

NEW THIADIAZOLES AND OXADIAZOLES AND THEIR USE AS
PHOSPHODIESTERASE-7 INHIBITORS

5 Field of the invention.

The invention relates to novel thiadiazoles and oxadiazoles, processes for their preparation, and their use as phosphodiesterase 7 (PDE7) inhibitors.

10 Background of the invention.

Phosphodiesterases (PDE) play an important role in various biological processes by hydrolysing the key second messengers adenosine and , guanosine 3',5'-cyclic monophosphates (cAMP and cGMP respectively) into their
15 corresponding 5'-monophosphate nucleotides. Therefore, inhibition of PDE activity produces an increase of cAMP and cGMP intracellular levels that activate specific protein phosphorylation pathways involved in a variety of functional responses.

20 At least eleven isoenzymes of mammalian cyclic nucleotide phosphodiesterases, numbered PDE 1 through PDE 11, have been identified on the basis of primary structure, substrate specificity or sensitivity to cofactors or inhibitory drugs.

25 Among these phosphodiesterases, PDE7 is a cAMP-specific PDE. The biochemical and pharmacological characterisation showed a high-affinity cAMP-specific PDE ($K_m=0.2 \mu M$), that was not affected by cGMP potent selective PDE isoenzyme inhibitors.

30 PDE7 activity or protein has been detected in T-cell lines, B-cell lines, airway epithelial (AE) cell lines and several foetal tissues.

Increasing cAMP levels by selective PDE7 inhibition appears to be a potentially promising approach to
35 specifically block T-cell mediated immune responses. Further studies have demonstrated that elevation of intracellular cAMP levels can modulate inflammatory and immunological processes. This selective approach could presumably be devoid



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of the side effects associated with known selective inhibitors (e.g. PDE3 or PDE4 selective inhibitors) and which limit their use.

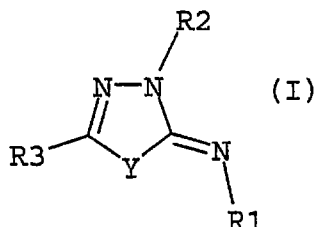
A functional role of PDE7 in T-cell activation has also been disclosed; therefore selective PDE7 inhibitors would be candidates for the treatment of T-cell-related diseases.

AE cells actively participate in inflammatory airway diseases by liberating mediators such as arachidonate metabolites and cytokines. Selective inhibition of PDE7 may be a useful anti-inflammatory approach for treating AE cells related diseases.

Thus, there is a need for selective PDE7 inhibitors, which are active at very low concentrations, i.e. micromolar inhibitor, preferably nanomolar inhibitors.

Summary of the invention.

The invention provides pharmaceutical compositions comprising a compound having the following formula (I):



wherein:

- Y is O or S;

- R1 is:

C₁-C₁₀ alkyl,

C₂-C₁₀ alkenyl,

C₂-C₁₀ alkynyl,

cycloalkyl,

cycloalkenyl,

heterocycle,

aryl,

or a polycyclic group;

each optionally substituted with one or several groups X₁-R₄,

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identical or different, in which:

- X_1 is:

a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene or divalent heterocycle, and,

- R_4 is:

1) H, =O, NO_2 , CN, halogen, lower haloalkyl, lower alkyl, carboxylic acid bioisostere,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5 , SOR_5 , SO_3R_5 , SR_5 , OR_5 ,

3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from OH, R_5 , R_6 , $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5 , $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ or $C(=S)NR_9R_{10}$;

- R_2 is:

lower alkyl,
 C_2-C_{10} alkenyl,
 C_2-C_{10} alkynyl,
cycloalkyl,
cycloalkenyl,
heterocycle,
aryl;

each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,

2) $COOR_5$, OR_5 , SO_2R_5 ,

3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ or $NR_{11}R_{12}$ in which R_{11} and R_{12} are the same or different and are selected from OH, R_5 , R_6 , $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5 , $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R_3 is $X_2-R'_3$ wherein:

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- X_2 is a single bond or,
a group selected from C_1-C_4 alkylene, C_2-C_6
alkenylene, C_2-C_6 alkynylene, each optionally
substituted with one or several groups which are
the same or different and which are selected from:

1) H, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, aryl,
heterocycle, =O, CN,

2) OR_5 , $=NR_5$ or,

3) $NR_{13}R_{14}$ in which R_{13} and R_{14} are the same or
different and are selected from R_5 , R_6 , $C(=O)NR_5R_6$,
 $C(=O)R_5$, SO_2R_5 , $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$,
 $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R'_3 is:

cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17} ,
identical or different, in which:

- X_3 is:

a single bond, lower alkylene, C_2-C_6 alkenylene,
 C_2-C_6 alkynylene, cycloalkylene, arylene, divalent
heterocycle or a divalent polycyclic group, and,

- R_{17} is:

1) H, =O, NO_2 , CN, lower haloalkyl, halogen,
carboxylic acid bioisostere, cycloalkyl,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5 , SOR_5 , SO_3R_5 , SR_5 ,
 OR_5 ,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-
SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$,
 $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$
or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or
different and are selected from OH, R_5 , R_6 ,
 $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5 , $C(=S)NR_9R_{10}$, $C(=CH-
NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$,
 $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,

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4) heterocycle optionally substituted with one or several groups R_5 ;

wherein,

5 - R_5 and R_6 are the same or different and are selected from :

- H,

- lower alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl;

10 - X_4 -cycloalkyl, X_4 -cycloalkenyl, X_4 -aryl, X_4 -heterocycle or X_4 -polycyclic group, in which X_4 is a single bond, lower alkylene or C_2 - C_6 alkenylene;

each optionally substituted with one or several groups which are the same or different and which are selected from:

15 - halogen, =O, $COOR_{20}$, CN, OR_{20} , lower alkyl optionally substituted with OR_{20} , O-lower alkyl optionally substituted with OR_{20} , $C(=O)$ -lower alkyl, lower haloalkyl, X_5-N-R_{18} in which X_5 is a single
 R_{19}

20 bond or lower alkylene and R_{18} , R_{19} and R_{20} are the same or different and are selected from H or lower alkyl;

25 - X_6 -heterocycle, X_6 -aryl, X_6 -cycloalkyl, X_6 -cycloalkenyl, X_6 -polycyclic group in which X_6 is selected from a single bond or lower alkylene, these groups being optionally substituted with one or several groups, identical or different, selected from halogens, $COOR_{21}$, OR_{21} , or $(CH_2)_nNR_{21}R_{22}$ in which n is 0, 1 or 2 and R_{21} and R_{22} are the same or different and
 30 are selected from H or lower alkyl;

- R_9 is selected from H, CN, OH, lower alkyl, O-lower alkyl, aryl, heterocycle, SO_2NH_2 or X_5-N-R_{18} in which X_5 is a
 R_{19}

35 single bond or lower alkylene and R_{18} and R_{19} are the same or different and are selected from H or lower alkyl;

- R_{10} is selected from hydrogen, lower alkyl, cyclopropyl or heterocycle;

or a pharmaceutically acceptable derivative thereof,

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together with a pharmaceutically acceptable carrier,
with the proviso that the compound of formula (I) is not 4-
[2-Formylimino-5-(4-methoxy-phenyl)-[1,3,4] thiadiazol-3-yl]-
butyric acid ethyl ester,
5 4-[5-(4-Chloro-phenyl)-2-formylimino-[1,3,4]thiadiazol-3-yl]-
butyric acid ethyl ester.

The invention also relates to novel compounds having the
following formula (I) above.

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These compounds are selective PDE7 inhibitors. They can
be used in the treatment of various diseases, such as T-cell-
related diseases, autoimmune diseases, inflammatory diseases,
respiratory diseases, central nervous system (CNS) diseases,
15 allergic diseases, endocrine or exocrine pancreas diseases,
gastrointestinal diseases, visceral pain, inflammatory bowel
disease, osteoarthritis, multiple sclerosis, chronic
obstructive pulmonary disease (COPD), asthma, cancer,
acquired immune deficiency syndrome (AIDS) or graft
20 rejection.

The invention also relates to a process for preparing
the above compounds.

The invention further concerns the use of a compound of
formula (I) for the preparation of a medicament for the
25 prevention or the treatment of disorders for which therapy by
a PDE7 inhibitor is relevant.

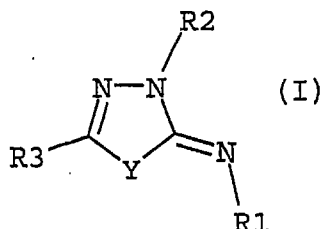
The invention also provides a method for the treatment
of a disorder for which therapy by a PDE7 inhibitor is
relevant, comprising administering to a mammal in need
30 thereof an effective amount of compound of formula (I).

The invention also concerns a pharmaceutical composition
comprising a compound of formula (I) together with a
pharmaceutically acceptable carrier.

The invention also relates to a pharmaceutical
35 composition for the treatment of a disorder for which therapy
by a PDE7 inhibitor is relevant, comprising a compound of
formula (I) together with a pharmaceutically acceptable
carrier.

Detailed description of the invention.

The present invention provides pharmaceutical compositions comprising compounds having formula I,



5 in which R1, R2, R3 and Y are as defined above with the exclusion of the compounds recited above.

In the following and in the foregoing text:

- aryl is understood to refer to an unsaturated carbocycle, exclusively comprising carbon atoms in the cyclic structure, the number of which is between 5 and 10, including phenyl, naphthyl or tetrahydronaphthyl;

- heterocycle is understood to refer to a non-saturated or saturated monocycle containing between 1 and 7 carbon atoms in the cyclic structure and at least one heteroatom in the cyclic structure, such as nitrogen, oxygen, or sulfur, preferably from 1 to 4 heteroatoms, identical or different, selected from nitrogen, sulfur and oxygen atoms. Suitable heterocycles include morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, pyrimidinyl, 2- and 3-furanyl, 2- and 3-thienyl, 2-pyridyl, 2- and 3-pyranyl, hydroxypyridyl, pyrazolyl, isoxazolyl, tetrazole, imidazole, triazole and the like;

- polycyclic groups include at least two cycles, identical or different, selected from aryl, heterocycle, cycloalkyl, cycloalkenyl groups fused together to form said polycyclic group such as 2- and 3-benzothienyl, 2- and 3-benzofuranyl, 2-indolyl, 2- and 3-quinolinyl, acridinyl, quinazolinyl, indolyl benzo[1,3]dioxolyl and 9-thioxantanyl; Preferred polycyclic groups include 2 or 3 cycles as defined above.

More preferred polycyclic groups include 2 cycles (bicyclic substituents) as defined above.

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- bicyclic groups refer to two cycles, which are the same or different and which are chosen from aryl, heterocycle, cycloalkyl or cycloalkenyl, fused together to form said bicyclic groups;

5 - halogen is understood to refer to fluorine, chlorine, bromine or iodine;

 - lower alkyl is understood to mean that the alkyl is linear or branched and contains 1 to 6 carbon atoms; Examples of lower alkyl groups include methyl, ethyl, propyl, butyl, 10 isopropyl, tert-butyl, isobutyl, n-butyl, pentyl, hexyl and the like.

 - alkenyl is understood to refer to a linear or branched unsaturated carbon atom chain, comprising one or several double bonds, preferably one or two double bonds. Preferred 15 alkenyls comprise from 3 to 6 carbon atoms and one double bonds.

 - alkynyl is understood to refer to a linear or branched unsaturated carbon atom chain, comprising one or several triple bonds, preferably one or two triple bonds. Preferred 20 alkynyls comprise from 3 to 6 carbon atoms and one triple bonds.

 - lower haloalkyl are understood to refer to a lower alkyl substituted with one or several halogens; Preferred lower haloalkyl groups include perhaloalkyl groups such as 25 CF₃.

 - cycloalkyl is understood to refer to saturated monocarbocycle containing from 3 to 10 carbon atoms; preferred cycloalkyl groups comprise cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

30 - cycloalkenyl is understood to refer to unsaturated monocarbocycle containing from 3 to 10 carbon atoms. Preferred cycloalkenyl groups contain 1 or 2 double bonds. Examples of suitable cycloalkenyl are 3-cyclohexene, 3-cycloheptene or the like.

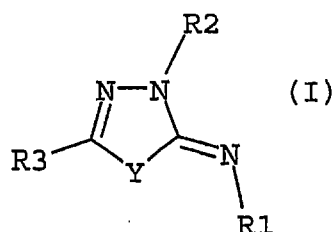
35 - carboxylic acid bioisostere has the classical meaning; common carboxylic acid bioisostere are tetrazol, hydroxamic acid, isoxazole, hydroxythiadiazole, sulfonamide, sulfonylcarboxamide, phosphonates, phosphonamides,

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phosphinates, sulfonates, acyl sulfonamide, mercaptoazole, acyl cyanamides.

Preferred pharmaceutical composition are those
 5 containing a compound of formula (I) in which R1, R2, R3 and Y are as defined above, with the proviso that when R1 is C(=O)-H, then R2 does not represent (CH₂)₃-C(=O)OCH₂CH₃.

The present invention also relates to compounds of formula
 10 (I),



in which

- Y is O or S;

- R1 is:

- 15 C₄-C₁₀ alkyl,
 C₂-C₁₀ alkenyl,
 C₂-C₁₀ alkynyl,
 cycloalkyl,
 cycloalkenyl,
 20 heterocycle,
 aryl,
 or a bicyclic group;

each optionally substituted with one or several groups X₁-R₄, identical or different, in which:

25 - X₁ is:

a single bond, lower alkylene, C₂-C₆ alkenylene, cycloalkylene, arylene or divalent heterocycle, and,

- R₄ is:

- 30 1) H, =O, NO₂, CN, halogen, lower haloalkyl, lower alkyl, carboxylic acid bioisostere,
 2) COOR₅, C(=O)R₅, C(=S)R₅, SO₂R₅, SOR₅, SO₃R₅, SR₅,

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OR₅,

3) C(=O)NR₇R₈, C(=S)NR₇R₈, C(=CH-NO₂)NR₇R₈, C(=N-CN)NR₇R₈, C(=N-SO₂NH₂)NR₇R₈, C(=NR₇)NHR₈, C(=NR₇)R₈, C(=NR₉)NHR₈, C(=NR₉)R₈, SO₂NR₇R₈ or NR₇R₈ in which
 5 R₇ and R₈ are the same or different and are selected from OH, R₅, R₆, C(=O)NR₅R₆, C(=O)R₅, SO₂R₅, C(=NR₉)NHR₁₀, C(=NR₉)R₁₀, C(=CH-NO₂)NR₉R₁₀, C(=N-SO₂NH₂)NR₉R₁₀, C(=N-CN)NR₉R₁₀ or C(=S)NR₉R₁₀;

10 - R₂ is:

lower alkyl,
 C₂-C₁₀ alkenyl,
 C₄-C₁₀ alkynyl,
 cycloalkyl,
 15 cycloalkenyl,
 heterocycle,
 aryl;

each optionally substituted with one or several groups which are the same or different and which are selected from:

20 1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,
 2) COOR₅, OR₅, SO₂R₅,
 3) SO₂NR₁₁R₁₂, C(=O)NR₁₁R₁₂ or NR₁₁R₁₂ in which R₁₁ and R₁₂ are the same or different and are selected
 25 from OH, R₅, R₆, C(=O)NR₅R₆, C(=O)R₅, SO₂R₅, C(=S)NR₉R₁₀, C(=CH-NO₂)NR₉R₁₀, C(=N-CN)NR₉R₁₀, C(=N-SO₂NH₂)NR₉R₁₀, C(=NR₉)NHR₁₀ or C(=NR₉)R₁₀;

- R₃ is X₂-R'₃ wherein:

30 - X₂ is a single bond or,
 a group selected from C₁-C₄ alkylene, C₂-C₆ alkenylene, C₂-C₆ alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:
 35 1) H, C₁-C₃ alkyl, C₃-C₄ cycloalkyl, aryl, heterocycle, =O, CN,
 2) OR₅, =NR₅ or,
 3) NR₁₃R₁₄ in which R₁₃ and R₁₄ are the same or

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different and are selected from R_5 , R_6 , $C(=O)NR_5R_6$,
 $C(=O)R_5$, SO_2R_5 , $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$,
 $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

5 - R'_3 is:

cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,

10 or a polycyclic group;

each optionally substituted with one or several groups X_3 - R_{17} ,
identical or different, in which:

- X_3 is:

15 a single bond, lower alkylene, C_2 - C_6 alkenylene,
 C_2 - C_6 alkynylene, cycloalkylene, arylene, divalent
heterocycle or a divalent polycyclic group, and,

- R_{17} is:

- 1) H, =O, NO_2 , CN, lower haloalkyl, halogen,
cycloalkyl,
- 20 2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5 , SOR_5 , SO_3R_5 , SR_5 ,
 OR_5 ,
- 3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-$
 $SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$,
 $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$
25 or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or
different and are selected from OH, R_5 , R_6 ,
 $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5 , $C(=S)NR_9R_{10}$, $C(=CH-$
 $NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$,
 $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;
- 30 4) heterocycle optionally substituted with one or
several groups R_5 ;

wherein, R_5 , R_6 , R_9 and R_{10} are as defined above,

with the proviso that,

35 - when R_1 is phenyl, it bears at least one substituent
other than H,

- when X_2 is a single bond and both R_1 and R'_3 are
phenyl, each of R_1 and R'_3 bear at least one substituent
other than H,

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- when X_2 is a single bond and R'_3 is phenyl, R'_3 is not substituted by an ester or a carboxylic acid in the ortho position,

- the atom of R_3 which is linked to the thiadiazole group is a carbon atom,
- with the exclusion of the following compounds,
- 1-Phenyl-1-[4-phenyl-5-(5-trifluoromethyl-2H-[1,2,4]triazol-3-ylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-methanone,
 - 1-[4-Phenyl-5-(5-trifluoromethyl-2H-[1,2,4]triazol-3-ylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-1-thiophen-2-yl-methanone,
 - 1-Phenyl-1-(4-phenyl-5-p-tolylimino-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-methanone,
 - Cyclohexyl-[3-(2,4,6-trichloro-phenyl)-5-(2,3,3-trimethylcyclopent-1-enylmethyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
 - 2-(3,5-Diphenyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-1,4-diphenyl-but-2-ene-1,4-dione,
 - 2-[3-Phenyl-5-(1-phenyl-methanoyl)-3H-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester,
 - 2-[5-(1-Phenyl-methanoyl)-3-p-tolyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester, and,
 - 2-[3-(4-Chloro-phenyl)-5-(1-phenyl-methanoyl)-3H-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester.

Preferred compounds of formula (I) are those in which R_1 , R_2 , R_3 and Y are as defined above, with the proviso that, when R_2 is a phenyl, unsubstituted or substituted with 1 to 3 chlorine or with a methyl, then R_3 does not represent $C(=O)$ -phenyl, $C(=O)$ -thienyl, phenyl or CH_2 -(2,3,3-trimethylcyclopent-1-enyl).

Other preferred compounds of formula (I) are those in which

- R_1 is:

- C_4 - C_6 alkyl,
- cycloalkyl,
- cycloalkenyl,

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heterocycle,

aryl,

or a bicyclic group;

each optionally substituted with one or several groups X_1 - R_4 ,

5 identical or different, in which:

- X_1 is a single bond, a divalent heterocycle or a lower alkylene, and,

- R_4 is selected from:

10 1) H, =O, halogen, CN, lower haloalkyl, preferably CF_3 , lower alkyl, carboxylic acid bioisostere,

2) $COOR_5$, SO_2R_5 , OR_5 , $C(=O)R_5$

3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from R_5 , R_6 , $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5 , $C(=NR_9)NHR_{10}$,

15 $C(=NR_9)R_{10}$ or $C(=S)NR_9R_{10}$.

Other preferred compounds of formula (I) are those in which R_2 is lower alkyl.

20 Further preferred compounds of formula (I) are those in which R_3 is X_2 - R'_3 wherein,

- X_2 is a single bond, C_1 - C_4 alkylene, C_2 - C_6 alkenylene or C_2 - C_6 alkynylene and,

- R'_3 is:

25 cycloalkyl,

cycloalkenyl,

aryl,

heterocycle,

or a polycyclic group;

30 each optionally substituted with one or several groups X_3 - R_{17} , identical or different, in which:

- X_3 is a single bond or lower alkylene, and,

- R_{17} is:

35 1) H, =O, NO_2 , CN, lower haloalkyl, halogen, cycloalkyl,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5 , SOR_5 , SO_3R_5 , SR_5 , OR_5 ,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$,

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$C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$,
 $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in
 which R_{15} and R_{16} are the same or different and are
 selected from OH, R_5 , R_6 , $C(=O)NR_5R_6$, $C(=O)R_5$,
 SO_2R_5 , $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$,
 $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,
 4) heterocycle optionally substituted with one or
 several groups R_5 .

10 Particularly preferred compounds of formula (I) are those in
 which R_1 is:

cycloalkyl, preferably cyclohexane,
 cycloalkenyl,
 aryl, preferably phenyl,
 15 or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4 ,
 identical or different, in which:

- X_1 is a single bond or a divalent heterocycle,
 and,
- 20 - R_4 is selected from:
 - 1) H, halogen, CF_3 , $=O$,
 - 2) $COOR_5$, OR_5 ,
 - 3) $C(=O)NR_5R_6$.

25 Other particularly preferred compounds of formula (I) are
 those in which R_2 is CH_3 .

Further particularly preferred compounds of formula (I) are
 those in which R_3 is $X_2-R'_3$ wherein,

- 30 - X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6
 alkenylene, and,
- R'_3 is:

cycloalkyl,
 aryl, preferably phenyl,
 35 heterocycle,
 or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17} ,
 identical or different, in which:

15

- X_3 is a single bond or $-\text{CH}_2-$, and,
- R_{17} is:
 - 1) H, CN, CF_3 , halogen, NO_2 ,
 - 2) COOR_5 , SO_2R_5 , OR_5 , $\text{C}(=\text{O})\text{R}_5$,
 - 5 3) $\text{C}(=\text{O})\text{NR}_{15}\text{R}_{16}$, $\text{SO}_2\text{NR}_{15}\text{R}_{16}$ or $\text{NR}_{15}\text{R}_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5 , R_6 , $\text{C}(=\text{O})\text{NR}_5\text{R}_6$, $\text{C}(=\text{O})\text{R}_5$, SO_2R_5 , $\text{C}(=\text{S})\text{NR}_9\text{R}_{10}$, $\text{C}(=\text{CH}-\text{NO}_2)\text{NR}_9\text{R}_{10}$, $\text{C}(=\text{NR}_9)\text{NHR}_{10}$, $\text{C}(=\text{NR}_9)\text{R}_{10}$ or $\text{C}(=\text{N}-\text{CN})\text{NR}_9\text{R}_{10}$,
 - 10 4) heterocycle optionally substituted with one or several groups R_5 .

More preferred compounds of formula (I) are those in which

- R_1 is:

15 C_4 - C_6 alkyl
cycloalkyl,
cycloalkenyl,
heterocycle,
aryl,

20 or a bicyclic group;

each optionally substituted with one or several groups X_1 - R_4 , identical or different, in which:

- X_1 is a single bond a divalent heterocycle or a lower alkylene, and,

25 - R_4 is selected from:

- 1) H, $=\text{O}$, halogen, CN, lower haloalkyl, preferably CF_3 , lower alkyl, carboxylic acid bioisostere,
- 2) COOR_5 , SO_2R_5 , OR_5 , $\text{C}(=\text{O})\text{R}_5$
- 3) $\text{C}(=\text{O})\text{NR}_7\text{R}_8$, $\text{SO}_2\text{NR}_7\text{R}_8$ or NR_7R_8 in which R_7 and R_8
- 30 are the same or different and are selected from R_5 , R_6 , $\text{C}(=\text{O})\text{NR}_5\text{R}_6$, $\text{C}(=\text{O})\text{R}_5$, SO_2R_5 , $\text{C}(=\text{NR}_9)\text{NHR}_{10}$, $\text{C}(=\text{NR}_9)\text{R}_{10}$ or $\text{C}(=\text{S})\text{NR}_9\text{R}_{10}$,

R_2 is lower alkyl, and,

35

R_3 is X_2 - R'_3 wherein,

- X_2 is a single bond, C_1 - C_4 alkylene, C_2 - C_6 alkenylene or C_2 - C_6 alkynylene and,

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- R'₃ is:

cycloalkyl,
cycloalkenyl,
aryl,

5 heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X₃-R₁₇,
identical or different, in which:

- X₃ is a single bond or lower alkylene, and,

10 - R₁₇ is:

1) H, =O, NO₂, CN, lower haloalkyl, halogen,
cycloalkyl,

2) COOR₅, C(=O)R₅, C(=S)R₅, SO₂R₅, SOR₅, SO₃R₅, SR₅,
OR₅,

15 3) C(=O)NR₁₅R₁₆, C(=S)NR₁₅R₁₆, C(=N-CN)NR₁₅R₁₆,
C(=CH-NO₂)NR₁₅R₁₆, SO₂NR₁₅R₁₆, C(=NR₁₅)NHR₁₆,
C(=NR₁₅)R₁₆, C(=NR₉)NHR₁₆, C(=NR₉)R₁₆ or NR₁₅R₁₆ in
which R₁₅ and R₁₆ are the same or different and are
selected from OH, R₅, R₆, C(=O)NR₅R₆, C(=O)R₅,
20 SO₂R₅, C(=S)NR₉R₁₀, C(=CH-NO₂)NR₉R₁₀, C(=N-CN)NR₉R₁₀,
C(=NR₉)NHR₁₀ or C(=NR₉)R₁₀,

4) heterocycle optionally substituted with one or
several groups R₅.

