine **7b** and from intermediate **12d** according to synthesis method **1**.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.51.

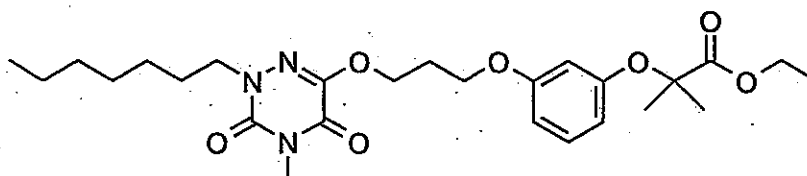
Example 32: Ethyl 2-{3-[3-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-propyl]-phenylsulfanyl}-2-methyl-propionate (32)



5 Compound 32 (oil) is prepared from triazine 4b and from intermediate 12e according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.37.

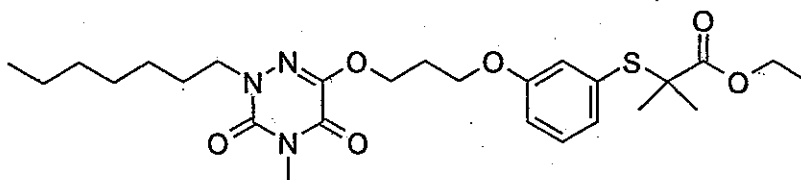
10 **Example 33:** Ethyl 2-{3-[3-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-propoxy]-phenoxy}-2-methyl-propionate (33)



15 Compound 33 is prepared according to synthesis method 2: 1.1 g (3.7 mmol) of triazine 9q, 0.83 g (3.7 mmol) of ester 10b and 1.25 g (4.7 mmol) of PPh₃ are placed in 30 ml of THF at 40 °C. 0.74 ml (4.7 mmol) of DEAD diluted in 10 ml of THF is added dropwise and the mixture is stirred for 1 h at 40°C. Afterwards, the reaction medium is dry concentrated and the residue obtained is purified by flash chromatography on neutral alumina (heptane:AcOEt 80:20). 0.8 g of compound 33 is isolated in the form of clear oil (yield=43%).

TLC silica gel 60 F 254 Merck, heptane:AcOEt 50:50,
Rf=0.30.

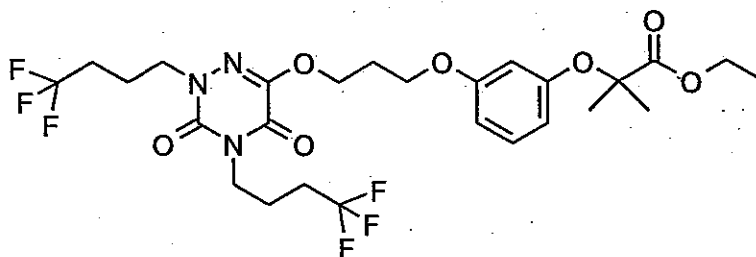
Example 34: Ethyl 2-{3-[3-(2-heptyl-4-methyl-3,5-dioxo-
5 2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-propoxy]-
phenylsulfanyl}-2-methyl-propionate (34)



Compound **34** (oil) is prepared from triazine **9q** and from
10 intermediate **11c** according to synthesis method 2.

TLC silica gel 60 F 254 Merck, heptane:AcOEt 50:50,
Rf=0.33.

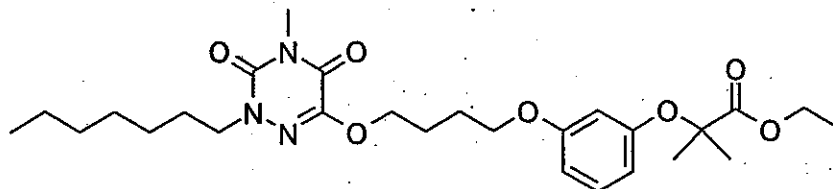
Example 35: Ethyl 2-(3-{3-[3,5-dioxo-2,4-bis-(4,4,4-
15 trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-
yloxy]-propoxy}-phenoxy)-2-methyl-propionate (35)



Compound **35** (oil) is prepared from triazine **9r** and from
intermediate **10b** according to synthesis method 2.

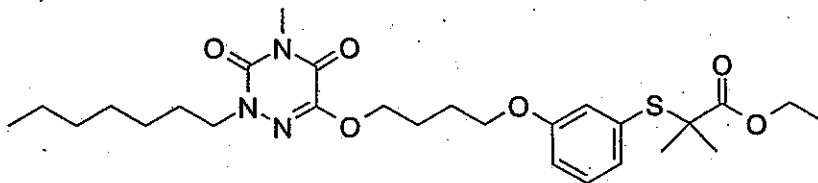
20 TLC silica gel 60 F 254 Merck, heptane:AcOEt 50:50,
Rf=0.50.

Example 36: Ethyl 2-{3-[4-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-butoxy]-phenoxy}-2-methyl-propionate (36)



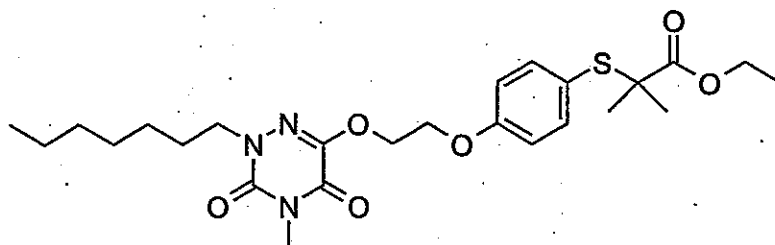
- 5 Compound 36 (oil) is prepared from triazine 9s and from intermediate 10b according to synthesis method 2.
TLC silica gel 60 F 254 Merck, heptane:AcOEt 50:50, Rf=0.34.

10 **Example 37:** Ethyl 2-{3-[4-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-butoxy]-phenylsulfanyl}-2-methyl-propionate (37)



- 15 Compound 37 (oil) is prepared from triazine 9s and from intermediate 11c according to synthesis method 2.
TLC silica gel 60 F 254 Merck, heptane:AcOEt 50:50, Rf=0.37.

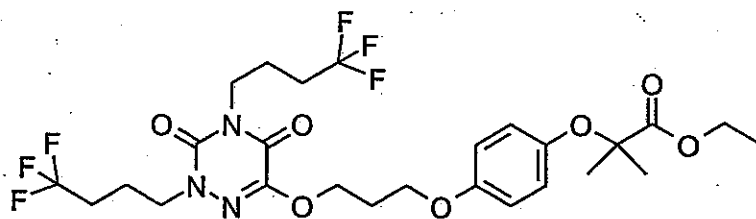
20 **Example 38:** Ethyl 2-{4-[2-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-ethoxy]-phenylsulfanyl}-2-methyl-propionate (38)



Compound **38** (oil) is prepared from triazine **9p** and from intermediate **11d** according to synthesis method 2.

TLC silica gel 60 F 254 Merck, heptane:AcOEt 50:50,
 5 R_f=0.33.

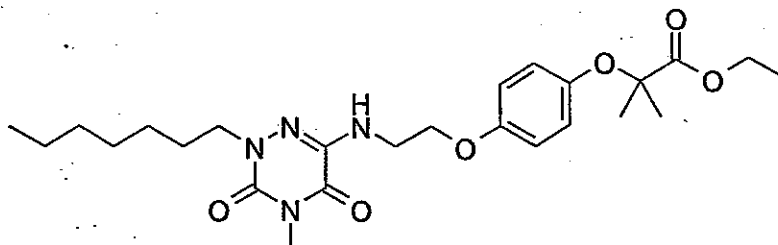
Example 39: Ethyl 2-(4-{3-[3,5-dioxo-2,4-bis-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-propoxy}-phenoxy)-2-methyl-propionate (**39**)



Compound **39** (oil) is prepared from triazine **9r** and from intermediate **10c** according to synthesis method 2.

TLC silica gel 60 F 254 Merck, heptane:AcOEt 50:50,
 15 R_f=0.50.

Example 40: Ethyl 2-{4-[2-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethoxy]-phenoxy}-2-methyl-propionate (**40**)

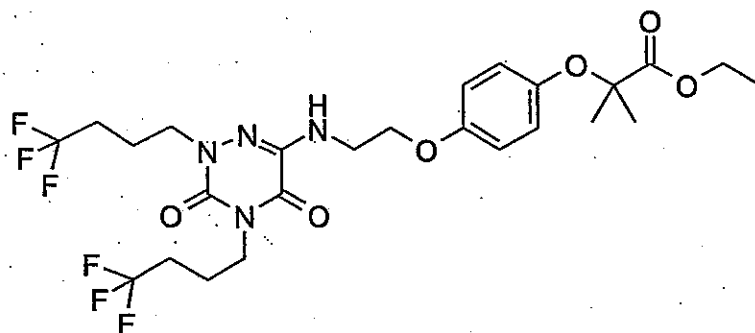


Compound **40** (oil) is prepared from triazine **9b** and from intermediate **10c** according to synthesis method 2.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.29.

5

Example 41: Ethyl 2-(4-{2-[3,5-dioxo-2,4-bis-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethoxy}-phenoxy)-2-methyl-propionate (**41**)



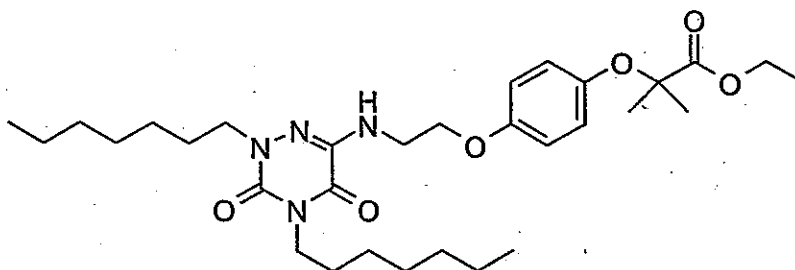
10

Compound **41** (oil) is prepared from triazine **9a** and from intermediate **10c** according to synthesis method 2.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.50.

15

Example 42: Ethyl 2-(4-[2-(2,4-diheptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethoxy]-phenoxy)-2-methyl-propionate (**42**)



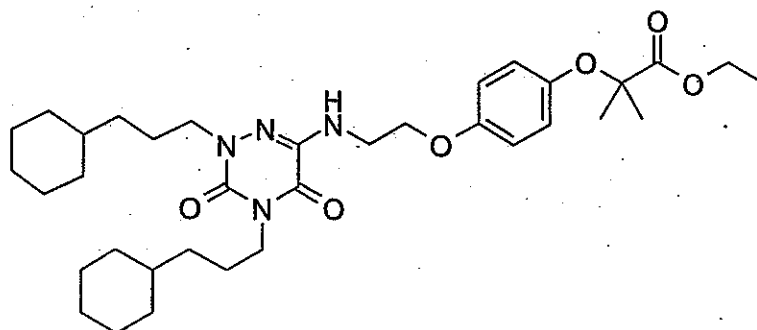
20

Compound **42** (oil) is prepared from triazine **9c** and from intermediate **10c** according to synthesis method 2.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, $R_f=0.85$.

5

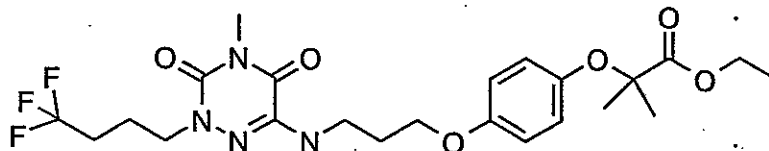
Example 43: Ethyl 2-(4-{2-[2,4-bis-(3-cyclohexyl-propyl)-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethoxy}-phenoxy)-2-methyl-propionate (**43**)



10 Compound **43** (oil) is prepared from triazine **9d** and from intermediate **10c** according to synthesis method 2.

TLC silica gel 60 F 254 Merck, heptane:AcOEt 80:20, $R_f=0.85$.

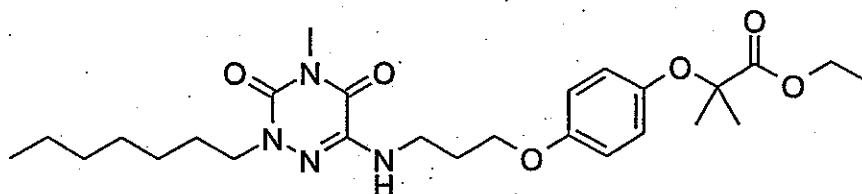
15 **Example 44:** Ethyl 2-methyl-2-(4-{3-[4-methyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-propoxy}-phenoxy)-propionate (**44**)



20 Compound **44** (oil) is prepared from triazine **9f** and from intermediate **10c** according to synthesis method 2.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, $R_f=0.36$.

Example 45: Ethyl 2-{4-[3-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-propoxy]-phenoxy}-2-methyl-propionate (45)



5

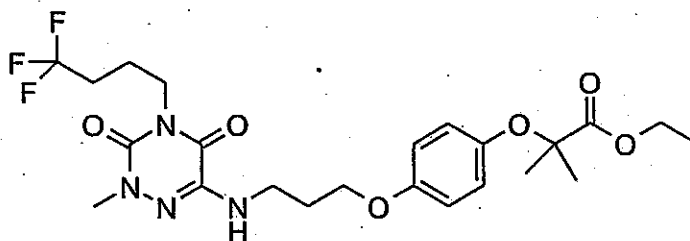
Compound 45 (oil) is prepared from triazine 9g and from intermediate 10c according to synthesis method 2.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, Rf=0.48.

10

Example 46: Ethyl 2-methyl-2-(4-{3-[2-methyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-propoxy}-phenoxy)-propionate (46)

15

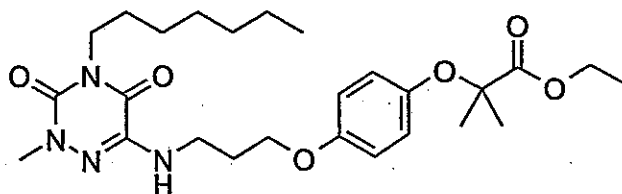


Compound 46 (solid) is prepared from triazine 9h and from intermediate 10c according to synthesis method 2.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, Rf=0.37. F=116 °C

20

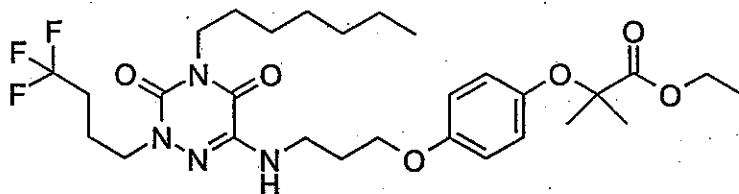
Example 47: Ethyl 2-{4-[3-(4-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-propoxy]-phenoxy}-2-methyl-propionate (47)



Compound 47 (oil) is prepared from triazine 9i and from intermediate 10c according to synthesis method 2.

5 TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.30.

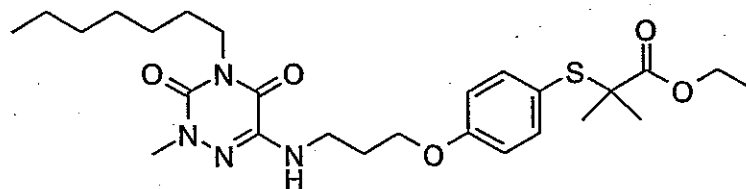
Example 48: Ethyl 2-(4-{3-[4-heptyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-propoxy}-phenoxy)-2-methyl-propionate (48)



Compound 48 (oil) is prepared from triazine 9j and from intermediate 10c according to synthesis method 2.

15 TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.50.

Example 49: Ethyl 2-(4-[3-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-propoxy]-phenylsulfanyl)-2-methyl-propionate (49)

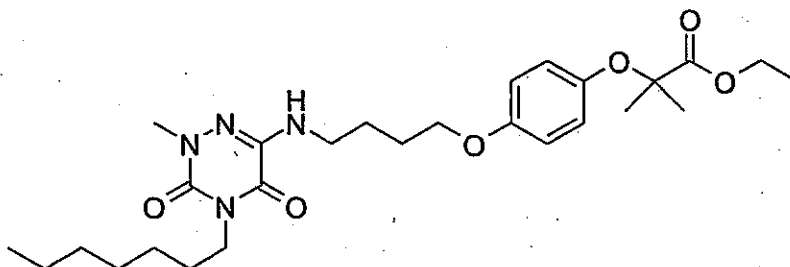


20

Compound 49 (oil) is prepared from triazine 9i and from intermediate 11d according to synthesis method 2.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.46.

