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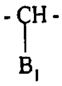
ABSTRACT

NEW HYDRAZIDE COMPOUNDS, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Compounds of formula (I) :

$$R - NH - A - CO - NH - NH - (W)_n - Z \qquad (I)$$

wherein :

- n is 0 or 1,
- W represents a -CO- group or an $S(O)_r$ group wherein r is 0, 1 or 2,
- Z represents a group selected from aryl, arylalkyl, heteroaryl and heteroarylalkyl, each optionally substituted,
- R represents a grouping selected from :
  Z_1-T-CO-, Z_1-O-T-CO-, Z_1-T-O-CO-, Z_1-T-$S(O)_q$-
  wherein Z_1, T and q are as defined in the description,
- A represents an alkylene, alkenylene or alkynylene group each having from 3 to 8 carbon atoms, an alkylenecycloalkylene, cycloalkylenealkylene or alkylenecycloalkylenealkylene, alkylenearylene, arylenealkylene, alkylenearylenealkylene a grouping  $-\underset{B_1}{\underset{|}{C}}H-$ wherein B_1 is as defined in the description, or A forms with the adjacent nitrogen atom a grouping  as defined in the description.

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Invention Title: NEW HYDRAZIDE COMPOUNDS, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The following statement is a full description of this invention, including the best method of performing it known to us :-

The present invention relates to new hydrazide compounds, to a process for their preparation and to pharmaceutical compositions containing them.

Hydrazide compounds have been described in the literature (J. Org. Chem., 1971, 36, 1580) although no pharmacological property has been mentioned. Other compounds of related structure are used in the composition of photographic films (JP 02008833), or have been used in the formation of polymers that are used to prepare semipermeable membranes (J. Appl. Polym. Sci., 1992, 44, 1383).

The compounds of the present invention have a novel structure which imparts to them great affinity for neuropeptide Y receptors.

Ligands of those receptors have been described recently. By way of example, there may be mentioned cyclic peptide compounds (WO 9400486), amino acid compounds of arginine (WO 9417035), or non-peptide compounds having a guanidine group (EP 448765, J. Med. Chem., 1994, 37, 2242).

Neuropeptide Y (NPY) is a peptide of 36 amino acids, related to the peptide YY (PYY) and to pancreatic polypeptides (PP). Originally isolated from pig brain (Proc. Natl. Acad. Sci., 1982, 79, 5485), NPY is widely distributed in mammals at the level of the central and peripheral nervous systems. This neurotransmitter is present in high concentrations in nerve fibres of the brain, but also of the heart, the sympathetic ganglia, blood vessels and smooth muscles of the vas deferens and of the gastrointestinal tract. It is responsible for various physiological effects which are exerted *via* the intermediary of specific receptors (Y). The latter form a heterogeneous group, 6 sub-types of which have been identified to date : Y_1 to Y_6 (Pharmacological Reviews, 1998, 50, 143). NPY is involved in eating behaviour by strongly stimulating food intake (Proc. Natl. Acad. Sci., 1985, 82, 3940) or by exerting a regulatory role on the HPA (hypothalamic-pituitary-adrenal) axis (J. of Neuroendocrinol., 1995, 7, 273). It also exhibits anxiolytic and sedative properties (Neuropsycho-pharmacology, 1993, 8, 357), a strong vasoconstrictive ability (Eur. J. Pharmacol., 1984, 85, 519) which induces an increase in blood pressure, and also has an effect on the circadian rhythm (Neuroscience and biobehavioral reviews, 1995, 19, 349).

In addition to the fact that the compounds of the invention are new, they have a structure which imparts to them great affinity for NPY receptors. It will thus be possible to use them in the treatment of pathologies in which an NPY receptor ligand is necessary, especially in the treatment of pathologies associated with eating behaviour disorders or energy balance disorders, such as diabetes, obesity, bulimia, anorexia nervosa, and also in the treatment of arterial hypertension, anxiety, depression, epilepsy, sexual dysfunctions and sleep disorders.

The present invention relates to compounds of formula (I) :

$$R - NH - A - CO - NH - NH - (W)_n - Z \qquad (I)$$

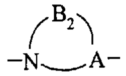
wherein :

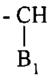
- n is 0 or 1,
- W represents a -CO- group or an $S(O)_r$ group wherein r is 0, 1 or 2,
- Z represents a group selected from optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl,
- R represents a group selected from :

  Z_1-T-CO-
  Z_1-O-T-CO-
  Z_1-T-O-CO-
  Z_1-T-$S(O)_q$-

  wherein :

  - Z_1 represents an optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl group,
  - T represents a σ bond or an alkylene, alkenylene or alkynylene group,
  - q represents an integer 0, 1 or 2,

- A represents a linear or branched alkylene group having from 3 to 8 carbon atoms, a linear or branched alkenylene group having from 3 to 8 carbon atoms, a linear or branched alkynylene group having from 3 to 8 carbon atoms, an alkylenecycloalkylene group, a cycloalkylenealkylene group, an alkylenecycloalkylenealkylene group, an alkylenearylene group, an arylenealkylene group, an alkylenearylenealkylene group, a grouping  $-\underset{B_1}{\underset{|}{C}}H-$ wherein B_1 represents an optionally substituted aryl, optionally substituted arylalkyl,optionally substituted heteroaryl or optionally substituted heteroarylalkyl group, or A forms with the nitrogen atom a grouping  wherein B_2 represents a saturated or unsaturated mono- or bi-cyclic system having from 5 to 11 ring members, optionally containing from 1 to 3 additional hetero atoms selected from nitrogen, oxygen and sulphur,

with the proviso that when simultaneously n is 0, A represents a grouping  $-\underset{B_1}{\underset{|}{C}}H-$, B_1 being a benzyl group, and Z represents an optionally substituted phenyl group, then R is other than a benzoyl group,

their enantiomers, diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base,

it being understood that :

the term "alkyl" denotes a linear or branched group having from 1 to 6 carbon atoms,

the term "alkylene" denotes a linear or branched bivalent radical containing from 1 to 6 carbon atoms, unless indicated otherwise,

the term "alkenylene" denotes a linear or branched bivalent radical containing from 2 to 6 carbon atoms and from 1 to 3 double bonds, unless indicated otherwise, the term "alkynylene" denotes a linear or branched bivalent radical containing from 2 to 6 carbon atoms and from 1 to 3 triple bonds, unless indicated otherwise,

the term "aryl" denotes a phenyl, naphthyl, dihydronaphthyl or tetrahydronaphthyl group, and the term "arylene" denotes a bivalent radical of the same type,

the term "heteroaryl" denotes an unsaturated or partially unsaturated mono- or bi-cyclic group having from 5 to 11 ring members, containing from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulphur,

the term "alkylenecycloalkylene" represents a grouping $-A_1-A_2-$, the term "cycloalkylene-alkylene" represents a grouping $-A_2-A_1-$, and the term "alkylenecycloalkylenealkylene" represents a grouping $-A_1-A_2-A_1$, the term "alkylenearylene" represents a grouping $-A_1-A_3-$, the term "arylenealkylene" represents a grouping $-A_3-A_1-$, the term "alkylenearylenealkylene" represents a grouping $-A_1-A_3-A_1-$, wherein A_1 is an alkylene group as defined hereinbefore, A_2 is a (C_4-C_8)cycloalkylene group, and A_3 is an arylene group as defined hereinbefore,

the expression "optionally substituted" applied to the terms "aryl", "arylalkyl", "heteroaryl" and "heteroarylalkyl" indicates that those groups are substituted on their cyclic moiety by from 1 to 5 identical or different substituents selected from linear or branched (C_1-C_6)alkyl, linear or branched (C_1-C_6)alkoxy, halogen, hydroxy, perhalo-(C_1-C_6)alkyl in which the alkyl moiety is linear or branched, nitro, linear or branched (C_1-C_6)acyl, linear or branched (C_1-C_6)alkylsulphonyl, and amino (amino optionally being substituted by one or two linear or branched (C_1-C_6)alkyl and/or linear or branched (C_1-C_6)acyl groups).

Among the pharmaceutically acceptable acids, there may be mentioned by way of non-limiting example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphonic acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulphonic acid, camphoric acid, etc..

Among the pharmaceutically acceptable bases, there may be mentioned by way of non-limiting example sodium hydroxide, potassium hydroxide, triethylamine, tert-butylamine, etc..

Advantageously, the invention relates to compounds of formula (I) wherein R represents a grouping Z_1-T-CO, Z_1 preferably being an optionally substituted aryl group, and T preferably being an alkylene group or a bond.

Another advantageous aspect of the invention relates to compounds of formula (I) wherein R represents a grouping Z_1-O-T-CO, Z_1 preferably being an optionally substituted aryl group, and T preferably being an alkylene group or a bond.

Another advantageous aspect of the invention relates to compounds of formula (I) wherein R represents a grouping Z_1-T-O-CO, Z_1 preferably being an optionally substituted aryl group, and T preferably being an alkylene group or a bond.

Another advantageous aspect of the invention relates to compounds of formula (I) wherein R represents a grouping Z_1-T-S(O)$_q$-, Z_1 preferably being an optionally substituted aryl group, and T preferably being an alkylene group or a bond, and q preferably being 2.

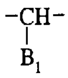
The preferred aryl group are phenyl or naphthyl.

Preferred compounds of the invention are those wherein W represents a -CO- group.

Other preferred compounds of the invention are those wherein W represents an SO_2 group.

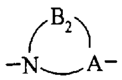
In the preferred compounds of the invention, Z represents a group selected from optionally substituted aryl and optionally substituted heteroaryl.

Preferred compounds of the invention are those wherein A represents a grouping $-\underset{B_1}{\underset{|}{CH}}-$ wherein B_1 is an optionally substituted arylalkyl group (for example a benzyl or tolylmethyl group).



Other preferred compounds of the invention are those wherein A represents an alkylene-cycloalkylene group (for example methylenecyclohexylene).