25 Other more preferred compounds of formula (I) are those in
which,

R₁ is:

cycloalkyl, preferably cyclohexane,
cycloalkenyl,

30 aryl, preferably phenyl,
or a bicyclic group;

each optionally substituted with one or several groups X₁-R₄,
identical or different, in which:

- X₁ is a single bond or a divalent heterocycle,
35 and,

- R₄ is selected from:

1) H, halogen, CF₃, =O,

2) COOR₅, OR₅,

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3) $C(=O)NR_5R_6$,

R2 is CH_3 , and,

5 R3 is $X_2-R'_3$ wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,

- R'3 is:

cycloalkyl,

10 aryl, preferably phenyl

heterocycle,

or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17} , identical or different, in which:

15 - X_3 is a single bond or $-CH_2-$, and,

- R_{17} is:

1) H, CN, CF_3 , halogen, NO_2

2) $COOR_5$, SO_2R_5 , OR_5 , $C(=O)R_5$

20 3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5 , R_6 , $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5 , $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=N-CN)NR_9R_{10}$,

25 4) heterocycle optionally substituted with one or several groups R_5 .

Other more preferred compounds of formula (I) are those in which,

Y is O,

30 R1 is:

cycloalkyl, preferably cyclohexane,

cycloalkenyl,

aryl, preferably phenyl,

or a bicyclic group;

35 each optionally substituted with one or several groups X_1-R_4 , identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,

18

- R_4 is selected from:

- 1) H, halogen, CF_3 , $=O$,
- 2) $COOR_5$, OR_5 ,
- 3) $C(=O)NR_5R_6$,

5

R_2 is CH_3 , and,

R_3 is $X_2-R'_3$ wherein,

10 - X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,

 - R'_3 is:

cycloalkyl,

aryl, preferably phenyl

heterocycle,

15 or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17} , identical or different, in which:

 - X_3 is a single bond or $-CH_2-$, and,

 - R_{17} is:

20

1) H, CN, CF_3 , halogen, NO_2

2) $COOR_5$, SO_2R_5 , OR_5 , $C(=O)R_5$

3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5 , R_6 , $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5 ,

25

$C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$,

$C(=NR_9)R_{10}$ or $C(=N-CN)NR_9R_{10}$,

4) heterocycle optionally substituted with one or several groups R_5 .

30 More specifically, a group of compounds of formula (I) which has been found to be of particular interest are those in which,

R_1 is:

cyclohexane,

35

phenyl

or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4 , identical or different, in which:

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- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:
 - 1) H, halogen, CF_3 ,
 - 2) $COOH$, OH ,
 - 3) $C(=O)NR_7R_8$ in which R_7 and R_8 are the same or different and are selected from H or lower alkyl,

R_2 is CH_3 , and,

R_3 is $X_2-R'_3$ wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'_3 is:

phenyl
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17} , identical or different, in which:

- X_3 is a single bond, and,
- R_{17} is:
 - 1) CN , OH , CF_3 , $=O$, C_1-C_6 alkoxy, halogen,
 - 2) $COOR_5$, SO_2R_5 ,
 - 3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH , $C(=O)R_5$, $C(=O)NR_5R_6$, R_5 or R_6 ,
 - 4) heterocycle optionally substituted with one or several groups R_5 .

Most preferred compounds of formula (I) are those in which Y is S.

Preferably, in each of the above definition of R_1 :

- R_5 is selected from
 - H, or,
 - lower alkyl, optionally substituted with OH , preferably CH_3 .
- R_6 is selected from

20

- H, or,
- lower alkyl, preferably CH₃.
- R₉ and R₁₀ are selected from
 - H, or,
 - 5 - lower alkyl, preferably CH₃.

Preferably, in each of the above definition of R₂:

- R₅ and R₆ are selected from
 - H, or,
 - 10 - lower alkyl, preferably CH₃.
- R₉ and R₁₀ are selected from:
 - H, or,
 - lower alkyl, preferably CH₃.

15 Preferred compounds are:

- I1 3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
- I1.1 (1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid
- I1.2 (S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-phenyl-ethanol
- I1.7 2-{2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-ethanol
- I1.9 {1-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclopentyl}-methanol
- I1,10 3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid
- I2.1 5-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid
- I2.2 3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2,5,6-trifluoro-benzoic acid
- I3 [5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-propyl-amine
- I3.1 (S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol

- I3.3 [5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclobutyl-amine
- I3.4 3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-azepan-2-one
- I3.7 [5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclopentyl-amine
- I3.8 [5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cycloheptyl-amine
- I3.10 (S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-3-methyl-butan-1-ol
- I3.11 2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-methyl-propan-1-ol
- I3.13 tert-Butyl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
- I3.14 [5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-isopropyl-amine
- I3.15 4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
- I3.16 [5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(1-ethyl-propyl)-amine
- I3.17 4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol
- I3.18 N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,2-diamine
- I3.19 [5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-fluoro-phenyl)-amine
- I3.20 N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,4-diamine
- I3.25 (1R*, 2S*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol
- I3.26 [5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-trifluoromethyl-phenyl)-amine
- I4 3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
- I5 3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol

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- I6 5-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid
- I6.1 (1-Aza-bicyclo[2.2.2]oct-3-yl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
- I6.3 2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol
- I6.5 (R)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol
- I6.7 [5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3-fluoro-phenyl)-amine
- I6.8 (3-Chloro-phenyl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
- I6.9 {3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-acetic acid
- I6.11 3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzamide
- I7 Bicyclo[2.2.1]hept-2-yl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
- I8 (1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol
- I8.1 5-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-2-methoxy-phenol
- I8.2 3-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-benzoic acid
- I8.3 3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-4-hydroxy-benzoic acid
- I8.4 (5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-(3-methanesulfonyl-phenyl)-amine
- I9 (1R*, 2R*)-2-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol
- I10 Cyclohexyl-[5-(2,4-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
- I10.1 [5-(2-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

- I11 Cyclohexyl-[3-methyl-5-(4-trifluoromethyl-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine
- I12 Cyclohexyl-(3-methyl-5-pyridin-4-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine
- I13 [5-(3-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine
- I14 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile
- I15 Cyclohexyl-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
- I15.1 [3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine
- I15.2 Cyclohexyl-[5-(3-methoxy-4-nitro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
- I16 2,4-Dichloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide
- I17 Cyclohexyl-(3-methyl-5-thiophen-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine
- I17.1 Cyclohexyl-[5-(3,5-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
- I17.2 Cyclohexyl-[5-(2-ethyl-5-methyl-2H-pyrazol-3-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
- I18 [5-(3-Chloro-2,6-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine
- I18.1 Cyclohexyl-(5-isoxazol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine
- I18.2 Cyclohexyl-[3-methyl-5-(5-pyridin-2-yl-thiophen-2-yl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine
- I18.3 5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2-methoxy-benzene-1,3-diol; compound with trifluoro-methanesulfonic acid
- I18.4 5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2,3-dimethoxy-phenol; compound with trifluoro-methanesulfonic acid
- I18.5 [5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

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- I18.6 2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-6-methoxy-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid
- I19 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide
- I19.1 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide
- I19.2 {5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine
- I19.3 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide
- I19.4 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide
- I19.5 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide
- I19.6 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide
- I19.7 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide
- I19.8 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide
- I19.9 C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-ethyl-benzenesulfonamide
- I19.10 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-benzenesulfonamide
- I19.11 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzenesulfonamide

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- I19.12 2-Chloro-5-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-diethylamino-ethyl)-N-ethyl-benzenesulfonamide
- I19.14 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-propyl)-N-ethyl-benzenesulfonamide
- I20 [5-(4-Chloro-phenyl)-2-cyclohexylimino-[1,3,4]thiadiazol-3-yl]-acetic acid methyl ester
- I21 3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester
- I21.1 3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid
- I21.2 3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide
- I21.3 3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-hydroxy-ethyl)-benzamide
- I21.4 3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide
- I22 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2-diol
- I23 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,6-dimethoxy-phenol
- I23.1 6-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-pyridin-2-ol
- I23.2 5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2,3-triol
- I24 2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinolin-8-ol
- I25 Cyclohexyl-(3-methyl-5-pyrazin-2-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine
- I26 5-[(E)-2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-vinyl]-2-methoxy-phenol
- I27 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol
- I28 Cyclohexyl-(3-methyl-5-quinolin-8-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

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- I29 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine
- I30 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide
- I31 [5-(5-Chloro-1H-indol-2-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine; compound with trifluoro-methanesulfonic acid
- I31.1 2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid
- I32 5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid
- I33 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid
- I34 Cyclohexyl-[5-(3,4-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
- I35 [5-(3-Bromo-4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine
- I35.1 Cyclohexyl-[5-(4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
- I35.2 Cyclohexyl-(3-methyl-5-phenyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine
- I36 3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol
- I37 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester
- I37.1 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid
- I37.2 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-hydroxy-benzamide
- I37.3 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide
- I37.4 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2H-tetrazol-5-yl)-benzamide hydrochloride salt

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- I37.5 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide
- I37.6 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2,6-dimethoxy-pyridin-3-yl)-benzamide
- I37.7 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide
- I37.8 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-ethyl-benzamide
- I37.8-1 Cyclohexyl-{5-[4-(1-ethyl-1H-tetrazol-5-yl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-amine
- I37.9 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-benzamide
- I37.10 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzamide
- I37.11 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide
- I37.12 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-isobutyl-benzamide
- I37.13 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide
- I37.13-1 4-(Cyclohexylimino-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-N-methyl-benzamide
- I37.14 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-phenyl]-1-(3-hydroxymethyl-piperidin-1-yl)-methanone
- I37.15 2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid tert-butyl ester,
- I37.15-a (S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid; compound with 2,2,2-trifluoro-acetic acid,

- I37.16 (S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid tert-butyl ester,
- I37.16-a (S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid; compound with 2,2,2-trifluoro-acetic acid
- I37.17 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyridin-2-yl-piperazin-1-yl)-methanone
- I37.18 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-[4-(4-fluorophenyl)-piperazin-1-yl]-methanone
- I37.19 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(3,4,5-trimethoxy-benzyl)-benzamide
- I37.20 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone,
- I37.21 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-methyl-piperazin-1-yl)-methanone
- I37.22 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzamide
- I37.23 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(1-ethyl-pyrrolidin-2-ylmethyl)-benzamide
- I37.24 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-3-ylmethylbenzamide
- I37.25 N-Benzyl-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide
- I37.26 N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide
- I37.27 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide

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- I37.28 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide
- I37.28-1 [5-(4-((N-cyano-N'-ethylmorpholine)-carboximidamide)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine
- I37.29 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide
- I38 Cyclohexyl-(3-methyl-5-pyridin-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine
- I39 3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide
- I40 (5-Benzo[1,3]dioxol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-cyclohexyl-amine
- I41 Cyclohexyl-[3-methyl-5-(3,4,5-trimethoxy-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine
- I42 4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile
- I43 4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile
- I44 4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
- I45 4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
- I46 5-[5-(4-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid
- I47-a 4-[4-Methyl-5-(cis-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
- I47-b 4-[4-Methyl-5-(trans-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
- I48 4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
- I49 4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

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- I50 4-[5-((1R*, 2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
- I51 4-[5-((1R*, 2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
- I52-a 4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
- I52-b 4-[5-((1R*, 3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
- I53 ((1R*, 3R*)) -3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol
- I54 4-[5-(1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid
- I55 4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide
- I56 4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid
- I57 4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide
- I58 4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide
- I59 N-tert-Butyl-4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
- I60 N-(1,1-dimethyl-3-oxo-butyl)-4-[5-(1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
- I61 N-(2-Cyano-1,2,2-trimethyl-ethyl)-4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

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- I62 1-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoylamino}-cyclopropanecarboxylic acid methyl ester
- I63 4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide
- I64 4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide
- I65 4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
- I66 4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
- I67 5-[5-(4-Carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid
- I68 4-[4-Methyl-5-(4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
- I69 4-[5-(4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
- I70 4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
- I71 4-[5-((1R*,2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
- I72 4-[5-((1R*,2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
- I73 4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
- I74 4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
- I74.1 4-[4-Methyl-5-(3-oxo-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
- I75 4-[5-(3,3-Difluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
- I76 4-[5-((1R*,3R*)-3-Fluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
- I77 4-[5-(Cyclohex-3-enylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

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- I78 (1R*,3R*)-3-{3-Methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylideneamino}-cyclohexanol
- I79 3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid
- I80 3-[5-(4-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
- I80.1 3-[5-(4-carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
- I81 2-Fluoro-5-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
- I82 3-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid
- I83 [5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-piperidin-1-yl amine
- I84 [5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(tetrahydro-pyran-4-yl)-amine
- I85 3-[5-(4-Acetyl-amino-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
- I86 N-{4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide
- I87 N-{4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide
- I88 N-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide
- I89 N-{5-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-pyridin-2-yl}-acetamide
- I90 3-[5-(4-Chloro-phenyl)-3-methyl-3H/[1,3,4]thiadiazol-2-ylideneamino]-benzonitrile
- I90.1 [5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(1H-tetrazol-5-yl)-phenyl]-amine

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- I90.2 3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-N-hydroxy-benzamidine
- I90.3 3-{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-[1,2,4]oxadiazol-5-ol
- I91 [5-(4-Bromo-3-methyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine
- I91.1 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzonitrile
- I91.2 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzamide
- I92 [5-(4-Bromo-3-methoxy-phenyl)-3-methyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine
- I92.1 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzamide
- I92.2 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-hydroxy-benzamide
- I93 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-nitro-benzoic acid methyl ester
- I93.1 2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester
- I93.2 2-Acetylamino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester
- I93.3 2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide
- I93.4 7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-3H-quinazolin-4-one
- I93.5 7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinazolin-4-ylamine
- I93.6 7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-1H-quinazoline-2,4-dione
- I94 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide
- I95 5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide

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- I96 3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid methyl ester
- I96.1 3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
- I97.1 3-[3-Methyl-5-pyridin-2-yl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
- I98 3-[5-(4-Chloro-3-sulfamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
- I99 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile
- I99.1 Cyclohexyl-{3-methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylidene}-amine
- I100 Cyclohexyl-[3-methyl-5-(4-nitro-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine
- I100.1 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenylamine
- I100.2 [5-(4-(N-cyano-N'-(2-dimethylaminoethyl)-carboximidamide)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine
- I100.3 N-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-acetamide
- I100.4 [5-(4-(bis-ethylsulfonylamino)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
- I100.5 [5-(4-(1-(2-dimethylaminoethyl)amino-2-nitro-vinylamino)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine
- I100.6 (E)-N¹-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-2-nitro-ethene-1,1-diamine
- I100.7 [5-(N-cyano-N'-methyl-4-carboximidamide-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine
- I100.8 [5-(4-(N-cyano-N'-amino-carboximidamide)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine
- I100.9 Ethanesulfonic acid [4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-amide

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- I100.10 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-urea
- I100.11 1-[4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-3-(2-dimethylaminoethyl)-urea
- I101 2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide
- I102 2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester
- I102.1 2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide
- I103 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide
- I104 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzoic acid methyl ester
- I104.1 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzamide

The compounds utilised in the invention include pharmaceutically acceptable derivatives of compounds of formula (I) such as solvates, hydrates, pharmaceutically acceptable salts and polymorphs (different crystalline lattice descriptors).

Pharmaceutically acceptable salts of a compound of formula (I) include salts having a basic part and salts having an acidic part.

The expression pharmaceutically acceptable salt of a compound of formula (I) having a basic part should be understood to refer to the addition salts of the compounds of formula (I) which may be formed from non-toxic inorganic or organic acids such as, for example, hydrobromic, hydrochloric, sulfuric, phosphoric, nitric, acetic, succinic, tartaric, citric, maleic, hydroxymaleic, benzoic, fumaric, toluenesulfonic and isethionic acid salts, and the like. The various quaternary ammonium salts of the derivatives (I) are also included in this category of compounds of the invention. In addition, the expression pharmaceutically acceptable salt of a compound of formula (I) having an acidic part is

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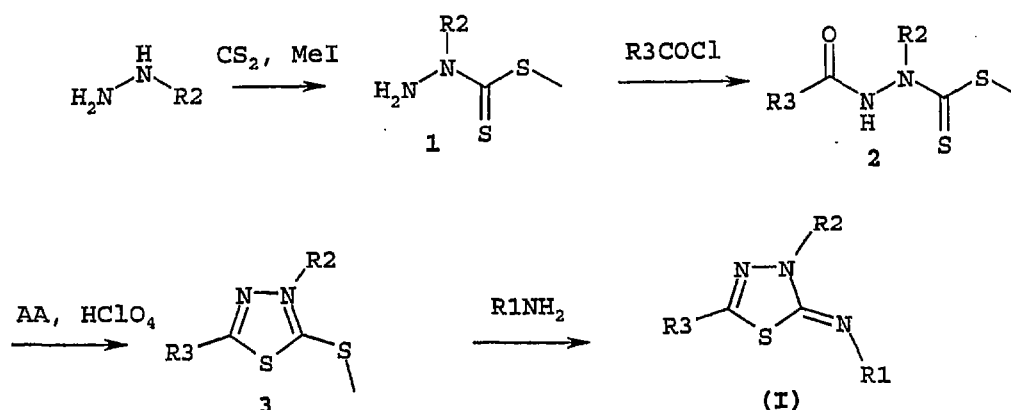
understood to refer to the usual salts of the compounds of formula (I) which may be formed from non-toxic inorganic or organic bases such as, for example, the hydroxides of alkali metals and alkaline-earth metals (sodium, potassium, magnesium and calcium), amines (dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like) or alternatively quaternary ammonium hydroxides such as tetramethylammonium hydroxide. (See also "Pharmaceutical salts" by Berge S.M. et al. (1997) J. Pharm. Sci. 66: 1-19, which is incorporated herein by reference.).

Use of a prodrug of a compound of the invention such as would occur to one skilled in the art (see Bundgaard, et al., Acta Pharm. Suec., 1987; 24: 233-246), is also contemplated.

Process for the preparation.

The compounds of this invention can be synthesised according to the general procedures of synthesis A-E, utilising methodology described herein which is known to a person skilled in the art.

Protocol A:



The starting compounds are either commercially available or can be prepared according to routes known to

the skilled man. See M. Akbar Ali, S.E. Livingston, and D.J. Philipps, *Inorganica Chimica Acta*, 6, 11 (1972); P. Molina, A. Tarraga, A. Espinosa; *Synthesis*, 690 (1988); P. Molina, A. Tarraga, A. Espinosa; *Heterocycles*, vol.29, N°12 (1989).

5

In step 1, the substituted hydrazine is reacted with carbon disulphide and with an alkyl-iodide such as methyl-iodide to form the desired 2-substituted S-alkyldithiocarbazate (1). Various solvents, operating
10 conditions, bases, can be used and will be easily determined by the skilled person. For example, and without any limitation, one can use for the reaction of the substituted hydrazine with carbon disulphide an alcoholic solution of potassium hydroxide with a temperature not exceeding 15°C.
15 Methyl iodide can be added to this solution or to a diluted solution (e.g. with water).

In step 2, the substituted S-methyldithiocarbazate is reacted with an appropriate group R₃CO-X in which X is a leaving group such as halogen. Preferably, R₃CO-X is an acyl
20 chloride (R₃COCl). The reaction can be carried out in e.g. toluene as the solvent at reflux. The corresponding acylated methyldithiocarbazate (2) is obtained.

In step 3, the acylated methyldithiocarbazate is cyclized into the desired 1,3,4-thiadiazole. The reaction
25 can be carried out in the presence of acetic anhydride (AA) and perchlorate HClO₄ in ether, preferably, at a temperature comprised between -5 and 5°C, preferably 0°C, or in the presence of trimethylsilyl trifluoromethanesulfonate in dichloromethane, preferably, at a temperature comprised
30 between 0 and 25°C. After stirring at room temperature several hours, an intermediate compound which is the 1,3,4-thiadiazolium perchlorate (3) is obtained.

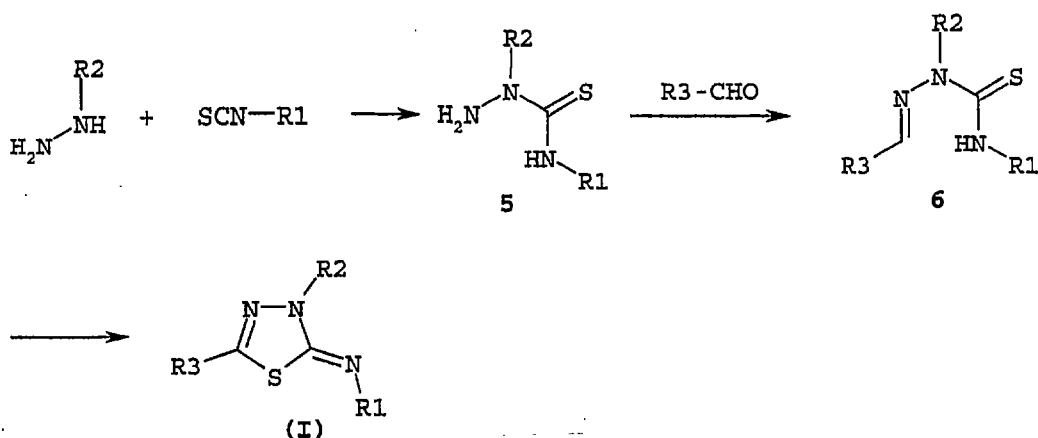
In step 4, the 1,3,4-thiadiazole (or its perchlorate or sulfonate) is reacted with a suitable amine R₁NH₂, to form
35 the final compound. The reaction can be carried out in alcohol such as ethanol as a solvent (the solvent may also be an aprotic solvent such as dioxane, dimethylformamide (DMF) or acetonitrile), in the presence of a base such as

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triethylamine, and preferably, at a temperature comprised between 40 and 110°C, preferably between 40 and 80°C.

Protocol B :

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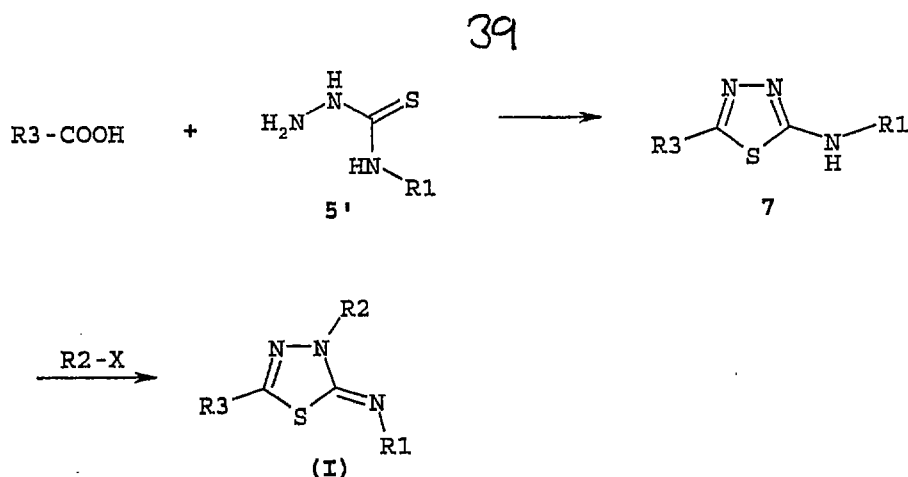
The starting compounds are either commercially available or can be prepared according to routes known to the skilled person. See R. Noto, P. Lo Meo, M. Gruttadauria, G. Werber ;
 10 *J. Heterocyclic Chem.*, 33, 863 (1996).

In step 1, the substituted isothiocyanate is reacted with the substituted hydrazine to form the desired substituted thiosemicarbazide (5). The reaction can be carried out in alcohol e.g. methanol and/or water at a
 15 temperature comprised between -5°C and 15°C, preferably 0°C.

In step 2, the substituted thiosemicarbazide is reacted with an aldehyde R_3CHO to form the desired thiosemicarbazone (6). The reaction can be carried out in alcohol e.g. methanol, at a temperature comprised between 50 and 90°C,
 20 preferably 75°C.

In step 3, the substituted thiosemicarbazone is cyclized to yield compound (I). The reaction can be carried out in alcohol, e.g. ethanol, at a temperature comprised between 20°C and 110°C, preferably 75°C, in the presence of
 25 an oxidant such as FeCl_3 .

Protocol C :

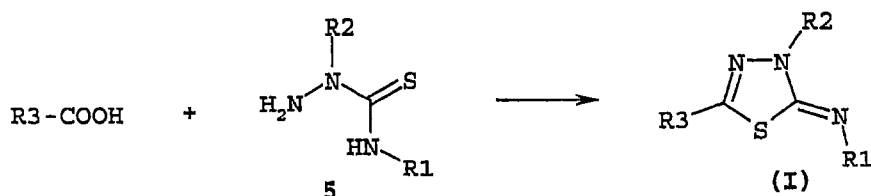


The starting compounds are either commercially available or can be prepared according to routes known to the skilled man. See FR-A-7712352, DE-A-4418066 and FR-A-8015072.

5 In the first step, the carboxylic acid is reacted with the thiosemicarbazide derivative (5') to yield the desired 1,3,4-thiadiazole (7). The reaction can be carried out in an aprotic solvent such as dioxane, at reflux, in the presence of a deshydrating agent, eg $POCl_3$.

10 In the second step, the desired 1,3,4-thiadiazole is reacted with R_2X , where X is a leaving group such as trifluoromethane sulfonate, iodide or bromide. The reaction can be carried out in an aprotic solvent such as dioxane or DMF (if R_2-X is alkyl-iodide or bromide), preferably at room
15 temperature (RT) or under heating to yield compound (I).

Protocol D : 1 step



20 The starting compounds are either commercially available or can be prepared according to routes known to the skilled man.