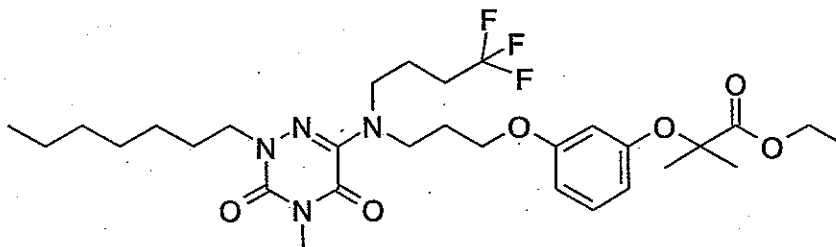
Example 50: Ethyl 2-{4-[4-(4-heptyl-2-methyl-3,5-dioxo-
5 2,3,4,5-tetrahydro-[1,2, 4]triazin-6-ylamino)-butoxy]-
phenoxy}-2-methyl-propionate (50)



Compound 50 (oil) is prepared from triazine 91 and from intermediate 10c according to synthesis method 2.

10 TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.50.

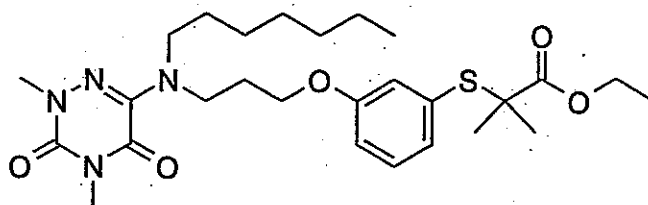
Example 51: Ethyl 2-(3-{3-[(2-heptyl-4-methyl-3,5-
dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-(4,4,4-
15 trifluoro-butyl)-amino]-propoxy}-phenoxy)-2-methyl-
propionate (51)



Compound 51 (oil) is prepared from triazine 9m and from intermediate 10b according to synthesis method 3 using
20 Mitsunobu coupling conditions such as those described for example 33.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 90:10, Rf=0.56.

Example 52: Ethyl 2-(3-{3-[(2,4-Dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-heptyl-amino]-propoxy}-phenylsulfanyl)-2-methyl-propionate (52)



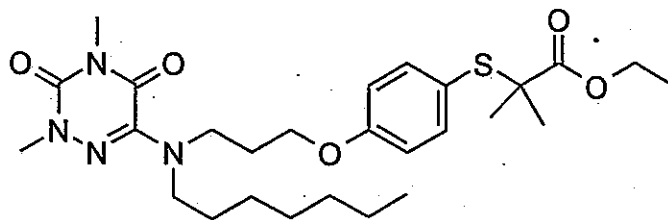
5

Compound **52** (oil) is prepared from triazine **9n** and from intermediate **11c** according to synthesis method **3** using coupling conditions such as those described for example **33**.

10 TLC silica gel 60 F 254 Merck, heptane:AcOEt 70:30, R_f=0.22.

Example 53: Ethyl 2-(4-{3-[(2,4-Dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-heptyl-amino]-propoxy}-phenylsulfanyl)-2-methyl-propionate (53)

15

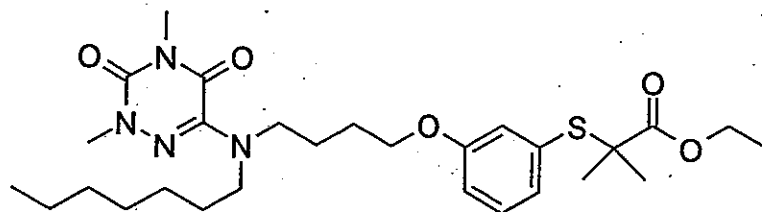


Compound **53** (oil) is prepared from triazine **9n** and from intermediate **11d** according to synthesis method **3** using coupling conditions such as those described for example **33**.

20

TLC silica gel 60 F 254 Merck, heptane:AcOEt 80:20, R_f=0.45.

Example 54: Ethyl 2-(3-{4-[(2,4-Dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-heptyl-amino]-butoxy}-phenylsulfanyl)-2-methyl-propionate (54)

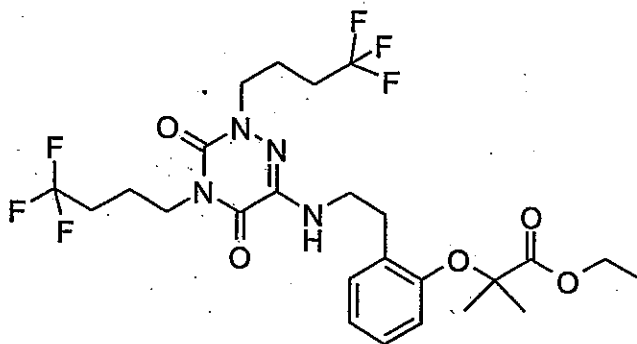


- 5 Compound **54** (oil) is prepared from triazine **9o** and from intermediate **11c** according to synthesis method **3** using coupling conditions such as those described for example **33**.

TLC silica gel 60 F 254 Merck, heptane:AcOEt 70:30,

10 R_f=0.25.

Example 55: Ethyl 2-(2-{2-[3,5-Dioxo-2,4-bis-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethyl}-phenoxy)-2-methyl-propionate (55)



15

- Compound **55** is prepared according to synthesis method **4**: 6.6 g (16.1 mmol) of triazine **1d**, 2 g (13.4 mmol) of 2 (2-methoxy-phenyl)-ethylamine and 4.7 ml (33.9 mmol) of triethylamine are placed in 20 ml of n-butanol at 120 °C for 28 h. After dry concentration of the reaction medium, the residue obtained is taken up in H₂O and extracted with AcOEt. The organic phases are
- 20

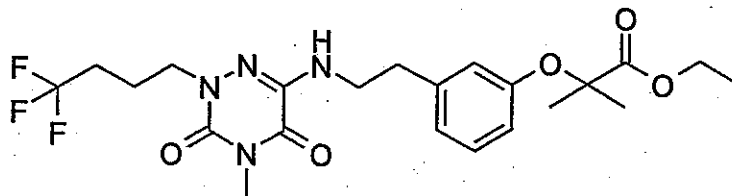
dried on MgSO_4 , then dry concentrated. The oil obtained is purified by flash chromatography on silica (petroleum ether:AcOEt 90:10). 3.1 g of intermediate are isolated in the form of an oil (yield=48%) which are then placed in 30 ml of CH_2Cl_2 at 0 °C under nitrogen. A solution of BBr_3 (12.8 ml at 1 M in CH_2Cl_2) is added dropwise and the reaction medium is stirred for 3.5 h at ambient temperature. It is then placed at 0 °C and acidified by a 0.1 N HCl solution until pH=1.

The organic phase is decanted and then washed with 100 ml of water. After drying on MgSO_4 , it is dry concentrated and the residue obtained is purified by flash chromatography on silica (CH_2Cl_2 :AcOEt 95:5). 1.9 g of the corresponding phenol is isolated (yield=65%) which is then placed in 2 ml of DMF in the presence of 1.9 ml (12.5 mmol) of ethyl bromoisobutyrate and 0.6 g (4.3 mmol) of K_2CO_3 . The reaction medium is heated at 130 °C for 22 h then filtered and dry concentrated. The oil obtained is purified by flash chromatography on silica (CH_2Cl_2 :AcOEt 98:2). 0.8g of compound 55 (yield=34%) is isolated in the form of an oil.

TLC silica gel 60 F 254 Merck, CH_2Cl_2 :AcOEt 95:5, R_f =0.66.

25

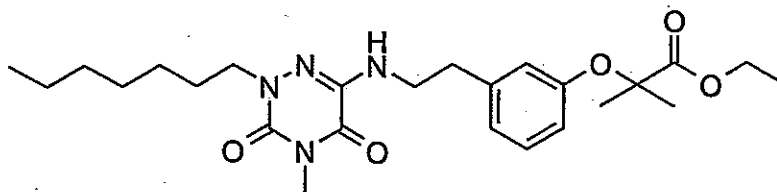
Example 56: Ethyl 2-methyl-2-(3-(2-[4-methyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethyl)-phenoxy)-propionate (56)



Compound **56** is prepared according to synthesis method
1: 1.1 g (4.4 mmol) of derivative **13b** and 1 g
 (3.7 mmol) of triazine **4a** are placed in 10 ml of nBuOH
 5 in the presence of 1.3 ml (9.3 mmol) of triethylamine.
 This mixture is stirred at 120 °C for 24 h. After dry
 concentration of the reaction medium, the residue
 obtained is taken up in H₂O and extracted with AcOEt.
 The organic phases are dried on MgSO₄, then dry
 10 concentrated. The oil obtained is purified by flash
 chromatography on silica (petroleum ether:AcOEt 90:10).
 0.4g of compound **56** is isolated in the form of an oil
 (yield=27%).

TLC silica gel 60 F 254 Merck, petroleum
 15 ether:AcOEt 80:20, R_f=0.19.

Example 57: Ethyl 2-{3-[2-(2-heptyl-4-methyl-3,5-dioxo-
 2,3,4,5-tetrahydro-[1,2, 4]triazin-6-ylamino)-ethyl]-
 phenoxy}-2-methyl-propionate (**57**)



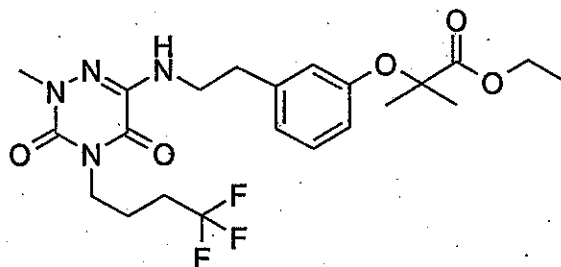
20

Compound **57** (oil) is prepared from triazine **4b** and from
 intermediate **13b** according to synthesis method **1**.

TLC silica gel 60 F 254 Merck, petroleum
 ether:AcOEt 70:30, R_f=0.44.

25

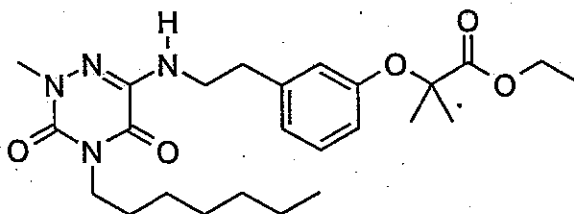
Example 58: Ethyl 2-methyl-2-(3-{2-[2-methyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethyl}-phenoxy)-propionate (58)



Compound **58** (oil) is prepared from triazine **6a** and from intermediate **13b** according to synthesis method **1**.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, R_f=0.33.

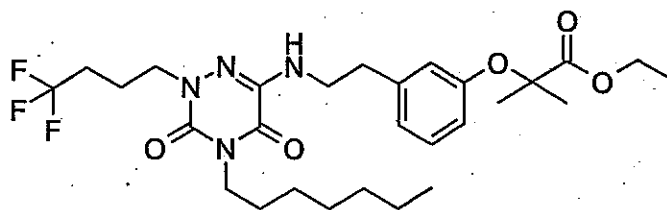
Example 59: Ethyl 2-{3-[2-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-phenoxy}-2-methyl-propionate (59)



Compound **59** (oil) is prepared from triazine **7a** and from intermediate **13b** according to synthesis method **1**.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, R_f=0.50.

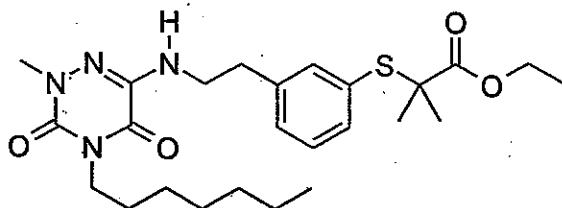
Example 60: Ethyl 2-(3-{2-[4-heptyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethyl}-phenoxy)-2-methyl-propionate (60)



Compound **60** (oil) is prepared from triazine **7b** and from intermediate **13b** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 90:10, R_f=0.22.

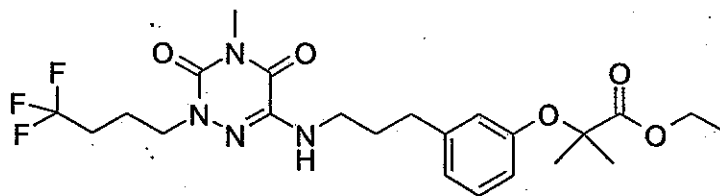
Example 61: Ethyl 2-{3-[2-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-phenylsulfanyl}-2-methyl-propionate (**61**)



Compound **61** (oil) is prepared from triazine **7a** and from intermediate **13d** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, R_f=0.61.

Example 62: Ethyl 2-methyl-2-(3-{3-[4-methyl-3,5-dioxo-2-(4,4,4-trifluorobutyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-propyl}-phenoxy)-propionate (**62**)

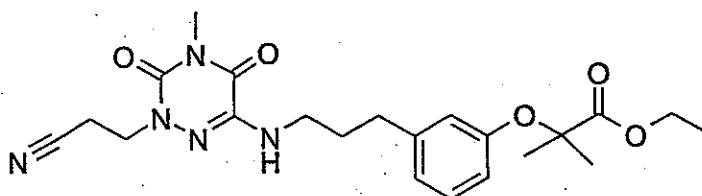


Compound **62** (oil) is prepared from triazine **4a** and from intermediate **13j** according to synthesis method **4**.

TLC silica gel 60 F 254 Merck, CH_2Cl_2 :AcOEt 90:10, $R_f=0.60$.

5

Example 63: Ethyl 2-(3-{3-[2-(2-cyano-ethyl)-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-propyl}-phenoxy)-2-methyl-propionate (**63**)



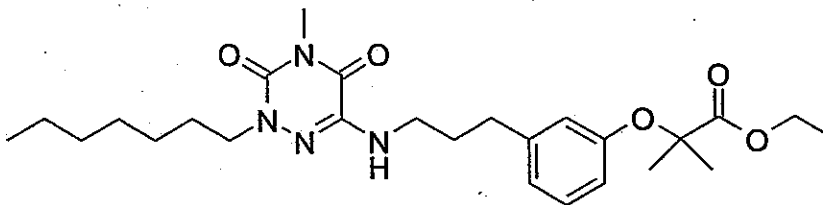
10

Compound **63** (oil) is prepared from triazine **3a** and from intermediate **13j** according to synthesis method **4**.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, $R_f=0.44$.

15

Example 64: Ethyl 2-{3-[3-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-propyl]-phenoxy}-2-methyl-propionate (**64**)

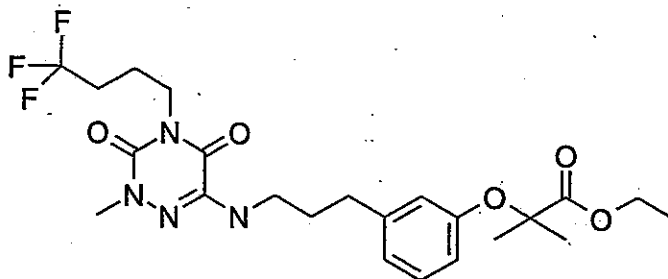


20 Compound **64** (oil) is prepared from triazine **4b** and from intermediate **13j** according to synthesis method **4**.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, $R_f=0.20$.

Example 65: Ethyl 2-methyl-2-(3-{3-[2-methyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-propyl}-phenoxy)-propionate (65)

5



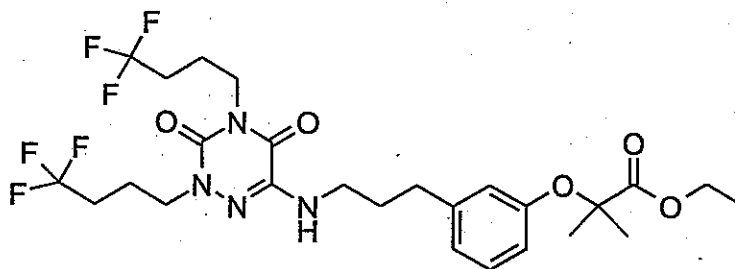
Compound **65** (oil) is prepared from triazine **6a** and from intermediate **13j** according to synthesis method **4**.

TLC silica gel 60 F 254 Merck, CH₂Cl₂:AcOEt 90:10, R_f=0.78.