Other preferred compounds of the invention are those wherein A represents an alkylenearylene group (for example methylenephenylene).

In the compounds of the invention, the cyclic groupings  are advantageously selected from pyrrolidine, perhydroindole and piperidine groups.

In an especially advantageous manner, the invention relates to compounds of formula (I) wherein W represents a -CO- group, Z represents a group selected from optionally substituted aryl and optionally substituted heteroaryl, R represents a grouping selected from Z_1-T-CO-, Z_1-O-T-CO-, Z_1-T-O-CO- and Z_1-T-S(O)$_q$- wherein Z_1 is preferably an optionally substituted aryl or optionally substituted heteroaryl group, T represents an alkylene group (for example methylene), and q is 2, and A represents an alkylene-cycloalkylene group, a grouping $-\underset{\mathrm{B}_1}{\underset{|}{\mathrm{C}}}\mathrm{H}-$ wherein B_1 is an optionally substituted arylalkyl group,or A forms with the adjacent nitrogen atom a pyrrolidine, perhydroindole or piperidine group.

Among the preferred compounds of the invention, there may be mentioned :

-N2-({4-[(2-benzoylhydrazino)carbonyl]cyclohexyl}methyl)-2-naphthalenesulphonamide

-N1-({4-[(2-benzoylhydrazino)carbonyl]cyclohexyl}methyl)-1-(2-nitrobenzene)-sulphonamide

-N1-[1-benzyl-2-oxo-2-(2-phenylhydrazino)ethyl]-1-(4-chlorobenzene)sulphonamide.

The present invention relates also to a process for the preparation of compounds of formula (I), characterised in that there is used as starting material a compound of formula (II) :

$$H_2N - A - COOH \qquad (II)$$

wherein A is as defined for formula (I), which is condensed in a basic medium with a halogen compound of formula (III) :

$$R - Cl \qquad (III)$$

wherein R is as defined for formula (I),

to yield a compound of formula (IV) :

$$R - NH - A - COOH \qquad (IV)$$

wherein R and A are as defined hereinbefore,

which compound (IV) is condensed, in the presence of a coupling agent, with a monosubstituted hydrazine of formula (V),

$$H_2N - NH - (W)_n - Z \qquad (V)$$

wherein n, W and Z are as defined for formula (I),

to yield compounds of formula (I) :

$$R - NH - A - CO - NH - NH - (W)_n - Z \qquad (I)$$

wherein R, A, n, W and Z are as defined hereinbefore,

which compound of formula (I) :

- may be purified, if necessary, according to a conventional purification technique,
- is separated, where appropriate, into its isomers according to a conventional separation technique,
- is converted, if desired, into an addition salt thereof with a pharmaceutically acceptable acid or base.

The present invention relates also to pharmaceutical compositions comprising as active ingredient at least one compound of formula (I), on its own or in combination with one or more inert non-toxic excipients or carriers.

Among the pharmaceutical compositions according to the invention, there may be mentioned more especially those that are suitable for oral, parenteral or nasal administration, tablets or dragées, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels, etc..

The useful dosage varies according to the age and weight of the patient, the nature and severity of the disorder and the route of administration, which may be oral, nasal, rectal or parenteral. Generally the unit dose ranges from 0.05 to 500 mg for a treatment in from 1 to 3 administrations per 24 hours.

The pharmaceutical composition referred to above may be used as a neuropeptide Y receptor ligand in the treatment of pathologies associated with eating behaviour disorders or energy balance disorders, selected from diabetes, obesity, bulimia, anorexia nervosa or in the treatment of arterial hypertension, anxiety, depression, epilepsy, sexual dysfunctions and sleep disorders.

The following Examples illustrate the invention but do not limit it in any way. The structures of the compounds described were confirmed by the usual spectroscopic techniques.

The starting materials used are known products or are prepared according to known procedures.

EXAMPLE 1 :

Benzyl n-[1-benzyl-2-oxo-2-(2-phenylhydrazino)ethyl]carbamate

Step a : ***2-Benzyloxycarbonylamino-3-phenylpropanoic acid***

82 mmol (13.9 g) of benzyl chloroformate and 20 ml of 4M aqueous sodium hydroxide are added over a period of 30 minutes to a solution, cooled to 0°C, of 80 mmol (13.2 g) of phenylalanine in 20 ml of 4M aqueous sodium hydroxide. The solution returns to room temperature during a period of 1 hour. The reaction mixture is extracted with ether. The aqueous phase is rendered acidic to pH = 2 with a dilute hydrochloric acid solution. The precipitate that forms is filtered off and washed to yield the expected compound.

Step b : ***Benzyl N-[1-benzyl-2-oxo-2-(2-phenylhydrazino)ethyl]carbamate***

3.25 mmol (0.63 g) of EDC are added to a solution, cooled to 0°C, of 2.85 mmol (0.8 g) of the compound described in the preceding Step and 3.25 mmol (0.43 g) of HOBT in 20 ml of dichloromethane. The reaction mixture is stirred at 0°C for 1 hour and then 3.25 mmol (0.32 ml) of phenylhydrazine are added. The reaction mixture is stirred at 0°C for 1 hour, and then at room temperature for 24 hours. The reaction mixture is filtered and the filtrate is concentrated. The resulting residue is taken up in ether (15 ml) and 10 ml of water are added. The resulting precipitate is filtered off, and washed with water and then with ether to yield the expected compound.

Melting point : *175-177°C*

Elemental microanalysis :

	C	*H*	*N*
% calculated	*70.95*	*5.91*	*10.79*
% found	*71.27*	*5.90*	*10.71*

EXAMPLE 2 : Benzyl N-[2-(2-benzoylhydrazino)-1-benzyl-2-oxoethyl]carbamate

The expected product is obtained according to the process described in Example 1, in Step b replacing phenylhydrazine by phenylhydrazide.

Melting point : *172-174°C*

Elemental microanalysis :

	C	*H*	*N*
% calculated	*69.06*	*5.52*	*10.07*
% found	*69.14*	*5.71*	*9.92*

EXAMPLE 3 : Benzyl N-[1-benzyl-2-oxo-2-(2-nicotinoylhydrazino)ethyl]carbamate

The expected product is obtained according to the process described in Example 1, in Step b replacing phenylhydrazine by 3-pyridinecarbohydrazide.

Elemental microanalysis:

	C	*H*	*N*
% calculated	*66.03*	*5.26*	*13.40*
% found	*66.00*	*5.72*	*13.68*

EXAMPLE 4 : Benzyl N-{1-benzyl-2-[2-(3-indolyl)acetyl]-2-oxoethyl}carbamate

The expected product is obtained according to the process described in Example 1, in Step b replacing phenylhydrazine by 3-indolylacetohydrazide.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*68.94*	*5.53*	*11.91*
% found	*69.23*	*5.81*	*11.57*

EXAMPLE 5 : N1-[1-Benzyl-2-oxo-2-(2-phenylhydrazino)ethyl]-2-phenoxyacetamide

Step a : 2-[(2-Phenoxyacetyl)amino]-3-phenylpropanoic acid

A solution of 6.6 mmol (1.0 g) of phenoxyacetic acid in 15 ml of dioxane is treated with 49.3 mmol (3.6 ml) of thionyl chloride. The reaction mixture is stirred at room temperature for 2 hours and then concentrated. The residue, taken up in 10 ml of dichloromethane, and 7.9 mmol (0.3 g) of sodium hydroxide in 10 ml of water are added in succession to a solution of 7.6 mmol (1.25 g) of phenylalanine and 7.6 mmol (0.3 g) of sodium hydroxide in 10 ml of water, the temperature being maintained at 10°C. The reaction mixture is then stirred for 1 hour at room temperature. After decanting, the aqueous phase is washed with dichloromethane, and then rendered acidic to pH = 2 with a dilute hydrochloric acid solution. The precipitate that forms is filtered off and recrystallised from water to yield the expected product.

Step b : N1-[1-Benzyl-2-oxo-2-(2-phenylhydrazino)ethyl]-2-phenoxyacetamide

3.7 mmol (0.71 g) of EDC are added to a solution, cooled to 0°C, of 3.35 mmol (1 g) of the compound described in the preceding Step and 3.7 mmol (0.56 g) of HOBT in 15 ml of dichloromethane. After one hour at 0°C, a solution of 3.7 mmol (0.4 g) of phenylhydrazine in 10 ml of dichloromethane is added. The reaction mixture is stirred at 0°C for 1 hour and then at room temperature for 24 hours. The organic phase is washed with water, dried over sodium sulphate and concentrated. The resulting residue is washed in ether and then filtered to yield the expected compound.

Melting point : 172-175°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*70.95*	*5.91*	*10.80*
% found	*70.91*	*6.06*	*10.68*

EXAMPLE 6 : N1-[2-(2-Benzoylhydrazino)-1-benzyl-2-oxoethyl]-2-phenoxyacetamide

The expected product is obtained according to the process described in Example 5, in Step b replacing phenylhydrazine by phenylhydrazide.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*69.06*	*5.12*	*10.07*
% found	*68.88*	*5.52*	*9.84*

EXAMPLE 7 : N1-{1-Benzyl-2-[2-(2-indolylcarbonyl)hydrazino]-2-oxoethyl}-2-phenoxyacetamide

The expected product is obtained according to the process described in Example 5, in Step b replacing phenylhydrazine by 2-indolecarbohydrazide.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*68.42*	*5.26*	*12.28*
% found	*67.97*	*5.44*	*12.42*

EXAMPLE 8 : N1-[1-Benzyl-2-oxo-2-(2-nicotinoylhydrazino)ethyl]-2-phenoxyacetamide

The expected product is obtained according to the process described in Example 5, in Step b replacing phenylhydrazine by 3-pyridinecarbohydrazide.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*64.29*	*5.36*	*12.50*
% found	*64.06*	*5.34*	*12.34*

EXAMPLE 9 : N2-[1-Benzyl-2-oxo-2-(2-phenylhydrazino)ethyl]-2-indole-carboxamide

Step a : 2-(2-Indolylcarbonylamino)-3-phenylpropanoic acid

The expected product is obtained according to the process described in Example 5, Step a, replacing phenoxyacetic acid by 2-indolecarboxylic acid.