In the first step, the carboxylic acid is reacted with the substituted thiosemicarbazide derivative (5) to yield

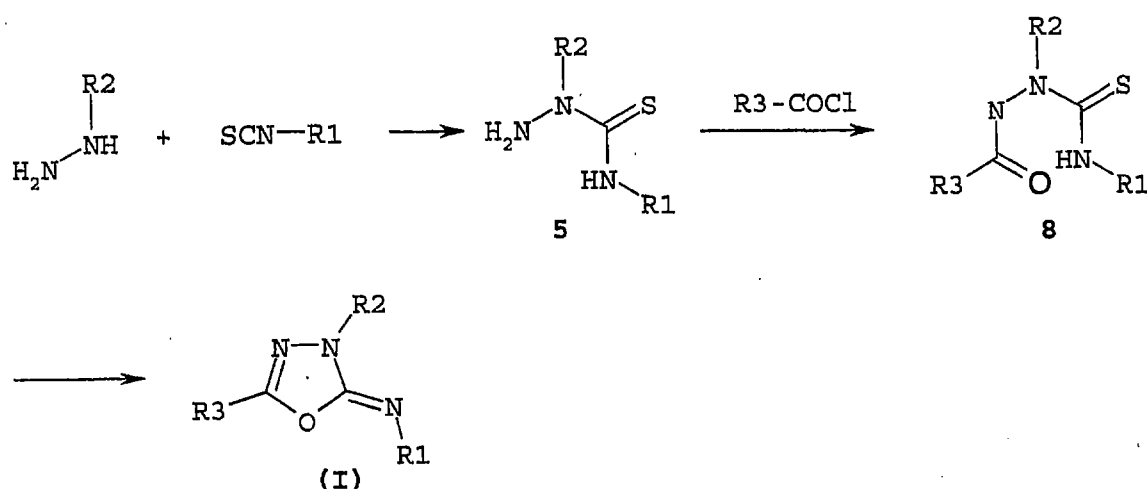
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the desired final 1,3,4-thiadiazole (I). The reaction can be carried out in an aprotic solvent such as dioxane, at reflux and at a temperature comprised between 75 and 120°C, in the presence of a deshydrating agent, e.g. POCl₃.

5

The solvent, reaction time, temperature, catalyst if any, can be varied in all steps described above for all routes, as the skilled man will appreciate.

10 Protocol E : 3 step



See J.M. Kane, M.A. Staeger, Synthetic communication, 22 (1), 1-11 (1992).

The starting compounds are either commercially available or can be prepared according to methods known to the skilled person. See R. Noto, P. Lo Meo, M. Gruttadauria, G. Werber ; J. Heterocyclic Chem., 33, 863 (1996).

In step 1, the substituted isothiocyanate is reacted with the substituted hydrazine to form the desired substituted thiosemicarbazide (5). The reaction can be carried out in alcohol e.g. methanol and/or water at a temperature comprised between -5 and 15°C preferably 0°C.

In step 2, the substituted thiosemicarbazide is reacted with the acid chloride to form the desired thiosemicarbazide (8). The reaction can be carried out in a basic medium such as pyridine at room temperature, or in an aprotic solvent in the presence of a base such as pyridine or triethylamine.

In step 3, the substituted thiosemicarbazide is

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cyclized to yield compound (I). The reaction can be carried out in alcohol, e.g. methanol, at a temperature of e.g. 75°C, in the presence of Mercuric oxide (HgO).

5 Pharmaceutical compositions.

The products of the invention are administered in the form of compositions, which are appropriate depending on the nature, and severity of the condition to be treated. The daily dose in humans is usually between 2 mg and 1 g of the active ingredient, which may be taken in one or more individual doses. The compositions are prepared in forms which are compatible with the intended route of administration, such as, for example, tablets, coated tablets, capsules, mouthwashes, aerosols, powders for inhalation, suppositories, enemas, foams (such as rectal foams) gels or suspensions. These compositions are prepared by methods which are familiar to those skilled in the art and comprise from 0.5 to 60% by weight of active ingredient (compound of the invention) and 40 to 99.5% by weight of a pharmaceutical vehicle or carrier which is appropriate and compatible with the active principle and the physical form of the intended composition.

Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders, tablets, cachets or encapsulated forms for capsules preferably contain 5% to about 70% of the active component. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl

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cellulose, a low-melting wax, cocoa butter, and the like.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration. The drug may be delivered as a spray (either in a pressurised container fitted with an appropriate valve or in a non-pressurised container fitted with a metering valve).

Liquid form preparations include solutions, suspensions, and emulsions.

Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavouring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

For preparing suppository preparations, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify. Enemas are obtained according to known procedures to prepare solutions adapted for rectal administration. Foams are prepared according to known methods (these foams can notably be similar to those used to administer a drug such as 5-ASA for treating rectocolite).

Preferably the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of drug. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for

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example, packaged tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

5

Methods of treatment.

The compounds of the invention are selective PDE7 inhibitors. They can be used in the treatment of various diseases, as they can modulate inflammatory and immunological processes due to an increase of intracellular cAMP levels.

The diseases that can be successfully treated include namely T-cell-related diseases, autoimmune diseases, inflammatory diseases, respiratory diseases, CNS diseases, allergic diseases, endocrine or exocrine pancreas diseases, gastrointestinal diseases, visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS) or graft rejection.

The compounds of the invention have low IC₅₀ values, typically at most 5 μ M, preferably below 1 μ M, and even below 100 nM.

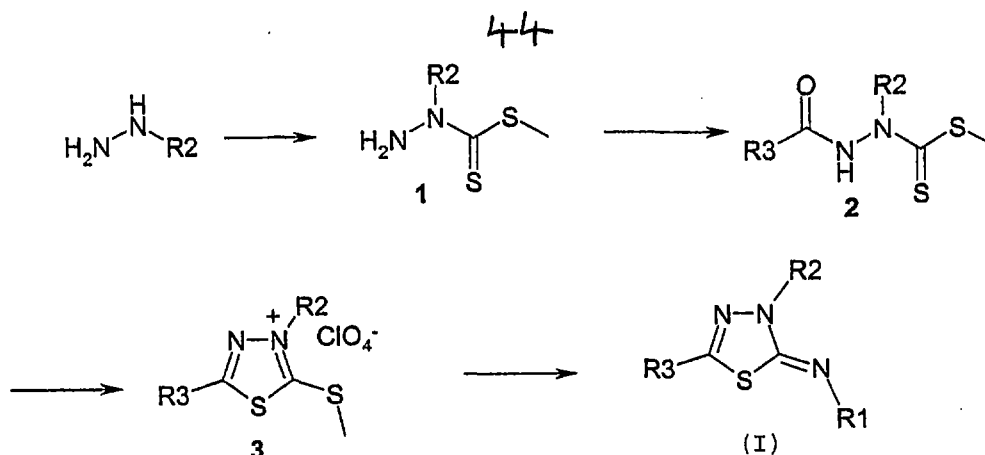
The invention finally relates to a method for the treatment of the above-mentioned diseases comprising administering to a mammal, particularly a human, in need thereof an effective amount of compound of the invention.

The following examples illustrate the invention without limiting it.

Examples

Compounds of the invention have been named with the software "AutoNom Version 4.0"

Protocol A :



Intermediate 1 : PROTOCOL A

5

Intermediate 1a: R2= methyl

N-Methyl-hydrazinecarbodithioic acid methyl ester

Methylhydrazine (370 mmol, 19.43 ml) was added to a solution of potassium hydroxide (370 mmol, 20.7 g) in 90% aqueous alcohol (130 mL). The mixture was cooled to 5°C, then carbon disulphide (370 mmol, 22.2 ml) was added dropwise with vigorous stirring, over 1h, while the temperature of the mixture was not allowed to rise above 7°C. The resulting yellow solution was diluted with water (300 ml) and the methyl iodide (370 mmol, 23.34 ml) was added slowly while the mixture was stirred vigorously. After the stirring had been continued for 3 h at 10-15°C, the white crystals of 2-methyl-S-methyldithiocarbazate (1a) were filtered off, washed with a mixture 1:1 of ethanol:petroleum ether to give 38 g of the desired compound.

15

20

Yield: 84%.

¹H-NMR (400MHz, DMSO) δ ppm: 2.32 (s, 3H), 3.60 (s, 3H), 5.55 (s, 2H).

25 Intermediate 2: PROTOCOL A

Intermediate 2a: R2= methyl, R3= 4-chloro-phenyl

N'-[1-(4-Chloro-phenyl)-methanoyl]-N-methyl-hydrazinecarbodithioic acid methyl ester

30 The appropriate acyl chloride (73.39 mmol, 9.30 ml) (R3COCl)

45

was added to a suspension of 2-methyl-S-methyldithiocarbazate (73.39 mmol, 10 g) in toluene (80 ml). The mixture was stirred at reflux for 4h then allowed to cool down overnight. The solids were isolated by filtration,
5 washed with water and then with ether to give 15 g of the expected 3-acyl-2-methyl-S-methyldithiocarbazate (2a).

Yield= 74%

¹H-NMR (400MHz, DMSO) δppm: 2.45 (s, 3H), 3.65 (s, 3H), 7.65 (dd, 2H), 7.90 (dd, 2H), 11.68 (s, 1H).

10

**Intermediate 2b: R2= methyl, R3= 4-(methylsulfonyl)-phenyl
N'-[1-(4-Methanesulfonyl-phenyl)-methanoyl]-N-methyl-
hydrazinecarbodithioic acid methyl ester**

The acid chloride was prepared from the corresponding
15 benzoic acid.

The appropriate acyl chloride (1.68 mmol, 0.39 g) was added to a suspension of 2-methyl-S-methyldithiocarbazate (1.77 mmol, 0.24 g) in toluene (2 ml). After 5h at reflux, the mixture was cooled down overnight, triturated in ether and
20 stirred over 2 h at RT to give 440 mg of the expected product (2b) as a white solid.

Yield= 82%

¹H-NMR (400MHz, DMSO) δ ppm: 2.5 (s, 3H), 3.30 (s, 3H), 3.65 (s, 3H), 8.15 (m, 4H), 11.9 (s, 1H).

25

**Intermediate 2c: R2= methyl, R3= 4-cyano-phenyl
N'-[1-(4-Cyano-phenyl)-methanoyl]-N-methyl-
hydrazinecarbodithioic acid methyl ester**

The appropriate acyl chloride (22.77 mmol, 3.77 g) (R3COCl) was added to a suspension of 2-methyl-S-methyldithio
30 carbazate (22.77 mmol, 3.10 g) in toluene (25 ml). The mixture was stirred at reflux for 3h-3h30 then allowed to cool down overnight. The solids were isolated by filtration, washed with water then with ether and dried to give 4.15 g
35 of the expected 3-acyl-2-methyl-S-methyldithiocarbazate (2c).

Yield= 68%

46

¹H-NMR (400MHz, DMSO) δppm: 2.45 (s, 3H), 3.65 (s, 3H), 8.05 (m, 4H), 11.85 (s, 1H).

Intermediate 2d: R2= methyl, R3= 4-acetylamino-phenyl

5 N'-(4-Acetylamino-benzoyl)-N-methyl-hydrazinecarbodithioic acid methyl ester

The acid chloride was prepared from the corresponding benzoic acid.

To a suspension of the appropriate acyl chloride (10 mmol, 1.4 g) in toluene (30 ml), was added triethylamine (20 mmol, 2.8 ml) followed by 2-methyl-S-methyldithiocarbazate (12 mmol, 2.4 g). The mixture was maintained at 90°C for 2 hours and was concentrated under reduced pressure. The residue was taken into dichloromethane, washed once with water, concentrated under reduced pressure and washed with AcOEt to give 1.28 g of the title compound.

Yield= 45%

¹H-NMR (400MHz, DMSO) δ ppm: 2.10 (s, 3H), 2.45 (s, 3H), 3.65 (s, 3H), 7.85 (d, 2H), 7.90 (d, 2H), 10.30 (s, 1H), 11.40 (s, 1H).

Intermediate 2e: R2= methyl, R3= 4-acetylamino-3-pyridyl

N'-(6-Acetylamino-pyridine-3-carbonyl)-N-methyl-hydrazinecarbodithioic acid methyl ester

25 The acid chloride was prepared from the corresponding benzoic acid.

To a suspension of the appropriate acyl chloride (63 mmol, 11 g) in toluene (150 ml) was added triethylamine (130 mmol) followed by 2-methyl-S-methyldithiocarbazate (62 mmol, 9 g). After 3h at room temperature, the mixture was concentrated under reduced pressure. The residue was taken into dichloromethane, washed once with water, concentrated under reduced pressure and purified by chromatography on silica gel (95:5 (dichloromethane (DCM)/MeOH) to give 9 g of the title compound.

Yield= 50%

47

¹H-NMR (400MHz, DMSO) δ ppm: 2.15 (s, 3H), 2.45 (s, 3H), 3.65 (s, 3H), 8.25 (m, 2H), 8.80 (s, 1H), 10.90 (s, 1H).
MS (m/z) / M+1 = 298.99

5 Intermediate 3: PROTOCOL A

**Intermediate 3a: R2= methyl, R3= 4-chloro-phenyl
1,3,4-Thiadiazolium, 5-(4-chlorophenyl)-3-methyl-2-(methylthio)-perchlorate**

- 10 To a suspension of the (2a) (54.4 mmol, 15 g) in ether (150 ml) at 0°C, acetic anhydride (30 ml) was added slowly and then HClO₄ 70% (65.33 mmol, 5.61 ml) was added dropwise at 0°C for 1 hour. The resultant mixture was stirred at RT overnight and the precipitate separated by filtration, was
15 washed with ether and then air dried to give 19 g of the title compound (3a) as white solid.
Yield= 97%.

¹H-NMR (400MHz, DMSO) δ ppm: 2.92 (s, 3H), 3.99 (s, 3H), 7.52 (dd, 2H), 7.82 (dd, 2H).

- 20 MS (m/z) / M+1 = 257/259

**Intermediate 3b : R2= methyl, R3= 4-(methanesulfonyl)phenyl
1,3,4 - Thiadiazolium, 5-(4-Methanesulfonyl-phenyl)-3-methyl-2-(methylthio)-perchlorate**

- 25 To a suspension of the (2b) (0.69 mmol, 0.22 g) in ether (3 ml) at 0°C, acetic anhydride (0.4 ml) was added slowly and then HClO₄ 70% (0.90 mmol, 0.080 mL) was added dropwise at 0°C for 1 hour. The resultant mixture was then allowed to rise to RT and stirred for 3h. The precipitate was isolated
30 by filtration then air dried to give 220 mg of the expected 3-methyl-2-methylthio[1,3,4]thiadiazolium perchlorate (3b) as a white solid.

Yield= 78%

¹H-NMR (400MHz, DMSO) δ ppm: 3.14 (s, 3H), 3.33 (s, 3H), 4.20 (s, 3H), 8.20 (dd, 2H), 8.25 (dd, 2H).

- 35 MS (m/z) / M+1 = 301/303

48

Intermediate 3c: R2= methyl, R3= 4-cyano-phenyl
1,3,4 - Thiadiazolium, 5-(4-cyanophenyl)-3-methyl-2-
(methylthio)-perchlorate

To a suspension of intermediate (2c) (15.64 mmol, 4.15 g) in
5 ether (50 ml) and acetic anhydride (13.3 ml), HClO₄ 70%
(18.76 mmol, 1.6 ml) was added dropwise at 0°C and stirred
during 15-30 minutes at 0°C. The resultant mixture was
stirred during 1h30 at room temperature and the precipitate,
separated by filtration, was washed with ether and then air
10 dried to give 5.22 g of the title compound (3c) as white
solid.

Yield= 96%.

¹H-NMR (400MHz, DMSO) δ ppm: 3.15 (s, 3H), 4.21 (s, 3H), 8.15
(m, 4H).

15

Intermediate 3d: R2= methyl, R3= 4-acetylamino-phenyl
1,3,4-thiadiazolium, 5-(4-Acetylaminophenyl)-3-methyl-2-
(methylthio)-trifluoromethanesulfonic acid

To a suspension of (2d) (4.3 mmol, 1.28 g) in
20 dichloromethane (15 ml) was added trimethylsilyl
trifluoromethane-sulfonate (12.9 mmol, 2.34 mL) dropwise.
The resulting mixture was stirred overnight. The precipitate
was isolated by filtration and then dried under reduced
pressure to give 1.3 g of the expected 3-methyl-2-
25 methylthio[1,3,4]thiadiazolium triflate (3d) as a white
solid.

Yield= 72%

¹H-NMR (400MHz, DMSO) δ ppm: 2.10 (s, 3H), 3.10 (s, 3H),
4.15 (s, 3H), 7.80 (dd, 2H), 7.95 (dd, 2H), 10.40 (s, 1H).

30

Intermediate 3e: R2= methyl, R3= 4-acetylamino-3-pyridyl
1,3,4-thiadiazolium, 5-(6-acetylamino-pyridin-3-yl)-3-
methyl-2-(methylthio)-perchlorate

To a suspension of (2e) (3.4 mmol, 1 g) in ether (11 ml) was
35 slowly added acetic anhydride (2 ml) followed by HClO₄ 70%
(4 mmol, 0.7 g) dropwise at 0°C over 1 hour. The resulting
mixture was then allowed to warm up to room temperature and
stirred overnight. Additional HClO₄ 70% (0.7 mmol, 0.1g) was

49

added at 0°C and the mixture was stirred for 2h. The precipitate was isolated by filtration washed with AcOEt then dried under reduced pressure to give 1 g of the expected (3e).

5 Yield = 77%

¹H-NMR (400MHz, DMSO) δ ppm: 2.15 (s, 3H), 3.15 (s, 3H), 4.20 (s, 3H), 8.30 (dd, 1H), 8.40 (dd, 2H), 8.90 (d, H), 11.05 (s, 1H).

MS (m/z) / M+1 = 280.92

10

Compound I : PROTOCOL A

Example I1: R1= 3-benzoic acid, R2= methyl, R3= 4-chloro-phenyl

15 3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

To a suspension of 1,3,4-thiadiazolium perchlorate (3a) (0.7 mmol, 0.25 g) in ethanol (3.5 ml), 3-aminobenzoic acid (1.05 mmol, 0.144 g) and triethylamine (0.7 mmol, 0.098 ml) were added, and the mixture was maintained at 70°C for 7 hours. On cooling to RT overnight, the solid formed was isolated by filtration to give 0.180 g of the expected compound.

Yield= 74.3%

25 ¹H-NMR (400MHz, DMSO) δ ppm: 3.72 (s, 3H), 7.30 (dd, 1H), 7.5 (dd, 1H), 7.54 (dd, 2H), 7.60 (s, 1H), 7.54 (dd, 1H), 7.71 (dd, 2H), 12.91-13.04 (b, 1H).

MS (m/z) / M+1= 346/348

HPLC (uv purity, λ= 214 nm)= 99.03%

30 The following compounds were prepared by the procedure described in example I.1 using appropriate intermediates and reagents. The desired products were obtained after purification by chromatography on silica gel.

I1.1	(1R*,2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid
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I1.2	(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-phenyl-ethanol
I1.3	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3-ethyl-phenyl)-amine
I1.4	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-pyrrolidin-3-yl-amine
I1.5	N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-N',N'-dimethyl-benzene-1,4-diamine
I1.6	2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-6-methyl-benzoic acid
I1.7	2-{2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-ethanol
I1.8	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-ethyl-phenyl)-amine
I1.9	{1-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclopentyl}-methanol

Example I1.10: R1= 3-carboxylic acid cyclohexyl, R2= methyl, R3= 4-chloro-phenyl

5 **3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid**

Compound I1.10 was prepared by the procedure described in example I1 (3h at 75°C) using appropriate intermediates and reagents (protocol A).

10 The mixture was filtered and the filtrate was evaporated to dryness. The residue was purified by silica gel chromatography eluting with dichloromethane containing from 0 to 5% of methanol and then isocratic elution with DCM / MeOH (90/10).

15 Yield= 7.0%

¹H-NMR (400MHz, DMSO) δppm: 0.95-1.20 (m, 4H), 1.62-1.74 (m, 3H), 1.74-1.80 (m 1H), 2.10-2.13 (b, 1H), 2.39-2.48 (b, 1H), 2.84-2.90 (m, 1H), 3.10 (3H, s), 7.33 (dd, 2H), 7.44 (dd, 2H), 11.89-11.84 (b, 1H).

51

MS (m/z) / M+1 = 352/354

HPLC (uv purity, λ = 214 nm) = 97.61%

5 **Example I2: R1= 2-benzoic acid, R2= methyl, R3= 4-chloro-phenyl**

2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

To a suspension of 1,3,4-thiadiazolium perchlorate (3a) (0.7 mmol, 0.25 g) in ethanol (3 ml), 2-aminobenzoic acid (0.84 mmol, 0.115 g) and triethylamine (0.7 mmol, 0.098 ml) were added, and the mixture was heated at 70°C for 7 hours. On cooling, the solid formed was filtered off to give 210 mg of the expected compound.

Yield= 87%

15 ¹H-NMR (400MHz, DMSO) δ ppm: 3.8 (s, 3H), 7.20 (m, 1H), 7.2.8 (dd, 1H), 7.56-7.64 (m, 3H), 7.78 (dd, 2H), 7.95 (dd, 1H), 13.52-13.59 (b, 1H).

MS (m/z) / M+1= 346/348

HPLC (uv purity, λ = 214 nm) = 97.64%

20

Example I2.1: R1= (4-fluoro)-3 benzoic acid, R2= methyl, R3= 4-chloro-phenyl

5-[5-(4-Chloro-phenyl)-3-methyl-3H[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid

25 Compound I2.1 was prepared by the procedure described in example I2 using appropriate intermediates and reagents(protocol A).

The precipitate obtained on cooling was washed with EtOH to give 0.250 g of the title compound.

30 Yield= 60%

¹H-NMR (400MHz, DMSO) δ ppm: 3.71 (s, 3H), 7.29-7.33 (m, 3H), 7.48-7.51(m 1H), 7.54 (dd, 2H), 7.70 (dd, 2H), 13.27-13.29 (b, 1H).

MS (m/z) / M+1= 364/366

35 HPLC (uv purity, λ = 214 nm) = 95.77%

52

Example I2.2: R1= (2,4,5-fluoro)-3 benzoic acid, R2= methyl, R3= 4-chloro-phenyl
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2,5,6-trifluoro-benzoic acid

- 5 Compound I2.2 was prepared by the procedure described in example I2 using the appropriate intermediates and reagents. Acetonitrile was used as solvent and the reaction was warmed at 80°C for 24h (protocol A).
The solid formed after cooling was filtered off and washed
10 with MeOH to give 0.250 g of the title compound.
Yield= 48.6%
¹H-NMR (400MHz, DMSO) δ ppm: 3.74 (s, 3H), 7.44-7.54 (m, 1H), 7.55 (dd, 2H), 7.73 (dd, 2H), 14.15-14.30 (b, 1H).
MS (m/z) / M+1= 400/402
15 HPLC (uv purity, λ = 214 nm) = 95.82%

Example I3: R1= propyl, R2= methyl, R3= 4-chloro-phenyl
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-propyl-amine

- 20 To a suspension of 1,3,4-thiadiazolium perchlorate (3a) (0.28 mmol, 0.10 g) in methanol (4 ml), propylamine (1.35 mmol, 0.115 ml) and triethylamine (0.28 mmol, 0.038 ml) were added, and the reaction was heated at 55°C for 5 hours. On cooling, the mixture was evaporated to dryness and the crude
25 was chromatographed on silica gel (Alltech column, 2 g silica) with a mixture of cyclohexane:EtOAc (98:2) to give the expected compound.
Yield= 0.03g, 45.2%.
¹H-NMR (400MHz, DMSO) δ ppm: 1.89 (t, 3H), 5.53-5.65 (m,
30 2H), 2.97 (t, 2H), 7.49 (dd, 2H), 7.62 (dd, 2H).
MS (m/z) / M+1= 268/270
HPLC (uv purity, λ = 214 nm) = 97.60%

- The following compounds were prepared by the procedure
35 described in example I3 using appropriate intermediates and reagents.

53

I3.1	(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol
I3.2	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(4-methyl-piperazin-1-yl)-propyl]-amine
I3.3	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclobutyl-amine
I3.4	3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-azepan-2-one
I3.5	(4-Chloro-benzyl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I3.6	Benzyl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I3.7	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclopentyl-amine
I3.8	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cycloheptyl-amine
I3.9	(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-3-phenyl-propan-1-ol
I3.10	(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-3-methyl-butan-1-ol

The following compounds were prepared by the procedure described in example I3 using appropriate intermediates and reagents and with isopropanol as solvent.

5

I3.11	2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-methyl-propan-1-ol
I3.12	2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxymethyl-propane-1,3-diol
I3.13	tert-Butyl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I3.14	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-

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	2-ylidene]-isopropyl-amine
I3.15	4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
I3.16	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(1-ethyl-propyl)-amine
I3.17	4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol
I3.18	N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,2-diamine
I3.19	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-fluoro-phenyl)-amine
I3.20	N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,4-diamine
I3.21	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3,4-dichloro-phenyl)-amine
I3.22	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-methoxy-phenyl)-amine
I3.23	(1R*,2S*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid
I3.24	N'-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-N,N-dimethyl-ethane-1,2-diamine

Example I3.25: R1= (1R*, 2S*)-cyclohexyl-2-ol, R2= methyl, R3= 4-chloro-phenyl

(1R*, 2S*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-

5 [1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol

The compound I3.25 was prepared by the procedure described in example I3 (protocol A) with isopropanol as solvent.

The title product was isolated by chromatography on silica gel (Alltech, 2g silica) eluting with dichloromethane containing from 0 to 1% methanol.

10 Yield= 0.015 g, 12%

¹H-NMR (400MHz, DMSO) δppm: 1.20-1.30 (b, 2H), 1.40-1.50 (b, 2H), 1.50-1.72 (b, 4H), 2.80-2.83 (b, 1H), 3.50 (s, 3H), 3.55-3.60 (b, 1H), 4.02-4.04 (b, 1H), 7.45 (d, 2H), 7.60 (d,

55

2H).