10

Example 66: Ethyl 2-(3-{3-[3,5-dioxo-2,4-bis-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-propyl}-phenoxy)-2-methyl-propionate (66)

15

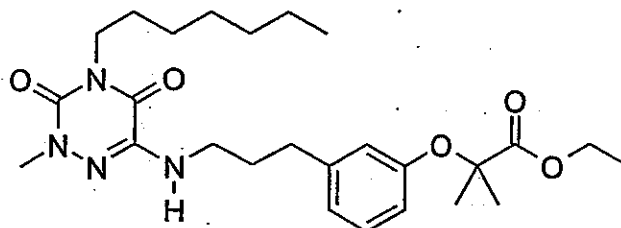


Compound **66** (oil) is prepared from triazine **1d** and from intermediate **13l** according to synthesis method **4**.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, R_f=0.49.

20

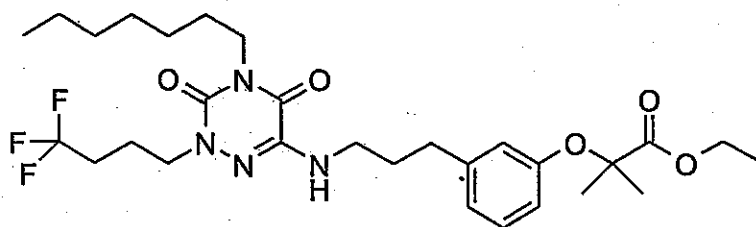
Example 67: Ethyl 2-{3-[3-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-propyl]-phenoxy}-2-methyl-propionate (67)



5 Compound **67** (oil) is prepared from triazine **7a** and from intermediate **13c** according to synthesis method **1**.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.50.

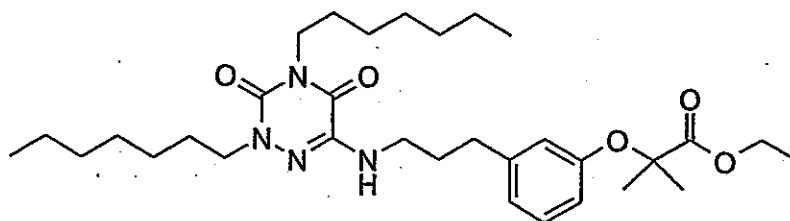
10 **Example 68:** Ethyl 2-(3-{3-[4-heptyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-propyl}-phenoxy)-2-methyl-propionate (68)



15 Compound **68** (oil) is prepared from triazine **7b** and from intermediate **13j** according to synthesis method **4**.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.63.

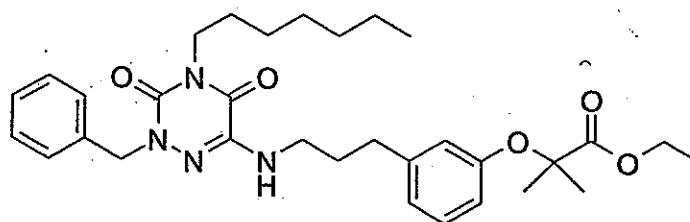
20 **Example 69:** Ethyl 2-{3-[3-(2,4-diheptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-propyl]-phenoxy}-2-methyl-propionate (69)



Compound **69** (oil) is prepared from triazine **1e** and from intermediate **13j** according to synthesis method 4.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.53.

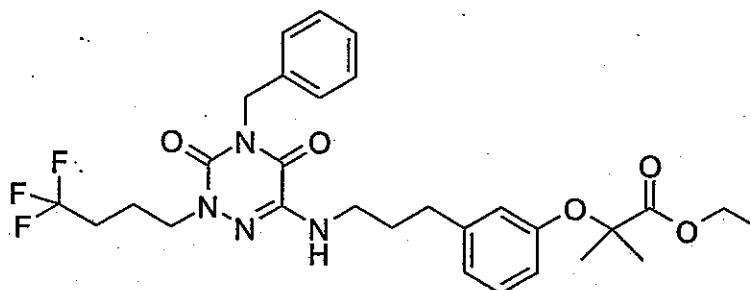
Example 70: Ethyl 2-(3-[3-(2-benzyl-4-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-propyl]-phenoxy)-2-methyl-propionate (**70**)



Compound **70** (oil) is prepared from triazine **7c** and from intermediate **13j** according to synthesis method 4.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.47.

Example 71: Ethyl 2-(3-[3-[4-benzyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-propyl]-phenoxy)-2-methyl-propionate (**71**)

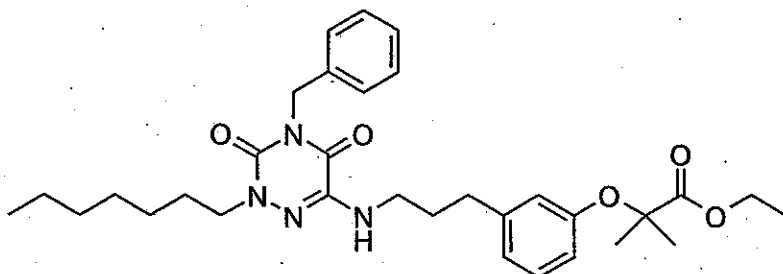


Compound **71** (oil) is prepared from triazine **8a** and from intermediate **13j** according to synthesis method 4.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.30.

5

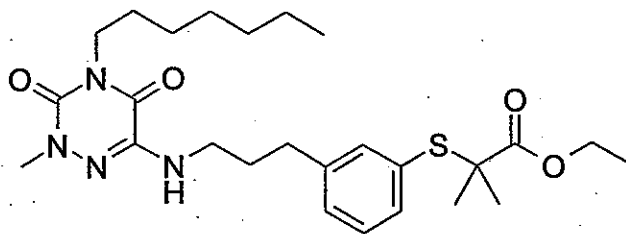
Example 72: Ethyl 2-{3-[3-(4-Benzyl-2-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-propyl]-phenoxy}-2-methyl-propionate (**72**)



10 Compound **72** (oil) is prepared from triazine **8b** and from intermediate **13j** according to synthesis method 4.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.42.

15 **Example 73:** Ethyl 2-{4-[3-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-propyl]-phenylsulfanyl}-2-methyl-propionate (**73**)

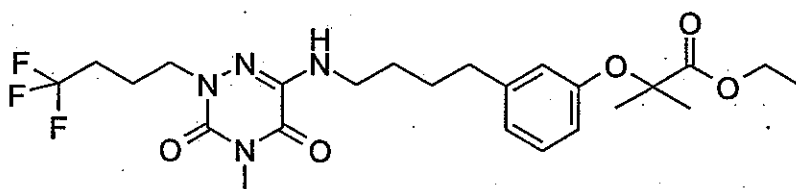


20

Compound **73** (oil) is prepared from triazine **7a** and from intermediate **13e** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.58.

Example 74: Ethyl 2-methyl-2-(3-{4-[4-methyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-propionate (74)



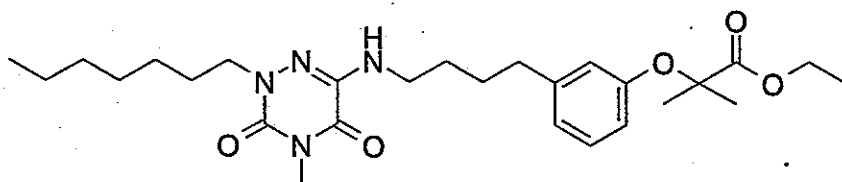
10

Compound **74** (oil) is prepared from triazine **4a** and from intermediate **13m** according to synthesis method **4**.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.21.

15

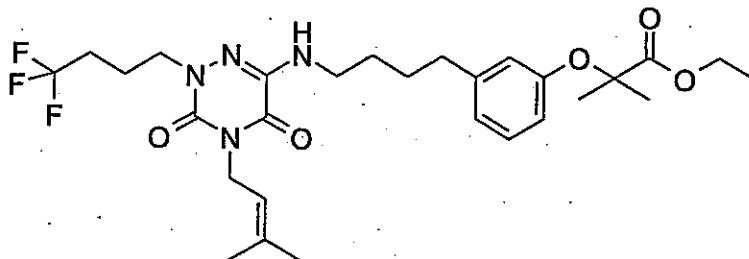
Example 75: Ethyl 2-{3-[4-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-butyl]-phenoxy}-2-methyl-propionate (75)



20 Compound **75** (oil) is prepared from triazine **4b** and from intermediate **13m** according to synthesis method **4**.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.44.

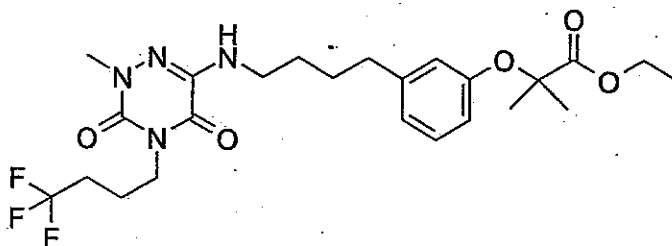
Example 76: Ethyl 2-methyl-2-(3-{4-[4-(3-methyl-but-2-enyl)-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-propionate (76)



Compound 76 (oil) is prepared from triazine 5d and from intermediate 13m according to synthesis method 4.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.50.

Example 77: Ethyl 2-methyl-2-(3-{4-[2-methyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-propionate (77)

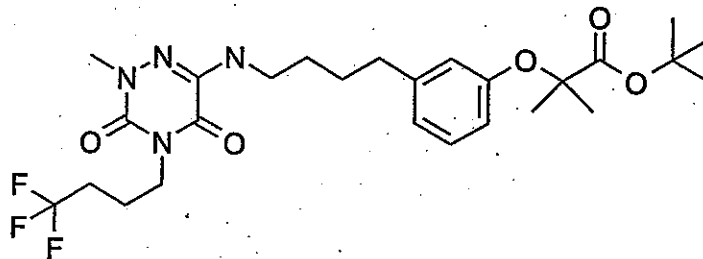


Compound 77 (oil) is prepared from triazine 6a and from intermediate 13k according to synthesis method 4.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.35.

Example 78: Tert-butyl 2-methyl-2-(3-{4-[2-methyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-

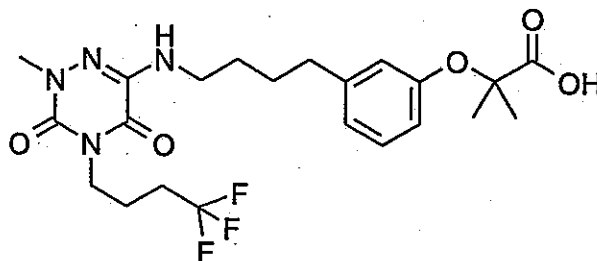
[1,2,4]triazin-6-ylamino]-butyl)-phenoxy)-propionate (78)



Compound **78** (oil) is prepared from triazine **6a** and from intermediate **13m** according to synthesis method **4** using tert-butyl bromoisobutyrate in the last step.

TLC silica gel 60 F 254 Merck, heptane:AcOEt 60:40, $R_f=0.35$.

- Example 79:** 2-Methyl-2-(3-(4-[2-methyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl)-phenoxy)-propionic acid (**79**)

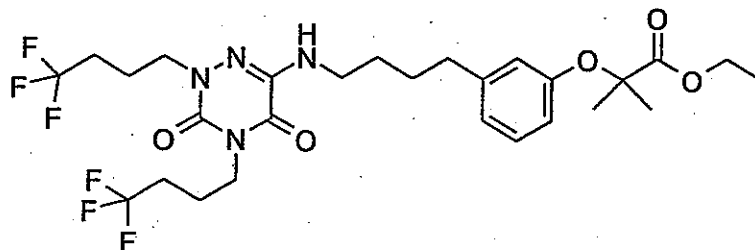


- After the hydrolysis of compound **78** (trifluoroacetic acid/ CH_2Cl_2 , yield=61%), compound **79** is isolated in the form of a solid.

TLC silica gel 60 F 254 Merck, CH_2Cl_2 :MeOH 90:10, $R_f=0.73$. $F=116^\circ\text{C}$

20

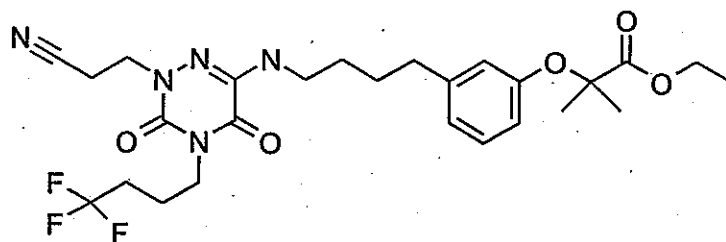
Example 80: Ethyl 2-(3-(4-[3,5-dioxo-2,4-bis-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl)-phenoxy)-2-methyl-propionate (**80**)



Compound **80** (oil) is prepared from triazine **1d** and from intermediate **13m** according to synthesis method 4.

TLC silica gel 60 F 254 Merck, petroleum
5 ether:AcOEt 80:20, R_f =0.32.

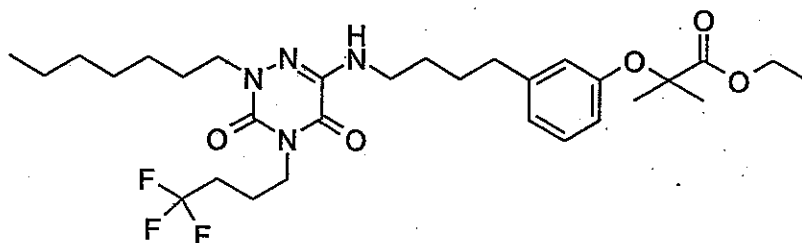
Example 81: Ethyl 2-(3-(4-[2-(2-cyano-ethyl)-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-
[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-2-methyl-
10 propionate (**81**)



Compound **81** (oil) is prepared from triazine **3b** and from intermediate **13k** according to synthesis method 4.

TLC silica gel 60 F 254 Merck, petroleum
15 ether:AcOEt 70:30, R_f =0.20.

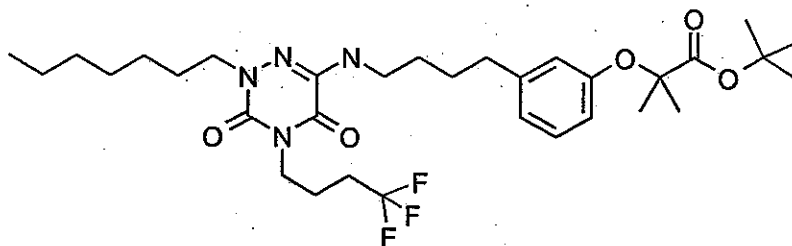
Example 82: Ethyl 2-(3-(4-[2-heptyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-2-methyl-propionate (**82**)



Compound **82** (oil) is prepared from triazine **6b** and from intermediate **13k** according to synthesis method 4.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, $R_f=0.37$.

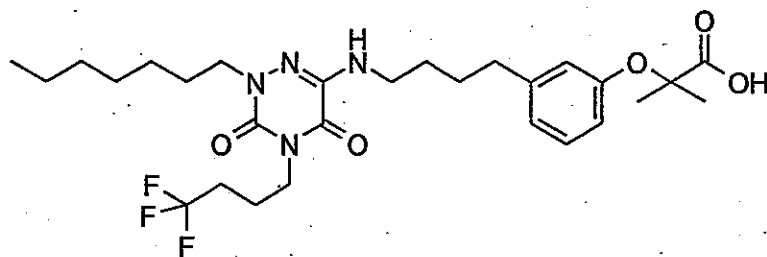
Example 83: Tert-butyl 2-(3-(4-[2-heptyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl)-phenoxy)-2-methyl-propionate (**83**)



Compound **83** (oil) is prepared from triazine **6b** and from intermediate **13m** according to synthesis method 4 using tert-butyl bromoisobutyrate in the last step.

TLC silica gel 60 F 254 Merck, heptane:AcOEt 60:40, $R_f=0.43$.

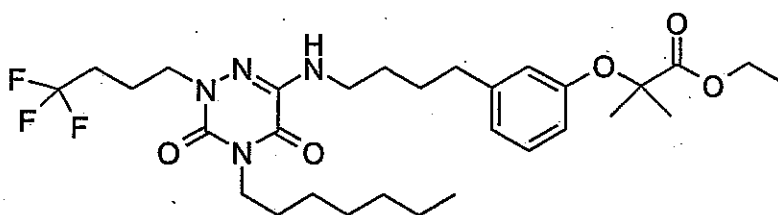
Example 84: 2-(3-(4-[2-Heptyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl)-phenoxy)-2-methyl-propionic acid (**84**)



After the hydrolysis of compound **83** (trifluoroacetic acid/ CH_2Cl_2 , yield=76%), compound **84** is isolated in the form of an oil.