Step b : N2-[1-Benzyl-2-oxo-2-(2-phenylhydrazino)ethyl]-2-indolecarboxamide

The expected product is obtained according to the process described in Example 5, Step b, using the compound described in the preceding Step as starting material.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*72.36*	*5.53*	*14.07*
% found	*72.05*	*5.82*	*14.60*

EXAMPLE 10 : N2-[1-Benzyl-2-oxo-2-(2-phenylhydrazino)ethyl]-2-naphthalenesulphonamide

Step a : 2-[(2-Naphthylsulphonyl)amino]-3-phenylpropanoic acid

A solution of 7.6 mmol (1.71 g) of 2-naphthylsulphonyl chloride in 10 ml of dichloromethane and a solution of 7.9 mmol (0.32 g) of sodium hydroxide in 10 ml of water are added slowly in succession to 7.6 mmol (1.25 g) of phenylalanine and 7.6 mmol (0.3 g) of sodium hydroxide in 10 ml of water. The reaction mixture is stirred for 1 hour at room temperature. After decanting, the aqueous phase is washed with dichloromethane and rendered acidic to pH = 2 with a dilute hydrochloric acid solution. After extraction with dichloromethane, the organic phase is dried over sodium sulphate and concentrated to yield the expected product.

Step b : N2-[1-Benzyl-2-oxo-2-(2-phenylhydrazino)ethyl]-2-naphthalenesulphonamide

The expected product is obtained according to the process described in Example 1, Step b, using the compound described in the preceding Step as starting material.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*67.41*	*5.17*	*9.44*
% found	*67.03*	*5.34*	*9.57*

EXAMPLE 11 : N2-[2-(2-Benzoylhydrazino)-1-benzyl-2-oxoethyl]-2-naphthalenesulphonamide

The expected product is obtained according to the process described in Example 1, Step b, using the compound described in Example 10, Step a, as starting material, and replacing phenylhydrazine by phenylhydrazide.

Melting point : 239-240°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*65.96*	*4.86*	*8.87*
% found	*65.55*	*4.99*	*8.88*

EXAMPLE 12 : N2-[1-Benzyl-2-oxo-2-(2-phenylhydrazino)ethyl]-2-naphthylamide

The expected product is obtained according to the process described in Example 1, in Step a replacing benzyl chloroformate by naphthoyl chloride.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*76.28*	*5.62*	*10.27*
% found	*76.25*	*5.76*	*10.03*

EXAMPLE 13 : N2-[2-(2-Benzoylhydrazino)-1-benzyl-2-oxoethyl]-2-naphthylamide

The expected product is obtained according to the process described in Example 1, in Step a replacing benzyl chloroformate by naphthoyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Elemental microanalysis :

	C	H	N
% calculated	*74.17*	*5.26*	*9.61*
% found	*74.21*	*5.38*	*9.49*

EXAMPLE 14 : N2-[1-Benzyl-2-oxo-2-(2-nicotinoylhydrazino)ethyl]-2-naphthylamide

The expected product is obtained according to the process described in Example 1, in Step a replacing benzyl chloroformate by naphthoyl chloride, and in Step b replacing phenylhydrazine by 3-pyridinecarbohydrazide.

Elemental microanalysis :

	C	H	N
% calculated	*71.23*	*5.02*	*12.79*
% found	*70.97*	*5.38*	*12.61*

EXAMPLE 15 : N2-{1-Benzyl-2-[2-(2-indolecarbonyl)hydrazino]-2-oxoethyl}-2-naphthylamide

The expected product is obtained according to the process described in Example 1, in Step a replacing benzyl chloroformate by naphthoyl chloride, and in Step b replacing phenylhydrazine by 2-indolecarbohydrazide.

Melting point : 214-215°C

Elemental microanalysis :

	C	H	N
% calculated	*73.11*	*5.25*	*11.76*
% found	*72.98*	*5.16*	*11.75*

EXAMPLE 16 : N1-[1-Benzyl-2-oxo-2-(2-phenylhydrazino)ethyl]-1-benzenesulphonamide

Step a : ***2-(Phenylsulphonylamino)-3-phenylpropanoic acid***

A mixture of 151 mmol (26.6 g) of benzenesulphonyl chloride and 50 ml of 4M aqueous sodium hydroxide is added to a solution of 37.8 mmol (6.25 g) of phenylalanine in 50 ml of 4M aqueous sodium hydroxide. The reaction mixture is stirred at room temperature for 24 hours. The solution is then rendered acidic to pH = 2 with dilute hydrochloric acid and extracted with ether. The organic phase is dried over magnesium sulphate and concentrated. The resulting residue is recrystallised from ethanol to yield the expected compound.

Step b : ***N1-[1-Benzyl-2-oxo-2-(2-phenylhydrazino)ethyl]-1-benzenesulphonamide***

The expected product is obtained according to the process described in Example 1, Step b, using the compound described in the preceding Step as starting material.

Melting point : 162-163°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*63.80*	*5.32*	*10.63*
% found	*63.03*	*5.38*	*10.38*

EXAMPLE 17 : N1-[2-(2-Benzoylhydrazino)-1-benzyl-2-oxoethyl]-1-benzenesulphonamide

The expected product is obtained according to the process described in Example 1, Step b, using the compound of Example 16, Step a, as starting material, and replacing phenylhydrazine by phenylhydrazide.

Melting point : 200°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*62.41*	*4.96*	*9.93*
% found	*62.59*	*5.06*	*9.84*

EXAMPLE 18 : N1-[1-Benzyl-2-oxo-2-(2-phenylhydrazino)ethyl]-1-(4-chlorobenzene)sulphonamide

The expected product is obtained according to the process described in Example 10, in Step a replacing 2-naphthylsulphonyl chloride by 4-chlorobenzenesulphonyl chloride.

Melting point : 174-175°C

Elemental microanalysis :

	C	H	N
% calculated	*58.67*	*4.66*	*9.78*
% found	*58.63*	*4.77*	*9.70*

EXAMPLE 19 : N1-[2-(2-Benzoylhydrazino)-1-benzyl-2-oxoethyl]-1-(4-chlorobenzene)sulphonamide

The expected product is obtained according to the process described in Example 10, in Step a replacing 2-naphthylsulphonyl chloride by 4-chlorobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Melting point : 192-193°C

Elemental microanalysis :

	C	H	N
% calculated	*57.70*	*4.37*	*9.18*
% found	*57.50*	*4.43*	*9.14*

EXAMPLE 20 : N1-[1-Benzyl-2-oxo-2-(2-phenylhydrazino)ethyl]-1-(3,4-dichlorobenzene)sulphonamide

The expected product is obtained according to the process described in Example 16, in Step a replacing benzenesulphonyl chloride by 3,4-dichlorobenzenesulphonyl chloride.

Melting point : 164-165°C

Elemental microanalysis :

	C	H	N
% calculated	*54.32*	*4.12*	*9.05*
% found	*54.14*	*4.16*	*8.87*

EXAMPLE 21 : N1-[2-(2-Benzoylhydrazino)-1-benzyl-2-oxoethyl]-1-(3,4-dichlorobenzene)sulphonamide

The expected product is obtained according to the process described in Example 16, in Step a replacing benzenesulphonyl chloride by 3,4-dichlorobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Melting point : 200-201°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*53.66*	*3.86*	*8.54*
% found	*53.45*	*3.93*	*8.28*

EXAMPLE 22 : Benzyl N-[1-(4-methoxybenzyl)-2-oxo-2-(2-phenylhydrazino)ethyl]-carbamate

The expected product is obtained according to the process described in Example 1, in Step a replacing phenylalanine by O-methyltyrosine.

Melting point : 182-185°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*68.74*	*5.97*	*10.02*
% found	*68.56*	*6.11*	*9.81*

EXAMPLE 23 : Benzyl N-[2-benzoylhydrazino-1-(4-methoxybenzyl)-2-oxoethyl]carbamate

The expected product is obtained according to the process described in Example 1, in Step a replacing phenylalanine by O-methyltyrosine, and in Step b replacing phenylhydrazine by phenylhydrazide.

Melting point : 208-209°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*67.11*	*5.59*	*9.40*
% found	*67.19*	*5.74*	*9.32*

EXAMPLE 24 : Benzyl N-{2-[2-(2-indolylcarbonyl)hydrazino]-1-(4-methoxybenzyl)-2-oxoethyl}carbamate

The expected product is obtained according to the process described in Example 1, in Step a replacing phenylalanine by O-methyltyrosine, and in Step b replacing phenylhydrazine by 2-indolecarbohydrazide.

Melting point : 185-186°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*66.67*	*5.35*	*11.52*
% found	*66.40*	*5.43*	*12.87*

EXAMPLE 25 : Benzyl N-[1-(4-methoxybenzyl)-2-(2-nicotinoylhydrazino)-2-oxoethyl]carbamate

The expected product is obtained according to the process described in Example 1, in Step a replacing phenylalanine by O-methyltyrosine, and in Step b replacing phenylhydrazine by 3-pyridinecarbohydrazide.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*64.29*	*5.36*	*12.50*
% found	*64.43*	*5.52*	*12.14*

EXAMPLE 26 : Benzyl N-(2-{2-[2-(3-indolyl)acetyl]hydrazino}-1-(4-methoxybenzyl)-2-oxoethyl)carbamate

The expected product is obtained according to the process described in Example 1, in Step a replacing phenylalanine by O-methyltyrosine, and in Step b replacing phenylhydrazine by 3-indolylacetohydrazide.