MS (m/z) / M+1= 324/3256

HPLC (uv purity, λ = 214 nm)= 96.62%

- 5 The following compound was prepared by the procedure described in example I3 with isopropanol as solvent.

I3.26	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-trifluoromethyl-phenyl)-amine
-------	--

Example I4: R1= 3-benzoic acid, R2= methyl, R3= 4-

- 10 (methanesulfonyl)-phenyl

3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

- To a suspension of 1,3,4-thiadiazolium perchlorate (3b) (0.547 mmol, 0.22 g) in ethanol (2.5 ml), 3-aminobenzoic acid (0.547 mmol, 0.075 g) and triethylamine (0.601 mmol, 0.084 ml) were added, and the reaction was maintained for 6 hours at 75°C. On cooling overnight, the precipitate was filtered off, washed with ethanol then purified on silica gel, eluted with a gradient of DCM then DCM:MeOH (95:5) to give 70 mg of the expected compound.

Yield= 33%

¹H-NMR (400MHz, DMSO) δ ppm: 3.78 (s, 3H), 7.31 (dd, 1H), 7.54 (dd, 1H), 7.60 (s, 1H), 7.65 (s, 1H), 7.97 (dd, 2H), 8.03 (dd, 2H), 12.92-12.03 (b, 1H).

- 25 MS (m/z) / M+1= 390

HPLC (uv purity, λ = 214 nm)= 95.14%

- The following compounds were prepared by the procedure described in example I4 with an excess of triethylamine (10eq) and of the appropriate amine (10eq). The reaction was refluxed for 5h.

I4.1	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclopropyl-amine
I4.2	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-

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2-ylidene]-cyclohexylmethyl-amine

Example I5: R1= 3-hydroxyphenyl, R2= methyl, R3= 4-chlorophenyl

3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol

In this example, polystyrene morpholine resin was used to replace triethylamine and the isocyanate resin to remove the remaining amino derivative.

The suspension of morpholine resin (0.70 mmol, 0.20 g) and 3-aminophenol (0.84 mmol, 0.09 g) in ethanol (3.5 ml) was stirred at RT for 5 min before the addition of 1,3,4-thiadiazolium perchlorate (3a) (0.70 mmol, 0.25 g). After 5 hours at 70°C, the mixture was allowed to cool down before the filtration of the resin. The crude obtained after the evaporation of the solvent was purified on chromatography gel (Alltech column, 2 g silica) and eluted with gradient of DCM and MeOH:DCM (99:1) to give a mixture (0.07 g) of the remained amino derivative and the expected compound. To this mixture in DCM (7 ml) / MeOH (0.5 ml), was added the isocyanate resin (2.44 mmol, 2.00 g) and the suspension was stirred at RT overnight. After filtration of the resin, the filtrate was evaporated to dryness to give 30 mg of the pure product.

Yield= 13.5%

¹H-NMR (400MHz, DMSO) δ ppm: 3.68 (s, 3H), 6.45-6.51 (m, 3H), 7.13-7.19 (m, 1H), 7.55 (dd, 2H), 7.71 (dd, 2H), 9.40-9.48 (b, 1H).

MS (m/z) / M+1= 318/320

HPLC (uv purity, λ = 214 nm)= 98.44%

Example I6: R1= 4-hydroxy-3-benzoic acid, R2= methyl, R3= 4-chlorophenyl

5-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid

The compound I6 was prepared by the procedure described in example I2 (protocol A). The precipitate obtained on cooling

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was washed with DCM then purified by chromatography on silica gel (Alltech column, 5g silica) eluted with a mixture of DCM/MeOH from 100/0 to 85/15.

Yield= 17.0%

5 ^1H -NMR (400MHz, DMSO) δ ppm: 3.07 (s, 1H), 3.59 (s, 3H), 6.70 (d, 1H), 6.93-6.98 (m 1H), 7.30 (s, 1H), 7.38-7.41 (m, 2H), 7.57-7.62 (m, 2H).

MS (m/z) / M+1= 362/364

HPLC (uv purity, λ = 214 nm)= 95.89%

10

The following compounds were prepared by the procedure described in example I6, using appropriate intermediates and reagents. Either morpholine resin or pyridine was used to replace triethylamine.

15

I6.1	(1-Aza-bicyclo[2.2.2]oct-3-yl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I6.2	4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-diethylaminomethyl-phenol
I6.3	2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol
I6.4	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(2-ethyl-phenyl)-amine
I6.5	(R)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol
I6.6	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3-methoxy-phenyl)-amine
I6.7	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3-fluoro-phenyl)-amine
I6.8	(3-Chloro-phenyl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I6.9	{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-acetic acid
I6.10	N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-N',N'-dimethyl-benzene-

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	1,3-diamine
I6.11	3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzamide

Example I7: R1= Exo-2-norbornyl, R2= methyl, R3= 4-chloro-phenyl

Bicyclo[2.2.1]hept-2-yl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

5

The compound I7 was prepared by the procedure described in example I3 using appropriate intermediates and reagents(protocol A).

The title product was isolated by chromatography on silica gel (Alltech, 2g silica) with a gradient of cyclohexane: EtOAc from 100: 0 to 97:3

10

Yield= 44.8 %

¹H-NMR (400MHz, DMSO) δ ppm: 1.09-1.18 (b, 3H), 1.27-1.33

(b, 1H), 1.40-1.52 (b, 2H), 1.58-1.62 (m, 1H), 1.70-1.76

15 (m, 1H), 1.99-2.10 (b, 1H), 2.24-2.27 (b, 1H), 3.45 (s, 3H), 7.53 (d, 2H) 7.64 (d, 2H).

MS (m/z) / M+1= 320/322

HPLC (uv purity, λ= 214 nm)= 93.17%

20 **Example I8:** R1= (1R*, 2R*)-cyclohexyl-2-ol, R2= methyl, R3= 4-chloro-phenyl

(1R*,2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol

The compound I8 was prepared by the procedure described in example I3 using appropriate intermediates and reagents(protocol A).

25

Triethylamine was replaced by morpholine resin (2.1 mmol, 0.61 g, loading 3.47 mmol/g); the mixture of morpholine resin and trans-2-aminocyclohexanol hydrochloride (2.1 mmol, 0.318 g) was stirred in ethanol (3.5 ml) at RT for 5 min before the addition of 3-methyl-2-methylthio[1,3,4]thiadiazolium perchlorate (3a) (0.7 mmol, 0.25 g). The residue was subjected to silica gel chromatography (Alltech column, 2g silica) eluting with

30

59

dichloromethane containing from 0 to 1% methanol.

Yield= 0.050g, 22%

¹H-NMR (400MHz, DMSO) δ ppm: 1.10-1.25 (m, 4H), 1.50-1.66 (m, 3H), 1.71-1.79 (b, 1H), 2.28-2.33 (m, 1H), 3.21-3.27 (m, 1H), 3.40 (s, 3H), 4.38 (s, 1H), 7.42 (dd, 2H), 7.54 (dd, 2H).

MS (m/z) / M+1= 324/326

HPLC (uv purity, λ= 214 nm)= 99.9%

- 10 The following compounds were prepared by the procedure described in example I8 using appropriate intermediates and reagents.

I8.1	5-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-2-methoxy-phenol
I8.2	3-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-benzoic acid
I8.3	3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-4-hydroxy-benzoic acid
I8.4	(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-(3-methanesulfonyl-phenyl)-amine

- 15 **Example I9:** R1= (1R*, 2R*)-cyclohexyl-2-ol, R2= methyl, R3= 4-(methanesulfonyl)-phenyl
(1R*, 2R*)-2-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol

The compound I9 was prepared by the procedure described in example I4 (protocol A).

- 20 3-methyl-2-methylthio[1,3,4]thiadiazolium perchlorate (3b) (0.372 mmol, 0.15 g), trans-2-aminocyclohexanol hydrochloride (0.410 mmol, 0.062 g) and triethylamine (0.7814 mmol, 0.109 ml) were reacted in ethanol (1.5 ml). The crude was twice
25 chromatographed on silica gel with a mixture of DCM: MeOH (98:2) to give the title product.

Yield= 0.030g, 23%

¹H-NMR (400MHz, DMSO) δ ppm: 1.20-1.37 (m, 5H), 1.60-1.78

60

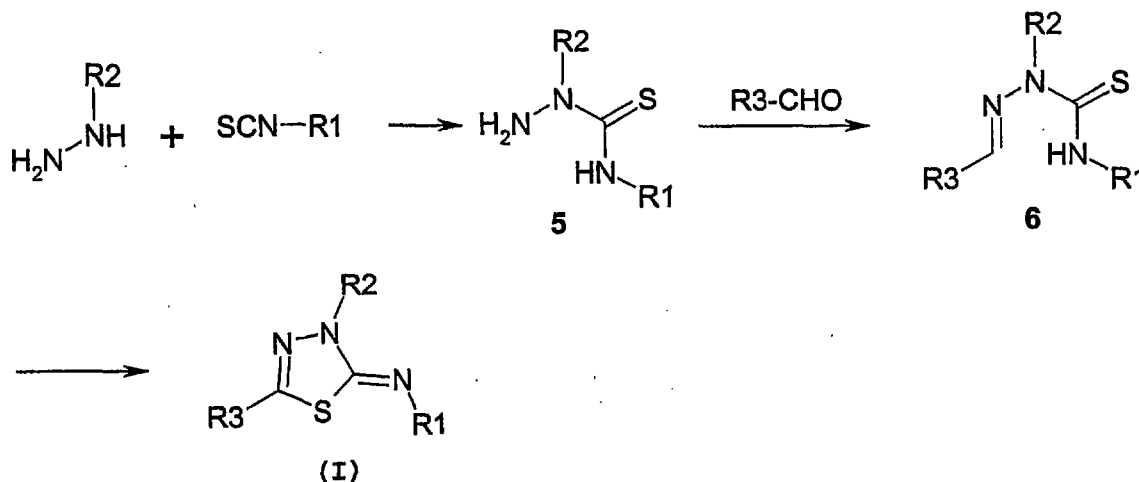
(b, 3H), 1.81-1.90 (b, 1H), 3.3 (s, 3H), 3.32-3.40 (b, 1H), 3.52 (s, 3H), 4.53 (s, 1H), 7.89 (d, 2H), 8.01 (d, 2H).

MS (m/z) / M+1 = 368/370

HPLC (uv purity, λ = 214 nm) = 99.17%

5

Protocol B



Intermediate 5 : PROTOCOL B

10

Intermediate 5a: R1= cyclohexyl, R2= methyl

Hydrazinecarbothioamide, N-(cyclohexyl)-1-methyl

The requisite cyclohexylisothiocyanate, (70.8 mmol, 10 g) was dissolved in methanol (35 ml) and this solution was added dropwise (30 min) to a stirred solution of methylhydrazine (134.5 mmol, 7 ml) in water (35 ml) at 0°C. After mixing, the solution was allowed to stir at RT overnight. The precipitate was removed by filtration. The solid was washed with cold EtOH to give 11.7 g of the expected derivative 5a.

Yield : 88.7%

¹H-NMR (400MHz , DMSO) δ ppm: 1.10-1.25 (m, 5H), 1.50-1.60 (m, 1H), 1.60-1.70 (m, 2H), 1.80-1.90 (m, 2H), 3.40 (s, 3H), 3.90-4.00 (m, 1H), 4.80 (s, 2H), 7.85 (d, 1H).

MS (m/z) / M+1 = 188, 33

25

Intermediate 5b: R1= cyclohexyl, R2= H

Hydrazinecarbothioamide, N-cyclohexyl

The requisite cyclohexylisothiocyanate, (141 mmol, 20 ml)

61

was dissolved in methanol (30 ml) and this solution was added dropwise (35 min) to a stirred solution of hydrazinehydrate (423 mmol, 13.2 ml) in methanol (200 ml) at 0°C. After mixing, the solution was allowed to stir at RT overnight. The precipitate was removed by filtration. The solid was washed with cold EtOH to give 14.9 g of the expected derivative (5b).

Yield: 61%

¹H-NMR (400MHz , DMSO) δ ppm : 1.10-1.35(m,5H), 1.50-1.60 (m,1H), 1.60-1.75(m,2H), 1.75-1.90 (m,2H), 4.00-4.10 (m,1H), 4.40 (s,2H), 7.50 (d,1H), 8.50 (s,1H).
MS (m/z) / M+1 =174,25

Intermediate 5c: R1= 3-benzoic-acid-methyl-ester, R2= H
Hydrazinecarbothioamide,N-(3-benzoic-acid-methyl-ester)
3-methoxycarbonylisothiocyanate(77.6 mmol, 15 g) was added dropwise (30 min) to a stirred solution of hydrazine hydrate (97 mmol, 4.7 mL) in methanol (40 mL) at -10°C. After stirring at -10°C for 5h, the solution was allowed to stir at room temperature overnight. The precipitate was filtered and washed with cold methanol to give 15.4 g of the expected compound (yield: 88%).

¹H-NMR (400 MHz , DMSO) δ ppm: 3.85 (s, 3H), 4.85 (brs, 1H), 7.43(t, 1H), 7.68 (d, 1H), 7.87 (d, 1H), 8.33 (s, 1H), 9.23 (s, 1H).
MS (m/z) / M+1 = 226

Intermediate 6: PROTOCOL B

Intermediate 6a: R1=cyclohexyl, R2=methyl , R3= 2,4-dichlorophenyl

Hydrazinecarbothioamide, N-cyclohexyl-2-[(2,4-dichlorophenyl)methylene]

A suspension of 2-methylthiosemicarbazide (5a) (2.67 mmol, 500 mg) in ethanol (5 ml) and 2,4-dichlorobenzaldehyde (2.94 mmol, 515 mg) were heated at 75°C for 18 hours. After cooling, the formed precipitate was filtered and washed with cold ethanol to give 876 mg of the title compound.

62

Yield: 95.3%

¹H-NMR (400MHz , DMSO) δ ppm: 1.10-1.25 (m, 1H), 1.25-1.35 (m, 2H), 1.35-1.55 (m, 2H), 1.60-1.70 (m, 1H), 1.70-1.80 (m, 1H), 1.90-2.00 (m, 2H), 3.80 (s, 3H), 4.10-4.30 (m, 1H),
5 7.50 (d, 1H), 7.70 (s, 1H), 8.00 (s, 1H), 8.20 (d, 1H), 8.50 (d, 1H).

EXAMPLE I : PROTOCOL B

10 **Example I10: R1= cyclohexyl, R2= methyl, R3= 2,4-dichlorophenyl**
Cyclohexyl-[5-(2,4-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

The appropriate thiosemicarbazone (prepared by the procedure
15 described in example 6a) (2.3 mmol, 800 mg) was suspended in ethanol (5ml) and the oxidant FeCl₃·6H₂O (5.06 mmol, 1.38 g) dissolved in ethanol (5 ml) was added. The mixture was heated at 75°C during 19h (TLC control). The oxidant (1.15 mmol, 0.31 g) was added to allow reaction to completion. The
20 mixture was concentrated by distillation of the solvent and the crude material was solubilized in ethyl acetate. The inorganic salts were removed by extraction with water. The organic layer was washed with a solution of NaCl, dried under magnesium sulphate, filtered, and distilled to give a
25 residue which was chromatographed on silica gel column (using a gradient of solvent ethyl acetate-cyclohexane starting with a ratio 5/95) to isolate 230 mg of the pure thiadiazoline. The byproduct mainly formed during this reaction is the 1,2,4-triazoline-5-thione.

30 Yield: 35%

¹H-NMR (400MHz , DMSO) δ ppm: 1.10-1.40 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.80 (m, 4H), 2.55-2.70 (m, 1H), 3.50 (s, 3H),
7.50 (d, 1H), 7.70-7.80 (m, 2H)

MS (m/z) / M+1= 344.1

35 HPLC (uv purity, λ= 214 nm): 99,9%

Example I10.1 : R1= cyclohexyl, R2= methyl, R3= 2-chloro-

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phenyl

[5-(2-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

Compound I10.1 was prepared by the procedure described in

5 I10 using appropriate intermediates and reagent.

The residue was subjected to silica gel chromatography, eluting with cyclohexane containing from 0 to 6% AcOEt.

Yield: 6%

¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.50-1.60
10 (m, 1H), 1.65-1.70 (m, 4H), 2.55-2.65 (m, 1H), 3.50 (s, 3H),
7.40-7.50 (m, 2H), 7.60 (d, 1H), 7.70 (d, 1H)

MS (m/z) / M+1= 310.2

HPLC (uv purity, λ= 214 nm): 99.9%

15 **Example I11: R1= cyclohexyl, R2= methyl, R3= 4-(trifluoromethyl)-phenyl**

Cyclohexyl-[3-methyl-5-(4-trifluoromethyl-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine

The appropriate thiosemicarbazone (prepared by the procedure
20 described in example 6a) (2 mmol, 700 mg) was suspended in ethanol (5 ml) and the oxidant FeCl₃ · 6H₂O (4.4 mmol, 1.21 g) dissolved in ethanol (5 mL) was added. The mixture was heated at 75°C during 19h. The mixture was concentrated by
25 distillation of the solvent and the crude material was solubilized in ethyl acetate. The inorganic salts were removed by extraction with water. The organic layer was washed with a solution of NaCl, dried under magnesium sulphate, filtered, and distilled to give a residue which
30 was chromatographed on silica gel column (using a gradient of solvent ethyl acetate-cyclohexane as eluent with a rapport 5/95) to isolate 290 mg the pure thiadiazoline.

Yield:42%

¹H-NMR (400MHz, DMSO) δ ppm: 1.25-1.50 (m, 5H), 1.60-1.70
(m, 1H), 1.75-1.90 (m, 4H), 2.65-2.75 (m, 1H), 3.60 (s, 3H),
35 7.85-7.95 (m, 4H)

MS (m/z) / M+1= 342.6.

HPLC (uv purity, λ= 214 nm): 99.9%

64

Example I12: R1= cyclohexyl, R2= methyl, R3= 4-pyridyl
Cyclohexyl-(3-methyl-5-pyridin-4-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

- 5 Compound I12 was prepared by the procedure described in example I11 using appropriate intermediates and reagents (protocol B).

The mixture was concentrated by distillation under reduced pressure and the residue was dissolved in water. The aqueous
10 mixture was then basified with saturated NaHCO₃ solution and extracted with ethyl acetate. The organic layer was washed with saturated solution of NaCl and dried over magnesium sulfate, filtered and distilled to give a residue which was purified by silica gel chromatography (eluent:
15 cyclohexane/ethyl acetate, 95/5).

Yield: 80%

¹H-NMR (400MHz , DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.55-2.70 (m, 1H), 3.55 (s, 3H), 7.60 (d, 2H), 8.65 (d, 2H)

20 MS (m/z) / M+1= 275.2

HPLC (uv purity, λ= 214 nm): 99.9%

Example I13: R1= cyclohexyl, R2= methyl, R3= 3-chloro-phenyl
[5-(3-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

- 25 Compounds I13 was prepared by the procedure described in example I10 using appropriate intermediates and reagents (protocol B).

The residue was subjected to silica gel chromatography,
30 eluting with cyclohexane containing from 0 to 6% AcOEt.

Yield: 23%

¹H-NMR (400MHz , DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.55-2.70 (m, 1H), 3.50 (s, 3H), 7.45-7.55 (m, 2H), 7.55-7.65 (m, 1H), 7.70 (s, 1H)

35 MS (m/z) / M+1= 308

HPLC (uv purity, λ= 214 nm): 99.9%

65

Example I14: R1= cyclohexyl, R2= methyl, R3= 4-cyano-phenyl
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile

Compounds I14 was prepared by the procedure described in
example I10 using appropriate intermediates and reagents
(protocol B).

The residue was subjected to silica gel chromatography,
eluting with cyclohexane containing from 0 to 8% AcOEt.

Yield: 10%

¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65
(m, 1H), 1.70-1.80 (m, 4H), 2.60-2.70 (m, 1H), 3.55 (s, 3H),
7.80 (d, 2H), 7.90 (d, 2H)

MS (m/z) / M+1= 299.2

HPLC (uv purity, λ= 214 nm): 99.3%

15

Example I15 : R1= cyclohexyl, R2= methyl, R3= 4-
methylsulfonyl-phenyl

Cyclohexyl-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-
[1,3,4]thiadiazol-2-ylidene]-amine

Compounds I15 was prepared by the procedure described in
example I10 using appropriate intermediates and reagents
(protocol B).

The residue was subjected to silica gel chromatography,
eluting with cyclohexane containing from 0 to 10% AcOEt.

Protocol D gave better yield to prepare I15.

Yield: 3%

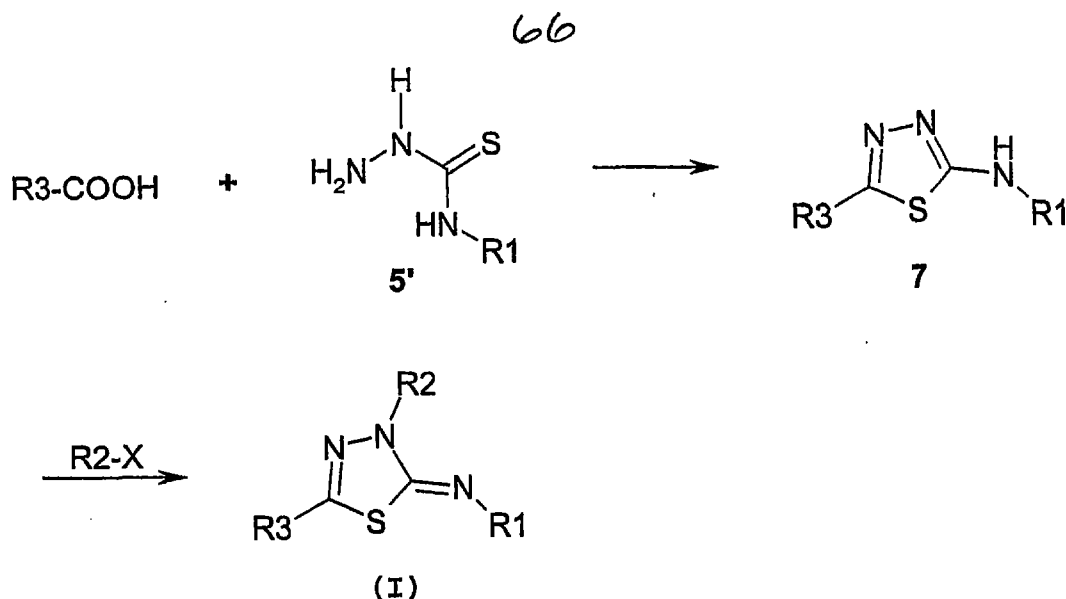
¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.45-1.55
(m, 1H), 1.60-1.75 (m, 4H), 2.50-2.60 (m, 1H), 3.20 (s, 3H),
3.45 (s, 3H), 7.80 (d, 2H), 7.90 (d, 2H).

MS (m/z) / M+1= 352.5

HPLC (uv purity, λ= 214 nm): 87.3%

Protocol C

35



Intermediate 7: PROTOCOL C

5 Intermediate 7a: R1= cyclohexyl, R3= 4-chloro-3-sulfamoyl-phenyl

2-Chloro-5-(5-cyclohexylamino-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

To a mixture of 4-chloro-3-sulfamoyl-benzoic acid (6.36 mmol, 1.5 g), thiosemicarbazide (5b) (6.36 mmol, 1.10 g) in dioxane (40 ml) at 60°C, POCl₃ (6.36 mmol, 600 μl) was added and the mixture was warmed at reflux for 2h30 and 16h at RT. The solvent was removed by distillation under reduced pressure to give a crude material which was basified with a solution of diluted NH₄OH. The yellow precipitate obtained was collected by filtration, washed with water before drying under vacuum over P₂O₅ to give 2g of the desired product. Yield = 84 % ;

¹H (400MHz, DMSO) δ ppm : 1.10-1.37 (m, 5H), 1.55 (m, 1H), 1.70 (m, 2H), 1.98 (m, 2H), 3.55 (m, 1H), 7.66-7.82 (m, 3H), 7.90 (m, 1H) ; 8.25-8.37 (br, 2H). MS (m/z) / M+1 = 373/375

25 Intermediate 7b: R1= cyclohexyl, R3= 2,4-dichloro-5-sulfamoyl-phenyl

2,4-Dichloro-5-(5-cyclohexylamino-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

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To a mixture of 2,4-dichlorobenzoic acid (1.85 mmol, 500 mg), thiosemicarbazide (5b) (1.85 mmol, 320 mg) in anhydrous dioxane (10 mL) at 70-80°C, POCl₃ (1.85 mmol, 173 µl) was added and the mixture was warmed at 95°C for 5 hours. The solvent was removed by distillation under reduced pressure to give a crude material which was basified at pH 8-7 with a saturated solution of NaHCO₃. The precipitate obtained was collected by filtration, washed with water and purified by silica gel chromatography using cyclohexane/ethyl acetate as eluent to give 351mg of the title compound.

Yield: 46.3%

¹H-NMR (400MHz, DMSO) δ ppm: 1.10-1.40 (m, 5H), 1.50-1.65 (m, 1H), 1.65-1.80 (m, 2H), 1.90-2.05 (m, 2H), 3.50-3.70 (m, 1H), 7.85 (d, 2H), 8.05 (s, 1H), 8.20-8.40 (m, 1H), 8.60 (s, 1H).

MS (m/z) / M+1= 407.1

HPLC (uv purity, λ= 214 nm): 97.1%

Intermediate 7c: R1= cyclohexyl, R3= 3-thienyl

Cyclohexyl-(5-thiophen-3-yl-[1,3,4]thiadiazol-2-yl)-amine

To a mixture of 3-thiophenecarboxylic acid (3.9 mmol, 500 mg), thiosemicarbazide 5b (3.9 mmol, 675 mg) in anhydrous dioxane (10 ml) at 60-65°C, POCl₃ (5 mmol, 473 µl) was added and the mixture was warmed at 95°C for 5 hours. The solvent was removed by distillation under reduced pressure to give a crude material which was basified at pH 8-7 with a saturated solution of NaHCO₃. The precipitate obtained was collected by filtration and washed with water. The solid was then dried under vacuum to provide 965 mg of the desired compound (7c).