5 TLC silica gel 60 F 254 Merck, CH_2Cl_2 :MeOH 95:5, R_f =0.39.

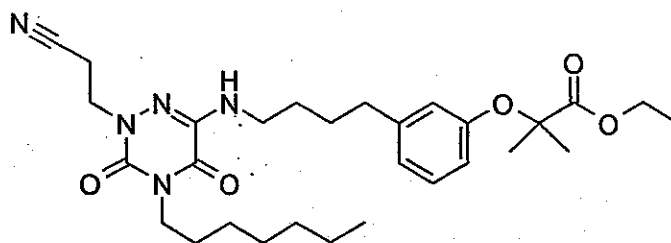
Example 85: Ethyl 2-(3-{4-[4-heptyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-2-methyl-propionate (**85**)



Compound **85** (oil) is prepared from triazine **7b** and from intermediate **13m** according to synthesis method 4.

15 TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, R_f =0.75.

Example 86: Ethyl 2-(3-{4-[2-(2-cyano-ethyl)-4-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-2-methyl-propionate (**86**)

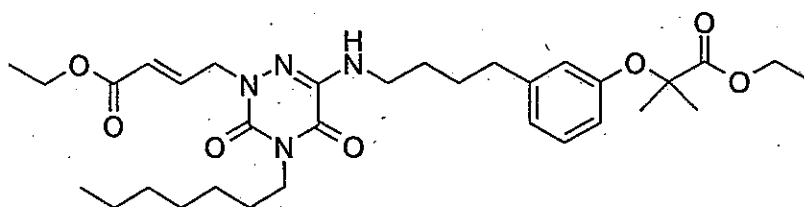


Compound **86** (oil) is prepared from triazine **3c** and from intermediate **13m** according to synthesis method **4**.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 70:30, R_f =0.51.

5

Example 87: Ethyl 4-(6-{4-[3-(1-ethoxycarbonyl-1-methyl-ethoxy)-phenyl]-butylamino}-4-heptyl-3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-but-2-enonate (87**)**

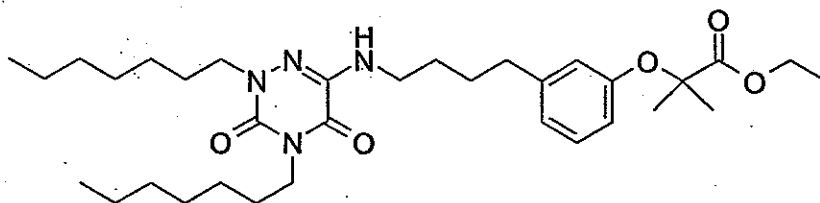


- 10 Compound **87** (oil) is prepared according to synthesis method **6**: 0.2g (5 mmol) of NaH (60% in paraffin) is placed in suspension in 10 ml of DMF at 0 °C under nitrogen. 1.4 g (2.6 mmol) of compound **86** diluted in 4 ml of DMF is added dropwise. The mixture is stirred
- 15 for 4.5h at ambient temperature then dry concentrated. The residue is taken up in H₂O and extracted with AcOEt. The organic phases are dried on MgSO₄, then dry concentrated. The oil obtained is purified by flash chromatography on silica (CH₂Cl₂:AcOEt 90:10) and 0.8 g
- 20 of solid is isolated (yield=63%). 78 mg (1.9 mmol) of NaH (60% in paraffin) is placed in suspension in 15 ml of DMF at 0 °C under nitrogen. The solid previously isolated (0.8 g, 1.6 mmol) diluted in 5 ml of DMF is added dropwise then this mixture is stirred for 1 h at
- 25 ambient temperature. 0.29 ml (2.1 mmol) of ethyl 4-bromo-but-2-enoate is added and then stirring is continued for 9 h. After dry concentration, the residue obtained is taken up in H₂O and extracted with AcOEt.

The organic phases are dried on MgSO_4 , then dry concentrated. The oil obtained is purified by flash chromatography on silica (petroleum ether:AcOEt 80:20). 0.6 g of compound **87** is isolated in the form of an oil (yield=56%).

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, R_f =0.33.

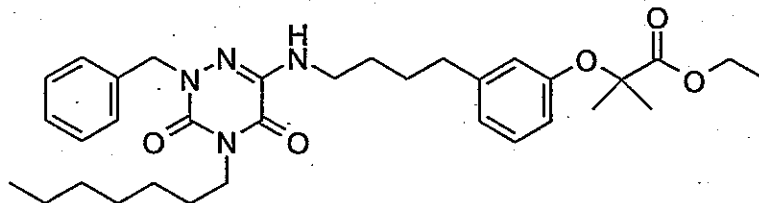
Example 88: Ethyl 2-{3-[4-(2,4-diheptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-butyl]-phenoxy}-2-methyl-propionate (**88**)



Compound **88** (oil) is prepared from triazine **1e** and from intermediate **13k** according to synthesis method 4.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, R_f =0.53.

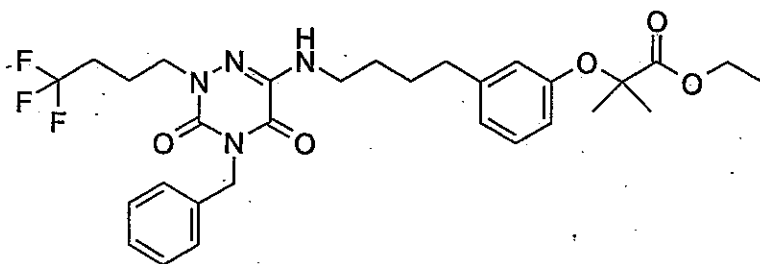
Example 89: Ethyl 2-{3-[4-(2-benzyl-4-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-butyl]-phenoxy}-2-methyl-propionate (**89**)



Compound **89** (solid) is prepared from triazine **7c** and from intermediate **13k** according to synthesis method 4.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.37. F=58 °C.

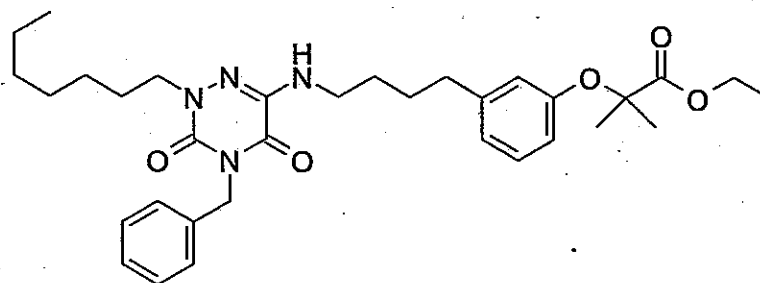
Example 90: Ethyl 2-(3-(3-[4-benzyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-2-methyl-propionate (90)



Compound 90 (oil) is prepared from triazine 8a and from intermediate 13k according to synthesis method 4.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.46.

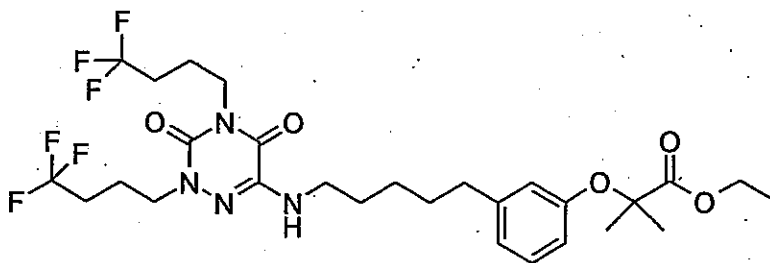
Example 91: Ethyl 2-(3-[4-(4-benzyl-2-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-butyl]-phenoxy)-2-methyl-propionate (91)



Compound 91 (oil) is prepared from triazine 8b and from intermediate 13k according to synthesis method 4.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.60.

Example 92: Ethyl 2-(3-{5-[3,5-dioxo-2,4-bis-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-pentyl}-phenoxy)-2-methyl-propionate (92)



5

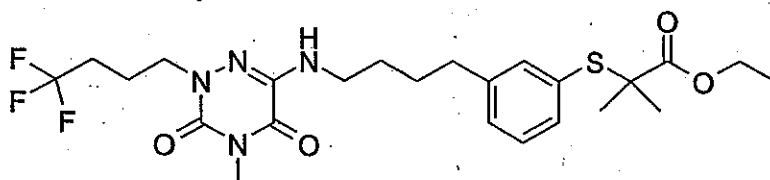
Compound 92 (oil) is prepared from triazine 1d and from intermediate 13n according to synthesis method 4.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.45.

10

Example 93: Ethyl 2-methyl-2-(3-{4-[4-methyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenylsulfanyl)-propionate (93)

15

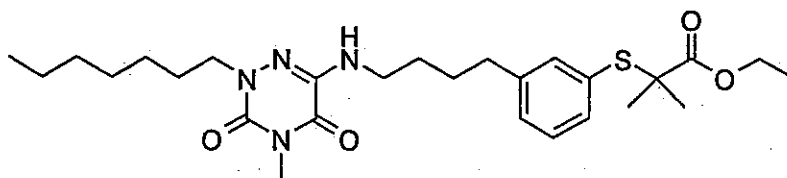


Compound 93 (oil) is prepared from triazine 4a and from intermediate 13f according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.45.

20

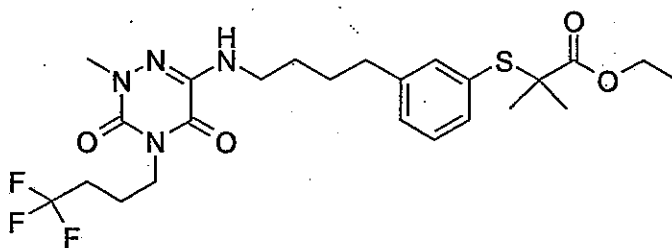
Example 94: Ethyl 2-{3-[4-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-butyl]-phenylsulfanyl}-2-methyl-propionate (94)



Compound **94** (oil) is prepared from triazine **4b** and from intermediate **13f** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, $R_f=0.26$.

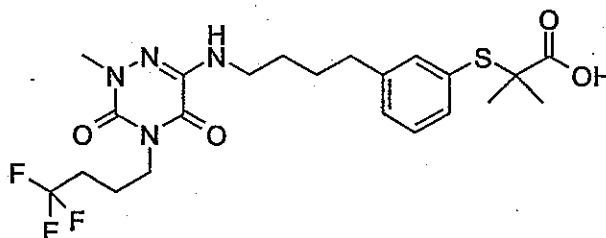
Example 95: Ethyl 2-methyl-2-(3-{4-[2-methyl-3,5-dioxo-4-(4,4,4-trifluorobutyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenylsulfanyl)-propionate (**95**)



Compound **95** (oil) is prepared from triazine **6a** and from intermediate **13f** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, $R_f=0.34$.

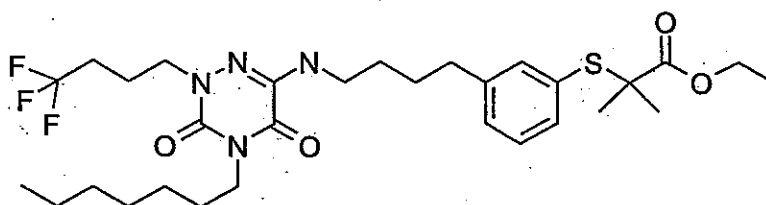
Example 96: 2-Methyl-2-(3-{4-[2-methyl-3,5-dioxo-4-(4,4,4-trifluorobutyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenylsulfanyl)-propionic acid (**96**)



After the hydrolysis of compound **95** ($\text{BBr}_3/\text{CH}_2\text{Cl}_2$, yield=49%), compound **96** is isolated in the form of a solid.

TLC silica gel 60 F 254 Merck, $\text{CH}_2\text{Cl}_2:\text{AcOEt}$ 80:20,
5 $R_f=0.24$. $F=106^\circ\text{C}$

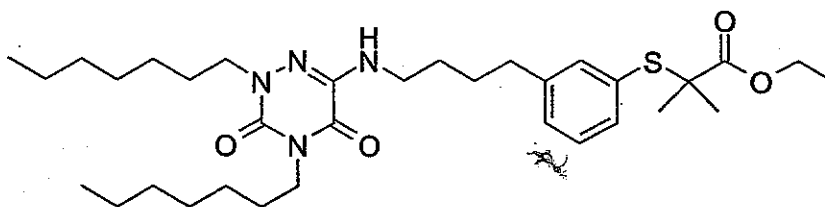
Example 97: Ethyl 2-(3-(4-[4-heptyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl)-phenylsulfanyl)-2-methyl-propionate
10 (97)



Compound **97** (oil) is prepared from triazine **7b** and from
15 intermediate **13f** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether: AcOEt 80:20, $R_f=0.74$.

Example 98: Ethyl 2-(3-[4-(2,4-diheptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-butyl]-phenylsulfanyl)-2-methyl-propionate (98)
20

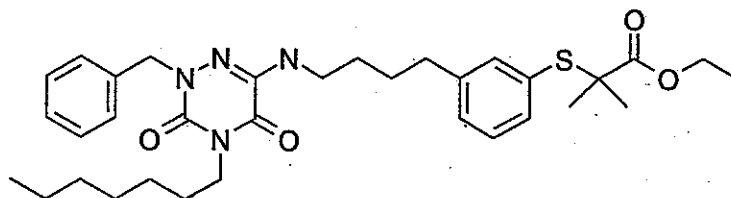


Compound **98** (oil) is prepared from triazine **1e** and from intermediate **13f** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, R_f=0.53.

5

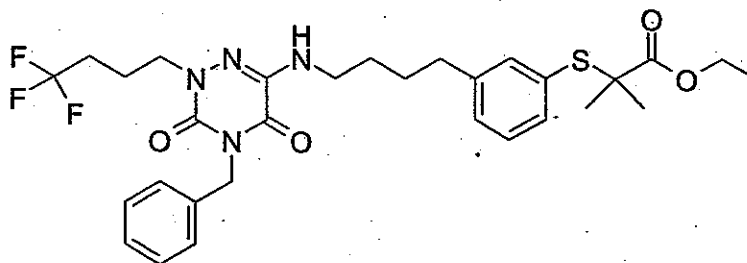
Example 99: Ethyl 2-{3-[4-(2-benzyl-4-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-butyl]-phenylsulfanyl}-2-methyl-propionate (**99**)



10 Compound **99** (oil) is prepared from triazine **7c** and from intermediate **13f** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, R_f=0.43.

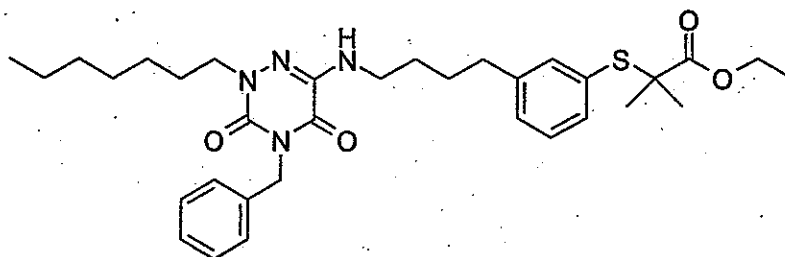
15 **Example 100:** Ethyl 2-(3-{4-[4-Benzyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenylsulfanyl)-2-methyl-propionate (**100**)



20 Compound **100** (oil) is prepared from triazine **8a** and from intermediate **13f** according to synthesis method 1.

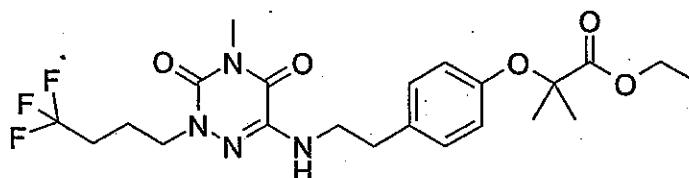
TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, R_f=0.27.

Example 101: Ethyl 2-{3-[4-(4-benzyl-2-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-butyl]-phenylsulfanyl}-2-methyl-propionate (101)



5 Compound 101 (oil) is prepared from triazine 8b and from intermediate 13f according to synthesis method 1. TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.39.

10 **Example 102:** Ethyl 2-methyl-2-(4-{2-[4-methyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethyl}-phenoxy)-propionate (102)

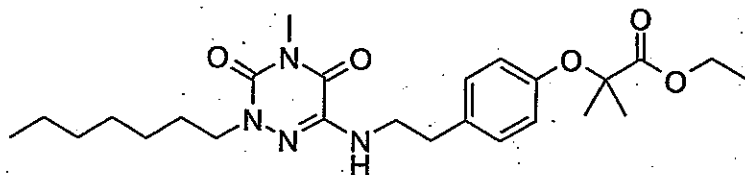


15

Compound 102 (oil) is prepared from triazine 4a and from intermediate 13a according to synthesis method 1. TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.22.