Melting point : 194-195°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*67.20*	*5.60*	*11.19*
% found	*67.01*	*5.59*	*11.12*

EXAMPLE 27 : N1-[1-(4-Methoxybenzyl)-2-oxo-2-(2-phenylhydrazino)ethyl]-2-phenoxyacetamide

The expected product is obtained according to the process described in Example 5, in Step a replacing phenylalanine by O-methyltyrosine.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*68.74*	*5.97*	*10.02*
% found	*68.37*	*6.06*	*9.86*

EXAMPLE 28 : N1-[2-(2-Benzoylhydrazino)-1-(4-methoxybenzyl)-2-oxoethyl]-2-phenoxyacetamide

The expected product is obtained according to the process described in Example 5, in Step a replacing phenylalanine by O-methyltyrosine, and in Step b replacing phenylhydrazine by phenylhydrazide.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*67.11*	*5.59*	*9.40*
% found	*67.19*	*5.81*	*9.60*

EXAMPLE 29 : N1-[1-(4-Methoxybenzyl)-2-(2-nicotinoylhydrazino)-2-oxoethyl]-2-phenoxyacetamide

The expected product is obtained according to the process described in Example 5, in Step a replacing phenylalanine by O-methyltyrosine, and in Step b replacing phenylhydrazine by 3-pyridinecarbohydrazide.

Elemental microanalysis :

	C	H	N
% calculated	*64.29*	*5.36*	*12.50*
% found	*64.06*	*5.34*	*12.34*

EXAMPLE 30 : N2-[1-(4-Methoxybenzyl)-2-oxo-2-(2-phenylhydrazino)ethyl]-2-naphthalenesulphonamide

The expected product is obtained according to the process described in Example 10, replacing phenylalanine by O-methyltyrosine.

Melting point : 210-212°C

Elemental microanalysis :

	C	H	N
% calculated	*64.47*	*5.37*	*8.87*
% found	*64.17*	*5.25*	*8.56*

EXAMPLE 31 : N2-[2-(2-Benzoylhydrazino)-1-(4-methoxybenzyl)-2-oxoethyl]-2-naphthalenesulphonamide

The expected product is obtained according to the process described in Example 10, in Step a replacing phenylalanine by O-methyltyrosine, and in Step b replacing phenylhydrazine by phenylhydrazide.

Melting point : 246-247°C

Elemental microanalysis :

	C	H	N
% calculated	*63.28*	*5.07*	*8.20*
% found	*63.14*	*5.01*	*8.55*

EXAMPLE 32 : N2-[1-(4-Methoxybenzyl)-2-oxo-2-(2-phenylhydrazino)ethyl]-2-naphthylamide

The expected product is obtained according to the process described in Example 1, in Step a replacing phenylalanine by O-methyltyrosine and benzyl chloroformate by naphthoyl chloride.

Elemental microanalysis :

	C	H	N
% calculated	73.80	5.70	9.57
% found	73.53	5.62	9.54

EXAMPLE 33 : N2-[1-(4-Methoxybenzyl)-2-(2-nicotinoylhydrazino)-2-oxoethyl]-2-naphthylamide

The expected product is obtained according to the process described in Example 1, in Step a replacing phenylalanine by O-methyltyrosine and benzyl chloroformate by naphthoyl chloride, and in Step b replacing phenylhydrazide by 3-pyridinecarbohydrazide.

Elemental microanalysis :

	C	H	N
% calculated	69.23	5.13	11.97
% found	69.25	5.13	11.72

EXAMPLE 34 : N1-[1-(4-Methoxybenzyl)-2-oxo-2-(2-phenylhydrazino)ethyl]-1-benzenesulphonamide

The expected product is obtained according to the process described in Example 16, in Step a replacing L-phenylalanine by O-methyltyrosine.

Melting point : 163-164°C

Elemental microanalysis :

	C	H	N
% calculated	62.12	5.41	9.88
% found	61.71	5.54	9.89

EXAMPLE 35 : N1-[2-(2-Benzoylhydrazino)-1-(4-methoxybenzyl)-2-oxoethyl]-1-benzenesulphonamide

The expected product is obtained according to the process described in Example 16, in Step a replacing L-phenylalanine by O-methyltyrosine, and in Step b replacing phenylhydrazine by phenylhydrazide.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*60.85*	*5.07*	*6.26*
% found	*60.81*	*5.23*	*9.20*

EXAMPLE 36 : N1-[1-(4-Methoxybenzyl)-2-oxo-2-(2-phenylhydrazino)ethyl]-1-(4-chlorobenzene)sulphonamide

The expected product is obtained according to the process described in Example 10, in Step a replacing phenylalanine by O-methyltyrosine and 2-naphthylsulphonyl chloride by 4-chlorobenzenesulphonyl chloride.

Melting point : *181-183°C*

Elemental microanalysis :

	C	*H*	*N*
% calculated	*56.31*	*4.92*	*9.39*
% found	*56.64*	*4.85*	*9.02*

EXAMPLE 37 : N1-[2-(2-Benzoylhydrazino)-1-(4-methoxybenzyl)-2-oxoethyl]-1-(4-chlorobenzene)sulphonamide

The expected product is obtained according to the process described in Example 10, in Step a replacing phenylalanine by O-methyltyrosine and 2-naphthylsulphonyl chloride by 4-chlorobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*56.61*	*4.54*	*8.61*
% found	*56.82*	*4.55*	*8.61*

EXAMPLE 38 : N1-[1-(4-Methoxybenzyl)-2-oxo-2-(2-phenylhydrazino)ethyl]-1-(3,4-dichlorobenzene)sulphonamide

The expected product is obtained according to the process described in Example 16, in Step a replacing phenylalanine by O-methyltyrosine and benzenesulphonyl chloride by 3,4-dichlorobenzenesulphonyl chloride.

Melting point : *153-154°C*

Elemental microanalysis :

	C	*H*	*N*
% calculated	*53.44*	*4.25*	*8.50*
% found	*53.80*	*4.38*	*8.30*

EXAMPLE 39 : N1-[2-(2-Benzoylhydrazino)-1-(4-methoxybenzyl)-2-oxoethyl]-1-(3,4-dichlorobenzene)sulphonamide

The expected product is obtained according to the process described in Example 16, in Step a replacing phenylalanine by O-methyltyrosine and benzenesulphonyl chloride by 3,4-dichlorobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by phenyl-hydrazide.

Melting point : *214-215°C*

Elemental microanalysis :

	C	*H*	*N*
% calculated	*52.87*	*4.03*	*8.05*
% found	*52.60*	*4.09*	*8.17*

EXAMPLE 40 : N2-[6-Oxo-6-(2-phenylhydrazino)hexyl]-2-naphthalenesulphonamide

Step a : *6-[(2-Naphthylsulphonyl)amino]hexanoic acid*

30.5 mmol (6.42 g) of 2-naphthylsulphonyl chloride and 15 ml of 4M aqueous sodium hydroxide are added in succession to a solution of 15.2 mmol (2 g) of 6-aminocaproic acid in 15 ml of 4M aqueous sodium hydroxide. The reaction mixture is stirred at room temperature for 24 hours. The solution is then rendered acidic to pH = 2 with concentrated hydrochloric acid, and extracted with dichloromethane. The organic phase is dried over sodium sulphate and concentrated, and the resulting residue is recrystallised from hexane to yield the expected compound.

Step b : ***N2-[6-Oxo-6-(2-phenylhydrazino)hexyl]-2-naphthalenesulphonamide***

The expected product is obtained according to the process described in Example 1, Step b, using the compound described in the preceding Step as starting material.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*64.16*	*6.08*	*10.21*
% found	*64.23*	*5.88*	*9.95*

EXAMPLE 41 : N2-[6-(2-Benzoylhydrazino)-6-oxohexyl]-2-naphthalene-sulphonamide

The expected product is obtained according to the process described in Example 40, in Step b replacing phenylhydrazine by phenylhydrazide.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*62.79*	*5.69*	*9.56*
% found	*62.50*	*5.70*	*9.49*

EXAMPLE 42 : N2-[6-(2-Benzoylhydrazino)-6-oxohexyl]-2-(2-nitrophenyl)-sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 2-naphthylsulphonyl chloride by 2-nitrophenylsulphonyl chloride.

Melting point : 106°C

Elemental microanalysis :

	C	H	N
% calculated	*52.53*	*5.10*	*12.89*
% found	*52.61*	*5.14*	*12.76*

EXAMPLE 43 : N2-({4-[(2-Phenylhydrazino)carbonyl]cyclohexyl}methyl)-2-naphthalenesulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid.

Elemental microanalysis : (x½ H_2O)

	C	H	N
% calculated	*64.50*	*6.27*	*9.41*
% found	*64.54*	*6.04*	*9.22*

EXAMPLE 44 : N2-({4-[(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-2-naphthalenesulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid, and in Step b replacing phenylhydrazine by phenylhydrazide.

Elemental microanalysis : (x½ H_2O)

	C	H	N
% calculated	*63.22*	*5.90*	*8.85*
% found	*63.59*	*5.68*	*8.76*

EXAMPLE 45 : N2-[(4-{[2-(2-Indolylcarbonyl)hydrazino]carbonyl}cyclohexyl)-methyl]-2-naphthalenesulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid, and in Step b replacing phenylhydrazine by 2-indolylcarbohydrazide.

Elemental microanalysis : (x½ H_2O)

	C	H	N
% calculated	*63.11*	*5.45*	*10.90*
% found	*63.11*	*5.72*	*11.10*

EXAMPLE 46 : N2-({4-[(2-Nicotinoylhydrazino)carbonyl]cyclohexyl}methyl)-2-naphthalenesulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid, and in Step b replacing phenylhydrazine by 3-pyridinecarbohydrazide.

Melting point : 204-205°C

Elemental microanalysis :

	C	H	N
% calculated	*61.76*	*5.57*	*12.01*
% found	*62.15*	*5.68*	*11.88*

EXAMPLE 47 : N2-{[4-({2-[2-(3-Indolyl)-acetyl]hydrazino}carbonyl)cyclohexyl]-methyl}-2-naphthalenesulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid, and in Step b replacing phenylhydrazine by 3-indolylacetohydrazide.