Yield : 93%

¹H-NMR (400MHz, DMSO) δ ppm: 1.10-1.40 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.75 (m, 2H), 1.90-2.00 (m, 2H), 3.45-3.55 (m, 1H), 7.45 (d, 1H), 7.65 (d, 1H), 7.80 (d, 1H), 7.85 (s, 1H).

Intermediate 7d: R1= cyclohexyl, R3= 3-chloro-2,6-dimethoxyphenyl

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[5-(3-Chloro-2,6-dimethoxy-phenyl)-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine

To a mixture of 3-chloro-2,6-dimethoxybenzoic acid (2.3 mmol, 500 mg), thiosemicarbazide **5b** (2.3 mmol, 399 mg) in anhydrous dioxane (10 ml) at 70-80°C, POCl₃ (2.3 mmol, 215 µl) was added and the mixture was warmed at 95°C for 5 hours. The solvent was removed by distillation under reduced pressure to give a crude material which was basified at pH 8-7 with a saturated solution of NaHCO₃. The precipitate obtained was collected by filtration, washed with water and dried under vacuum. The solid was subjected to flash chromatography eluting with ethyl acetate/cyclohexane to give 115 mg of the title compound.

Yield: 14%

¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.80 (m, 2H), 1.95-2.05 (m, 2H), 3.50-3.60 (m, 1H), 3.70 (s, 3H), 3.80 (s, 3H), 7.00 (d, 1H), 7.55 (d, 1H), 7.75 (d, 1H).

MS (m/z) / M+1 = 354.1

Intermediate 7e: R1= cyclohexyl, R3= 3-bromo-4-methoxyphenyl
[5-(3-Bromo-4-methoxy-phenyl)-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine

To a mixture of 3-bromo-4-methoxybenzoic acid (2.16 mmol, 500 mg), thiosemicarbazide **5b** (2.16 mmol, 375 mg) in anhydrous dioxane (10 ml) at 60-65°C, POCl₃ (2.8 mmol, 262 µl) was added and the mixture was warmed at 95°C for 5 hours. The solvent was removed by distillation under reduced pressure to give a crude material which was basified at pH 8-7 with a saturated solution of NaHCO₃. The precipitate obtained was collected by filtration, washed with water and dried under vacuum. The solid was solubilized in 50 ml of dichloromethane/methanol (7/3) to which was additionned a morpholine resin (13.88 mmol, 4 g). The mixture was stirred overnight to remove the excess of acid. The resin morpholine salt was filtered and the organic layer was concentrated by distillation under reduced pressure to give 740 mg of the

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purified product (7e).

Yield: 92.8%

¹H-NMR (400MHz , DMSO) δ ppm: 1.10-1.40 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.75 (m, 2H), 1.90-2.00 (m, 2H), 3.45-3.55 (m, 1H), 7.45 (dd, 1H), 7.65 (dd, 1H), 7.80 (dd, 1H), 7.85 (dd, 1H).

Intermediate 7f: R1= cyclohexyl, R3= 2-pyrazinyl

Cyclohexyl-(5-pyrazin-2-yl-[1,3,4]thiadiazol-2-yl)-amine

10 To a mixture of 2-pyrazine carboxylic acid (2.885 mmol, 0.358 g), thiosemicarbazide (5b) (2.885 mmol, 0.5 g) in anhydrous dioxane (10 ml), was added phosphorus oxychloride (3.751 mmol, 0.350 ml) at 90°C and the mixture was heated at 95°C for 5 hours. The mixture was then basified to pH 7 with
15 a saturated solution of sodium bicarbonate then extracted with EtOAc. The organic phase was dried over MgSO₄ and evaporated to dryness to give the expected product.

Yield= 0.6 g, 79.6%

¹H-NMR (400MHz, DMSO) δ ppm: 1.20-1.44 (m, 5H), 1.56-1.63 (b, 1H), 1.70-1.77 (b, 2H), 2.00-2.05 (b, 2H), 3.60-3.68 (b, 1H), 8.22 (d, 1H), 8.67-8.69 (m, 2H), 9.28 (s, 1H).

Intermediate 7g: R1= cyclohexyl, R3 =3,4-dihydroxyphenyl

4-(5-Cyclohexylamino-[1,3,4]thiadiazol-2-yl)-benzene-1,2-diol

25 To a mixture of 3,4-dihydroxybenzoic acid (2.885 mmol, 0.445 g), thiosemicarbazide (5b) (2.885 mmol, 0.500 g) in anhydrous dioxane (10 ml), was added phosphorus oxychloride (3.751 mmol, 0.350 ml) at 90°C and the mixture was heated at 95°C for 5 hours. The mixture was basified with a saturated
30 solution of sodium bicarbonate to pH 7 then stirred at RT overnight. The precipitate was filtered, washed with hexane then dried to give the title compound.

Yield: 71%

¹H-NMR (400MHz , DMSO) δ ppm: 1.15-1.39 (m, 5H), 1.55-1.62 (b, 1H), 1.70-1.78 (b, 2H), 1.95-2.00 (b, 2H), 3.48-3.53 (b, 1H), 6.80 (d, 1H), 6.98 (d, 1H), 7.19 (s, 1H), 7.68 (d, 1H), 9.20-9.40 (b, 2H).

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Intermediate 7h: R1 = cyclohexyl, R3= 4-chloro-phenyl

[5-(4-Chloro-phenyl)-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine

Thiosemicarbazone (6b) (obtained from 5b following the

5 protocol 6a) (10 mmol, 3 g) was suspended in ethanol (50 ml)

and the oxidant $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (23 mmol, 6.3 g) was added. The

mixture was heated at reflux for 3h. The mixture was

concentrated by distillation of the solvent and the crude

material was solubilized in ethyl acetate. The organic layer

10 was washed with water, dried under magnesium sulphate,

filtered, and distilled to give a residue submitted to

another oxidative process with $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (3 g) in ethanol

(50 ml). The mixture was heated at reflux for 3h and 12h at

RT. The mixture was concentrated by distillation of the

15 solvent and the crude material was solubilized in ethyl

acetate. The inorganic salts were removed by extraction with

water. The organic layer was washed with a solution of NaCl,

dried under magnesium sulphate, filtered, and distilled to

give a residue which was triturated and wash with

20 cyclohexane to give 2.5g of the title product.

Yield: 85%

$^1\text{H-NMR}$ (400MHz, DMSO) δ ppm: 0.95-1.22 (m, 5H), 1.35-1.45

(b, 1H), 1.50-1.60 (m, 2H), 1.80-1.87 (m, 2H), 3.32-3.42 (b,

1H), 7.35 (d, 2H), 7.55 (d, 2H), 7.75 (d, 1H)

25 MS (m/z) / M+1 = 294.1

HPLC (uv purity, λ = 214 nm): 97.21%

Intermediate 7i: R1= cyclohexyl, R3= 3-chloro-4-hydroxy-5-methoxyphenyl

30 2-chloro-4-(5-cyclohexylamino-[1,3,4]thiadiazol-2-yl)-6-methoxy-phenol

To a mixture of 3-chloro-4-hydroxy-5-methoxybenzoic acid (2.468 mmol, 500 g), thiosemicarbazide (5b) (2.468 mmol, 427

mg) in dioxane (10 ml) at 65°C, POCl_3 (3.2 mmol, 300 μl) was

35 added and the mixture was warmed at 95°C for 3h30. The

solvent was removed by distillation under reduced pressure

to give a crude material which was basified with a solution

of diluted NH_4OH . The precipitate obtained was collected by

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filtration, washed with water before drying under vacuum over P_2O_5 to give 675 mg of the desired product.

Yield = 80%

1H -NMR (400MHz, DMSO) δ ppm: 1.15-1.36 (m, 5H), 1.53-1.63 (m, 1H), 1.67-1.80 (m, 2H), 1.95-2.05 (m, 2H), 3.45-3.57 (m, 1H), 3.90 (s, 3H), 7.25 (s, 1H) ; 7.30 (s, 1H), 7.85 (d, 1H), 9.90 (s, 1H)

Intermediate 7j: R1= 3-benzoic-acid-methyl-ester, R3= 3-cyano-phenyl
3-[5-(3-Cyano-phenyl)-[1,3,4]thiadiazol-2-ylamino]-benzoic acid methyl ester

To a mixture of 3-cyanobenzoic acid (2.92 mmol, 0.43 g), (5c) (3 mmol, 0.7 g) in dioxane (10 mL) at 85°C, $POCl_3$ (3.8 mmol, 350 μ L) was added and the mixture was heated at 95°C for 3h30. The solvent was removed by distillation under reduced pressure to give a crude material which was basified with an aqueous saturated solution of $NaHCO_3$. The precipitate obtained was collected by filtration, washed successively with water and with ether before being dried under vacuum to give 0.5 g of the desired product (yield: 49%).

1H -NMR (400 MHz, DMSO) δ ppm: 3.88 (s, 3H), 7.53 (t, 1H), 7.63 (d, 1H), 7.72 (t, 1H), 7.86 (d, 1H), 7.96 (d, 1H), 8.23 (d, 1H), 8.32 (s, 1H), 8.43 (s, 1H), 10.89 (s, 1H).

MS (m/z) / M+1 = 337

Intermediate 7k: R1= 3-benzoic-acid-methyl-ester, R3= 2-pyridyl
3-(5-Pyridin-2-yl-[1,3,4]thiadiazol-2-ylamino)-benzoic acid methyl ester

To a mixture of picolinic acid (2.92 mmol, 0.36 g), (5c) (3 mmol, 0.7 g) in dioxane (10 mL) at 85°C, $POCl_3$ (3.8 mmol, 350 μ L) was added and the mixture was heated at 95°C for 5h. The solvent was removed by distillation under reduced pressure to give a crude material. Methanol was added and the precipitate obtained was collected by filtration, washed with methanol and dried under vacuum to give 0.59 g (61%) of

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the desired product. The crude material was engaged in the next step without purification.

¹H-NMR (400 MHz, DMSO) δ ppm: 3.8 (s, 3H), 7.5 (m, 2H), 7.6 (d, 1H), 7.88 (d, 1H), 7.98 (t, 1H), 8.12 (d, 1H), 8.42 (s, 1H), 8.63 (d, 1H), 10.9 (s, 1H).
MS (m/z) / M+1 = 313/314/315

EXAMPLE I : PROTOCOL C

10 **Example I16: R1= cyclohexyl, R2= methyl, R3= 2,4-dichloro-5-sulfamoyl-phenyl**

2,4-Dichloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

To a solution of 1,3,4-thiadiazole 7b (0.195 mmol, 80 mg) in anhydrous dioxane (10 mL), methyltrifluoromethane sulfonate (0.23 mmol, 27 μ l) was added. The resultant mixture was stirred for 24 h. To this solution was added 0.527 mmol (64 μ l) of methyltrifluoromethane sulfonate to allow reaction to completion, and 0.585 mmol (82 μ l) of triethylamine. The filtrate is concentrated by distillation under reduced pressure. The product was purified via column chromatography on silica gel (eluted with cyclohexane/ethyl acetate, 80/20) to give 48 mg of the title product.

Yield: 58%

25 ¹H-NMR (400MHz , DMSO) δ ppm: 1.20-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 3.55 (s, 3H), 7.80 (d, 2H), 8.0 (s, 1H), 8.35 (s, 1H).

MS (m/z) / M+1: 421.3

HPLC (uv purity, λ = 214 nm): 99.4%

30

Example I17: R1= cyclohexyl, R2= methyl, R3= 3-thienyl
Cyclohexyl-(3-methyl-5-thiophen-3-yl-3H-[1,3,4] thiadiazol-2-ylidene)-amine

To a solution of 1,3,4-thiadiazole 7c (0.75 mmol, 200 mg) in anhydrous dioxane (10 mL), methyltrifluoromethane sulfonate (1.13 mmol, 128 μ l) was added. The resultant mixture was stirred for 24 h. To this solution was added 0.225 mmol (26

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μl) of methyltrifluoromethanesulfonate to allow reaction to completion, and 0.675 mmol (94 μl) of triethylamine. The mixture is concentrated by distillation under reduce pressure and the residue was dissolved in water. The aqueous mixture was then basified (pH= 5-6) with saturated NaHCO₃ solution with ethyl acetate. The organic layer was saturated with NaCl and dried over magnesium sulfate, filtered and distilled to give a residue which was purified by silica gel chromatography, eluting with cyclohexane containing from 0 to 15% AcOEt to provide 80 mg of the desired product.
Yield : 38%

¹H-NMR (400MHz , DMSO): δ ppm= 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.7-1.8 (m, 4H), 2.55-2.65 (m, 1H), 3.45 (s, 3H), 7.40 (d, 1H), 7.70 (d, 1H), 7.85 (s, 1H).

MS (m/z) / M+1= 280.23

HPLC (uv purity, λ= 214 nm): 99.9%

Example I17.1: R1= cyclohexyl, R2= methyl, R3= 3,5-dichloro-phenyl

Cyclohexyl-[5-(3,5-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

Compound I17.1 was prepared by the procedure described in example I17 using appropriate intermediates and reagents.
Yield: 43%

¹H-NMR (400MHz , DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.90 (m, 4H), 2.55-2.65 (m, 1H), 3.50 (s, 3H), 7.65 (s, 2H), 7.70 (s, 1H)

MS (m/z) / M+1= 342.2

HPLC (uv purity, λ = 214 nm): 99.9%

Compound I17.2 was prepared by the procedure described in example I17 using appropriate intermediates and reagents.

I17.2	Cyclohexyl-[5-(2-ethyl-5-methyl-2H-pyrazol-3-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
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Example I18: R1= cyclohexyl, R2= methyl, R3= 3-chloro-2,6-

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dimethoxyphenyl

[5-(3-Chloro-2,6-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

To a solution of the 1,3,4-thiadiazole 7d (0.226 mmol, 80 mg) in anhydrous dioxane (10 mL), methyltrifluoromethanesulfonate (0.27 mmol, 31 μ l) was added. The resultant mixture was stirred for 24 h. To this solution was added 0.068 mmol (7 μ l) of methyltrifluoromethanesulfonate to allow reaction to completion. The mixture was concentrated by distillation under reduced pressure and the residue was dissolved in water. The aqueous mixture was then basified (pH= 5-6) with saturated NaHCO₃ solution and extracted with ethyl acetate. The organic layer was washed with saturated solution of NaCl and dried over magnesium sulfate, filtered and distilled to give a residue which was purified by silica gel chromatography. (eluent: cyclohexane/ethyl acetate, 80/20). 11 mg of desired product was obtained.

Yield: 13%

¹H-NMR (400MHz , DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.80 (m, 4H), 2.50-2.60 (m, 1H), 3.50 (s, 3H), 3.75 (s, 3H), 3.80 (s, 3H), 7.00 (d, 1H), 7.60 (d, 1H)
MS (m/z) / M+1= 368.26

HPLC (uv purity, λ = 214 nm): 99.7%

Compound I18.1 was prepared by the procedure described in example I18 using appropriate intermediates and reagents:

I18.1	Cyclohexyl-(5-isoxazol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine
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Example I18.2: R1= cyclohexyl, R2= methyl, R3= 2-(5-pyridin-2-yl)-thienyl

Cyclohexyl-[3-methyl-5-(5-pyridin-2-yl-thiophen-2-yl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine

Compound I18.2 was prepared by the procedure described in example I18 using appropriate intermediates and reagents. The residue was purified by silica gel chromatography

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eluting with a gradient of cyclohexane containing from 0 to 10% ethyl acetate.

Yield: 57%

¹H-NMR (400MHz , DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.80 (m, 4H), 2.55-2.65 (m, 1H), 3.45 (s, 3H), 7.30 (m, 1H), 7.35 (d, 1H), 7.80 (d, 1H), 7.85 (m, 1H), 7.95 (d, 1H), 8.55 (d, 1H).

MS (m/z) / M+1= 357.3

HPLC (uv purity, λ= 214 nm): 99.5%

10

Example I18.3: R1= cyclohexyl, R2= methyl, R3= 3,5-dihydroxy-4-methoxy-phenyl

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2-methoxy-benzene-1,3-diol; compound with trifluoromethanesulfonic acid

15

Compound I18.3 was prepared from the appropriate 1,3,4-thiadiazole 7 prepared by the procedure described in example I18. In this particular case, the mixture was concentrated and the formed precipitate was filtered and washed with ethyl acetate to give the expected compound as a salt of trifluoromethansulfonic acid.

20

Yield: 45%

¹H-NMR (400MHz , DMSO) δ ppm: 1-1.40 (m, 5H), 1.45-1.55 (m, 1H), 1.65-1.75 (m, 2H), 1.85-1.95 (m, 2H), 3.05-3.20 (m, 1H), 3.6 (s, 3H), 4.00 (bs, 3H), 6.65 (s, 2H), 9.60 (bs, 2H), 10.00 (bs, 1H).

25

MS (m/z) / M+1= 336.4

HPLC (uv purity, λ= 214 nm): 99.7%

30

Example I18.4: R1= cyclohexyl, R2= methyl, R3= 3-hydroxy-4,5-dimethoxy-phenyl

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2,3-dimethoxy-phenol; compound with trifluoromethanesulfonic acid

35

Compound I18.4 was prepared from the appropriate 1,3,4-thiadiazole 7 prepared by the procedure described example I18. In this particular case, the mixture was concentrated

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and the formed precipitate was filtered and washed with ethyl acetate to give the expected compound as a salt of trifluoromethanesulfonic acid.

Yield: 11%

5 ¹H-NMR (400MHz , DMSO) δ ppm: 1.10-1.50 (m, 5H), 1.60-1.70 (m, 1H), 1.75-1.85 (m, 2H), 1.95-2.10 (m, 2H), 3.10-3.25 (m, 1H), 3.75 (s, 3H), 3.85 (s, 6H), 6.85 (s, 1H), 6.95 (s, 1H), 9.80 (bs, 1H), 9.90 (bs, 1H).

MS (m/z) / M+1= 350.45

10 HPLC (uv purity, λ= 214 nm): 99.9%

Example I18.5: R1= cyclohexyl, R2= methyl, R3= 4-chloro-phenyl

15 **[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine**

Compound I18.5 was prepared by the procedure described in example I18 using appropriate intermediates and reagents.

¹H-NMR (400MHz , DMSO) δ ppm: 1.20-1.40 (m, 5H), 1.57-1.63 (m, 1H), 1.70-1.82 (m, 4H), 2.60 (br, 1H), 3.50 (s, 3H),
20 7.52(d, 2H), 7.65 (d, 2H).

MS (m/z) / M+1= 308/310

HPLC (uv putrity, λ= 214nm): 94.24%

Example I18.6: R1= cyclohexyl, R2= methyl, R3= 3-chloro-4-hydroxy-5-methoxy-phenyl

25 **2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-6-methoxy-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid**

Compound I18.6 was prepared from the appropriate 1,3,4-thiadiazole 7i. To a solution of intermediate 7i (2 mmol, 675 mg) in anhydrous dioxane (10 mL), methyltrifluoromethane sulfonate (3 mmol, 337 μl) was added. The resultant mixture was stirred for 48 h to give a precipitate. The mixture was filtered and washed with ethyl acetate to give 400 mg of
30 desired product as a salt of trifluoromethanesulfonic acid.
Yield: 40%

¹H-NMR (400MHz , DMSO) δ ppm: 1.15-1.55 (m, 5H), 1.60-1.70

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(m, 1H), 1.76-1.88 (m, 2H), 2.00-2.11 (m, 2H), 3.11-3.25 (m, 1H), 3.85 (s, 3H), 3.95 (s, 3H), 7.30 (s, 1H), 7.48 (s, 1H), 9.90 (s, 1H), 10.50 (s, 1H).

MS (m/z) / M+1= 354/356

5 HPLC (uv purity, λ = 214 nm): 99.4%

Example I19: R1= cyclohexyl, R2= methyl, R3= 4-chloro-3-sulfamoyl-phenyl

10 **2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide**

To a solution of 1,3,4-thiadiazole 7a (0.215 mmol, 80 mg) in anhydrous dioxane (10 mL), methyltrifluoromethane sulfonate (0.257 mmol, 29 μ l) was added. The resultant mixture was stirred for 24 h. To this solution was added (0.065 mmol, 7 μ l) of methyltrifluoromethanesulfonate to allow reaction to completion. The filtrate is concentrated by distillation under reduced pressure and the residue was dissolved in water. The aqueous mixture was then basified (pH= 5-6) with saturated NaHCO₃ solution and extracted with ethyl acetate. The organic layer was washed with a saturated solution of NaCl and dried over magnesium sulfate, filtered and distilled to give a residue which was purified by silica gel chromatography. (eluted with a gradient of cyclohexane/ethyl acetate) to afford 59 mg of pure product.

Yield: 71%

¹H-NMR (400MHz, DMSO) δ ppm: 1.25-1.55 (m, 5H), 1.65-1.75 (m, 1H), 1.75-1.95 (m, 4H), 2.70-2.80 (m, 1H), 3.65 (s, 3H), 7.80-7.95 (m, 4H), 8.30 (dd, 1H).

30 MS (m/z) / M+1: 387.3

HPLC (uv purity, λ = 214 nm): 99.7%

Example I19.1: R1= cyclohexyl, R2= methyl, R3= 4-chloro- N,N-diethyl-3-sulfonamide-phenyl

35 **2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide**
To a mixture of compound I19 (0.258 mmol, 0.100 g), tetra-n-

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butylammonium hydrogen sulphate (0.0258 mmol, 0.090 g), 50% aqueous sodium hydroxide (0.300 ml) and toluene (2.2 ml), was added ethylbromide (0.310 mmol, 0.023 ml). The reaction was stirred at RT for 2h and then heated to 90°C for 1h30 before a second addition of ethylbromide (0.310 mmol, 0.023 ml). The mixture was heated at 90°C for 2h30 and the volatiles were removed by distillation. The crude material was solubilized with ethyl acetate and the organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure to give 0.1 g of the expected product as a white solid.

Yield= 87.7%

¹H-NMR (400MHz, DMSO) δ ppm: 1.00 (t, 6H), 1.10-1.32 (b, 5H), 1.48-1.54 (m, 1H), 1.65-1.73 (b, 4H), 2.53-2.62 (b, 1H), 3.20-3.30 (m, 4H), 3.48 (s, 3H), 7.68-7.79 (m, 2H), 8.11 (s, 1H).

MS (m/z) / M+1= 443/445

HPLC (uv purity, λ= 214 nm)= 99.72%

Example I19.2: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl

{5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine

To a solution of I19 (0.516 mmol, 0.2 g) in DMF (13 ml) were added potassium carbonate (1.548 mmol, 0.214 g) and water (3 ml). The mixture was stirred at RT until obtaining an homogenous solution and then the bis-(2-chloro-ethyl)methyl-amine hydrochloride (0.516 mmol, 0.10 g) was added. After a day of stirring, the mixture was warmed at 80°C for 15h. The solvents were then evaporated and the crude material was solubilized in dicloromethane. The organic layer was washed with a saturated solution of bicarbonate of sodium, then with brine. After filtration, the filtrate was dried over MgSO₄ and concentrated by distillation. The crude material was chromatographed on silica gel, eluting with dichloromethane containing from 0 to 5% methanol. The solid product was then washed with ethyl acetate.

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Yield= 10%

¹H-NMR (400MHz, CDCl₃ + D₂O) δ ppm: 1.20-1.48 (m, 5H), 1.62-1.68 (m, 1H), 1.79-1.89 (m, 4H), 2.45 (s, 3H), 2.45 (t, 4H), 2.55-2.65 (m, 1H), 3.33 (t, 4H), 3.60 (s, 3H), 7.52 (d, 1H),
5 7.72 (d, 1H), 8.24 (s, 1H).

MS (m/z) / M+1= 470

HPLC (uv purity, λ= 214 nm): 99.53%

**Example I19.3: R1= cyclohexyl, R2= methyl, R3= 4-chloro-3-
10 [(pyridin-4-ylmethyl)-sulfamoyl]-phenyl
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-
benzenesulfonamide**

To a mixture of I19 (0.258 mmol, 0.1 g), triethylamine (0.516
15 mmol, 0.072 ml) and acetic acid (0.516 mmol, 0.03 ml) in 1,2-
dichloroethane, 4-pyridine carboxaldehyde (0.387 mmol, 0.037
ml) was added. The mixture was cooled to 0°C and sodium
triacetoxyborohydride (0.516 mmol, 0.135 g) was added. After
24h of stirring at RT the same quantities of borohydride and
20 aldehyde were added and the reaction was stirred for 15h.

The mixture was then filtered and the filtrate was diluted
with dichloromethane, washed with water, brine, dried over
MgSO₄, filtered and then evaporated to dryness. The residue
was purified on silica gel eluting with dichloromethane
25 containing from 0 to 7% of methanol. The solid product was
then washed with ether to give the title product.

Yield= 40%

¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.39 (m, 5H), 1.54-1.60
(m, 1H), 1.70-1.80 (m, 4H), 2.60-2.67 (m, 1H), 3.50 (s, 3H),
30 4.18 (s, 2H), 7.22 (d, 2H), 7.67 (dd, 1H), 7.76 (dd, 1H),
8.06 (d, 1H), 8.39 (d, 2H), 8.73-8.78 (b, 1H).

MS (m/z) / M+1= 478

HPLC (uv purity, λ= 214 nm): 99.99%

**Example I19.4: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-(2-
35 morpholin-4-yl-ethyl-sulfamoyl)-phenyl
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-**

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benzenesulfonamide

2-Chloro-N-(2-chloro-ethyl)-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide was prepared by the procedure described in example I19.3 using an appropriate aldehyde and I19. The residue was purified by silica gel chromatography eluting with a gradient cyclohexane containing from 0 to 20% of ethyl acetate followed by an isocratic elution with ethyl acetate/cyclohexane (4/6).