20

Example 103: Ethyl 2-{4-[2-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-phenoxy}-2-methyl-propionate (103)



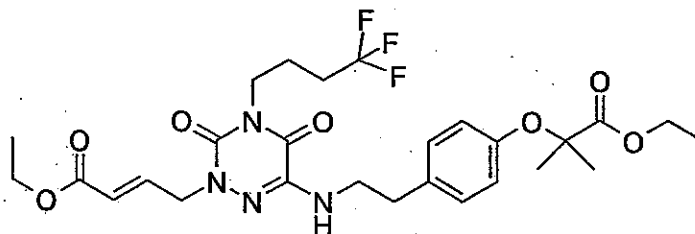
5

Compound **103** (oil) is prepared from triazine **4b** and from intermediate **13a** according to synthesis method 1. TLC silica gel 60 F 254 Merck, CH₂Cl₂:AcOEt 90:10, R_f=0.54.

10

Example 104: Ethyl 4-[6-{2-[4-(1-ethoxycarbonyl-1-methyl-ethoxy)-phenyl]-ethylamino}-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-4,5-dihydro-3H-[1,2,4]triazin-2-yl]-but-2-enoate (104)

15



Compound **104** (oil) is prepared from triazine **3b** and from intermediate **13a** according to synthesis method 6 with ethyl 4-bromo-but-2-enoate used in the alkylation step.

20

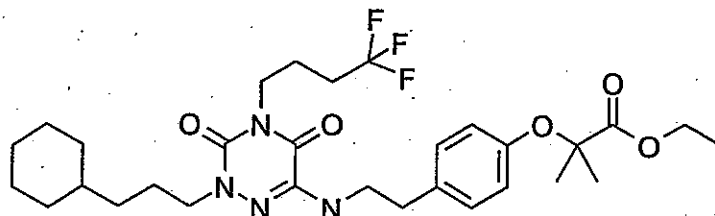
TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, R_f=0.34.

Example 105: Ethyl 2-(4-{2-[2-(3-cyclohexyl-propyl)-

25

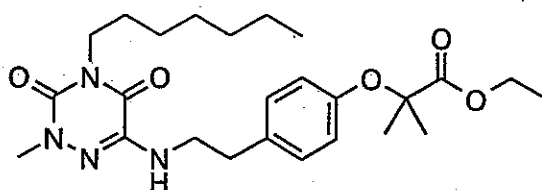
3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-

[1,2,4]triazin-6-ylamino]-ethyl}-phenoxy)-2-methyl-propionate (105)



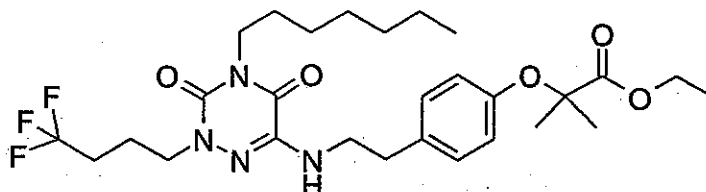
Compound 105 (oil) is prepared from triazine 6c and
 5 from intermediate 13a according to synthesis method 1.
 TLC silica gel 60 F 254 Merck, petroleum
 ether:AcOEt 80:20, Rf=0.44.

Example 106: Ethyl 2-(4-[2-(4-heptyl-2-methyl-3,5-dioxo-
 10 2,3,4,5-tetrahydro-[1, 2,4]triazin-6-ylamino)-ethyl]-
 phenoxy)-2-methyl-propionate (106)



Compound 106 (solid) is prepared from triazine 7a and
 from intermediate 13a according to synthesis method 1.
 15 TLC silica gel 60 F 254 Merck, petroleum
 ether:AcOEt 70:30, Rf=0.60. F=54 °C.

Example 107: Ethyl 2-(4-{2-[4-heptyl-3,5-dioxo-2-
 (4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-
 20 [1,2,4]triazin-6-ylamino]-ethyl}-phenoxy)-2-methyl-
 propionate (107)

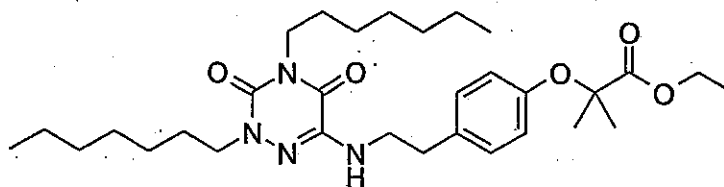


Compound **107** (solid) is prepared from triazine **7b** and from intermediate **13a** according to synthesis method **1**.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.47. F=63 °C.

5

Example 108: Ethyl 2-{4-[2-(2,4-diheptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-phenoxy}-2-methyl-propionate (**108**)



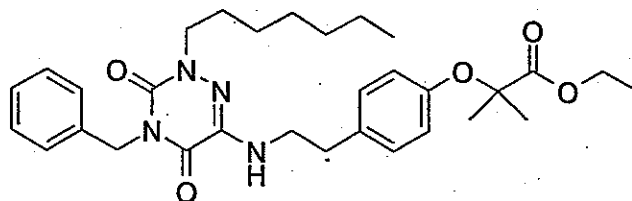
10

Compound **108** (oil) is prepared from triazine **1e** and from intermediate **13a** according to synthesis method **1**.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.57.

15

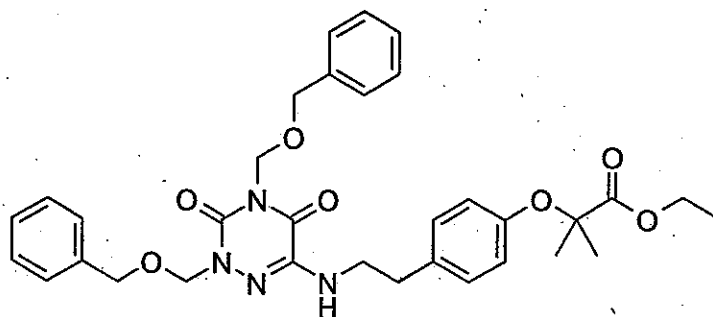
Example 109: Ethyl 2-{4-[2-(4-benzyl-2-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-phenoxy}-2-methyl-propionate (**109**)



20 Compound **109** (solid) is prepared from triazine **8b** and from intermediate **13a** according to synthesis method **1**.

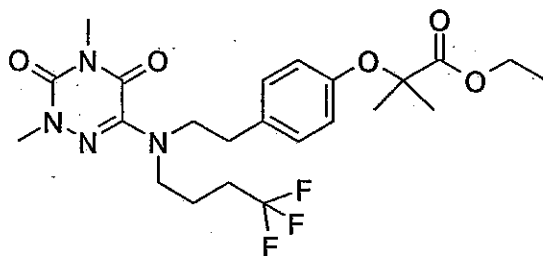
TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.60. F=65 °C.

Example 110: Ethyl 2-{4-[2-(2,4-bis-benzyloxymethyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-phenoxy}-2-methyl-propionate (110)



- 5 Compound **110** (oil) is prepared from triazine **1g** and from intermediate **13a** according to synthesis method **1**.
TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, R_f=0.34.

- 10 **Example 111:** Ethyl 2-(4-{2-[(2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-(4,4,4-trifluoro-butyl)-amino]-ethyl}-phenoxy)-2-methyl-propionate (111)

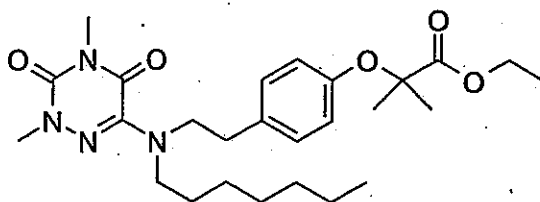


- 15 Compound **111** is prepared according to synthesis method **5**: 3.2 g (14.7 mmol) of triazine **1b** and 5.4 ml (36.8 mmol) of 2-(4-methoxy-phenyl)-ethylamine are placed in 30 ml of nBuOH in the presence of 5.1 ml (36.8 mmol) of triethylamine at 130 °C for 10.5 h.
20 After dry concentration, the residue obtained is taken up in H₂O and extracted with AcOEt. The organic phases are dried on MgSO₄, then dry concentrated. The oil

obtained is purified by flash chromatography on silica (heptane:AcOEt 50:50) and 2.3g of solid is isolated (yield=54%). 0.48 g (12 mmol) of NaH (60% in paraffin) is placed in suspension in 15 ml of DMF at 0 °C under nitrogen. 2.3g (7.9 mmol) of the previously isolated solid diluted in 5 ml of DMF are added dropwise. The mixture is stirred for 0.5 h at ambient temperature and then 4.7 g (19.8 mmol) of 1,1,1-trifluoro-4-iodo-butane are added and stirring is continued for 6.5 h. After dry concentration, the residue obtained is taken up in H₂O and extracted with AcOEt. The organic phases are dried on MgSO₄, then dry concentrated. The oil obtained is purified by flash chromatography on silica (CH₂Cl₂:AcOEt 95:5) and 0.82 g of oil is isolated (yield=26%). 0.4 g of the latter is then placed in 15 ml of CH₂Cl₂ at -60 °C under nitrogen, a BBr₃ solution (1 M in CH₂Cl) (0.24 ml diluted in 2 ml of CH₂Cl₂) is added dropwise and the reaction medium is stirred for 2 h at ambient temperature. It is next placed at 0 °C and neutralized by a 1 N HCl solution. The organic phase is decanted and then washed with 100 ml of water. After drying on MgSO₄, it is dry concentrated and 0.38g of the corresponding phenol is isolated (quantitative yield). It is then placed in 0.5 ml of ethyl bromoisobutyrate in the presence of 0.14 g (1 mmol) of K₂CO₃ at 150 °C for 5 h. After filtration and dry concentration, the residue obtained is purified by flash chromatography on silica (CH₂Cl₂:AcOEt 95:5) and 0.25 g of compound **111** is isolated in the form of an oil (yield=51%).

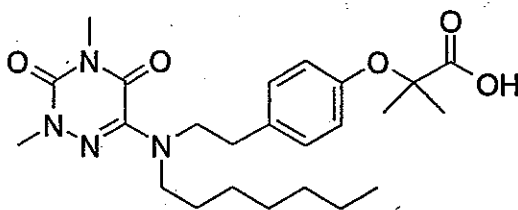
TLC silica gel 60 F 254 Merck, CH_2Cl_2 :AcOEt 90:10,
 Rf=0.65.

Example 112: Ethyl 2-(4-{2-[(2,4-dimethyl-3,5-dioxo-
 2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-heptyl-amino]-
 ethyl}-phenoxy)-2-methyl-propionate (112)



Compound **112** (oil) is prepared from triazine **1b** and from intermediate **14a** according to synthesis method **1**.
 TLC silica gel 60 F 254 Merck, CH_2Cl_2 :AcOEt 70:30,
 Rf=0.70.

Example 113: 2-(4-{2-[(2,4-Dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-heptyl-amino]-ethyl}-phenoxy)-2-methyl-propionic acid (113)



20

Compound **113** is prepared from triazine **1b** and from 2-(4-methoxy-phenyl)-ethylamine according to synthesis method **5** by alkylating nitrogen with 1-bromoheptane and by using tert-butyl bromoisobutyrate. After hydrolysis

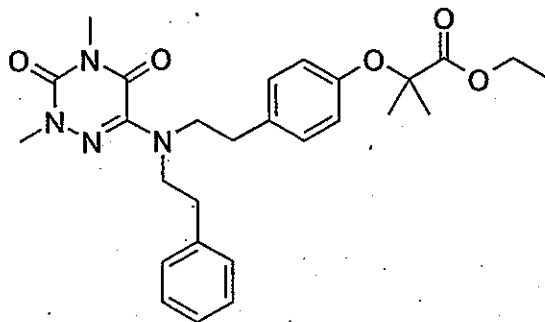
with trifluoroacetic acid in CH_2Cl_2 , compound **113** is isolated in the form of oil.

TLC silica gel 60 F 254 Merck, $\text{CH}_2\text{Cl}_2:\text{MeOH}$ 90:10, $R_f=0.43$.

5

Example 114: Ethyl 2-(4-{2-[(2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-phenethyl-amino]-ethyl}-phenoxy)-2-methyl-propionate (**114**)

10

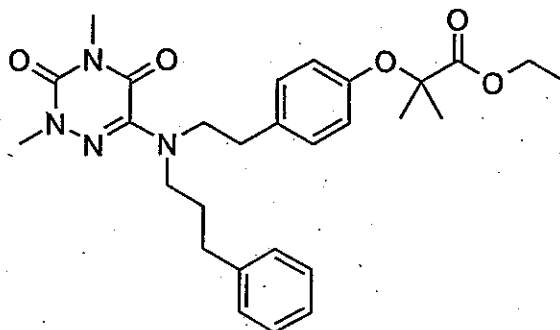


Compound **114** (oil) is prepared from triazine **1b** and from intermediate **14b** according to synthesis method **1**.

15 TLC silica gel 60 F 254 Merck, $\text{CH}_2\text{Cl}_2:\text{AcOEt}$ 90:10, $R_f=0.74$.

Example 115: Ethyl 2-(4-{2-[(2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-(3-phenyl-propyl)-amino]-ethyl}-phenoxy)-2-methyl-propionate (**115**)

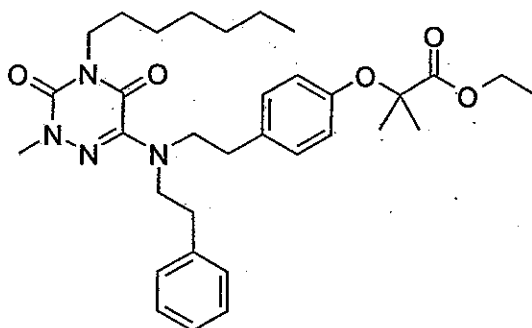
20



Compound **115** (oil) is prepared from triazine **1b** and from intermediate **14c** according to synthesis method 1.

5 TLC. silica gel 60 F 254 Merck, CH_2Cl_2 :AcOEt 90:10, R_f =0.63.

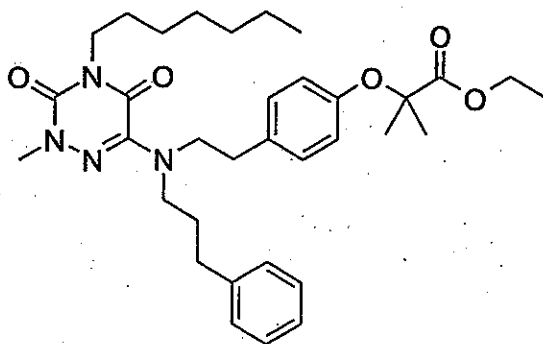
Example 116: Ethyl 2-(4-{2-[(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-phenethyl-amino]-ethyl}-phenoxy)-2-methyl-propionate (116)



Compound **116** (oil) is prepared from triazine **7a** and from intermediate **14b** according to synthesis method 1.

15 TLC silica gel 60 F 254 Merck, CH_2Cl_2 , R_f =0.52.

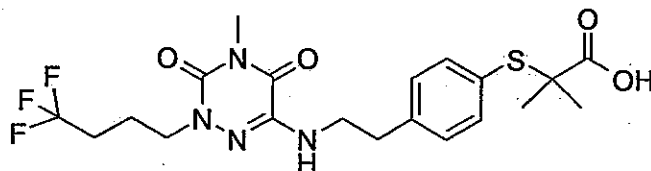
Example 117: Ethyl 2-(4-{2-[(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-(3-phenyl-propyl)-amino]-ethyl}-phenoxy)-2-methyl-propionate (117)



Compound **117** (oil) is prepared from triazine **7a** and from intermediate **14c** according to synthesis method 1. TLC silica gel 60 F 254 Merck, CH₂Cl₂, R_f=0.46.