Elemental microanalysis :

	C	H	N
% calculated	*62.61*	*5.77*	*10.44*
% found	*62.11*	*5.99*	*10.41*

EXAMPLE 48 : N1-({4-[(2-Phenylhydrazino)carbonyl]cyclohexyl}methyl)-1-benzylsulphonamide

The expected product is obtained according to the process described in Example 40, in

Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by benzenesulphonyl chloride.

Melting point : 194-196°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*61.99*	*6.50*	*10.84*
% found	*62.81*	*6.60*	*10.83*

EXAMPLE 49 : N1-({4-[(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-1-benzenesulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by benzenesulphonyl chloride, and in Step b replacing phenyl-hydrazine by phenylhydrazide.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*60.70*	*6.06*	*10.11*
% found	*60.25*	*6.24*	*10.07*

EXAMPLE 50 : N1-({4-[(2-Nicotinoylhydrazino)carbonyl]cyclohexyl}methyl)-1-benzenesulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by benzenesulphonyl chloride, and in Step b replacing phenyl-hydrazine by 3-pyridinecarbohydrazide.

Melting point : 213-215°C

Elemental microanalysis : (x½ H_2O)

	C	*H*	*N*
% calculated	*56.41*	*5.64*	*13.16*
% found	*56.45*	*5.74*	*13.56*

EXAMPLE 51 : N1-[(4-{[2-(4-Chlorophenyl)hydrazino]carbonyl}cyclohexyl)methyl]-1-benzenesulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by benzenesulphonyl chloride, and in Step b replacing phenyl-hydrazine by 4-chlorophenylhydrazine.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*56.93*	*5.73*	*9.96*
% found	*56.91*	*5.82*	*9.86*

EXAMPLE 52 : N1-[(4-{2-(4-Chlorobenzoyl)hydrazino]carbonyl}cyclohexyl)methyl]-1-benzenesulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by benzenesulphonyl chloride, and in Step b replacing phenyl-hydrazine by 4-chlorophenylhydrazide.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*56.01*	*5.33*	*9.33*
% found	*55.98*	*5.43*	*9.41*

EXAMPLE 53 : N1-({4-[(2-Phenylhydrazino)carbonyl]cyclohexyl}methyl)-1-(2-nitrobenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 2-nitrobenzenesulphonyl chloride.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*55.54*	*5.59*	*12.95*
% found	*55.35*	*5.49*	*12.70*

EXAMPLE 54 : N1-({4-[(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-1-(2-nitrobenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 2-nitrobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Elemental microanalysis : (x½ H_2O)

	C	*H*	*N*
% calculated	*53.72*	*5.15*	*11.93*
% found	*53.57*	*5.19*	*11.76*

EXAMPLE 55 : N1-{[4-(2-[2-(3-Indolyl)-acetyl]hydrazino}carbonyl)cyclohexyl]-methyl}-1-(2-nitrobenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 2-nitrobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by 3-indolylacetohydrazide.

Elemental microanalysis : (x½ H_2O)

	C	*H*	*N*
% calculated	*55.11*	*5.17*	*13.39*
% found	*55.13*	*5.14*	*13.35*

EXAMPLE 56 : N1-[(4-{2-(2-Indolylcarbonyl)hydrazino]carbonyl}cyclohexyl)-methyl]-1-(2-nitrobenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 2-nitrobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by 2-indolylcarbohydrazide.

Melting point : 249-251°C

Elemental microanalysis :

	C	H	N
% calculated	*55.27*	*5.01*	*14.02*
% found	*55.02*	*5.28*	*14.39*

<u>EXAMPLE 57</u> : N1-({4-[(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-1-(2-nitro-4-trifluoromethylphenyl)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 2-nitro-4-trifluoromethylphenylsulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Elemental microanalysis :

	C	H	N
% calculated	*50.00*	*4.36*	*10.61*
% found	*49.97*	*4.46*	*10.68*

<u>EXAMPLE 58</u> : N1-({4-[(2-Phenylhydrazino)carbonyl]cyclohexyl}methyl)-1-(4-bromobenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 4-bromobenzenesulphonyl chloride.

Melting point : 192-194°C

Elemental microanalysis : (x½ H_2O)

	C	H	N
% calculated	*50.48*	*5.05*	*8.83*
% found	*50.38*	*5.15*	*8.69*

EXAMPLE 59 : N1-({4-[(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-1-(4-bromobenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 4-bromobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Melting point : 251-253°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*51.02*	*4.89*	*8.50*
% found	*50.47*	*4.92*	*8.34*

EXAMPLE 60 : N1-[(4-{[2-(4-Chlorophenyl)hydrazino]cyclohexyl}carbonyl)methyl]-1-(4-bromobenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 4-bromobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by 4-chlorophenylhydrazine.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*47.96*	*4.63*	*8.39*
% found	*47.99*	*4.63*	*8.29*

EXAMPLE 61 : N1-[(4-{[2-(4-Chlorobenzoyl)hydrazino]cyclohexyl}carbonyl)methyl]-1-(4-bromobenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 4-bromobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by 4-chlorophenylhydrazide.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*47.69*	*4.38*	*7.95*
% found	*47.78*	*4.45*	*8.05*

EXAMPLE 62 : N'-Phenyl-1-(phenylsulphonyl)perhydro-2-indolecarbohydrazide

Step a : 1-(Phenylsulphonyl)-2-perhydroindolecarboxylic acid

29.8 mmol (3.8 ml) of benzenesulphonyl chloride and 7.4 ml of 4M sodium hydroxide solution are added in succession to a solution, cooled to 0°C, of 29.6 mmol (5 g) of 2-perhydroindolecarboxylic acid in 7.4 ml of 4M NaOH. The reaction mixture is left at room temperature, with stirring, for 24 hours. The mixture is then rendered acidic to pH 2-3 and filtered. The resulting solid is washed with ether to yield the expected product.

Step b : N'-Phenyl-1-(phénylsulphonyl)perhydro-2-indolecarbohydrazide

The expected product is obtained according to the process described in Step b of Example 1, using the compound described in the preceding Step as starting material.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*63.16*	*6.27*	*10.53*
% found	*63.37*	*6.43*	*10.38*

EXAMPLE 63 : N'-(2-Indolylcarbonyl)-1-(phenylsulphonyl)perhydro-2-indolecarbohydrazide

The expected product is obtained according to the process described in Example 62, in Step b replacing phenylhydrazine by 2-indolecarbohydrazide.

Melting point : 134-137°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*61.80*	*5.58*	*12.02*
% found	*61.34*	*5.74*	*11.62*

EXAMPLE 64 : N'-Nicotinoyl-1-(phenylsulphonyl)perhydro-2-indolecarbohydrazide

The expected product is obtained according to the process described in Example 62, in Step b replacing phenylhydrazine by 3-pyridinecarbohydrazide.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*58.88*	*5.61*	*13.08*
% found	*58.41*	*5.74*	*13.64*

EXAMPLE 65 : N2-({4-[(2-Phenylhydrazino)carbonyl]cyclohexyl}methyl)-1-naphthalenesulphonamide

Step a : 6-(1-Naphthylsulphonyl)aminomethyl]cyclohexanecarboxylic acid

The expected product is obtained according to the process described in Example 40, Step a, replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and using 1-naphthylsulphonyl chloride.

Step b : N2-({4-[(2-Phenylhydrazino)carbonyl]cyclohexyl}methyl)-1-naphthalenesulphonamide

The expected product is obtained according to the process described in Example 1, Step b, using the compound described in the preceding Step as starting material, and replacing phenylhydrazine by phenylhydrazide.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*64.44*	*5.80*	*9.02*
% found	*64.59*	*5.96*	*8.76*

EXAMPLE 66 : N1-({4-[(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-1-(4-isopropylbenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 4-isopropylbenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Melting point : 232-236°C

Elemental microanalysis :

	C	H	N
% calculated	62.46	6.77	9.10
% found	62.32	7.20	9.18

EXAMPLE 67 : N1-({4-[(2-Naphthoylhydrazino)carbonyl]cyclohexyl}methyl)-1-(2-nitrobenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 2-nitrobenzenesulphonyl choride, and in Step b replacing phenylhydrazine by 2-naphthylhydrazide.

Melting point : 263-264°C

Elemental microanalysis :

	C	H	N
% calculated	58.81	5.13	10.97
% found	58.87	5.32	11.25

EXAMPLE 68 : N1-({4-[(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-1-(3-nitrobenzene)sulphonamide

The expected product is obtained according to the process described in Example 54, replacing 2-nitrobenzenesulphonyl chloride by 3-nitrobenzenesulphonyl chloride.

Melting point : 198-201°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*51.69*	*4.92*	*11.48*
% found	*51.58*	*4.83*	*11.61*

EXAMPLE 69 : N1-({4-[(2-Phenylhydrazino)carbonyl]cyclohexyl}methyl)-1-(4-nitrobenzene)sulphonamide

The expected product is obtained according to the process described in Example 53, replacing 2-nitrobenzenesulphonyl chloride by 4-nitrobenzenesulphonyl chloride.

Melting point : 200-201°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*54.36*	*5.44*	*12.68*
% found	*53.99*	*5.33*	*12.46*

EXAMPLE 70 : N1-({4-[(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-1-(4-nitrobenzene)sulphonamide

The expected product is obtained according to the process described in Example 54, replacing 2-nitrobenzenesulphonyl chloride by 4-nitrobenzenesulphonyl chloride.

Melting point : 262-264°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*53.67*	*5.11*	*11.93*
% found	*53.68*	*5.21*	*11.96*

EXAMPLE 71 : N1-[(4-{[2-(4-Chlorophenyl)hydrazino]carbonyl}cyclohexyl)-methyl]-1-(4-nitrobenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and

2-naphthylsulphonyl chloride by 4-nitrobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by 4-chlorophenylhydrazine.