Yield= 84%

- 10 To a mixture of this intermediate (0.866 mmol, 0.390 g), in presence of sodium iodide in ethanol (10 ml), morpholine (8.66 mmol, 0.756 ml) was added. After 15 h at reflux, the mixture was evaporated to dryness and the crude material was basified with a saturated solution of sodium bicarbonate.
- 15 After extraction with ethyl acetate, the organic layer was washed with brine, dried over MgSO_4 , filtered and then evaporated to dryness. The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 50% of ethyl acetate.

20 Yield= 65%

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ ppm: 1.20-1.50 (m, 5H), 1.61-1.69 (m, 1H), 1.80-1.89 (b, 4H), 2.30-2.39 (m, 4H), 2.41-2.49 (m, 2H), 2.59-2.68 (m, 1H), 3.00-3.09 (m, 2H), 3.60-3.73 (m, 7H), 5.81-5.89 (b, 1H), 7.54 (d, 1H), 7.73 (d, 1H), 8.32 (s, 1H).

MS (m/z) / M+1= 500/501

HPLC (uv purity, λ = 214 nm): 97.76%

Example I19.5: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-ethylsulfamoyl-phenyl

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide

The title compound was prepared as described in example I19.3. In this particular case, a large excess of

- 35 acetaldehyde (20 equivalents) and triacetoxy borohydride (4 equivalents) were used and added once.

Yield= 50%

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¹H-NMR (400MHz, CDCl₃) δ ppm: 1.13 (t, 3H), 1.22-1.50 (m, 5H), 1.61-1.68 (m, 1H), 1.78-1.87 (b, 4H), 2.57-2.64 (m, 1H), 2.97-3.04 (q, 2H), 3.60 (s, 3H), 4.90 (t, 1H), 7.53 (d, 1H), 7.77 (d, 1H), 8.30 (s, 1H).

5 MS (m/z) / M+1 = 415/416

HPLC (uv purity, λ = 214 nm): 99.36%

Example I19.6: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-[ethyl-(2-morpholin-4-yl-ethyl)-sulfamoyl]-phenyl

10 **2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide**

To a mixture of I19.4 (0.100 mmol, 0.05 g), N-tetrabutyl ammonium hydrogen sulfate (0.02 mmol, 0.008 g), a solution
15 of 50% of sodium hydroxide (1.25 mmol, 0.1 ml) in toluene (2 ml), ethylbromide (1 mmol, 0.075 ml) was added. The mixture was heated to 90°C for 5h and then evaporated to dryness. The residue was solubilized in ethyl acetate and the organic layer was washed with brine, dried over MgSO₄, filtered and
20 then distilled under vacuum. The crude material was purified on silica gel chromatography eluting with a mixture of ethylacetate/cyclohexane in a ratio 1/9 then 2/8 to give the expected product.

Yield= 60%

25 ¹H-NMR (400MHz, CDCl₃) δ ppm: 1.13 (t, 3H), 1.22-1.45 (m, 5H), 1.61-1.68 (m, 1H), 1.78-1.84 (b, 4H), 2.38-2.43 (m, 4H), 2.50-2.53 (t, 2H), 2.57-2.64 (m, 1H), 3.40-3.50 (m, 4H), 3.60-3.65 (m, 7H), 7.50 (d, 1H), 7.70 (d, 1H), 8.30 (s, 1H).

MS (m/z) / M+1 = 528/529

30 HPLC (uv purity, λ = 214 nm): 98.57%

Example I19.7: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-[isopropyl-(2-morpholin-4-yl-ethyl)-sulfamoyl]-phenyl

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide

The title compound was prepared as described in example I19.6 with 13 equivalents of isopropylbromide. The residue was

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purified by silica gel chromatography eluting with a gradient of cyclohexane containing from 0 to 20% ethylacetate.

Yield= 74%

¹H-NMR (400MHz, CDCl₃) δ ppm: 1.50 (d, 6H), 1.22-1.47 (m, 5H),
5 1.61-1.68 (m, 1H), 1.78-1.83 (b, 4H), 2.44-2.50 (m, 4H),
2.57-2.63 (m, 3H), 2.47-2.51 (t, 2H), 3.60 (s, 3H), 3.68-
3.70 (m, 4H), 3.98-4.04 (m, 1H), 7.50 (d, 1H), 7.70 (d, 1H),
8.30 (s, 1H).

MS (m/z) / M+1= 542/543

10 HPLC (uv purity, λ= 214 nm): 96.86%

**Example I19.8: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-
{ethyl-[2-(2-methoxy-ethoxy)-ethyl]-sulfamoyl}-phenyl
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-
15 [1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-
ethyl]-benzenesulfonamide**

To a solution of I19.5 (0.241 mmol, 0.1 g) in EtOH (4 ml),
potassium carbonate (0.289 mmol, 0.040 g) was addedd and then
the reaction mixture was heated at reflux for 30 min before
20 the addition of 1-bromo-2-(2-methoxyethoxy)ethane (0.289
mmol, 0.040 ml). After 3h at reflux, 2.4 equivalents of the
bromo derivative were added and the mixture was kept at
reflux for additional 15h. The mixture was then evaporated to
dryness and the residue was diluted in water and extracted
25 with dichloromethane. The organic layer was washed with
water, brine, dried over MgSO₄, filtered and evaporated to
dryness. The crude material was purified by silica gel
chromatography eluting with a gradient of cyclohexane
containing from 10 to 60% ethylacetate.

30 Yield= 64%

¹H-NMR (400MHz, CDCl₃) δ ppm: 1.11 (t, 3H), 1.20-1.47 (m, 5H),
1.61-1.68 (m, 1H), 1.79-1.89 (b, 4H), 2.59-2.68 (m, 1H), 3.36
(s, 3H), 3.43-3.50 (m, 4H), 3.54-3.58 (m, 4H), 3.61-3.65 (m,
5H), 7.50 (d, 1H), 7.70 (d, 1H), 8.28 (s, 1H).

35 MS (m/z) / M+1= 518/520

HPLC (uv purity, λ= 214 nm): 99.9%

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Example I19.9: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-
[(3-dimethylamino-2-hydroxy-propyl)-ethyl-sulfamoyl]-phenyl
C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-
ethyl-benzenesulfonamide

An excess of epibromohydrin (3 molar equivalents) was reacted with I19.5 following the procedure described in example I19.8. The intermediate was isolated by chromatography on silica gel eluting with a mixture of cyclohexane/ethylacetate in a ratio 1/9. To a solution of this intermediate (0.106 mmol, 0.05 g) in EtOH (2 ml) at 50°C, dimethylamine (0.318 mmol, 0.041 ml) was added and the mixture was heated at 70°C for 15h. The solvent was then removed under reduced pressure. The residue was diluted in water and extracted with dichloromethane. The organic layer was washed with water, brine, dried over MgSO₄, filtered and the volatile was evaporated to give the desired product.

Yield= 64%

¹H-NMR (400MHz, CDCl₃) δ ppm: 1.10 (t, 3H), 1.22-1.49 (m, 5H), 1.60-1.70 (m, 1H), 1.79-1.89 (b, 4H), 2.254-2.36 (m, 8H), 2.58-2.66 (m, 1H), 3.31-3.34 (dd, 1H), 3.42-3.60 (m, 6H), 3.79-3.87 (m, 1H), 7.50 (d, 1H), 7.70 (d, 1H), 8.30 (s, 1H).

MS (m/z) / M+1= 516/517

HPLC (uv purity, λ= 214 nm): 96.60%

Example I19.10: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-
[(2,3-dihydroxy-propyl)-ethyl-sulfamoyl]-phenyl
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-
benzenesulfonamide

The title compound was prepared as described in example I19.8 with 3 eq. of 3-bromo-1,2-propane-diol and the reaction mixture was heated at reflux for 12h. The desired product was obtained after purification of the crude material by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 3% methanol.

Yield= 38%

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¹H-NMR (400MHz, CDCl₃) δ ppm: 1.10 (t, 3H), 1.22-1.49 (m, 5H),
1.62-1.68 (m, 1H), 1.79-1.89 (m, 4H), 2.17-2.22 (m, 1H),
2.59-2.66 (m, 2H), 3.40-3.48 (m, 3H), 3.51-3.57 (dd, 1H),
3.61 (s, 3H), 3.89-3.94 (m, 1H), 7.53 (d, 1H), 7.73 (d, 1H),
5 8.30 (s, 1H).
MS (m/z) / M+1= 489/490
HPLC (uv purity, λ= 214 nm): 98.41%

Example I19.11: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-
10 **[ethyl-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-sulfamoyl]-**
phenyl
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-
yl-propyl)-benzenesulfonamide

15 The title compound was prepared as described in example
I19.9 using the same intermediate and pyrrolidine (3eq) as
nucleophile. The residue was purified by silica gel
chromatography eluting with a gradient of dichloromethane
containing from 2 to 3% of methanol.

20 Yield= 27%

¹H-NMR (400MHz, CDCl₃) δ ppm: 1.10 (t, 3H), 1.19-1.47 (m, 5H),
1.64-1.70 (m, 1H), 1.77-1.90 (m, 4H), 2.48-2.51 (dd, 1H),
2.53-2.78 (m, 7H), 3.33-3.37 (dd, 1H), 3.45-3.54 (m, 2H),
3.56 (d, 2H), 3.61 (s, 3H), 3.87-3.95 (m, 1H), 7.51 (d, 1H),
25 7.72 (d, 1H), 8.30 (s, 1H).

MS (m/z) / M+1= 542/543

HPLC (uv purity, λ= 214 nm): 95.50%

Example I19.12: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-
30 **[(2-diethylamino-ethyl)-ethyl-sulfamoyl]-phenyl**
2-Chloro-5-(cyclohexylimino-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-(2-diethylamino-ethyl)-N-ethyl-
benzenesulfonamide

The title compound was prepared as described in example
35 I19.8 using 3.3 eq of potassium carbonate and 2eq of 2-
diethylaminoethylchloride hydrochloride. The residue was
purified by silica gel chromatography eluting with a mixture

85

of MeOH/DCM (10/90).

Yield= 32%

¹H-NMR (400MHz, CDCl₃) δ ppm: 1.00 (t, 6H), 1.17 (t, 3H),
1.22-1.48 (m, 5H), 1.61-1.70 (b, 1H), 1.80-1.90 (m, 4H),
5 2.48-2.53 (q, 4H), 2.59-2.63 (m, 3H), 3.40-3.45 (m, 4H), 3.63
(s, 3H), 7.50 (d, 1H), 7.72 (d, 1H), 8.30 (s, 1H).

MS (m/z) / M+1= 514/ 515

HPLC (uv purity, λ= 214 nm): 99.34%

10 **Example I19.13: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-
[(2-dimethylamino-1-methyl-ethyl)-ethyl-sulfamoyl]-phenyl
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-methyl-ethyl)-N-
ethyl-benzenesulfonamide (minor isomer)**

15 **and Example I19.14: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-
3-[(2-dimethylamino-propyl)-ethyl-sulfamoyl]-phenyl
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-propyl)-N-ethyl-
benzenesulfonamide (major isomer)**

20 The title compounds were prepared by the procedure described
in example I19.8 using 3.3 eq of potassium carbonate and 2eq
of the of 2-dimethylaminoisopropylchloride hydrochloride.
Two "isomers" were obtained from this reaction:
The crude material was purified by silica gel chromatography
25 eluting with dichloromethane/methanol (99/1) to afford two
isomers.

The minor isomer:

Yield= 10%

¹H-NMR (400MHz, CDCl₃) δ ppm: 1.20-1.47 (m, 11H), 1.64-1.72 (m,
30 1H), 1.77-1.86 (m, 4H), 2.10 (s, 6H), 2.23-2.36 (m, 2H),
2.54-2.66 (m, 1H), 3.31-3.39 (m, 1H), 3.42-3.52 (m, 1H), 3.59
(s, 3H), 3.88-3.93 (m, 1H), 7.50 (d, 1H), 7.70 (d, H), 8.30
(s, 1H).

MS (m/z) / M+1= 500/ 501

35 HPLC (uv purity, λ= 214 nm): 98.67%

The major isomer:

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Yield= 30%

¹H-NMR (400MHz, CDCl₃) δ ppm: 0.92 (d, 3H), 1.11 (t, 3H),
1.23-1.50 (m, 5H), 1.62-1.70 (m, 1H), 1.79-1.89 (m, 4H),
2.14 (s, 6H), 2.59-2.64 (m, 1H), 2.77-2.86 (m, 1H), 3.33-
5 3.51 (m, 4H), 3.59 (s, 3H), 7.50 (d, 1H), 7.70 (d, H), 8.30
(s, 1H).

MS (m/z) / M+1= 500/ 501

HPLC (uv purity, λ= 214 nm): 99.67%

10 **Example I20: R1= cyclohexyl, R2= methylacetate, R3= 4-chlorophenyl**

[5-(4-Chloro-phenyl)-2-cyclohexylimino-[1,3,4]thiadiazol-3-yl]-acetic acid methyl ester

To a solution of the appropriate 1,3,4-thiadiazole 7h (0.34
15 mmol, 100 mg) in anhydrous dioxane (3mL), an excess of
methyl bromoacetate (3.4 mmol) was added. The resultant
mixture was stirred for 48 h at 90°C. The mixture was
concentrated and a saturated solution of K₂CO₃ was added.
The solution was extracted with ethylacetate, the organic
20 layer was dried over MgSO₄, filtered and concentrated to
dryness. The residue was purified by chromatography on silica
gel using a gradient of solvent cyclohexane/ethylacetate to
afford 66 mg of product.

Yield= 52%

25 ¹H-NMR (400MHz, DMSO) δ ppm: 1.20-1.35 (m, 5H), 1.55-1.60
(m, 1H), 1.65-1.75 (m, 4H), 2.65 (br, 1H), 3.65 (s, 3H),
4.77 (s, 2H), 7.53 (d, 2H), 7.67 (d, 2H).

MS (m/z) / M+1= 366/368

HPLC (uv putrity, λ= 214nm): 99.70%

30

The compounds of the following examples were prepared by the
procedure described in example I20 using appropriate
intermediates and reagents:

I20.1	[5-(4-Chloro-phenyl)-3-cyclopropylmethyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine
I20.2	3-[5-(4-Chloro-phenyl)-2-cyclohexylimino-

	[1,3,4]thiadiazol-3-yl]-propane-1,2-diol
I20.3	[5-(4-Chloro-phenyl)-3-(2-diethylamino-ethyl)-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

Example I21: R1= cyclohexyl, R2= methyl, R3= 3- benzoic acid methyl ester

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester

To a solution of the appropriate 1,3,4-thiadiazole 7 (1.86 mmol, 590 mg) prepared by the procedure described in **example 7g** in anhydrous dioxane (20 mL), methyltrifluoromethane sulfonate (2.79 mmol, 316 μ l) and triethylamine (2.23 mmol, 310 μ l) were added. The mixture was stirred for 7h at RT. The mixture was filtered and the precipitate was then poured into diluted NaHCO₃ solution and washed with dichloromethane. The organic layer was washed with saturated solution of NaCl and dried over magnesium sulfate, filtered and concentrated under reduce pressure to give 200 mg of the title product.

Yield: 37%

¹H-NMR (400MHz , DMSO) δ ppm: 1.10-1.35 (m, 5H), 1.45-1.55 (m, 1H), 1.60-1.75 (m, 4H), 2.50-2.60 (m, 1H), 3.45 (s, 3H), 3.80 (s, 3H), 7.55 (t, 1H), 7.80 (d, 2H), 7.95 (d, 2H), 8.10 (s, 1H).

MS (m/z) / M+1= 332.3

HPLC (uv purity, λ = 214 nm): 99.9%

Example I21.1: R1= cyclohexyl, R2= methyl, R3= 3-benzoic acid

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid

To a solution of compound I21 (30 mg, 0.09 mmol) in methanol (10 ml) and water (2.5 ml), K₂CO₃ (163 mg, 1.17 mmol) was added. The mixture was heated at reflux for 3h, allowed to cool and concentrated in vacuo to give a crude material. This residue was poured into water and the suspension was carefully neutralised with a solution of HCl (0.1N) and the

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aqueous phase was extracted with ethyl acetate. The organic layer was washed with saturated solution of NaCl, dried over magnesium sulfate, filtered and distilled to give 10 mg of the title product.

5 Yield: 35%

¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.80 (m, 4H), 2.55-2.65 (m, 1H), 3.50 (s, 3H), 7.55 (t, 1H), 7.80 (d, 1H), 7.95 (d, 1H), 8.15 (s, 1H), 13.3 (bs, 1H).

10 MS (m/z) / M+1= 318.3

HPLC (uv purity, λ = 214 nm): 99.6%

**Example I21.2: R1= cyclohexyl, R2= methyl, R3= 3-benzamide
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-
15 2-yl)-benzamide**

To a solution of LiOH monohydrate (96 mg, 2.26 mmol) in 1.6 ml of water, a solution of I21 (500 mg, 1.51 mmol) in tetrahydrofuran (THF)/MeOH (50/50) (8 ml) was added. The mixture was stirred at RT for 24H and then concentrated
20 under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 38 ml) was added. The resulting mixture was stirred for 2 hours. After distillation of water, the product was dried over P₂O₅ in vacuo. To a solution of this crude material (1.51 mmol) in toluene (10 ml),
25 thionylchloride (10 ml) was added dropwise and the mixture was heated at reflux for 5H. The mixture was concentrated under reduced pressure. A solution of ammonia (1 ml at 28%) was added to a solution of the residue (150 mg, 0.32 mmol) in THF (2 ml) cooled to 10°C. After 3 hours at RT, the
30 mixture was concentrated to dryness, poured into water and extracted with ethyl acetate. The combined organic extracts were washed with water and with a saturated solution of NaCl, dried over magnesium sulfate, filtered and distilled under reduced pressure. The white solid material was
35 purified by silica gel chromatography (eluted with dichloromethane/methanol at 99/1) to afford 14mg of the title product.

Yield: 14%

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¹H-NMR (400MHz, DMSO) δ ppm: 1.20-1.45 (m, 5H), 1.60-1.70 (m, 1H), 1.75-1.90 (m, 4H), 2.65-2.75 (m, 1H), 3.60 (s, 3H), 7.52 (s, 1H), 7.60 (dd, 1H), 7.85 (d, 1H), 7.98 (d, 1H), 8.15 (s, 1H), 8.18 (s, 1H).

5 MS (m/z) / M+1= 317

HPLC (uv purity, λ= 214 nm): 99.9%

Example I21.3: R1= cyclohexyl, R2= methyl, R3= 3-[N-(2-hydroxy-ethyl)]-benzamide

10 **3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-hydroxy-ethyl)-benzamide**

To a solution of LiOH monohydrate (96 mg, 2.26 mmol) in 1.6 ml of water, a solution of I21 (500 mg, 1.51 mmol) in THF/MeOH (50/50) (8 ml) was added. The mixture was stirred
15 at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 38 ml) was added. The resulting mixture was stirred for 2 hours. After distillation of water, the product was dried over P₂O₅ in vacuo. To a solution of this crude
20 material (1.51 mmol) in toluene (10 ml), thionylchloride (10 ml) was added dropwise and the mixture was heated at reflux for 5H. The mixture was concentrated under reduced pressure. To a suspension of this residue (150 mg, 0.32 mmol) in THF (2ml) with triethylamine (90 μl, 0.64 mmol) was added at 0°C
25 ethanolamine (20 μl, 0.32 mmol) and stirred at room temperature during 4 hours. Water was added in the mixture and extracted with ethyl acetate, washed with water and brine, dried with magnesium sulfate, filtered and reduce under pressure vacuum. The residue was purified by silica
30 gel chromatography with a gradient of dichlorometane containig from 0 to 2% methanol to afford 50 mg of the good product.

Yield: 43%

¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.55-1.65
35 (m, 1H), 1.70-1.83 (m, 4H), 2.55-2.75 (m, 1H), 3.30-3.37 (m, 2H), 3.45-3.55 (m, 5H), 4.70 (t, 1H), 7.55 (dd, 1H), 7.80 (d, 1H), 7.90 (d, 1H), 8.05 (s, 1H), 8.60 (t, 1H).

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MS (m/z) / M+1= 361

HPLC (uv purity, λ = 214 nm): 99.7%

Example I21.4: R1= cyclohexyl, R2= methyl, R3= 3-(N-methyl)-benzamide

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide

To a solution of LiOH monohydrate (96 mg, 2.26 mmol) in 1.6 ml of water, a solution of I21 (500 mg, 1.51 mmol) in THF/MeOH (50/50) (8 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 38 ml) was added. The resulting mixture was stirred for 2 hours. After distillation of water, the product was dried over P₂O₅ in vacuo. To a solution of this crude material (1.51 mmol) in toluene (10 ml), thionylchloride (10 ml) was added dropwise and the mixture was heated at reflux for 5H. The mixture was concentrated under reduced pressure. To a suspension of this residue (150 mg, 0.32 mmol) in THF (4 ml) with triethylamine (90 μ l, 0.64 mmol) was added at 0°C methylamine hydrochloride (44 mg, 0.64 mmol) and stirred at room temperature during 4 hours. Water was added in the mixture and basified with a solution of NaHCO₃, extracted with ethyl acetate, washed with water and brine, dried with magnesium sulfate, filtered and reduce under pressure vacuum. The residue was purified by silica gel chromatography with a gradient of dichlorometane containig from 0 to 2% methanol to afford the desired product.

Yield: 9%

¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 2.82 (s, 3H), 3.55 (s, 3H), 7.60 (t, 1H), 7.80 (d, 1H), 7.90 (d, 1H), 8.05 (s, 1H), 8.55-8.65 (m, 1H).

MS (m/z) / M+1= 331

HPLC (uv purity, λ = 214 nm): 96.6%

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Example I22: R1= cyclohexyl, R2= methyl, R3= 3,4-dihydroxyphenyl

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4] thiadiazol-2-yl)-benzene-1,2-diol; compound with trifluoro

5 methanesulfonic acid

Compound I22 was prepared from 1,3,4-thiadiazole 7g by the procedure described in example I18 using appropriate intermediates and reagents (protocol C).

10 In this particular case, the mixture was filtered and the precipitate was washed with dioxane and diethylether to give the expected compound as a trifluoromethanesulfonic acid salt.

Yield= 54.1%

¹H-NMR (400MHz, DMSO) δ ppm: 1.10-1.53 (m, 5H), 1.64-1.69 (b, 1H), 1.78-1.84 (b, 1H), 2.03-2.10 (b, 2H), 3.19-3.27 (b, 1H), 3.84 (s, 3H), 6.90 (d, 1H), 7.13 (d, 1H), 7.20 (s, 1H), 9.55-9.63 (b, 1H), 9.75-9.81 (b, 1H), 9.96-10.3 (b, 1H).

MS (m/z) / M+1= 306/307

HPLC (uv purity, λ= 214 nm)= 97.35 %

20

Example I23: R1= cyclohexyl, R2= methyl, R3= 3,5-dimethoxy-4-hydroxy-phenyl

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4] thiadiazol-2-yl)-2,6-dimethoxy-phenol

25 Compound I23 was prepared from the appropriate 1,3,4-thiadiazole 7 by the procedure described in example I18 using appropriate intermediates and reagents (protocol C).

In this particular case, the mixture was filtered and the precipitate was washed with dioxane and diethylether to give the expected compound as a trifluoromethanesulfonic acid salt.

Yield= 13.9%

¹H-NMR (400MHz, DMSO) δ ppm: 1.12-1.27 (b, 1H), 1.27-1.41 (b, 2H), 1.41-1.54 (b, 2H), 1.63-1.70 (b, 1H), 1.80-1.87 (b, 2H), 2.03-2.11 (b, 2H), 3.17-3.26 (b, 1H), 3.88 (9H, s), 7.06 (s, 2H), 9.38-9.47 (b, 1H), 9.80-9.88 (b, 1H).

MS (m/z) / M+1= 350/351

35

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HPLC (uv purity, λ = 214 nm) = 96.00%

Compounds I23.1 and I23.2 were prepared by the procedure described in example I18 using appropriate intermediates and reagents (protocol C).

I23.1	6-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-pyridin-2-ol
I23.2	5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2,3-triol

Example I24: R1= cyclohexyl, R2= methyl, R3= 8-hydroxyquinolin-2-yl

10 **2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinolin-8-ol**

Compound I24 was prepared from the appropriate 1,3,4-thiadiazole 7 (procedure described in example 7d) by the procedure described in example I18.6. In this particular case, the mixture was filtered and the precipitate was washed with dioxane and diethylether to give the expected compound as a trifluoromethansulfonic acid salt.

Yield = 58.1%

¹H-NMR (400MHz, DMSO) δ ppm: 1.25-1.36 (b, 1H), 1.45-1.67 (b, 4H), 1.74-1.81 (b, 1H), 1.90-1.96 (b, 2H), 2.18-2.22 (b, 2H), 3.40-3.50 (b, 1H), 4.02 (s, 3H), 7.35 (d, 1H), 7.63 (d, 1H), 7.69 (t, 1H), 8.21 (d, 1H), 8.64 (d, 1H), 10.08-10.13 (b, 1H), 10.21-10.28 (b, 1H).

MS (m/z) / M+1 = 341/342

25 HPLC (uv purity, λ = 214 nm) = 94.88%

**Example I25: R1= cyclohexyl, R2= methyl, R3= 2-pyrazyl
Cyclohexyl-(3-methyl-5-pyrazin-2-yl-3H-[1,3,4] thiadiazol-2-ylidene)-amine**

30 The 1,3,4-thiadiazole 7f (0.770 mmol, 0.200 g) and methyltrifluoromethane sulfonate (0.924 mmol, 0.104 ml) were reacted in dioxane (7 ml). The residue, obtained after basification to pH 9-10 with a saturated solution of

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carbonate of potassium, was subjected to silica gel chromatography, eluting with dichloromethane containing from 0 to 10% methanol to give the expected product.