5

Example 118: 2-Methyl-2-(4-{2-[4-methyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethyl}-phenylsulfanyl)-propionic acid (**118**)

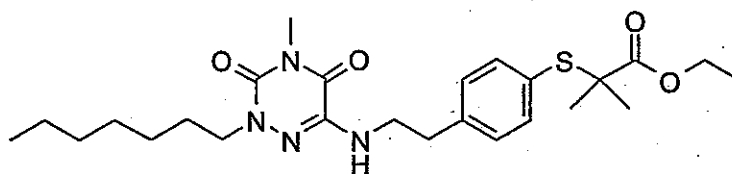


10

Compound **118** is prepared from triazine **4a** and from intermediate **13i** according to synthesis method 1. After hydrolysis with trifluoroacetic acid in CH₂Cl₂, compound **118** is isolated in the form of a solid.

15 TLC silica gel 60 F 254 Merck, AcOEt, R_f=0.42. F=128 °C

Example 119: Ethyl 2-{4-[2-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-phenylsulfanyl}-2-methyl-propionate (**119**)



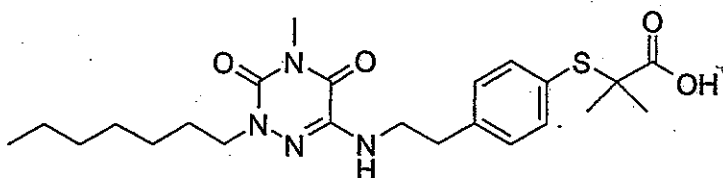
20

Compound **119** (oil) is prepared from triazine **4b** and from intermediate **13g** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, R_f =0.60.

5

Example 120: 2-{4-[2-(2-Heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-phenylsulfanyl}-2-methyl-propionic acid (**120**)

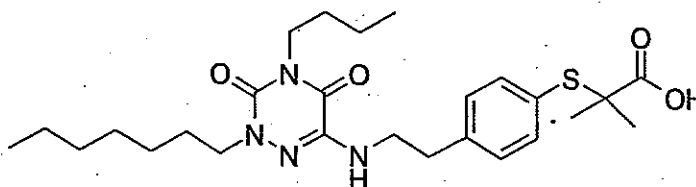


10 Compound **120** is prepared from triazine **4b** and from intermediate **13i** according to synthesis method 1. After hydrolysis with trifluoroacetic acid in CH_2Cl_2 , compound **120** is isolated in the form of a solid.

TLC silica gel 60 F 254 Merck, CH_2Cl_2 :MeOH 90:10,

15 R_f =0.34. $F=70^\circ\text{C}$.

Example 121: 2-{4-[2-(4-Butyl-2-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-phenylsulfanyl}-2-methyl-propionic acid (**121**)



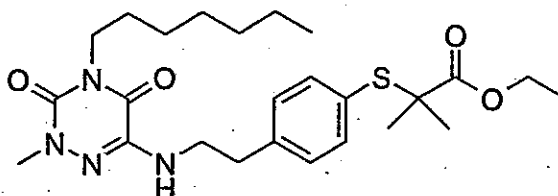
20

Compound **121** is prepared from triazine **5c** and from intermediate **13i** according to synthesis method 1. After hydrolysis with trifluoroacetic acid in CH_2Cl_2 , compound **121** is isolated in the form of oil.

25 TLC silica gel 60 F 254 Merck, CH_2Cl_2 :MeOH 98:2, R_f =0.46.

Example 122: Ethyl 2-{4-[2-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-phenylsulfanyl}-2-methyl-propionate (122)

5



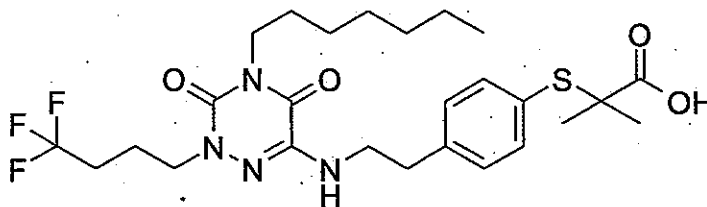
Compound **122** (solid) is prepared from triazine **7a** and from intermediate **13g** according to synthesis method 1.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, R_f=0.67. F=49 °C.

10

Example 123: 2-(4-{2-[4-Heptyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethyl}-phenylsulfanyl)-2-methyl-propionic acid (123)

15

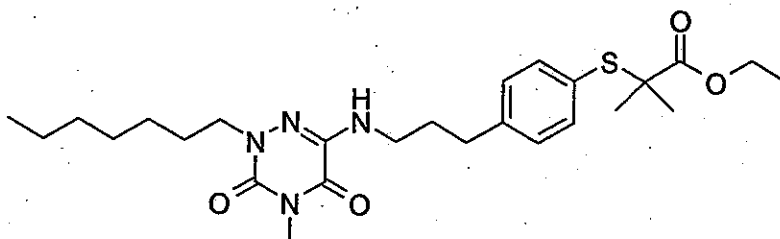


Compound **123** is prepared from triazine **7b** and from intermediate **13i** according to synthesis method 1. After hydrolysis with trifluoroacetic acid in CH₂Cl₂, compound **123** is isolated in the form of a solid.

TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, R_f=0.19. F=86 °C.

25

Example 124: Ethyl 2-{4-[3-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-propyl]-phenylsulfanyl}-2-methyl-propionate (124)



5

Compound **125** (oil) is prepared from triazine **4b** and from intermediate **13h** according to synthesis method 1. TLC silica gel 60 F 254 Merck, petroleum ether:AcOEt 80:20, Rf=0.20.

PHARMACOLOGICAL EVALUATION

In vitro

5 Activation of transcription (transactivation)
of the reporter gene controlled by specific response
elements after binding of the ligand to the receptor
(reporter gene assay).

 These experiments were carried out according to
J.M. Lehmann et al. (J. Biol. Chem 1995, 270:12953-
10 12956) with several modifications. Subconfluent Cos-7
cells (ATCC, CRL-1651) were transfected with (i)
chimeric receptors containing the binding domain for
human PPAR α or PPAR γ or PPAR δ ligand bound to the DNA
binding domain of yeast galactosidase (Gal-4), and (ii)
15 the reporter plasmid containing five copies of the Gal-
4 response element upstream of the thymidine kinase
promoter adjacent to the luciferase gene (p5xUAS-tk-
Luc). After 24 hours, these cells were treated for the
following 24 hours by compounds and their vehicle and
20 luciferase activity were evaluated after cellular
extraction according to the manufacturer's (Promega)
recommendations.

 The results are reported in table 17 below, in
which the designation "hit" indicates a compound whose
25 transactivation level is significant but for which
definition of an EC₅₀ is not possible, and in which the
designation "nd" indicates that no data was collected.

Table 17: reporter gene transactivation by various human PPAR subtypes

Examples	hPPAR-GAL4 alpha EC ₅₀ (μM)	hPPAR-GAL4 gamma EC ₅₀ (μM)	hPPAR-GAL4 delta EC ₅₀ (μM)
Fenofibric acid	16.9	65.2	>100
Rosiglitazone	0	1.12	0
Pioglitazone	>10	4.77	0
1	3-10	0	0
2	>10	~10	0
3	~3	0	0
4	>10	0	0
5	~3	~10	0
6	~0.3	0	0
7	0.3-1	1-3	0
8	~0.3	3-10	0
9	3-10	~10	0
10	0.3-1	~1	0
11	0.3-1	1-3	0
12	~0.03	1-3	hit
13	0.01-0.03	0.1-0.3	~3
14	0.01-0.03	~1	~10
15	0.001-0.003	0.1-0.3	hit
16	~0.1	3-10	0
17	0.3-1	~0.3	0
18	0.03-0.1	~1	0
19	~3	3-10	0
20	hit	hit	0
21	3-10	0	0
22	10	hit	0
23	1	hit	0
24	>10	0	0
25	hit	>10	hit
26	>10	0	0
27	~3	3-10	3-10
28	~10	hit	0
29	3-10	3-10	3-10
30	0.03-0.1	>10	hit
31	~0.1	~1	3-10
32	1-3	hit	0
33	~3	~3	0
34	>10	>10	0
35	0.03-0.1	3-10	~10

Examples	hPPAR-GAL4 alpha EC ₅₀ (μM)	hPPAR-GAL4 gamma EC ₅₀ (μM)	hPPAR-GAL4 delta EC ₅₀ (μM)
36	0.3-1	3-10	hit
37	>10	~10	0
38	>10	>10	0
39	0.1-0.3	3-10	~3
40	3-10	~10	>10
41	~0.1	~10	1-3
42	~1	>10	1-3
43	~3	hit	0
44	>10	3-10	0
45	1-3	~3	hit
46	0.3-1	0	0
47	~0.3	~0.3	hit
48	0.3-1	0.3-1	~3
49	>10	>10	0
50	>10	~10	0
51	3-10	>10	0
52	hit	0	0
53	1-3	0	0
54	>10	0	0
55	>10	0	0
56	hit	hit	0
57	~3	1-3	hit
58	>10	0	0
59	1-3	nd	0
60	>10	hit	0
61	~3	nd	0
62	>10	0	0
63	0	hit	0
64	>10	3-10	hit
65	0.1-0.3	>10	0
66	0.03-0.1	>10	~10
67	~1	nd	0
68	0.1-0.3	3-10	0
69	1-3	~10	0
70	~1	~10	0
71	~1	hit	0
72	3-10	3-10	0
73	0.1-0.3	nd	0
74	~1	3-10	0
75	3-10	3-10	0
76	0.01-0.03	1-3	3-10
77	~0.3	3-10	0
78	>10	0	0
79	~0.03	3-10	0
80	0.01-0.03	0.3-1	>10

Examples	hPPAR-GAL4 alpha EC ₅₀ (μM)	hPPAR-GAL4 gamma EC ₅₀ (μM)	hPPAR-GAL4 delta EC ₅₀ (μM)
81	0.3-1	>10	0
82	~0.01	0.1-0.3	hit
83	>10	0	0
84	0.003-0.01	~0.3	1-3
85	~0.03	1-3	hit
86	>10	~1	hit
87	~0.3	0.1-0.3	hit
88	~0.3	~10	0
89	>10	1-3	3-10
90	~0.1	~10	0
91	0.3-1	3-10	0
92	0.003-0.01	3-10	0
93	>10	hit	0
94	3-10	3-10	0
95	1-3	>10	0
96	0.03-0.1	~10	>10
97	1-3	hit	0
98	>10	0	0
99	>10	3-10	0
100	1-3	>10	0
101	1-3	0	0
102	>10	hit	0
104	1-3	>10	0
105	1-3	~10	0
106	~1	nd	>10
107	~1	hit	0
108	>10	hit	0
109	~1	nd	3-10
110	1-3	hit	>10
111	0	hit	0
112	1-3	~10	1-3
113	0.3-1	3-10	0.3-1
114	~10	nd	0
115	~3	nd	>10
116	~10	nd	0
117	~10	nd	0
118	1-3	~10	0
119	0.3	0.3	hit
120	0.3-1	1-3	hit
121	0.03-0.1	1-3	hit
122	~0.3	nd	>10
123	0.1-0.3	~10	0
124	0.3-1	>10	0

In vivo

Normalization of metabolic parameters (cholesterol, plasma triglycerides) in an insulin-resistant male rat (Ico: ZUCKER-fa/fa), unfed for 16-18 hours, after treatment by oral route, once per day for four days, with the compounds to be evaluated or their administration vehicle.

These metabolic parameters are measured by spectrophotometry at the beginning and the end of each animal's treatment.

Table 18: Normalization of metabolic parameters

Examples	Plasma triglycerides	Plasma cholesterol
11	inactive at 2.5 mg/kg -37% at 10 mg/kg	-25% at 2.5 mg/kg -25% at 10 mg/kg
13	inactive at 2.5 mg/kg -28% at 10 mg/kg	-8% at 2.5 mg/kg -12% at 10 mg/kg
15	-22% at 2.5 mg/kg -63% at 10 mg/kg	-4% at 2.5 mg/kg -8% at 10 mg/kg
16	inactive at 2.5 mg/kg -15% at 10 mg/kg	-14% at 2.5 mg/kg -25% at 10 mg/kg
17	-37% at 10 mg/kg	active at 10 mg/kg
41	inactive at 10 mg/kg	-28% at 10 mg/kg
45	inactive at 10 mg/kg	-16% at 10 mg/kg
46	-32% at 10 mg/kg	-13% at 10 mg/kg
47	-45% at 10 mg/kg	-25% at 10 mg/kg
53	inactive at 10 mg/kg	-7% at 2.5 mg/kg -28% at 10 mg/kg
59	-13% at 2.5 mg/kg	-37% at 2.5 mg/kg
65	inactive at 2.5 mg/kg -13% at 10 mg/kg	-13% at 2.5 mg/kg -23% at 10 mg/kg
66	inactive at 10 mg/kg	-9% at 10 mg/kg
67	-23% at 10 mg/kg	-14% at 10 mg/kg

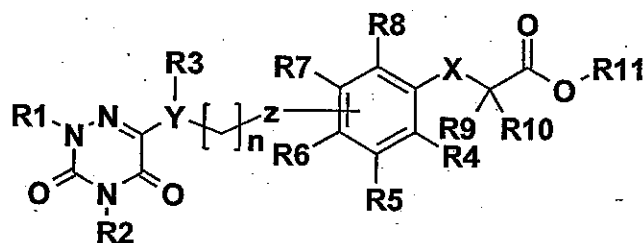
Examples	Plasma triglycerides	Plasma cholesterol
68	active at 10 mg/kg	-21% at 10 mg/kg
72	inactive at 10 mg/kg	-21% at 10 mg/kg
73	inactive at 10 mg/kg	-14% at 10 mg/kg
74	inactive at 2.5 mg/kg -26% at 10 mg/kg	-18% at 2.5 mg/kg -29% at 10 mg/kg
75	active at 10 mg/kg	-19% at 2.5 mg/kg -13% at 10 mg/kg
76	-7% at 10 mg/kg	-16% at 2.5 mg/kg -22% at 10 mg/kg
77	active at 10 mg/kg	-29% at 2.5 mg/kg -35% at 10 mg/kg
79	-55% at 2.5 mg/kg	-32% at 2.5 mg/kg
80	inactive at 10 mg/kg	-16% at 10 mg/kg
81	-17% at 10 mg/kg	-12% at 10 mg/kg
82	active at 10 mg/kg	-13% at 10 mg/kg
84	inactive at 2.5 mg/kg -7% at 10 mg/kg	inactive at 2.5 mg/kg -13% at 10 mg/kg
85	active at 10 mg/kg	-21% at 10 mg/kg
92	inactive at 10 mg/kg	-18% at 10 mg/kg
95	inactive at 10 mg/kg	-18% at 2.5 mg/kg -40% at 10 mg/kg
96	-26% at 2.5 mg/kg -60% at 10 mg/kg	-28% at 2.5 mg/kg -21% at 10 mg/kg
112	-31% at 10 mg/kg	-43% at 10 mg/kg
113	inactive at 2.5 mg/kg -26% at 10 mg/kg	-30% at 2.5 mg/kg -40% at 10 mg/kg
119	active at 2.5 mg/kg -29% at 10 mg/kg	-21% at 2.5 mg/kg -32% at 10 mg/kg
120	-27% at 2.5 mg/kg -73% at 10 mg/kg	-32% at 2.5 mg/kg -33% at 10 mg/kg
121	-24% at 2.5 mg/kg	-7% at 2.5 mg/kg
122	-35% at 10 mg/kg	-22% at 10 mg/kg
123	-6% at 2.5 mg/kg -20% at 10 mg/kg	-8% at 2.5 mg/kg -14% at 10 mg/kg

Thus, the present invention relates to the compounds of formula I previously defined as novel medicines of use in the treatment of diseases requiring PPAR alpha and/or PPAR gamma receptor agonists. These
5 compounds are of use in the prevention and the treatment of diseases such as diabetic dyslipidemia, hypertriglyceridemia, hypercholesterolemia, hyperinsulinemia, hyperglycemia, metabolic syndrome, obesity, atherosclerosis, and in dermatology in
10 pathologies with an inflammatory component or resulting from abnormal cell differentiation as well as in the treatment of diseases such as psoriasis, acne, atopic dermatitis, cutaneous aging and photoaging.

Lastly, the invention relates to pharmaceutical
15 compounds containing as an active ingredient at least one compound of formula I previously defined, preferably in association with a suitable excipient.