Melting point : 211-213°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*51.45*	*4.96*	*12.00*
% found	*51.52*	*5.12*	*11.81*

EXAMPLE 72 : N1-[(4-{[2-(4-Chlorobenzoyl)hydrazino]carbonyl}cyclohexyl)-methyl]-1-(4-nitrobenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 4-nitrobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by 4-chlorophenylhydrazide.

Melting point : 272-273°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*50.91*	*4.65*	*11.31*
% found	*50.89*	*4.76*	*11.29*

EXAMPLE 73 : N1-({4-[(2-(4-Phenylhydrazino)carbonyl]cyclohexyl}methyl)-1-(2-bromobenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 2-bromobenzenesulphonyl chloride.

Melting point : 165-167°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*51.46*	*5.14*	*9.01*
% found	*51.54*	*5.29*	*9.03*

EXAMPLE 74 : N1-({4-[(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-1-(2-bromobenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 2-bromobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Melting point : *231-232°C*

Elemental microanalysis :

	C	*H*	*N*
% calculated	*50.97*	*4.85*	*8.49*
% found	*51.11*	*4.98*	*8.51*

EXAMPLE 75 : N1-[(4-{[(2-(4-Chlorophenyl)hydrazino]carbonyl}cyclohexyl)-methyl]-1-(2-bromobenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 2-bromobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by 4-chlorophenylhydrazine.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*47.92*	*4.59*	*8.39*
% found	*48.15*	*4.73*	*8.37*

EXAMPLE 76 : N1-[(4-{[2-(4-Chlorophenyl)hydrazino]cyclohexyl}carbonyl)-methyl]-1-(2-bromobenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 2-bromobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by 4-chlorophenylhydrazide.

Melting point : 263-264°C

Elemental microanalysis :

	C	H	N
% calculated	47.65	4.35	7.94
% found	47.65	4.44	7.87

EXAMPLE 77 : N1-({4-[(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-1-(4-chlorobenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 4-chlorobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Melting point : 254-256°C

Elemental microanalysis :

	C	H	N
% calculated	56.01	5.33	9.33
% found	56.00	5.22	9.24

EXAMPLE 78 : N1-({4-[(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-1-(3,4-dichlorobenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 3,4-dichlorobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Melting point : 251-252°C

Elemental microanalysis :

	C	H	N
% calculated	52.07	4.75	8.67
% found	51.91	5.32	8.71

EXAMPLE 79 : **N1-({4-[(2-Phenylhydrazino)carbonyl]cyclohexyl}methyl)-1-(4-fluorobenzene)sulphonamide**

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 4-fluorobenzenesulphonyl chloride.

Melting point : *192-193°C*

Elemental microanalysis :

	C	*H*	*N*
% calculated	*59.19*	*5.92*	*10.36*
% found	*59.03*	*5.98*	*10.23*

EXAMPLE 80 : **N1-({4-([(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-1-(4-fluorobenzene)sulphonamide**

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 4-fluorobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Melting point : *264-265°C*

Elemental microanalysis :

	C	*H*	*N*
% calculated	*58.13*	*5.54*	*9.69*
% found	*58.04*	*5.60*	*9.71*

EXAMPLE 81 : **N1-[(4-{[2-(4-Chlorophenyl)hydrazino]carbonyl}cyclohexyl)methyl]-1-(4-fluorobenzene)sulphonamide**

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 4-fluorobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by 4-chlorophenylhydrazine.

Melting point : 216-217°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*54.31*	*5.20*	*9.50*
% found	*54.39*	*5.22*	*9.45*

EXAMPLE 82 : N1-[(4-{[2-(4-Chlorobenzoyl)hydrazino]carbonyl}cyclohexyl)-methyl]-1-(4-fluorobenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 4-fluorobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by 4-chlorophenylhydrazide.

Melting point : 257-258°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*53.85*	*4.92*	*8.98*
% found	*53.90*	*5.00*	*8.89*

EXAMPLE 83 : N1-({4-[(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-1-(4-methylbenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 4-methylbenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*61.52*	*6.34*	*9.78*
% found	*61.71*	*6.32*	*9.67*

EXAMPLE 84 : N1-({4-[(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-1-(4-methoxybenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 4-methoxybenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*59.25*	*6.06*	*9.43*
% found	*59.25*	*6.26*	*9.49*

EXAMPLE 85 : N1-({4-[(2-Benzoylhydrazino]carbonyl]cyclohexyl}methyl)-1-(3,4-dimethoxybenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 3,4-dimethoxybenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Melting point : 244-245°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*57.02*	*5.99*	*8.68*
% found	*56.91*	*6.33*	*8.84*

EXAMPLE 86 : N1-({4-[(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-1-(4-acetylaminobenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 4-(N-acetylamino)benzenesulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Elemental microanalysis :

	C	H	N
% calculated	*58.46*	*5.97*	*11.86*
% found	*58.29*	*6.04*	*11.73*

EXAMPLE 87 : N1-({4-[(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-1-(2-methylsulphonylbenzene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by 2-(methylsulphonyl)benzenesulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Melting point : *193-194°C*

Elemental microanalysis :

	C	H	N
% calculated	*53.55*	*5.48*	*8.52*
% found	*53.17*	*5.74*	*8.49*

EXAMPLE 88 : N1-({4-[(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-1-(β-styrene)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by (β-styrene)sulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Melting point : *208-209°C*

Elemental microanalysis :

	C	H	N
% calculated	*60.13*	*6.32*	*9.15*
% found	*60.06*	*6.45*	*9.05*

EXAMPLE 89 : N1-({4-[(2-Phenylhydrazino)carbonyl]cyclohexyl}methyl)-1-(2-thienyl)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by (2-thienyl)sulphonyl chloride.

Melting point : 218-221°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*54.89*	*5.84*	*10.67*
% found	*54.50*	*6.05*	*10.82*

EXAMPLE 90 : N1-({4-[(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-1-(2-thienyl)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by (2-thienyl)sulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Melting point : 221-222°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*52.96*	*5.34*	*9.76*
% found	*53.14*	*5.50*	*9.82*

EXAMPLE 91 : N1-[(4-{[2-(4-Chlorophenyl)hydrazino]carbonyl}cyclohexyl)-methyl]-1-(2-thienyl)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by (2-thienyl)sulphonyl chloride, and in Step b replacing phenylhydrazine by 4-chlorophenylhydrazine.

Melting point : 193-194°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*50.47*	*5.14*	*9.81*
% found	*50.50*	*5.27*	*9.73*

EXAMPLE 92 : N1-[(4-{[(2-(4-Chlorobenzoyl)hydrazino]carbonyl}cyclohexyl)-methyl]-1-(2-thienyl)sulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-naphthylsulphonyl chloride by (2-thienyl)sulphonyl chloride, and in Step b replacing phenylhydrazine by 4-chlorophenylhydrazide.

Melting point : 237-239°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*50.00*	*4.82*	*9.21*
% found	*49.93*	*4.97*	*9.37*

EXAMPLE 93 : N1-[6-Oxo-6-(2-phenylhydrazino)hexyl]-1-benzenesulphonamide

The expected product is obtained according to the process described in Example 40, replacing 2-naphthylsulphonyl chloride by benzenesulphonyl chloride.

Melting point : 123-124°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*59.81*	*6.41*	*11.62*
% found	*59.92*	*6.58*	*11.52*

EXAMPLE 94 : N1-[6-(2-Benzoylhydrazino)-6-oxohexyl]-1-phenylsulphonamide

The expected product is obtained according to the process described in Example 40, replacing 2-naphthylsulphonyl chloride by benzenesulphonyl chloride, and phenylhydrazine by phenylhydrazide.

Melting point : 150°C

Elemental microanalysis :

	C	H	N
% calculated	*58.59*	*5.95*	*10.79*
% found	*58.52*	*6.10*	*10.90*

EXAMPLE 95 : Benzyl N-[1-(4-methoxybenzyl)-2-oxo-2-(2-phenylsulphonylhydrazino)ethyl]carbamate

The expected product is obtained according to the process described in Example 1, in Step a replacing phenylalanine by O-methyltyrosine, and in Step b replacing phenylhydrazine by phenylsulphonylhydrazine.

Elemental microanalysis :

	C	H	N
% calculated	*59.63*	*5.18*	*8.70*
% found	*60.03*	*5.41*	*8.65*

EXAMPLE 96 : N1-[1-(4-Methoxybenzyl)-2-oxo-2-(2-phenylsulphonylhydrazino)-ethyl]-2-phenoxyacetamide

The expected product is obtained according to the process described in Example 5, in Step a replacing phenylalanine by O-methyltyrosine, and in Step b replacing phenylhydrazine by phenylsulphonylhydrazine.

Elemental microanalysis :

	C	H	N
% calculated	*59.63*	*5.18*	*8.70*
% found	*59.52*	*5.06*	*8.59*

EXAMPLE 97 : N1-[1-Benzyl-2-oxo-2-(2-phenylsulphonylhydrazino)ethyl]-1-phenylsulphonamide

The expected product is obtained according to the process described in Example 10, in Step a replacing 2-naphthylsulphonyl chloride by benzenesulphonyl chloride, and in Step b replacing phenylhydrazine by phenylsulphonylhydrazine.

Melting point : 182-183°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*54.90*	*4.58*	*9.15*
% found	*54.70*	*4.79*	*8.91*

EXAMPLE 98 : N2-[1-Benzyl-2-oxo-2-(2-phenylsulphonylhydrazino)ethyl]-2-naphthylamide

The expected product is obtained according to the process described in Example 1, in Step a replacing benzyl chloroformate by naphthoyl chloride, and in Step b replacing phenylhydrazine by phenylsulphonylhydrazine.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*64.41*	*4.97*	*8.35*
% found	*63.95*	*5.01*	*8.29*

EXAMPLE 99 : 1-[(4-Chlorophenyl)sulphonyl]-N'-phenylperhydro-2-indolecarbohydrazide

The expected product is obtained according to the process described in Example 62, in Step a replacing benzenesulphonyl chloride by 4-chlorobenzenesulphonyl chloride.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*58.13*	*5.54*	*9.68*
% found	*58.66*	*5.63*	*9.18*

EXAMPLE 100 : 1-[(4-Chlorophenyl)sulphonyl]-N'-nicotinoyl-perhydro-2-indolecarbohydrazide

The expected product is obtained according to the process described in Example 62, in Step a replacing benzenesulphonyl chloride by 4-chlorobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by 3-pyridinecarbohydrazide.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*54.49*	*4.97*	*12.11*
% found	*54.54*	*5.21*	*12.32*

EXAMPLE 101 : 1-[(2-Nitrophenyl)sulphonyl]-N'-phenylperhydro-2-indolecarbohydrazide

The expected product is obtained according to the process described in Example 62, in Step a replacing benzenesulphonyl chloride by 2-nitrobenzenesulphonyl chloride.