Yield= 0.075g, 35.37%

5 $^1\text{H-NMR}$ (400MHz, DMSO) δ ppm: 1.20-1.43 (b, 5H), 1.56-1.65 (b, 1H), 1.90-2.00 (b, 4H), 2.63-2.70 (b, 1H), 3.56 (s, 3H), 8.67 (s, 2H), 9.12 (s, 1H).

HPLC (uv purity, λ = 214 nm)= 98.32%

MS (m/z) / M+1= 276/277

10

Example I26: R1 =cyclohexyl, R2= methyl, R3= (E)-2-(3-hydroxy-4-methoxy-phenyl)-vinyl

5-[(E)-2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-vinyl]-2-methoxy-phenol

15 Compounds I26 was prepared by the procedure described in example I18 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7d) and reagents. The desired product was isolated by chromatography on silica gel eluting with dichloromethane containing from 0 to 7% methanol.

Yield= 0.025g, 24.1%

$^1\text{H-NMR}$ (400MHz, DMSO) δ ppm: 1.10-1.36 (b, 6H), 1.52-1.59 (b, 1H), 1.66-1.78 (b, 4H), 3.39 (s, 3H), 3.76 (s, 3H), 6.70-6.80 (b, 1H), 6.85-6.97 (b, 2H), 6.97-7.07 (b, 2H),

25 9.04 (s, 1H).

MS (m/z) / M+1= 346/347

HPLC (uv purity, λ = 214 nm)= 98.64%

30 **Example I27:** R1= cyclohexyl, R2= methyl, R3= 3-methoxy-4-hydroxy-phenyl

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol

35 Compounds I27 was prepared by the procedure described in example I18 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7d) and reagents. The desired product was isolated by chromatography on silica gel (Alltech, 2g silice) eluting with cyclohexane

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containing from 0 to 4% ethylacetate.

Yield= 0.015 g, 14.2%

¹H-NMR (400MHz, DMSO) δ ppm: 1.01-1.20 (b, 5H), 1.39-1.44 (b, 1H), 1.53-1.63 (b, 4H), 2.4-2.48 (b, 1H), 3.30 (s, 3H), 3.65 (s, 3H), 6.64 (d, 1H), 6.87 (d, 1H), 7.00 (d, 1H), 9.38-9.43 (b, 1H).

MS (m/z) / M+1= 320/321

HPLC (uv purity, λ = 214 nm)= 99.08%

10 **Example I28: R1= cyclohexyl, R2= methyl, R3= quinolin-8-yl**
Cyclohexyl-(3-methyl-5-quinolin-8-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

Compounds I28 was prepared by the procedure described in example I18 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7b) and reagents. The residue was subjected to silica gel chromatography, eluting with cyclohexane containing from 0 to 20% AcOEt.

Yield: 41%

20 ¹H-NMR (400MHz, DMSO) δ ppm: 1.10-1.35 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.80 (m, 4H), 2.70-2.80 (m, 1H), 3.45 (s, 3H), 7.55-7.60 (m, 1H), 7.60-7.70 (m, 1H), 7.95-8.05 (m, 1H), 8.35-8.40 (m, 1H), 8.40-8.45 (m, 1H), 8.20-8.80 (m, 1H).

MS (m/z) / M+1= 325.3

25 HPLC (uv purity, λ = 214 nm): 99.9%

Example I29: R1= cyclohexyl, R2= methyl, R3= 4-dimethylamino-phenyl

30 **[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine**

Compounds I29 was prepared by the procedure described in example I18 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7b) and reagents. The product was chromatographed on silica gel column using cyclohexane/ethyl acetate with a ratio 8/2 as solvent.

Yield: 27%

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¹H-NMR (400MHz, DMSO) δ ppm: 1.10-1.35 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.80 (m, 4H), 2.50-2.60 (m, 1H), 3.45 (s, 3H), 6.70 (d, 2H), 7.40 (d, 2H).

MS (m/z) / M+1= 317.3

5 HPLC (uv purity, λ = 214 nm): 99.5%

Example I30: R1= cyclohexyl, R2= methyl, R3= 4-sulfonamide-phenyl

10 **4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide**

Compounds I30 was prepared by the procedure described in example I18 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7b) and reagents.

15 The residue was subjected to silica gel chromatography, eluting with cyclohexane containing from 0 to 20% AcOEt.

Yield: 21%

¹H-NMR (400MHz, DMSO) δ ppm: 1.10-1.35 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.75 (m, 4H), 2.50-2.60 (m, 1H), 3.45 (s, 3H),
20 7.40 (s, 2H), 7.75 (d, 2H), 7.85 (d, 2H).

MS (m/z) / M+1= 353.2

HPLC (uv purity, λ = 214 nm): 98.5%

Example I31: R1= cyclohexyl, R2= methyl, R3= 5-chloroindol-2-yl

25 **[5-(5-Chloro-1H-indol-2-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine; compound with trifluoromethanesulfonic acid**

Compounds I31 was prepared by the procedure described in
30 example I18.6 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7b) and reagents.

In this particular case, the mixture was filtered and the precipitate was washed with ethyl acetate to give the
35 expected compound as a salt of trifluoromethanesulfonic acid.

Yield: 88%

¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.55 (m, 5H), 1.60-1.70

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(m, 1H), 1.75-1.85 (m, 2H), 1.95-2.10 (m, 2H), 3.10-3.30 (m, 1H), 3.85 (bs, 3H), 7.10-7.15 (m, 1H), 7.15-7.20 (m, 1H), 7.40-7.50 (m, 1H), 7.75 (bs, 1H), 10 (bs, 1H), 12.40 (bs, 1H).

5 MS (m/z) / M+1= 347.3

HPLC (uv purity, λ = 214 nm): 95.2%

Compound I31.1 was prepared by the procedure described in example I31 using appropriate intermediates and reagents:

10

I31.1	2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid
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Example I32: R1= cyclohexyl, R2= methyl, R3= 3-hydroxy-4-methoxy-phenyl

15 5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid

Compounds I32 was prepared by the procedure described in example I18.6 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7b) and reagents.

In this particular case, the mixture was concentrated, filtered and the precipitate was washed with ethyl acetate to give the expected compound as a salt of trifluoromethansulfonic acid.

25 Yield: 69%

¹H-NMR (400MHz, DMSO) δ ppm: 1.05-1.45 (m, 5H), 1.50-1.60 (m, 1H), 1.70-1.80 (m, 2H), 1.90-2.05 (m, 2H), 3.05-3.20 (m, 1H), 3.8 (2s, 6H), 7.00 (d, 1H), 7.15-7.20 (m, 2H), 9.60 (bs, 1H), 9.75 (bs, 1H).

30

MS (m/z) / M+1= 320.3

HPLC (uv purity, λ = 214 nm): 98%

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Example I33: R1= cyclohexyl, R2= methyl, R3= 4-hydroxy-phenyl
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-
2-yl)-phenol; compound with 1,1,1-trifluoro-methanesulfonic
acid

5 Compounds I33 was prepared by the procedure described in
example I18.6 using appropriate intermediate (1,3,4-
thiadiazole 7 - procedure described in example 7b) and
reagents.

10 In this particular case, the mixture was filtered and the
precipitate was washed with ethyl acetate to give the
expected compound as a salt of trifluoromethanesulfonic acid.
Yield: 95%

¹H-NMR (400MHz, DMSO) δ ppm: 1.05-1.45 (m, 5H), 1.50-1.60
(m, 1H), 1.65-1.75 (m, 2H), 1.90-2.00 (m, 2H), 3.30-3.40 (m,
15 1H), 3.75 (s, 3H), 6.85 (d, 2H), 7.60 (d, 2H), 9.70 (bd,
1H), 10.25 (bd, 1H).

MS (m/z) / M+1= 290.3

HPLC (uv purity, λ= 214 nm): 95.6%

20 Example I34: R1= cyclohexyl, R2= methyl, R3= 3,4-dimethoxy-
phenyl

Cyclohexyl-[5-(3,4-dimethoxy-phenyl)-3-methyl-3H-
[1,3,4]thiadiazol-2-ylidene]-amine

Compound I34 was prepared from the appropriate 1,3,4-
25 thiadiazole 7 by the procedure described in example I17
(protocol C) using appropriate intermediates and reagents.
The desired product was isolated by chromatography on silica
gel eluting with cyclohexane containing from 0 to 20%
ethylacetate.

30 Yield: 28%

¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.30 (m, 5H), 1.45-1.55
(m, 1H), 1.60-1.75 (m, 4H), 2.45-2.60 (m, 1H), 3.40 (s, 3H),
3.70 (2s, 6H), 6.95 (d, 1H), 7.05 (d, 1H), 7.10 (s, 1H)

MS (m/z) / M+1= 334.3

35 HPLC (uv purity, λ= 214 nm): 98.2%

Example I35: R1= cyclohexyl, R2= methyl, R3= 3-bromo-4-

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methoxy-phenyl

[5-(3-Bromo-4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

Compound I35 was prepared from 1,3,4-thiadiazole 7e, by the
5 procedure described in example I17 (protocol C) using appropriate intermediates and reagents.

The desired product was isolated by chromatography on silica gel eluting with cyclohexane containing from 0 to 15% ethylacetate.

10 Yield: 13%

¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.55-2.65 (m, 1H), 3.50 (s, 3H), 3.90 (s, 3H), 7.20 (d, 1H), 7.60 (d, 1H), 7.85 (s, 1H)
MS (m/z) / M+1= 384.2

15 HPLC (uv purity, λ= 214 nm): 95%

The compounds of the following examples were prepared by the procedure described in example I35 using appropriate intermediates and reagents:

20

I35.1	Cyclohexyl-[5-(4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I35.2	Cyclohexyl-(3-methyl-5-phenyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

Example I36: R1= cyclohexyl, R2= methyl, R3= 3-hydroxy-phenyl
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol

25 Compound I36 was prepared from the appropriate 1,3,4-thiadiazole 7 by the procedure described in example I17 (protocol C), using appropriate intermediates and reagents.
The product was chromatographed on silica gel column using a gradient of cyclohexane/ethyl acetate.

30 Yield: 14%

¹H-NMR (400MHz, DMSO) δ ppm : 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.55-2.65 (m, 1H), 3.50 (s, 3H), 6.85 (d, 1H), 7.00-7.05 (m, 2H), 7.25 (t, 1H), 9.75 (s, 1H)

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MS (m/z) / M+1 =290.29

HPLC (uv purity, λ = 214 nm): 93.9%

Example I37: R1= cyclohexyl, R2= methyl, R3= 4-benzoic acid methyl ester

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester

Compound I37 was prepared from the appropriate 1,3,4-thiadiazole 7 by the procedure described in example I17 (protocol C) using appropriate intermediates and reagents. The product was chromatographed on silica gel column using a gradient of cyclohexane/ethyl acetate.

Yield: 47%

$^1\text{H-NMR}$ (400MHz, DMSO) δ ppm: 1.10-1.35 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.75 (m, 4H), 2.50-2.65 (m, 1H), 3.50 (s, 3H), 3.80 (s, 3H), 7.70 (d, 2H), 8.00 (d, 2H).

MS (m/z) / M+1= 332.3

HPLC (uv purity, λ = 214 nm): 99.9%

Example I37.1: R1= cyclohexyl, R2= methyl, R3= 4-benzoic acid

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid

To a solution of 1,3,4-thiadiazol I37 (80 mg, 0.24 mmol) in methanol (10 ml) and water (2.5 ml), K_2CO_3 (434 mg, 3.14 mmol) was added. The mixture was heated at 65°C during 3h then at RT over night. The solvent was removed by distillation under reduced pressure to give a crude material. This residue was poured into water, the suspension was carefully neutralised with a solution of HCl (0.1N) and the aqueous phase was extracted with dichloromethane. The organic layer was washed with saturated solution of NaCl, dried over magnesium sulfate, filtered and distilled to give 40 mg of the title product.

Yield: 52%

$^1\text{H-NMR}$ (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.55-2.70 (m, 1H), 3.55 (s, 3H),

100

7.75 (d, 2H), 8.00 (d, 2H), 13.15 (bs, 1H).

MS (m/z) / M+1= 318.4

HPLC (uv purity, λ = 214 nm): 99.9%

5 **Example I37.2: R1= cyclohexyl, R2= methyl, R3= 4-hydroxamic acid phenyl**

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-hydroxy-benzamide

To a solution of LiOH monohydrate (37 mg, 0.75 mmol) in 0.8
10 ml of water, a solution of compound I37 (250 mg, 0.75 mmol)
in THF/MeOH (50/50) (4 ml) was added. The mixture was
stirred at RT for 24H and then concentrated under reduced
pressure. The residue was dissolved in water (2 ml) and a
solution of HCl (0.1N, 15 ml) was added. The resulting
15 mixture was stirred for 20 min. After distillation of water,
the crude product was dried over P₂O₅ in vacuo. To a
solution of 75 mg (0.19 mmol) of this crude material in
toluene (1 ml), a drop of pyridine, and thionylchloride (70
 μ l) were added and reacted at reflux during 4H. The
20 volatiles were removed under reduced pressure. To a solution
of this residue in anhydrous THF, O-(trimethylsilyl)
hydroxylamine (230 μ l, 0.47 mmol) was added with molecular
sieves (3A) and the reaction mixture was stirred for 18H at
RT. After filtration, the filtrate was concentrated under
25 reduced pressure and the residue was treated with a 1 M
solution of HCl, stirred at RT and then basified with a
solution of NaHCO₃. The aqueous phase was extracted with
dichloromethane. The organic layer was washed with brine,
dried over magnesium sulfate, filtered and concentrated in
30 vacuo. The title product was isolated by preparative HPLC on
inverse phase (HYPERSYL C18) eluting with water containing
from 5 to 95% acetonitrile during 20 mn.

Yield: 12 mg, 20%

¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65
35 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 3.50 (s, 3H),
7.65 (d, 2H), 7.85 (d, 2H):

MS (m/z) / M+1= 333.2

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HPLC (uv purity, $\lambda = 214$ nm): 94.9%

Example I37.3: R1= cyclohexyl, R2= methyl, R3= 4-benzamide
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-
5 2-yl)-benzamide

To a solution of LiOH monohydrate (126 mg, 3.0 mmol) in 0.8 ml of water, a solution of I37 (1.0g, 3mmol) in THF/MeOH (50/50) (4 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The
10 residue was dissolved in water (8 ml) and a solution of HCl (0.1N, 60 ml) was added. The resulting mixture was stirred for 20 min. After distillation of water, the product was dried over P₂O₅ in vacuo. To a solution of 120 mg (0.3 mmol) of this crude material in 2 ml of toluene, thionylchloride
15 (2 ml) was added dropwise and the mixture was heated at reflux for 4H. The mixture was concentrated under reduced pressure. A solution of ammonia (1 ml at 28%) was added to a solution of the residue in THF (2 ml) cooled to 10°C. After allowing to stand 5 hours at RT, the mixture was
20 concentrated to dryness, poured into water and extracted with ethyl acetate. The combined organic extracts were washed with water and with a saturated solution of NaCl, dried over magnesium sulfate, filtered and distilled under reduced pressure. The white solid material was purified by
25 silica gel chromatography (eluted with dichloromethane) to afford 64mg of the title product.

Yield: 67%

¹H-NMR (400MHz, DMSO) δ ppm: 1.20-1.45 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 3.55 (s, 3H),
30 7.45(bs, 1H), 7.75 (d, 2H), 7.95 (d, 2H), 8.05 (bs, 1H).

MS (m/z) / M+1= 317.35

HPLC (uv purity, $\lambda = 214$ nm): 99.3%

Example I37.4: R1= cyclohexyl, R2= methyl, R3= 4-N-(2H-
35 tetrazol-5-yl)-benzamide.

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4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2H-tetrazol-5-yl)-benzamide hydrochloride salt

To a solution of LiOH monohydrate (187 mg, 4.5 mmol) in 0.8 ml of water, a solution of compound I37 (250 mg, 0.75 mmol) in THF/MeOH (50/50) (4 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water (2 ml) and a 0.1 M solution of HCl was added to reach pH 6-7. After distillation of water, the crude material was dried over P₂O₅ in vacuo. Morpholine type resin (180 mg, 0.62 mmol) was added to a solution of 450 mg (0.62 mmol) of this crude material in 15ml of THF cooled to -15°C. Then isobutylchloroformate (105 µl, 0.8mmol) was added and the mixture was stirred at -15°C for 1H30 before addition of a suspension of amino-1H-tetrazole (80 mg, 0.74 mmol) in THF (10 ml). The reaction mixture was allowed to stand overnight at RT and the mixture was filtered over a silica gel. The filtrate was concentrated to dryness, and purified by preparative HPLC on inverse phase C18 (HYPERSYL), eluting with water containing from 5 to 95% acetonitrile in 20 min to afford 10 mg of the title product. The compound was treated with a solution of ethanol/HCl to give the corresponding hydrochloride salt.

Yield: 4%

¹H-NMR (400MHz, DMSO) δ ppm: 1.10-2.15 (m, 10H), 3.10-3.30 (m, 1H), 4.00 (bs, 3H), 8.10 (bd, 2H), 8.35 (bd, 2H), 12.70 (bs, 1H).

MS (m/z) / M+1= 385.46

HPLC (uv purity, λ= 214 nm): 99.9%

30

Example I37.5: R1= cyclohexyl, R2= methyl, R3= 4-(N-quinolin-8-yl)-benzamide**4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide**

To a solution of LiOH monohydrate (794 mg, 19mmol) in 18 ml of water, a solution of I37 (5.7 g, 17.2mmol) in THF/MeOH (50/50) (100 ml) was added. The mixture was stirred at RT

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for 24H and then concentrated under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 361 ml) was added. The resulting mixture was stirred for 3H30. After distillation of water, the crude product was
5 dried over P₂O₅ in vacuo. To a suspension of 200 mg (0.5 mmol) of this crude material in CH₂Cl₂/DMF (50/50) (6 ml) were added cyclocarbodiimide-N-methyl resin (1.03 g, 1.5 mmol), 1-hydroxy-7-azabenzotriazol (14 mg, 0.1mmol), N,N-diisopropylethylamine (175 µl, 1 mmol), 8-aminoquinoline
10 (145 mg, 1 mmol), molecular sieves (3A) and the reaction mixture was stirred 24H at RT. After filtration, methylisocyanate resin (1 g, 1 mmol) was added to the filtrate and the mixture was stirred for another 24H at RT. The mixture was filtered, the filtrate was concentrated
15 under reduced pressure. The residue was purified by silica gel chromatography eluting with a gradient of cyclohexane containing from 0 to 20% ethyl acetate to afford 10 mg of the title product.

Yield: 4.5%

- 20 ¹H-NMR (400MHz , DMSO) δ ppm: 1.20-1.40 (m, 5H), 1.60-1.65 (m, 1H), 1.75-1.85 (m, 4H), 2.65-2.75 (m, 1H), 3.55 (s, 3H), 7.65-7.75 (m, 2H), 7.80 (d, 1H), 7.90 (d, 2H), 8.15 (d, 2H), 8.5 (d, 1H), 8.75 (d, 1H), 9.00 (d, 1H), 10.70 (s, 1H).
MS (m/z) / M+1= 444.13
25 HPLC (uv purity, λ = 214 nm): 96.4%

Example I37.6: R1= cyclohexyl, R2= methyl, R3= 4-N-(2,6-dimethoxy-pyridin-3-yl)-benzamide

**4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-
30 2-yl)-N-(2,6-dimethoxy-pyridin-3-yl)-benzamide**

To a solution of LiOH monohydrate (794 mg, 19 mmol) in 18 ml of water, a solution of I37 (5.7 g, 17.2 mmol) in THF/MeOH (50/50) (100 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The
35 residue was dissolved in water and a solution of HCl (0.1N, 361 ml) was added. The resulting mixture was stirred for 3H30. After distillation of water, the crude product was

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dried over P_2O_5 in vacuo. To a suspension of 200 mg (0.5 mmol) of this crude material in CH_2Cl_2 /DMF (50/50) (6 ml) were added cyclocarbodiimide-N-methyl resin (1.03 g, 1.5 mmol), 1-hydroxy-7-azabenzotriazol (14 mg, 0.1 mmol),
5 N,N-diisopropylethylamine (260 μ l, 1.5 mmol), 3-amino-2,6-dimethoxypyridine monohydrochloride (190 mg, 1mmol), molecular sieves (3A) and the reaction mixture was stirred 24h at RT. After filtration, methylisocyanate resin (1 g, 1 mmol) was added to the filtrate and the mixture was stirred
10 for another 24H at RT. The mixture was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with a gradient of cyclohexane containing from 0 to 10% ethyl acetate to afford 60 mg of the title product.

15 Yield: 26%

1H -NMR (400MHz, DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.50-1.60 (m, 1H), 1.70-1.80 (m, 4H), 2.55-2.65 (m, 1H), 3.50 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 6.35 (d, 1H), 7.70-7.80 (m, 3H), 8.00 (d, 2H), 9.65 (s, 1H).

20 MS (m/z) / M+1= 454

HPLC (uv purity, λ = 214 nm): 99.9%

Example I37.7: R1= cyclohexyl, R2= methyl, R3= 4-N-isopropyl-benzamide

25 **4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide**

To a solution of LiOH monohydrate (794 mg, 19 mmol) in 18 ml of water, a solution of I37 (5.7g, 17.2 mmol) in THF/MeOH (50/50) (100 ml) was added. The mixture was stirred at RT
30 for 24H and then concentrated under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 361 ml) was added. The resulting mixture was stirred for 3H30. After distillation of water, the crude product was dried over P_2O_5 in vacuo. To a suspension of 200 mg (0.5
35 mmol) of this crude material in CH_2Cl_2 /DMF (50/50) (6 ml) were added cyclocarbodiimide-N-methyl resin (1.03 g, 1.5 mmol), 1-hydroxy-7-azabenzotriazol (15 mg, 0.1mmol),

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N,N-diisopropylethylamine (175 μ l, 1 mmol), isopropylamine (85 μ l, 1 mmol), molecular sieves (3A) and the reaction mixture was stirred 24H at RT. After filtration, Methylisocyanate resin (1 g, 1 mmol) was added to the
5 filtrate and the mixture was stirred for another 24H at RT. The mixture was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with a gradient of cyclohexane containing from 0 to 20% ethyl acetate to afford 40 mg of
10 the title product.

Yield: 22%

¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 11H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 3.55 (s, 3H), 4.05-4.15 (m, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.30 (d, 1H).

15 MS (m/z) / M+1= 359

HPLC (uv purity, λ = 214 nm): 99.9%

Example I37.8: R1= cyclohexyl, R2= methyl, R3= 4-N-ethyl-benzamide

20 **4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-ethyl-benzamide**

To a solution of 2M ethylamine (1.8 ml, 3.6 mmol) in dichloroethane (5 ml) under nitrogen at 0°C, was added 2M trimethylaluminium (1.8 ml, 3.6 mmol) and the mixture was
25 stirred at RT for 15min. Then, a solution of compound I37 (180 mg, 0.54 mmol) in dichloroethane (5 ml) was added and the reaction mixture was allowed to stir for 48 h at RT. A solution of 2M ethylamine (0.8 ml, 1.6 mmol) and of 2M trimethylaluminium (0.8 ml, 1.6 mmol) were added to allow
30 reaction to completion and the mixture was stirred at RT for another 24H. The mixture was diluted with 50 ml of dichloromethane and 30 ml of water, stirred for 2H, and filtered through Celite. The filtrate was washed with water, brine and the organic layer was dried over MgSO₄, filtered,
35 and concentrated under reduced pressure. The residue was subjected to flash chromatography eluting with a gradient of cyclohexane containing from 0 to 20% ethyl acetate to afford

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60 mg of the title product.

Yield: 32%

¹H-NMR (400MHz, DMSO) δ ppm: 1.20 (t, 3H), 1.20-1.50 (m, 5H), 1.60-1.70 (m, 1H), 1.80-1.95 (m, 4H), 2.70-2.80 (m, 1H), 3.35-3.45 (m, 2H), 3.65 (s, 3H), 7.90 (d, 2H), 8.05 (d, 2H), 8.65 (m, 1H).

MS (m/z) / M+1= 344.7

HPLC (uv purity, λ = 214 nm): 99.9%

10 **Example I37.8-1: R1= cyclohexyl, R2= methyl, R3= 4-(1-ethyl-1H-tetrazol-5-yl)-phenyl**

Cyclohexyl-{5-[4-(1-ethyl-1H-tetrazol-5-yl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-amine

To a solution of I37.8 (0.29 mmol, 100 mg) in acetonitrile (3 ml) at 0°C under a nitrogen atmosphere, sodium azide (0.44mmol, 28mg) and trifluoromethanesulfonic anhydride (0.44 mmol, 73 μl) were added. Then, the mixture was stirred overnight at room temperature and a saturated solution of NaHCO₃ to pH=7 was added. The aqueous layer was extracted with dichloromethane and the organic layer was washed with water, brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with a gradient of dichloromethane/methanol, then by HPLC (C₁₈-HYPERSYL column), eluting with water containing from 5 to 95% acetonitrile in 20 min to afford the title product.

Yield: 9%

¹H-NMR (400MHz, DMSO) δ ppm: 1.20-1.40 (m, 5H), 1.47 (t, 3H), 1.55-1.65 (m, 1H), 1.70-1.82 (m, 4H), 2.50-2.55 (m, 1H), 3.55 (s, 3H), 4.52 (q, 2H), 7.85-7.90 (m, 4H).