CLAIMS

1) 3,5-Dioxo-(2H,4H)-1,2,4-triazine derivatives of general formula I



I

in which

-R₁ and R₂ can be identical or different and represent an alkyl or alkenyl radical, linear or branched, at C₁-C₇, an alkyl radical at C₁-C₆ substituted by groups such as trifluoromethyl, cycloalkyl at C₅-C₆, nitrile, alkoxy carbonyl vinyl at C₁-C₄, hydroxycarbonyl vinyl, alkoxy carbonyl at C₁-C₄, carboxylate, benzyloxy or phenyl (for which the core phenyl is possibly substituted by one or more groups such as alkyl at C₁-C₄, alkoxy at C₁-C₄, nitro, halogen or trifluoromethyl),

-YR₃ represents oxygen or NR₃ in which R₃ represents hydrogen, an alkyl or alkenyl radical, linear or branched at C₁-C₇, an alkyl radical at C₁-C₆ substituted by groups such as trifluoromethyl or phenyl (for which the core phenyl is possibly substituted by one or more groups such as alkyl at C₁-C₄,

alkoxy at C₁-C₄, nitro, halogen or trifluoromethyl),

-Z represents an oxygen atom or a carbon atom which can be bound in ortho, meta or para position on the phenyl group of formula I

-n can range from 0 to 5 when Z=C or from 2 to 4 when Z=O,

-X represents oxygen or sulfur,

10 -R₄, R₅, R₆, R₇ and R₈ represent hydrogen or fluorine,

-R₉, R₁₀ and R₁₁ represent hydrogen or an alkyl group, linear or branched, at C₁-C₅,

as well as additive salts with pharmaceutically acceptable bases and the various enantiomers of compounds having asymmetrical carbons, as well as their mixtures in all proportions, including racemic mixtures in particular.

2) 3,5-Dioxo-(2H,4H)-1,2,4-triazine

derivatives of general formula I according to claim 1 in which:

-R₁ and R₂ represent, independently one from the other, an alkyl or alkenyl radical, linear or branched, at C₁-C₇, an alkyl radical at C₁-C₆ substituted by groups such as trifluoromethyl, cycloalkyl at C₆, nitrile, or phenyl (for which the core phenyl is possibly substituted by one or more groups such as alkyl at C₁-C₄, alkoxy at C₁-C₄, nitro, halogen or trifluoromethyl),

30 -YR₃ represents oxygen or NR₃ in which R₃ represents hydrogen, an alkyl or alkenyl

- radical, linear or branched, at C₁-C₇, an alkyl radical at C₁-C₆ substituted by groups such as trifluoromethyl or phenyl,
- 5 -Z represents an oxygen atom or a carbon atom which can be bound in ortho, meta or para position on the phenyl group of formula I
- n can range from 0 to 5 when Z=C or from 2 to 4 when Z=O,
- X represents oxygen or sulfur,
- 10 -R₄, R₅, R₆, R₇ and R₈ represent hydrogen or fluorine, -R₉, R₁₀ and R₁₁ represent hydrogen or an alkyl group, linear or branched, at C₁-C₅.
- 3) 3,5-Dioxo-(2H,4H)-1,2,4-triazine derivatives of general formula I according to one of
- 15 the claims 1 and 2 in which:
- R₁ and R₂ represent independently one from the other, an alkyl or alkenyl radical, linear or branched, at C₁-C₇, an alkyl radical at C₁-C₆ substituted by groups such as trifluoromethyl or nitrile,
- 20 -YR₃ represents oxygen or NR₃ in which R₃ represents hydrogen or a linear or branched alkyl radical at C₁-C₇,
- Z represents a carbon atom which can be bound
- 25 in ortho, meta or para position on the phenyl group of formula I,
- n can range from 0 to 5,
- X represents oxygen or sulfur,
- R₄, R₅, R₆, R₇ and R₈ represent hydrogen or fluorine,
- 30 -R₉, R₁₀ and R₁₁ represents hydrogen or a linear or branched alkyl group at C₁-C₅, in particular R₉ and R₁₀

represent a methyl group and R_{11} hydrogen or an ethyl group.

4) 3,5-Dioxo-(2H,4H)-1,2,4-triazine derivatives of general formula I according to one of the claims 1 and 3 in which:

- R_1 and R_2 represent independently one from the other, an alkyl or alkenyl radical, linear or branched, at C_1-C_7 , possibly substituted at the end of the chain by a trifluoromethyl group,
- 10 - YR_3 represents oxygen or NR_3 in which R_3 represents hydrogen or a linear or branched alkyl radical at C_1-C_7 ,
- Z represents a carbon atom which can be bound in meta or para position on the phenyl group of
- 15 formula I,
- n can range from 1 to 5,
- X represents oxygen or sulfur,
- R_4 to R_8 represent hydrogen,
- R_9 and R_{10} represent a methyl radical
- 20 - R_{11} represents hydrogen or an ethyl radical.

5) Compounds of general formula I according to claim 1) wherein they are selected among:

- 25 1. Ethyl 2-{2-[2-(4-butyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-ethyl]-phenoxy}-2-methyl-propionate
- 2. Ethyl 2-{3-[2-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-ethyl]-phenoxy}-
- 30 2-methyl-propionate

3. Ethyl 2-methyl-2-(3-{2-[2-methyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-ethyl}-phenoxy)-propionate
4. Ethyl 2-methyl-2-(3-{3-[4-methyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-ethyl}-phenoxy)-propionate
5. Ethyl 2-{3-[3-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-propyl]-phenoxy}-2-methyl-propionate
- 10 6. Ethyl 2-methyl-2-(3-{3-[2-methyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-ethyl}-phenoxy)-propionate
7. Ethyl 2-{3-[3-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-propyl]-phenoxy}-2-methyl-propionate
- 15 8. Ethyl 2-(3-{3-[4-heptyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-propyl}-phenoxy)-2-methyl-propionate
9. Ethyl 2-methyl-2-(3-{5-[4-methyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-pentyl}-phenoxy)-propionate
- 20 10. Ethyl 2-{3-[5-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-pentyl]-phenoxy}-2-methyl-propionate
- 25 11. Ethyl 2-{3-[5-(4-butyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-pentyl]-phenoxy}-2-methyl-propionate
12. 2-{3-[5-(4-Butyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-pentyl]-phenoxy}-2-methyl-propionic acid
- 30

13. Ethyl 2-{3-[5-(2,4-dibutyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-pentyl]-phenoxy}-2-methyl-propionate
- 5 14. Ethyl 2-(3-{5-[4-butyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-pentyl}-phenoxy)-2-methyl-propionate
15. Ethyl 2-{3-[5-(4-butyl-2-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-pentyl]-phenoxy}-2-methyl-propionate
- 10 16. Ethyl 2-methyl-2-(3-{5-[2-methyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-pentyl}-phenoxy)-propionate
17. Ethyl 2-{3-[5-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-pentyl]-phenoxy}-2-methyl propionate
- 15 18. Ethyl 2-(3-{5-[4-heptyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-pentyl}-phenoxy)-2-methyl-propionate
19. Ethyl 2-{3-[5-(2-benzyl-4-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-pentyl]-phenoxy}-2-methyl-propionate
- 20 20. Ethyl 2-[4-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxymethyl)-phenoxy]-2-methyl-propionate
- 25 21. Ethyl 2-methyl-2-{4-[2-methyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxymethyl]-phenoxy}-propionate
22. Ethyl 2-[4-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxymethyl)-phenoxy]-2-methyl-propionate
- 30

23. Ethyl 2-{4-[4-heptyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxymethyl]-phenoxy}-2-methyl-propionate
24. Ethyl 2-methyl-2-(4-{2-[4-methyl-3,5-dioxo-2-
5 (4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-ethyl}-phenoxy)-propionate
25. Ethyl 2-{4-[2-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-ethyl]-phenoxy}-2-methyl-propionate
- 10 26. Ethyl 2-{4-[2-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-ethyl]-phenoxy}-2-methyl-propionate
27. Ethyl 2-{4-[3-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-propyl]-
15 phenoxy}-2-methyl-propionate
28. Ethyl 2-methyl-2-(4-{4-[4-methyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-ethyl}-phenoxy)-propionate
29. Ethyl 2-{4-[4-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-ethyl]-phenoxy}-
20 2-methyl-propionate
30. Ethyl 2-methyl-2-(4-{4-[2-methyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-ethyl}-phenoxy)-propionate
- 25 31. Ethyl 2-(4-{4-[4-heptyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-butyl}-phenoxy)-2-methyl-propionate
32. Ethyl 2-{3-[3-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-propyl]-
30 phenylsulfanyl}-2-methyl-propionate

33. Ethyl 2-{3-[3-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-propoxy]-phenoxy}-2-methyl-propionate
- 5 34. Ethyl 2-{3-[3-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-propoxy]-phenylsulfanyl}-2-methyl-propionate
35. Ethyl 2-(3-{3-[3,5-dioxo-2,4-bis-(4,4,4-trifluorobutyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-propoxy}-phenoxy)-2-methyl-propionate
- 10 36. Ethyl 2-{3-[4-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-butoxy]-phenoxy}-2-methyl-propionate
37. Ethyl 2-{3-[4-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-butoxy]-phenylsulfanyl}-2-methyl-propionate
- 15 38. Ethyl 2-{4-[2-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy)-ethoxy]-phenylsulfanyl}-2-methyl-propionate
39. Ethyl 2-(4-{3-[3,5-dioxo-2,4-bis-(4,4,4-trifluorobutyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yloxy]-propoxy}-phenoxy)-2-methyl-propionate
- 20 40. Ethyl 2-{4-[2-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethoxy]-phenoxy}-2-methyl-propionate
- 25 41. Ethyl 2-(4-{2-[3,5-dioxo-2,4-bis-(4,4,4-trifluorobutyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethoxy}-phenoxy)-2-methyl-propionate
42. Ethyl 2-{4-[2-(2,4-diheptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethoxy]-phenoxy}-2-methyl-propionate
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43. Ethyl 2-(4-{2-[2,4-bis-(3-cyclohexyl-propyl)-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethoxy}-phenoxy)-2-methyl-propionate
- 5 44. Ethyl 2-methyl-2-(4-{3-[4-methyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-propoxy}-phenoxy)-propionate
- 10 45. Ethyl 2-{4-[3-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-propoxy]-phenoxy}-2-methyl-propionate
46. Ethyl 2-methyl-2-(4-{3-[2-methyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-propoxy}-phenoxy)-propionate
- 15 47. Ethyl 2-{4-[3-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-propoxy]-phenoxy}-2-methyl-propionate
48. Ethyl 2-(4-{3-[4-heptyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-propoxy}-phenoxy)-2-methyl-propionate
- 20 49. Ethyl 2-{4-[3-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-propoxy]-phenylsulfanyl}-2-methyl-propionate
- 25 50. Ethyl 2-{4-[4-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-butoxy]-phenoxy}-2-methyl-propionate
- 30 51. Ethyl 2-(3-{3-[(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-(4,4,4-trifluoro-butyl)-amino]-propoxy}-phenoxy)-2-methyl-propionate

52. Ethyl 2-(3-{3-[(2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-heptyl-amino]-propoxy}-phenylsulfanyl)-2-methyl-propionate
53. Ethyl 2-(4-{3-[(2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-heptyl-amino]-propoxy}-phenylsulfanyl)-2-methyl-propionate
54. Ethyl 2-(3-{4-[(2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-heptyl-amino]-butoxy}-phenylsulfanyl)-2-methyl-propionate
55. Ethyl 2-(2-{2-[3,5-dioxo-2,4-bis-(4,4,4-trifluorobutyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethyl}-phenoxy)-2-methyl-propionate
56. Ethyl 2-methyl-2-(3-{2-[4-methyl-3,5-dioxo-2-(4,4,4-trifluorobutyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethyl}-phenoxy)-propionate
57. Ethyl 2-{3-[2-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-phenoxy}-2-methyl-propionate
58. Ethyl 2-methyl-2-(3-{2-[2-methyl-3,5-dioxo-4-(4,4,4-trifluorobutyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethyl}-phenoxy)-propionate
59. Ethyl 2-{3-[2-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-phenoxy}-2-methyl-propionate
60. Ethyl 2-(3-{2-[4-heptyl-3,5-dioxo-2-(4,4,4-trifluorobutyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethyl}-phenoxy)-2-methyl-propionate

61. Ethyl 2-{3-[2-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-phenylsulfanyl}-2-methyl-propionate
- 5 62. Ethyl 2-methyl-2-(3-{3-[4-methyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethyl}-phenoxy)-propionate
- 10 63. Ethyl 2-(3-{3-[2-(2-cyano-ethyl)-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-propyl}-phenoxy)-2-methyl-propionate
64. Ethyl 2-{3-[3-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-propyl]-phenoxy}-2-methyl-propionate
- 15 65. Ethyl 2-methyl-2-(3-{3-[2-methyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethyl}-phenoxy)-propionate
- 20 66. Ethyl 2-(3-{3-[3,5-dioxo-2,4-bis-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-propyl}-phenoxy)-2-methyl-propionate
67. Ethyl 2-{3-[3-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-propyl]-phenoxy}-2-methyl-propionate
- 25 68. Ethyl 2-(3-{3-[4-heptyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-propyl}-phenoxy)-2-methyl-propionate
69. Ethyl 2-{3-[3-(2,4-diheptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-propyl]-phenoxy}-2-methyl-propionate

70. Ethyl 2-{3-[3-(2-benzyl-4-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-propyl]-phenoxy}-2-methyl-propionate
- 5 71. Ethyl 2-(3-{3-[4-benzyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-propyl}-phenoxy)-2-methyl-propionate
72. Ethyl 2-{3-[3-(4-benzyl-2-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-propyl]-phenoxy}-2-methyl-propionate
- 10 73. Ethyl 2-{3-[3-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-propyl]-phenylsulfanyl}-2-methyl-propionate
74. Ethyl 2-methyl-2-(3-{4-[4-methyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-
- 15 [1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-propionate
75. Ethyl 2-{3-[4-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-butyl]-phenoxy}-2-methyl-propionate
- 20 76. Ethyl 2-methyl-2-(3-{4-[4-(3-methyl-but-2-enyl)-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-propionate
77. Ethyl 2-methyl-2-(3-{4-[2-methyl-3,5-dioxo-4-
- 25 (4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-propionate
78. Tert-butyl 2-methyl-2-(3-{4-[2-methyl-3,5-dioxo-4-
- 30 (4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-propionate

79. 2-Methyl-2-(3-{4-[2-methyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-propionic acid
- 5 80. Ethyl 2-(3-{4-[3,5-dioxo-2,4-bis-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-2-methyl-propionate
81. Ethyl 2-(3-{4-[2-(2-cyano-ethyl)-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-2-methyl-10 propionate
82. Ethyl 2-(3-{4-[2-heptyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-2-methyl-propionate
- 15 83. Tert-butyl 2-(3-{4-[2-heptyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-2-methyl-propionate
84. 2-(3-{4-[2-Heptyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-2-methyl-propionic acid
- 20 85. Ethyl 2-(3-{4-[4-heptyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-2-methyl-propionate
86. Ethyl 2-(3-{4-[2-(2-cyano-ethyl)-4-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-2-methyl-propionate 25
87. Ethyl 4-(6-{4-[3-(1-ethoxycarbonyl-1-methyl-ethoxy)-phenyl]-butylamino}-4-heptyl-3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-but-2-enonate
- 30 88. Ethyl 2-{3-[4-(2,4-diheptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-butyl]-phenoxy}-2-methyl-propionate

89. Ethyl 2-{3-[4-(2-benzyl-4-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-butyl]-phenoxy}-2-methyl-propionate
- 5 90. Ethyl 2-(3-{4-[4-benzyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenoxy)-2-methyl-propionate
91. Ethyl 2-{3-[4-(4-benzyl-2-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-butyl]-phenoxy}-2-methyl-propionate
- 10 92. Ethyl 2-(3-{5-[3,5-dioxo-2,4-bis-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-pentyl}-phenoxy)-2-methyl-propionate
- 15 93. Ethyl 2-methyl-2-(3-{4-[4-methyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenylsulfanyl)-propionate
94. Ethyl 2-{3-[4-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-butyl]-phenylsulfanyl}-2-methyl-propionate
- 20 95. Ethyl 2-methyl-2-(3-{4-[2-methyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenylsulfanyl)-propionate
- 25 96. 2-Methyl-2-(3-{4-[2-methyl-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenylsulfanyl)-propionic acid
- 30 97. Ethyl 2-(3-{4-[4-heptyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenylsulfanyl)-2-methyl-propionate