Melting point : 86-89°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*56.88*	*5.19*	*12.64*
% found	*56.78*	*5.49*	*12.26*

EXAMPLE 102 : N'-Benzoyl-1-[(2-nitrophenyl)sulphonyl]-perhydro-2-indolecarbohydrazide

The expected product is obtained according to the process described in Example 62, in Step a replacing benzenesulphonyl chloride by 2-nitrobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Melting point : 109-113°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*55.93*	*5.08*	*11.86*
% found	*56.21*	*5.24*	*12.05*

EXAMPLE 103 : 1-[(4-Chlorophenyl)sulphonyl]-N'-phenyl-2-pyrrolidinecarbohydrazide

The expected product is obtained according to the process described in Example 62, in Step a replacing perhydroindolecarboxylic acid by proline and benzenesulphonyl chloride by 4-chlorobenzenesulphonyl chloride.

Melting point : 133-135°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*53.75*	*4.74*	*11.07*
% found	*53.94*	*4.89*	*10.81*

EXAMPLE 104 : N'-Benzoyl-1-[(4-chlorophenyl)sulphonyl]-2-pyrrolidinecarbohydrazide

The expected product is obtained according to the process described in Example 62, in Step a replacing perhydroindolecarboxylic acid by proline and benzenesulphonyl chloride by 4-chlorobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by phenylhydrazide.

Melting point : 171-172°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*53.01*	*4.42*	*10.31*
% found	*53.26*	*4.53*	*10.36*

EXAMPLE 105 : 1-[(4-Chlorophenyl)sulphonyl]-N'-nicotinoyl-2-pyrrolidinecarbohydrazide

The expected product is obtained according to the process described in Example 62, in Step a replacing perhydroindolecarboxylic acid by proline and benzenesulphonyl chloride by 4-chlorobenzenesulphonyl chloride, and in Step b replacing phenylhydrazine by 3-pyridinecarbohydrazide.

Melting point : *107-108°C*

Elemental microanalysis :

	C	*H*	*N*
% calculated	*49.94*	*4.16*	*13.71*
% found	*50.51*	*4.40*	*13.47*

EXAMPLE 106 : 1-[(4-Chlorophenyl)sulphonyl]-N'-naphthyl-2-pyrrolidinecarbohydrazide

The expected product is obtained according to the process described in Example 62, in Step a replacing perhydroindolecarboxylic acid by proline and phenylhydrazine by naphthylhydrazine.

Melting point : *178-180°C*

Elemental microanalysis :

	C	*H*	*N*
% calculated	*60.80*	*4.58*	*6.76*
% found	*60.78*	*4.73*	*6.79*

EXAMPLE 107 : N-({4-[(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-5-(dimethylamino)-1-napthalenesulphonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-napthylsulphonyl chloride by 5-dimethylamino-1-naphthyl sulphonyle chloride and in step b replacing phenylhydrazine by phenylhydrazide.

Melting point : *201-203°C*

Elemental microanalysis :

	C	*H*	*N*
% calculated	*61.99*	*6.50*	*10.84*
% found	*62.81*	*6.60*	*10.83*

EXEMPLE 108 : 4-Bromo-N-({4-[(2-{[4-(trifluoromethyl)-2-pyrimidinyl]carbonyl} hydrazino)carbonyl]cyclohexyl}methyl)benzenesulfonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-napthylsulphonyl chloride by 4-bromobenzenesulphonyl chloride and in step b replacing phenylhydrazine by 4-(trifluorométhyl)-2-pyrimidinecarbohydrazide.

Melting point : 229-230°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*41,16*	*4,15*	*12,64*
% found	*41,06*	*4,03*	*12,75*

EXEMPLE 109 : 3,4-Dimethoxy-N-[(4-{[2-(3-pyridylcarbonyl)hydrazino]carbonyl} cyclohexyl)methyl]benzenesulfonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-napthylsulphonyl chloride by 3,4-dimethoxybenzenesulphonyl chloride and in step b replacing phenylhydrazine by 3-pyridinecarbohydrazide.

Melting point : 211-212°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*55,46*	*5,88*	*11,76*
% found	*55,43*	*5,75*	*11,86*

EXEMPLE 110 : N-({4-[(2-Benzoylhydrazino)carbonyl]cyclohexyl}methyl)-5-quinoleinesulfonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)cyclohexanecarboxylic acid and 2-napthylsulphonyl chloride by 5-quinoleïnesulphonyl chloride and in step b replacing phenylhydrazine by phenylhydrazide.

Melting point : 215-216°C

Elemental microanalysis :

	C	H	N
% calculated	61,80	5,58	12,02
% found	61,69	5,66	12,13

EXEMPLE 111 : N-{4-[(2-Benzoylhydrazino)carbonyl]benzyl}benzenesulfonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)benzoïc acid and 2-napthylsulphonyl chloride by benzenesulphonyl chloride and in step b replacing phenylhydrazine by phenylhydrazide.

Melting point : 191-193°C

Elemental microanalysis :

	C	H	N
% calculated	61,54	4,64	10,26
% found	61,57	4,81	10,22

EXEMPLE 112 : N2-{4-[(2-Benzoylhydrazino)carbonyl]benzyl} naphthalenesulfonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)benzoïc acid and 2-napthylsulphonyl chloride by benzenesulphonyl chloride and in step b replacing phenylhydrazine by phenylhydrazide.

Elemental microanalysis :

	C	H	N
% calculated	65,29	4,57	9,14
% found	65,69	4,70	8,87

EXEMPLE 113 : N-{4-[(2-Benzoylhydrazino)carbonyl]benzyl}-2-nitrobenzenesulfonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)benzoïc acid and 2-napthylsulphonyl chloride by 2-nitrobenzenesulphonyl chloride and in step b replacing phenylhydrazine by phenylhydrazide.

Elemental microanalysis :

	C	*H*	*N*
% calculated	*55,45*	*3,96*	*12,32*
% found	*55,36*	*4,11*	*12,56*

EXEMPLE 114 : N-{4-[(2-Benzoylhydrazino)carbonyl]benzyl}-4-bromobenzenesulfonamide

The expected product is obtained according to the process described in Example 40, in Step a replacing 6-aminocaproic acid by 4-(aminomethyl)benzoïc acid and 2-napthylsulphonyl chloride by 2-bromobenzenesulphonyl chloride and in step b replacing phenylhydrazine by phenylhydrazide.

Melting point : 208-210°C

Elemental microanalysis :

	C	*H*	*N*
% calculated	*50,71*	*3,82*	*8,45*
% found	*50,85*	*3,61*	*8,42*

PHARMACOLOGICAL STUDY

EXAMPLE A : Measurement of the *in vitro* affinity for NPY receptors

The capacity of the compounds of the invention to bind to NPY receptors was measured on various cell lines, each expressing one of the receptor sub-types studied. Competition binding experiments were carried out using the peptide [^{125}I]-PYY as radioligand at concentrations ranging from 15 to 65 pM. The non-specific fraction is measured in the presence of a concentration of 1 μM NPY. The cells are incubated for a period ranging from 1 to 2 hours depending upon the lines, and the radioactivity is collected after filtration over a GF/C filter treated with 0.1% PEI, before being measured.

Results :

The results are expressed as IC_{50}. The compounds of the invention appear to be capable of significantly displacing the reference ligand : the IC_{50} values vary from a few nanomoles to some hundreds of nanomoles.

By way of example, the compound of Example 44 has an IC_{50} of 14.5 nM for the Y_5 receptor.

EXAMPLE B : Measurement of the effect on food intake and weight development in the obese mouse

The compounds of the invention were administered *in vivo* to the obese ob/ob mouse in order to evaluate their influence on food intake and weight development. The animals used are 13- to 18-week-old female ob/ob C57B1/6J mice. They are divided into groups each comprising 4 animals per cage, the cages being fitted with a grating floor, and the mice having free access to food.

Before the experiments, the animals are conditioned for a period ranging from 2 to 3 weeks until their food consumption has stabilised. The experiments may be summarised as follows :

- D -14 to D -7 : conditioning
- D -7 to D -3 : measurement of the basal food intake
- D0 to D +3 : animals treated twice daily, the control groups being given the carrier
- D0 to D +4 : daily measurement of food intake and body weight

The test products are dissolved, immediately before use, in water, 0.9% sodium chloride, propylene glycol or dimethyl sulphoxide, depending upon their solubility, and are administered intraperitoneally (IP), in a volume of 2.5 ml/kg.

The parameters measured are the weight of the feed troughs containing the food and the body weight.

Results :

The results are expressed as :

- percentage variation in food intake under treatment compared with the basal food intake ;
- percentage variation in body weight between the first and last day of treatment.

By way of example, the results obtained with the compound of Example 44 are as follows :

Product	Dose (mg/kg)	Food intake % variation (D1)		Body weight % variation (D4/D0)
		Control	Treated	
Example 44	5	- 25.3	- 75.2	- 6.0

EXAMPLE C : ACUTE TOXICITY STUDY

The acute toxicity was evaluated after oral administration of increasing doses of the test compound to groups each comprising 8 mice (26 ± 6 gramms). The animals were observed at regular intervals over the course of the first day and daily for the two weeks following treatment.