MS (m/z) / M+1= 370

HPLC (uv purity, λ = 214 nm)= 96.8%

35 **Example I37.9: R1= cyclohexyl, R2= methyl, R3= 4-N-(2-dimethylamino-ethyl)-benzamide**

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-benzamide

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To a solution of N,N-dimethylethylenediamine (335 μ l, 3 mmol) in dichloroethane (5 ml) under nitrogen atmosphere at 0°C, was added 2M trimethylaluminium (1.5 ml, 3 mmol), and the mixture was stirred at RT for 1H30. Then, a solution of compound I37 (180 mg, 0.54 mmol) in dichloroethane (5 ml) was added and the reaction mixture was allowed to stir for 24 h at RT and 24h at 45°C. The mixture was diluted with 10ml of dichloromethane and 20ml of water, stirred for 1H30, and filtered through Celite. The filtrate was washed with water, brine and the organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with a gradient of dichloromethane containing 0 to 5% methanol to afford 140 mg of the title product.

Yield: 60%

¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.25 (s, 6H), 2.60-2.70 (m, 1H), 3.55 (s, 3H), 7.75 (d, 2H), 7.90 (d, 2H), 8.50 (m, 1H)

MS (m/z) / M+1= 388

HPLC (uv purity, λ = 214 nm): 99.4%

Example I37.10: R1= cyclohexyl, R2= methyl, R3= 4-N-pyridin-4-ylmethyl-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzamide

To a solution of LiOH monohydrate (794 mg, 19 mmol) in 18 ml of water, a solution of compound I37 (5.7 g, 17.2 mmol) in THF/MeOH (50/50) (100 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 361 ml) was added. The resulting mixture was stirred for 3H30. After distillation of water, the crude product was dried over P₂O₅ in vacuo. To a suspension of 200 mg (0.5 mmol) of the crude material in CH₂Cl₂/DMF (50/50) (6 ml) were added cyclocarbodiimide-N-methyl resin (1.03 g, 1.5 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (38 mg, 0.1mmol),

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N,N-diisopropylethylamine (175 μ l, 1 mmol), 4-picolyamine (105 μ l, 1 mmol), molecular sieves (3A) and the reaction mixture was stirred 3 days at RT. This mixture was filtered, and in the organic layer was added methylisocyanate resin (1 g, 1 mmol) and stirred 3 days at RT. After filtration, the filtrate was concentrated under reduced pressure. The solid was poured into water and the mixture was stirred for 1 h, before extraction with dichloromethane. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 5% methanol to afford 30 mg of the title product.

Yield: 15%

1H -NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.75 (m, 1H), 3.55 (s, 3H), 4.50 (d, 2H), 7.35 (d, 2H), 7.75 (d, 2H), 8.00 (d, 2H), 8.50 (d, 2H), 9.25 (m, 1H).

MS (m/z) / M+1 = 408

HPLC (uv purity, λ = 214 nm): 99.7%

Example I37.11: R1= cyclohexyl, R2= methyl, R3= 4-N-methyl-N-(1-methyl-piperidin-4-yl)-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-N-(1-methyl-piperidin-4-yl)-benzamide

To a solution of I37.1 (0.5 mmol, 200 mg) in DMF (2.5 ml), ethyl-diisopropyl-amine (1.6 mmol, 190 μ l), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.6 mmol, 265 mg), 1-hydroxy-7-azabenzotriazole (0.25 mmol, 34 mg) and 1-methyl-4-(methylamino)piperidine (0.6 mmol, 87 μ l) were added and the reaction mixture was stirred at room temperature overnight. The solvent was distilled under reduced pressure and the residue was poured into water before extraction with dichloromethane. The organic layer was washed with brine and then with a saturated solution of $NaHCO_3$, dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was purified by

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silica gel chromatography using a gradient of dichloromethane containing 0 to 15% methanol, to give the desired product.

Yield: 93.5%

5 ¹H-NMR (400MHz, DMSO) δ ppm: 1.23-1.45 (m, 5H), 1.55-1.65 (m, 1H), 1.68-1.85 (m, 6H), 1.85-2.00 (m, 2H), 2.23-2.44 (m, 5H), 2.55-2.65 (m, 1H), 2.83 (s, 3H), 3.00-3.10 (m, 2H), 3.55 (s, 3H), 3.85-4.03 (m, 1H), 7.48 (dd, 2H), 7.70 (dd, 2H).

10 MS (m/z) / M+1= 428

HPLC (uv purity, λ = 214 nm) = 99.4%

Example I37.12: R1= cyclohexyl, R2= methyl, R3= 4-N-isobutyl-benzamide

15 **4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isobutyl-benzamide**

To a solution of I37.1 (0.5 mmol, 200 mg) in DMF (2.5 ml), ethyl-diisopropyl-amine (1.6 mmol, 190 μl), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.6
20 mmol, 265 mg), 1-hydroxy-7-azabenzotriazole (0.25 mmol, 34 mg) and isobutylamine (2.3 mmol, 80 μl) were added and the reaction mixture was stirred at room temperature overnight. The solvent was distilled and the residue was poured into water before extraction with dichloromethane. The organic
25 layer was washed with brine, a saturated solution of NaHCO₃, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the desired product.

Yield: 86%

30 ¹H-NMR (400MHz, DMSO) δ ppm: 0.90 (d, 6H), 1.20-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.72-1.90 (m, 5H), 2.60-2.70 (m, 1H), 3.10 (t, 2H), 3.55 (s, 3H), 7.72 (dd, 2H), 7.92 (dd, 2H), 8.55 (t, 1H).

MS (m/z) / M+1= 373

HPLC (uv purity, λ = 214 nm) = 98.4%

35

Example I37.13: R1= cyclohexyl, R2= methyl, R3: 4-N-methyl-benzamide

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4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide

To a solution of I37.1 (4.25 mmol, 1,7 g) in DMF (20,5 ml) was added N-ethyldiisopropylamine-N,N-diisopropylethylamine (13.6 mmol, 1.615 ml), benzotriazol-1-yloxytris (dimethylamino) phosphonium hexafluorophosphate (5.1 mmol, 2.265 g), 1-hydroxy-7-azabenzotriazole (2.125 mmol, 290 mg) and a solution of methylamine at [2N] in methanol (5.1 mmol, 3.55 ml). The mixture was stirred at room temperature overnight. The mixture was reduced under pressure vacuum, extracted with dichloromethane in water. The organic layer was washed with brine, dried over magnesium sulfate and reduced under pressure vacuum. The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 4% methanol, to give a residue which was stirred in diethylether during one hour. The precipitate was filtered and dried under vacuum over P₂O₅ to give 550 mg of the desired product.

Yield: 44%

¹H-NMR (400MHz, DMSO) δ ppm: 1.18-1.45 (m, 5H), 1.55-1.68 (m, 1H), 1.68-1.83 (m, 4H), 2.60-2.70 (m, 1H), 2.80 (d, 3H), 3.55 (s, 3H), 7.82 (dd, 2H), 7.92 (dd, 2H), 8.55 (q, 1H).

MS (m/z) / M+1= 331

HPLC (uv purity, λ = 214 nm)= 99.9%

25

Example I37.13-1: R1= cyclohexyl, R2= methyl, R3= 4-N-(2-dimethylamino-ethyl)-N-methyl-benzamide

4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-N-methyl-benzamide

To a suspension of I37.13 (0.3 mmol, 100 mg) in dimethylformamide (1 ml), sodium hydride at 60% dispersion in mineral oil (0.6 mmol, 24 mg), 2-dimethylaminoethylchloride hydrochloride (0.36 mmol, 52 mg) and K₂CO₃ (0.36 mmol, 50 mg) were added. The mixture was stirred overnight at 40°C. Then, potassium ter-butoxyde (0.18 mmol, 20 mg) was added and the mixture was stirred during 24h. 2-dimethylaminoethylchloride hydrochloride (0.18 mmol, 26 mg), and K₂CO₃ (0.18 mmol, 25 mg) were added and

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warmed at 40°C overnight. The mixture was reduced under pressure vacuum to give a residue which was purified by silica gel chromatography, eluting with a gradient of dichloromethane containing from 0 to 6% methanol to afford the title product.

Yield: 16%

¹H-NMR (400MHz, DMSO) δ ppm: 1.20-1.42 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.00 (s, 3H), 2.25 (s, 3H), 2.30-2.40 (m, 1H), 2.60-2.70 (m, 1H), 2.88-3.02 (m, 3H), 3.55 (s, 3H), 7.45 (dd, 2H), 7.70 (dd, 2H).

MS (m/z) / M+1 = 402

HPLC (uv purity, λ = 214 nm) = 98.8%

Example I37.14: R1= cyclohexyl, R2= methyl, R3= 4-(3-hydroxy-methyl-piperidin-1-carbonyl)-phenyl

[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-1-(3-hydroxymethyl-piperidin-1-yl)-methanone

Compound I37.14 was prepared by the procedure described in example I37.11 using I37.1 as a starting material. The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 5% methanol, to give the desired product.

Yield: 34%

¹H-NMR (350K, 400MHz, DMSO) δ ppm: 1.20-1.50 (m, 7H), 1.50-1.70 (m, 3H), 1.70-1.85 (m, 5H), 2.63-2.78 (m, 2H), 2.88-2.98 (m, 1H), 3.18-3.28 (m, 1H), 3.28-3.38 (m, 1H), 3.50 (s, 3H), 3.75-4.10 (m, 2H), 4.18-4.28 (m, 1H), 7.45 (dd, 2H), 7.68 (dd, 2H).

MS (m/z) / M+1 = 415

HPLC (uv purity, λ = 214 nm) = 95.4%

Example I37.15: R1= cyclohexyl, R2= methyl, R3= 4-{N-[(S)-1-tert-butoxycarbonyl-2-(4-hydroxy-phenyl)-ethyl]}benzamide
2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid tert-butyl ester

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Compound I37.15 was prepared by the procedure described in example I37.11 using I37.1 as a starting material. The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 2% methanol and then the product was washed with water, extracted with ethylacetate and the organic layer was washed with brine, dried over magnesium sulfate and reduced under pressure vacuum to give the title product.

Yield: 70%

¹H-NMR (400MHz, DMSO) δ ppm: 1.20-1.40 (m, 14H), 1.55-1.65 (m, 1H), 1.70-1.80 (m, 4H), 2.58-2.68 (m, 1H), 2.91-3.01 (m, 2H), 3.52 (s, 3H), 4.45-4.51 (m, 1H), 6.65 (dd, 2H), 7.08 (dd, 2H), 7.71 (dd, 2H), 7.90 (dd, 2H), 8.75 (d, 1H), 9.15 (s, 1H).

MS (m/z) / M+1= 537

HPLC (uv purity, λ = 214 nm)= 96.3%

Example I37.15-a: R1= cyclohexyl, R2= methyl, R3= 4-[N-((S)-1-carboxy-2-(4-hydroxy-phenyl)-ethyl)]benzamide

(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid; compound with 2,2,2-trifluoro-acetic acid

To a solution of I37.15 (0.186 mmol, 100 mg) in dichloromethane (1.5 ml), trifluoroacetic acid (4.4 mmol, 378 μ l) was added and the mixture was stirred at reflux during 2 hours. The mixture was purified by silica gel chromatography, eluting with a gradient of dichloromethane containing from 0 to 10% methanol to afford 60 mg of the title product.

Yield: 54%

¹H-NMR (400MHz, DMSO) δ ppm: 1.12-1.52 (m, 5H), 1.58-1.68 (m, 1H), 1.73-1.85 (m, 2H), 1.85-2.05 (m, 2H), 2.88-3.11 (m, 3H), 3.75 (s, 3H), 4.48-4.60 (m, 1H), 6.62 (dd, 2H), 7.08 (dd, 2H), 7.85 (dd, 2H), 7.95 (dd, 2H), 9.15 (s, 1H), 12.75 (s, 1H).

MS (m/z) / M+1= 481

HPLC (uv purity, λ = 214 nm)= 98%

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Example I37.16: R1= cyclohexyl, R2= methyl, R3= 4-(N-((S)-1-tert-butoxycarbonyl)-ethyl)benzamide

(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-

5 [1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid tert-butyl ester

Compound I37.16 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material.

10 The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 2% methanol, and the product was washed with water, filtrered and dried under pressure vacuum with P₂O₅ to give the title compound.

Yield: 65%

¹H-NMR (400MHz , DMSO) δ ppm: 1.20-1.40 (m, 17H), 1.55-1.65
15 (m, 1H), 1.70-1.82 (m, 4H), 2.58-2.68 (m, 1H), 3.52 (s, 3H), 4.35 (q, 1H), 7.73 (dd, 2H), 7.95 (dd, 2H), 8.75 (d, 1H).

MS (m/z) / M+1= 445

HPLC (uv purity, λ= 214 nm)= 99.3%

20 Example I37.16-a: R1= cyclohexyl, R2= methyl, R3= 4-(N-((S)-1-carboxy)-ethyl)benzamide

(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]

thiadiazol-2-yl)-benzoylamino]-propionic acid; compound with 2,2,2-trifluoro-acetic acid

25 To a solution of I37.16 (0.225 mmol, 100 mg) in dichloromethane (1 ml) at 0°C, trifluoroacetic acid (5.85 mmol, 457 µl) was added and the mixture was stirred at room temperature overnight. The mixture was purified by silica gel chromatography, eluting with a gradient of
30 dicloromethane containing from 0 to 5% methanol to afford 40 mg of the title product.

Yield: 35%

¹H-NMR (400MHz, DMSO) δ ppm: 1.10-1.48 (m, 8H), 1.55-1.65
(m, 1H), 1.70-1.81 (m, 2H), 1.81-2.00 (m, 2H), 2.89-3.05 (m,
35 1H), 3.71 (s, 3H), 4.44 (q, 1H), 7.87 (dd, 2H), 8.03 (dd, 2H), 8.82 (d, 1H), 12.57 (s, 1H).

MS (m/z) / M+1= 388/389

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HPLC (uv purity, λ = 214 nm) = 97.9%

Example I37.17: R1= cyclohexyl, R2= methyl, R3= 4-(4-pyridin-2-yl-piperazine-1-carbonyl)-phenyl
5 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyridin-2-yl-piperazin-1-yl)-methanone

Compound I37.17 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material.

10 The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 5% methanol, and then the product was washed with water, filtered and dried under reduced pressure over P₂O₅ to give the desired product.

15 Yield: 82%

¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.48 (m, 5H), 1.55-1.65 (m, 1H), 1.70-2.00 (m, 4H), 2.62-2.92 (m, 1H), 3.35-3.87 (m, 11H), 6.67 (dd, 1H), 6.88 (d, 1H), 7.45-7.63 (m, 3H), 7.78 (dd, 2H), 8.12 (d, 1H).

20 MS (m/z) / M+1= 463

HPLC (uv purity, λ = 214 nm) = 99.9%

Example I37.18: R1= cyclohexyl, R2= methyl, R3= 4-[4-(4-fluoro-phenyl)-piperazine-1-carbonyl]-phenyl

25 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-[4-(4-fluoro-phenyl)-piperazin-1-yl]-methanone

Compound I37.18 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material.

30 The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 5% methanol, and then the product was washed with water, filtered and dried under reduced pressure over P₂O₅ to give the desired product.

35 Yield: 31%

¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.65-1.86 (m, 4H), 2.56-2.70 (m, 1H), 2.96-3.10 (m,

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4H), 3.37-3.85 (m, 7H), 6.67 (dd, 1H), 6.92-7.12 (m, 4H),
7.51 (dd, 2H), 7.71 (dd, 2H).

MS (m/z) / M+1= 480

HPLC (uv purity, λ = 214 nm)= 98.6%

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Example I37.19: R1= cyclohexyl, R2= methyl, R3= 4-[N-(3,4,5-trimethoxy-benzyl)]-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(3,4,5-trimethoxy-benzyl)-benzamide

10 Compound I37.19 was prepared by the procedure described in example I37.11 using I37.1 as a starting material.

The residue was purified by silica gel chromatography using a gradient of cyclohexane containing 0 to 30% ethylacetate, to give a product which was washed with water, filtered and
15 dried under reduced pressure over P₂O₅ to give the desired product.

Yield: 52%

¹H-NMR (400MHz, DMSO) δ ppm: 1.19-1.42 (m, 5H), 1.55-1.65 (m, 1H), 1.71-1.88 (m, 4H), 2.60-2.70 (m, 1H), 3.50-3.55 (m,
20 3H), 3.55 (s, 3H), 3.75 (s, 6H), 4.42 (d, 2H), 6.65 (s, 4H), 7.70-7.80 (m, 1H), 8.00 (d, 1H), 9.10 (t, 1H).

MS (m/z) / M+1= 497

HPLC (uv purity, λ = 214 nm)= 99.5%

25 **Example I37.20: R1= cyclohexyl, R2= methyl, R3= 4-(4-pyrimidin-2-yl-piperazin-1-carbonyl)-phenyl**
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone

30 Compound I37.20 was prepared by the procedure described in example I37.11 using I37.1 as a starting material.

The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 1% methanol, to give a product which was washed with water, filtered and
35 dried under reduced pressure over P₂O₅ to give the desired product.

Yield: 4%

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¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.41 (m, 5H), 1.55-1.65 (m, 1H), 1.68-1.75 (m, 4H), 2.55-2.70 (m, 1H), 3.00-3.90 (m, 11H), 6.65 (t, 1H), 6.88 (d, 1H), 7.50 (dd, 2H), 7.70 (dd, 2H), 8.38 (d, 2H).

5 MS (m/z) / M+1= 464

HPLC (uv purity, λ= 214 nm)= 97%

Example I37.21: R1= cyclohexyl, R2= methyl, R3= 4-(4-methyl-piperazine-1-carbonyl)-phenyl

10 **[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-methyl-piperazin-1-yl)-methanone**

Compound I37.21 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material.

15 The residue was purified by silica gel chromatography using a gradient of of dichloromethane containing 0 to 10% methanol, to give a product which was washed with water, filtred and dried under reduced pressure over P₂O₅ to give the desired product.

20 Yield: 55%

¹H-NMR (400MHz, DMSO) δ ppm: 1.18-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.69-1.81 (m, 4H), 2.25 (s, 3H), 2.33-2.52 (m, 4H), 2.59-2.69 (m, 1H), 3.25-3.45 (m, 2H), 3.52 (s, 3H), 3.55-3.70 (m, 2H), 7.78 (dd, 2H), 7.71 (dd, 2H).

25 MS (m/z) / M+1= 400

HPLC (uv purity, λ= 214 nm)= 99.6%

Example I37.22: R1= cyclohexyl, R2= methyl, R3= 4-[N-(3-(4-methyl-piperazin-1-yl)-propyl)]benzamide

30 **4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzamide**

Compound I37.22 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material.

35 The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 10% methanol, to give a product which was stirred in diethylether, filtred and dried under reduced pressure over P₂O₅ to give the

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desired product.

Yield: 3.5%

¹H-NMR (400MHz, CDCl³): δ ppm: 1.20-1.50 (m, 5H), 1.60-2.05 (m, 7H), 2.35 (s, 3H), 2.48-2.85 (m, 11H), 3.52-3.64 (m, 2H), 3.50 (s, 3H), 7.68 (dd, 2H), 7.87 (dd, 2H), 8.00-8.08 (m, 1H).

MS (m/z) / M+1= 457

HPLC (uv purity, λ= 214 nm)= 97.2%

10 **Example I37.23: R1= cyclohexyl, R2= methyl, R3= 4-N-[(1-ethyl-pyrrolidin-2-ylmethyl)-benzamide**

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(1-ethyl-pyrrolidin-2-ylmethyl)-benzamide

To a solution of 2-(aminomethyl)-1-ethylpyrrolidine (7.5 mmol, 967 mg) in dichloroethane (10 ml) under nitrogen atmosphere, was added dropwise trimethylaluminium [2N] in toluene (7.5 mmol, 3.8 ml) and the mixture was stirred at room temperature during 2 hours. A solution of compound I37 (1.5 mmol, 500 mg) in dichloroethane (10 ml) was then added and the stirring was pursued at 65°C overnight. At room temperature, dichloromethane (30 ml) and water (50 ml) were added and the mixture was stirred several hours. The mixture was filtered through celite, extracted with dichloromethane, washed with water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 10% methanol to afford the desired product.

Yield: 79%

30 ¹H-NMR (400MHz, DMSO) δ ppm: 1.05 (t, 3H), 1.20-1.42 (m, 5H), 1.55-1.70 (m, 4H), 1.70-1.85 (m, 5H), 2.10-2.18 (m, 1H), 2.25-2.35 (m, 1H), 2.55-2.70 (m, 2H), 2.80-2.90 (m, 1H), 3.00-3.12 (m, 2H), 3.39-3.49 (m, 1H), 3.55 (s, 3H), 7.71 (dd, 2H), 7.92 (dd, 2H), 8.49 (t, 1H).

35 MS (m/z) / M+1= 428

HPLC (uv purity, λ= 214 nm)= 99.2%

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Example I37.24: R1= cyclohexyl, R2= methyl, R3= 4-N-
[(pyridin-3-ylmethyl)-benzamide
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-
2-yl)-N-pyridin-3-ylmethyl-benzamide

5 Compound I37.24 was prepared by the procedure described in
example I37.23 using appropriate intermediates and reagents
(I37 and 2-(aminoethyl)pyridine).

The residue was purified by silica gel chromatography
eluting with a gradient of dichloromethane containing from 0
10 to 8% methanol to afford the desired product.

Yield: 34%

¹H-NMR (400MHz, DMSO) δ ppm: 1.20-1.42 (m, 5H), 1.55-1.65
(m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 3.55 (s, 3H),
4.50 (d, 2H), 7.35-7.40 (m, 1H), 7.70-7.80 (m, 3H), 8.00
15 (dd, 2H), 8.45-8.50 (m, 1H), 8.57 (s, 1H), 9.30 (t, 1H).

MS (m/z) / M+1= 408

HPLC (uv purity, λ= 214 nm)= 98.6%

Example I37.25: R1= cyclohexyl, R2= methyl, R3= 4-(N-
20 benzyl)-benzamide
N-Benzyl-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-benzamide

Compound I37.25 was prepared by the procedure described in
example I37.23 using appropriate intermediates and reagents
25 (I37 and benzylamine).

The residue was purified by silica gel chromatography
eluting with a gradient of dichloromethane containing from 0
to 2% methanol to afford the desired product.

Yield: 34%

30 ¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65
(m, 1H), 1.65-1.85 (m, 4H), 2.55-2.70 (m, 1H), 3.52 (s, 3H),
4.48 (d, 2H), 7.19-7.39 (m, 5H), 7.72 (dd, 2H), 7.98 (dd,
2H), 9.13 (t, 1H)

MS (m/z) / M+1= 407

35 HPLC (uv purity, λ= 214 nm)= 99.2%

Example I37.26: R1= cyclohexyl, R2= methyl, R3= 4-[N-(1-

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benzyl-piperidin-4-yl)]-benzamide**N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide**

Compound I37.26 was prepared by the procedure described in example I37.23 using appropriate intermediates and reagents (I37 and 4-amino-1-benzylpiperidine).

The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 8% methanol to afford the desired product.

Yield: 50%

¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.53-1.65 (m, 3H), 1.70-1.83 (m, 6H), 1.97-2.07 (m, 2H), 2.70-2.80 (m, 1H), 2.77-2.87 (m, 2H), 3.47 (s, 2H), 3.55 (s, 3H), 3.70-3.85 (m, 1H), 7.22-7.35 (m, 5H), 7.70 (dd, 2H), 7.93 (dd, 2H), 8.35 (d, 1H).

MS (m/z) / M+1= 490

HPLC (uv purity, λ= 214 nm)= 96.4%

Example I37.27: R1= cyclohexyl, R2= methyl, R3= 4-[N-(2-ethyl-2H-pyrazol-3-yl)]-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide

Compound I37.27 was prepared by the procedure described in example I37.23 using appropriate intermediates and reagents (I37 and 5-amino-1-ethylpyrazole).

The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 6% methanol and then the solid was stirred in diethylether during 15 min, filtered and dried under reduced pressure to give the title product.

Yield: 26%

¹H-NMR (400MHz, DMSO) δ ppm: 1.20-1.45 (m, 8H), 1.60-1.70 (m, 1H), 1.75-1.87 (m, 4H), 2.63-2.73 (m, 1H), 3.55 (s, 3H), 4.05 (q, 2H), 6.25 (d, 1H), 7.45 (d, 1H), 7.83 (dd, 2H), 8.10 (dd, 2H), 10.40 (s, 1H).

MS (m/z) / M+1= 411

HPLC (uv purity, λ= 214 nm)= 99.7%

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Example I37.28: R1= cyclohexyl, R2= methyl, R3= 4-(2-morpholin-4-yl-ethyl)-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide

Compound I37.28 was prepared by the procedure described in example I37.23 using appropriate intermediates and reagents (I37 and N-(2-aminoethyl)morpholine).

The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 6% methanol and then the solid was stirred in diethylether during 15 min, filtered and dried under reduced pressure to give the title product.

Yield: 21%

¹H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.63 (m, 1H), 1.70-1.83 (m, 5H), 2.35-2.50 (m, 6H), 2.57-2.67 (m, 1H), 3.38 (q, 2H), 3.50 (s, 3H), 3.52-3.57 (m, 4H), 7.80 (dd, 2H), 7.90 (dd, 2H), 8.50 (t, 1H)

MS (m/z) / M+1= 430

HPLC (uv purity, λ= 214 nm)= 99.9%

Example I37.28-1: R1= cyclohexyl, R2= methyl, R3= 4-[(N-cyano-N'-ethylmorpholine)-carboxyimidamine]-phenyl

[5-(4-((N-cyano-N'-ethylmorpholine)-carboximidamide)-

phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexylamine

To a solution of I37.28 (2.33 mmol, 1 g) in toluene (15 ml), Lawesson's reagent (4.65 mmol, 1.88 g) was added and the mixture was stirred overnight at reflux. After cooling at room temperature, the mixture was acidified with a solution of HCl at 5% (3.5 ml) then basified with a solution of NaHCO₃. The aqueous layer was extracted with ethylacetate and the combined organic layers were washed with water, brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N(2-morpholin-4-yl-ethyl)thiobenzamide.