98. Ethyl 2-{3-[4-(2,4-diheptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-butyl]-phenylsulfanyl}-2-methyl-propionate
99. Ethyl 2-{3-[4-(2-benzyl-4-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-butyl]-phenylsulfanyl}-2-methyl-propionate
100. Ethyl 2-(3-{4-[4-benzyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-butyl}-phenylsulfanyl)-2-methyl-propionate
101. Ethyl 2-{3-[4-(4-benzyl-2-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-butyl]-phenylsulfanyl}-2-methyl-propionate
102. Ethyl 2-methyl-2-(4-{2-[4-methyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethyl}-phenoxy)-propionate
103. Ethyl 2-{4-[2-(2-heptyl-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-phenoxy}-2-methyl-propionate
104. Ethyl 4-[6-{2-[4-(1-ethoxycarbonyl-1-methyl-ethoxy)-phenyl]-ethylamino}-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-4,5-dihydro-3H-[1,2,4]triazin-2-yl]-but-2-enoate
105. Ethyl 2-(4-{2-[2-(3-cyclohexyl-propyl)-3,5-dioxo-4-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethyl}-phenoxy)-2-methyl-propionate
106. Ethyl 2-{4-[2-(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-phenoxy}-2-methyl-propionate

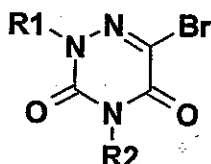
107. Ethyl 2-(4-{2-[4-heptyl-3,5-dioxo-2-(4,4,4-trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-ethyl}-phenoxy)-2-methyl-propionate
108. Ethyl 2-{4-[2-(2,4-diheptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-phenoxy}-2-methyl-propionate
109. Ethyl 2-{4-[2-(4-benzyl-2-heptyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-phenoxy}-2-methyl-propionate
110. Ethyl 2-{4-[2-(2,4-bis-benzyloxymethyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-phenoxy}-2-methyl-propionate
111. Ethyl 2-(4-{2-[(2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-(4,4,4-trifluoro-butyl)-amino]-ethyl}-phenoxy)-2-methyl-propionate
112. Ethyl 2-(4-{2-[(2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-heptyl-amino]-ethyl}-phenoxy)-2-methyl-propionate
113. 2-(4-{2-[(2,4-Dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-heptyl-amino]-ethyl}-phenoxy)-2-methyl-propionic acid
114. Ethyl 2-(4-{2-[(2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-phenethyl-amino]-ethyl}-phenoxy)-2-methyl-propionate
115. Ethyl 2-(4-{2-[(2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-(3-phenyl-propyl)-amino]-ethyl}-phenoxy)-2-methyl-propionate
116. Ethyl 2-(4-{2-[(4-heptyl-2-methyl-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-phenethyl-amino]-ethyl}-phenoxy)-2-methyl-propionate

117. Ethyl 2-(4-{2-[(4-heptyl-2-methyl-3,5-dioxo-
2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-(3-phenyl-
propyl)-amino]-ethyl}-phenoxy)-2-methyl-propionate
118. 2-Methyl-2-(4-{2-[4-methyl-3,5-dioxo-2-(4,4,4-
trifluoro-butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-
6-ylamino]-ethyl}-phenylsulfanyl)-propionic acid
119. Ethyl 2-(4-[2-(2-heptyl-4-methyl-3,5-dioxo-
2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-
ethyl]-phenylsulfanyl)-2-methyl-propionate
120. 2-(4-[2-(2-Heptyl-4-methyl-3,5-dioxo-2,3,4,5-
tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-
phenylsulfanyl)-2-methyl-propionic acid
121. 2-(4-[2-(4-Butyl-2-heptyl-3,5-dioxo-2,3,4,5-
tetrahydro-[1,2,4]triazin-6-ylamino)-ethyl]-
phenylsulfanyl)-2-methyl-propionic acid
122. Ethyl 2-(4-[2-(4-heptyl-2-methyl-3,5-dioxo-
2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-
ethyl]-phenylsulfanyl)-2-methyl-propionate
123. 2-(4-{2-[4-Heptyl-3,5-dioxo-2-(4,4,4-trifluoro-
butyl)-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino]-
ethyl}-phenylsulfanyl)-2-methyl-propionic acid
124. Ethyl 2-(4-[3-(2-heptyl-4-methyl-3,5-dioxo-
2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylamino)-
propyl]-phenylsulfanyl)-2-methyl-propionate

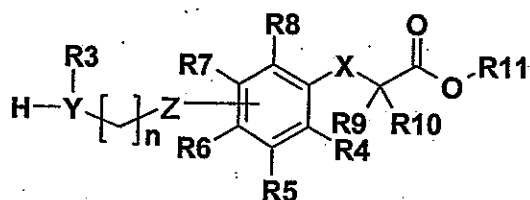
6) Method of preparation of the chemical
compounds according to one of the claims 1) to 5)
wherein:

a derivative of general formula II is condensed

II



in which R_1 and R_2 represent the groups as previously described in formula I with a derivative of general formula III



III

- 15 where YR_3 , n , Z , X , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} and R_{11} are such as described previously in formula I, notably in the presence of a base such as triethylamine in n-butanol (when $Y=N$) or potassium carbonate in dimethylformamide (when $YR_3=O$).

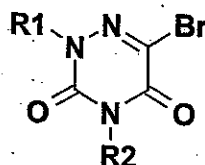
20

7) Method of preparation according to one of the claims 1) to 5) of the chemical compounds of general formula I in which $Z=O$ wherein:

- a) a derivative of general formula II is

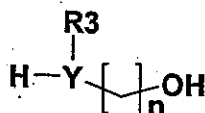
25 condensed

II



- 30 in which R_1 and R_2 represent the groups as previously described in formula I with a derivative of general formula IV

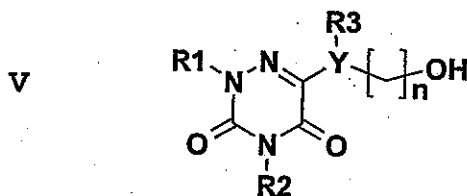
IV



- in which R_3Y can be equal to NH or O and n is such as
- 40 described previously in formula I, notably in the

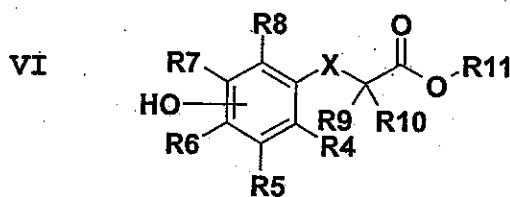
absence of solvent without adding base (in the case where $R_3Y=NH$) or in the presence of a base such as K_2CO_3 (in the case where $R_3Y=O$).

5 b) the derivative obtained **V** is condensed



15

with a compound of general formula **VI**



25

where **X**, R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} and R_{11} are as described previously in formula **I**, notably under conditions such as those of the Mitsunobu reaction in the presence of triphenylphosphine and diethylazodicarboxylate in THF.

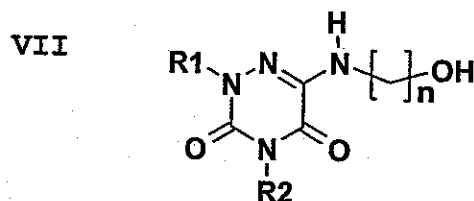
30

8) Method of preparation according to one of the claims 1) to 5) of the chemical compounds of general formula **I** in which $Z=O$ wherein:

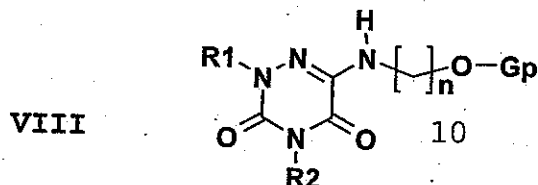
35

a) the alcohol function of a derivative of general formula **VII** is protected

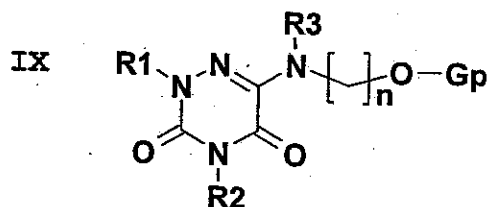
40



in which R_1 , R_2 and n are such as described previously in formula I by a protection group such as tertbutyldimethylsilane, in particular under conditions
 5 such as THF using chlorotertbutyldimethylsilane and imidazole.

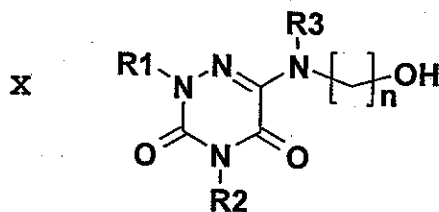


15 b) the nitrogen of compound VIII previously obtained is alkylated by a halogenated derivative $R_3\text{Hal}$ in which the Hal group represents a halogen such as Cl, Br or I and R_3 is as described previously in formula I, under operating conditions such as NaH or tBuOK in DMF.

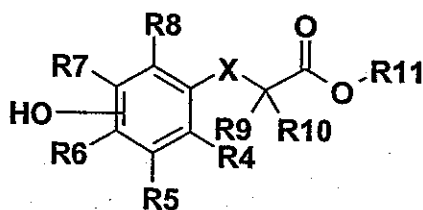


30 c) the compound IX thus obtained is deprotected under operating conditions such as tetrabutylammonium fluoride in THF.

35 d) the derivative obtained X is condensed



with a compound of general formula VI



VI

5 where X , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} and R_{11} are as described previously in formula I, notably under conditions such as those of the Mitsunobu reaction in the presence of triphenylphosphine and diethylazodicarboxylate in THF.

10

9) Method of preparation of chemical compounds of general formula I according to one of the claims 1) to 5) when $Y=N$ and which $Z=C$ wherein:

15

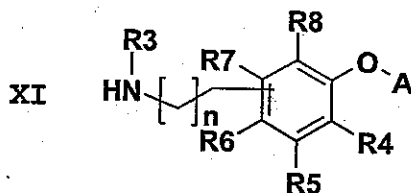
a) a derivative of general formula II is
20 condensed

II



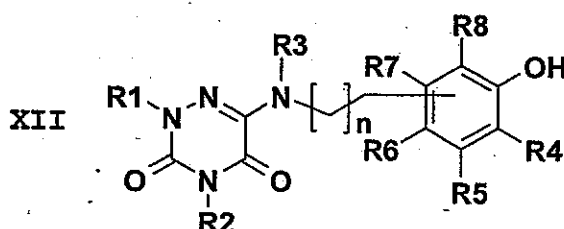
25 in which R_1 and R_2 represent the groups as previously described in formula I with a derivative of general formula XI

30

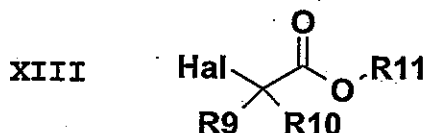


in which n , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are as described previously in formula I and A can be hydrogen or a methyl group, notably in the presence of a base such as triethylamine in *n*-butanol.

5 b) after demethylation (if **A**=Me, under conditions such as BBr₃ in dichloromethane), the phenol function of derivative **XII** is alkylated



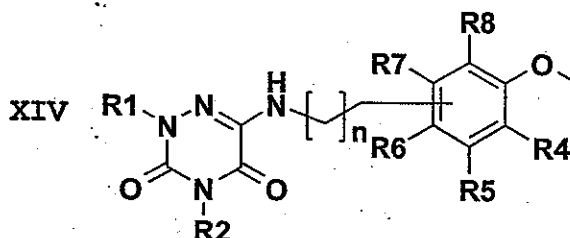
by a halogenated derivative of general formula **XIII**
(used as a solvent in the presence of a base such as
potassium carbonate)



in which the Hal group represents a halogen such as Cl, Br or I, and R₉, R₁₀ and R₁₁ are as previously described in general formula I.

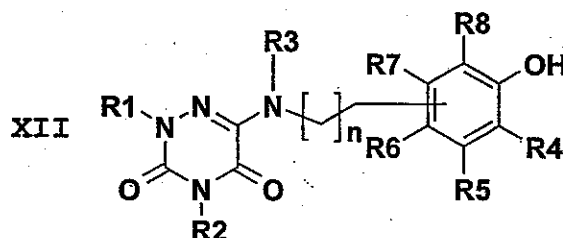
10) Method of preparation of chemical compounds of general formula I according to one of the claims 1) to 5) when $Y=N$ and $Z=C$ wherein:

a) a derivative of general formula **XIV** is alkylated

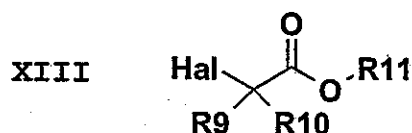


in which R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 et n are as described previously in formula I with a derivative of formula $R_3\text{Hal}$ in which the **Hal** group represents a halogen such as Cl, Br or I and R_3 is as described previously in formula I, under operating conditions such as NaH or tBuOK in DMF.

b) after demethylation under conditions such as BBr_3 in dichloromethane, the phenol function of the derivative **XII** thus obtained is alkylated



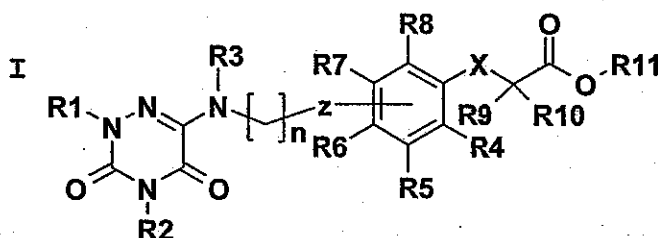
by a halogenated derivative of general formula **XIII** (used as a solvent in the presence of a base such as potassium carbonate)



in which the **Hal** group represents a halogen such as Cl, Br or I, and R_9 , R_{10} and R_{11} are as previously described in general formula I.

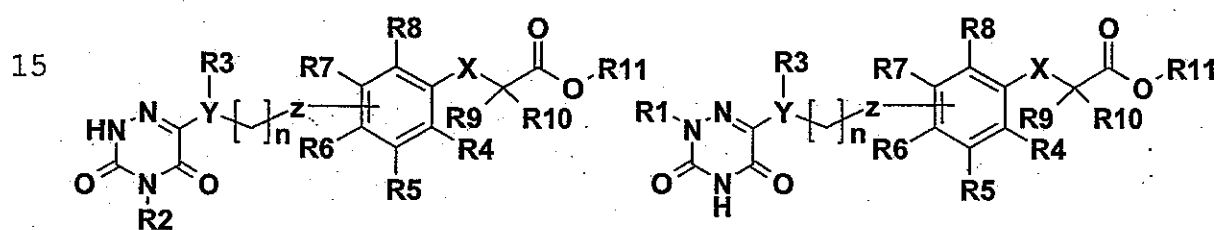
11) Method of preparation of the chemical compounds according to one of the claims 1) to 5) wherein:

a) a derivative of general formula I is placed



in which $R_1 = (CH_2)_2CN$ and $R_2, R_3, n, Z, X, R_4, R_5, R_6, R_7,$
 5 R_8, R_9, R_{10} and R_{11} are as described previously in
 formula I or $R_2 = (CH_2)_2CN$ and $R_1, R_3, n, Z, X, R_4, R_5, R_6,$
 R_7, R_8, R_9, R_{10} and R_{11} are as described previously in
 formula I under operating conditions such as in the
 presence of a base NaH in DMF.

10 b) the nitrogen of the triazine of derivative
XIVa or **XIVb** thus obtained is then alkylated

**XIVa****XIVb**

by a halogenated derivative of general formula R_1Hal in
 the case of the intermediate **XIVa** and of general
 25 formula R_2Hal in the case of the intermediate **XIVb** in
 which the **Hal** group represents a halogen such as Cl, Br
 or I and R_1 and R_2 are as described previously in
 formula I, under operating conditions such as in the
 presence of NaH or tBuOK in DMF.

30

12) As novel medicines of use in the
 treatment of disorders requiring PPAR alpha and/or PPAR
 gamma receptor agonists, the compounds defined
 according to one of the claims 1) to 5).

35

13) As novel medicines of use in the
 prevention and the treatment of diseases such as

diabetic dyslipidemia, hypertriglyceridemia,
hypercholesterolemia, hyperinsulinemia, hyperglycemia,
metabolic syndrome, obesity and atherosclerosis, the
compounds defined according to one of the claims 1) to
5).

14) As novel medicines of use in dermatology
in pathologies with an inflammatory component or
resulting from abnormal cell differentiation, the
compounds defined according to one of the claims 1) to
5).

15) As novel medicines of use in the
treatment of diseases such as psoriasis, acne, atopic
dermatitis, cutaneous aging and photoaging, the
compounds defined according to one of the claims 1) to
5).

16) Pharmaceutical compound wherein it
contains as an active ingredient a compound defined
according to one of the claims 1) to 5) in association
with a suitable excipient.