The compounds of the invention appear to be not very toxic at all.

EXAMPLE D : PHARMACEUTICAL COMPOSITION

Formulation for the preparation of 1000 tablets each comprising a dose of 10 mg

Compound of Example 44	10 g
Hydroxypropyl cellulose	2 g
Wheat starch	10 g
Lactose	100 g
Magnesium stearate	3 g
Talc	3 g

Comprises/comprising and grammatical variations thereof when used in this specification are to be taken to specify the presence of stated features, integers, steps or components or groups thereof, but do not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof.

~~CLAIMS~~

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1- Compounds of formula (I) :

$$R - NH - A - CO - NH - NH - (W)_n - Z \qquad (I)$$

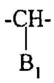
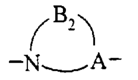
wherein :

- n is 0 or 1,
- W represents a -CO- group or an $S(O)_r$ group wherein r is 0, 1 or 2,
- Z represents a group selected from optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl,
- R represents a group selected from :

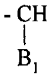
  Z_1-T-CO-
  Z_1-O-T-CO-
  Z_1-T-O-CO-
  Z_1-T-$S(O)_q$-

  wherein :

  - Z_1 represents an optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl group,
  - T represents a σ bond or an alkylene, alkenylene or alkynylene group,
  - q represents an integer 0, 1 or 2,
- A represents a linear or branched alkylene group having from 3 to 8 carbon atoms, a linear or branched alkenylene group having from 3 to 8 carbon atoms, a linear or branched alkynylene group having from 3 to 8 carbon atoms, an alkylenecycloalkylene group, a cycloalkylenealkylene group, an alkylenecycloalkylenealkylene group, an alkylenearylene group, an arylenealkylene group, an alkylenearylenealkylene group, a

grouping  $-\underset{B_1}{\underset{|}{C}}H-$ wherein B_1 represents an optionally substituted aryl, optionally substituted arylalkyl,optionally substituted heteroaryl or optionally substituted heteroarylalkyl group, or A forms with the nitrogen atom a grouping 

wherein B_2 represents a saturated or unsaturated mono- or bi-cyclic system having from 5 to 11 ring members, optionally containing from 1 to 3 additional hetero atoms selected from nitrogen, oxygen and sulphur,

with the proviso that when simultaneously n is 0, A represents a grouping  $-\underset{B_1}{\underset{|}{C}}H-$, B_1 being a benzyl group, and Z represents an optionally substituted phenyl group, then R is other than a benzoyl group,

their enantiomers, diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base,

it being understood that :

the term "alkyl" denotes a linear or branched group having from 1 to 6 carbon atoms,

the term "alkylene" denotes a linear or branched bivalent radical containing from 1 to 6 carbon atoms, unless indicated otherwise,

the term "alkenylene" denotes a linear or branched bivalent radical containing from 2 to 6 carbon atoms and from 1 to 3 double bonds, unless indicated otherwise,

the term "alkynylene" denotes a linear or branched bivalent radical containing from 2 to 6 carbon atoms and from 1 to 3 triple bonds, unless indicated otherwise,

the term "aryl" denotes a phenyl, naphthyl, dihydronaphthyl or tetrahydronaphthyl group, and the term "arylene" denotes a bivalent radical of the same type, the term "heteroaryl" denotes an unsaturated or partially unsaturated mono- or bi-cyclic group having from 5 to 11 ring members, containing from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulphur,

the term "alkylenecycloalkylene" represents a grouping -A_1-A_2-, the term "cycloalkylene-alkylene" represents a grouping -A_2-A_1-, and the term "alkylenecycloalkylenealkylene" represents a grouping -A_1-A_2-A_1, the term "alkylenearylene" represents a grouping -A_1-A_3-, the term "arylenealkylene" represents a grouping –A_3-A_1-, the term "alkylenearylenealkylene" represents a grouping -A_1-A_3-A_1-, wherein A_1 is an alkylene group as defined hereinbefore, A_2 is a (C_4-C_8)cycloalkylene group, and A_3 is an arylene group as defined hereinbefore,

the expression "optionally substituted" applied to the terms "aryl", "arylalkyl", "heteroaryl" and "heteroarylalkyl" indicates that those groups are substituted on their cyclic moiety by from 1 to 5 identical or different substituents selected from linear or branched (C_1-C_6)alkyl, linear or branched (C_1-C_6)alkoxy, halogen, hydroxy, perhalo-(C_1-C_6)alkyl in which the alkyl moiety is linear or branched, nitro, linear or branched (C_1-C_6)acyl, linear or branched (C_1-C_6)alkylsulphonyl, and amino (amino optionally being substituted by one or two linear or branched (C_1-C_6)alkyl and/or linear or branched (C_1-C_6)acyl groups).

2- Compounds of formula (I) according to claim 1 wherein W represents a -CO- group, their enantiomers, diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

3- Compounds of formula (I) according to claim 1 wherein W represents a –SO_2- group, their enantiomers, diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

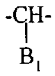
4- Compounds of formula (I) according to claim 1 wherein R represents a grouping Z_1-T-CO, T being an alkylene group or a bond, their enantiomers, diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

5- Compounds of formula (I) according to claim 1 wherein R represents a grouping Z_1-O-T-CO, T being an alkylene group or a bond, their enantiomers, diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

6- Compounds of formula (I) according to claim 1 wherein R represents a grouping Z_1-T-O-CO, T being an alkylene group or a bond, their enantiomers, diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

7- Compounds of formula (I) according to claim 1 wherein R represents a grouping Z_1-T-S(O)$_q$-, T being an alkylene group or a bond, their enantiomers, diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

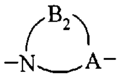
8- Compounds of formula (I) according to claim 1 wherein Z represents an optionally substituted aryl or optionally substituted heteroaryl group, their enantiomers, diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

9- Compounds of formula (I) according to claim 1 wherein A represents a grouping  $\underset{B_1}{\underset{|}{-\mathrm{CH}-}}$ wherein B_1 is an optionally substituted arylalkyl group, their enantiomers, diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

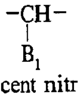
10- Compounds of formula (I) according to claim 1 wherein A represents an alkylenecycloalkylene group, their enantiomers, diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

11- Compounds of formula (I) according to claim 1 wherein A represents an alkylenearylene group, their enantiomers, diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

12- Compounds of formula (I) according to claim 1 wherein A represents a grouping



their enantiomers, diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

13- Compound of formula (I) according to claim 1 wherein W represents a -CO- group, Z represents a group selected from optionally substituted aryl and optionally substituted heteroaryl, R represents a grouping selected from Z_1-T-CO-, Z_1-O-T-CO-, Z_1-T-O-CO- and Z_1-T-S(O)$_q$- wherein Z_1 is an optionally substituted aryl or optionally substituted heteroaryl group, T represents an alkylene group, and q is 2, and A represents an alkylenecycloalkylene group, a grouping  $-\underset{B_1}{\underset{|}{C}}H-$ wherein B_1 is an optionally substituted arylalkyl group, or A forms with the adjacent nitrogen atom a pyrrolidine, perhydroindole or piperidine group, and its enantiomers, diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

14- Compound of formula (I) according to claim 1 which is N2-({4-[(2-benzoylhydrazino)-carbonyl]cyclohexyl}methyl)-2-naphthalenesulphonamide, and its enantiomers, diastereo-isomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

15- Compound of formula (I) according to claim 1 which is N1-({4-[(2-benzoylhydrazino)-carbonyl]cyclohexyl}methyl)-1-(2-nitrobenzene)sulphonamide, and its enantiomers, diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

16- Compound of formula (I) according to claim 1 which is N1-[1-benzyl-2-oxo-2-(2-phenylhydrazino)ethyl]-1-(4-chlorobenzene)sulphonamide, and addition salts thereof with a pharmaceutically acceptable acid or base.

17- Process for the preparation of compounds of formula (I) characterised in that there is used as starting material a compound of formula (II) :

$$H_2N - A - COOH \qquad (II)$$

wherein A is as defined for formula (I), which is condensed in a basic medium with a halogen compound of formula (III) :

$$R - Cl \qquad (III)$$

wherein R is as defined for formula (I),

to yield a compound of formula (IV) :

$$R - NH - A - COOH \qquad (IV)$$

wherein R and A are as defined hereinbefore,

which compound (IV) is condensed, in the presence of a coupling agent, with a monosubstituted hydrazine of formula (V),

$$H_2N - NH - (W)_n - Z \qquad (V)$$

wherein n, W and Z are as defined for formula (I),

to yield compounds of formula (I) :

$$R - NH - A - CO - NH - NH - (W)_n - Z \qquad (I)$$

wherein R, A, n, W and Z are as defined hereinbefore,

which compound of formula (I) :

may be purified, if necessary, according to a conventional purification technique,

is separated, where appropriate, into its isomers according to a conventional separation technique,

is converted, if desired, into an addition salt thereof with a pharmaceutically acceptable acid or base.

18. Pharmaceutical compositions comprising as active ingredient at least one compound according to any one of claims 1 to 16, on its own or in combination with one or more inert, non-toxic pharmaceutically acceptable excipients or carriers.

19. Pharmaceutical compositions according to claim 18 comprising at least one active ingredient according to any one of claims 1 to 16 for use as a neuropeptide Y receptor ligand in the treatment of pathologies associated with eating behaviour disorders or energy balance disorders, selected from diabetes, obesity, bulimia, anorexia nervosa, or in the treatment of arterial hypertension, anxiety, depression, epilepsy, sexual dysfunctions and sleep disorders.

20. A method of treatment of the pathologies associated with eating behaviour disorders or energy balance disorders, selected from diabetes, obesity, bulimia, anorexia nervosa or in the treatment of arterial hypertension, anxiety, depression, epilepsy, sexual dysfunctions and sleep disorders comprising administration of a neuropeptide Y receptor ligand according to any one of claims 1 to 16 to a mammal in need of such treatment.

DATED this 22nd day of April 2003
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