1-Aminotriazolo[4,3-a]quinazolin-5-ones and/or -5-thiones, inhibiting phosphodiesterases IV

Field of the invention

The present invention relates to novel triazolo[4,3-a]quinazolin-5-ones and/or –5-thiones which are useful for the preparation of medicinal products for treating complaints that fall within the domain of a treatment with a phosphodiesterase-4 inhibitor. These medicinal products are useful in particular as anti-inflammatory agents, antiallergic agents, bronchodilators, anti-asthmatic agents or TNFα inhibitors.

Technological background of the invention

Cyclic adenosine 3',5'-monophosphate (cAMP) is a ubiquitous intracellular second messenger, which is intermediate between a first messenger (hormone, neurotransmitter or autacoid) and the cellular functional responses: the first messenger stimulates the enzyme responsible for the synthesis of cAMP; depending on the cells concerned, the cAMP then intervenes in a great number of functions: metabolic, contractile or secretory.

The effects of cAMP end when it is degraded by cyclic nucleotide phosphodiesterases, which are intracellular enzymes that catalyse its hydrolysis into inactive adenosine 5'-monophosphate.

At least seven major families of cyclic nucleotide phosphodiesterases (PDE) have been distinguished in mammals, numbered from 1 to 7 according to their structure, their kinetic behaviour, their substrate specificity or their sensitivity to effectors (Beavo J.A. *et al.* (1990) Trends Pharmacol. Sci. 11, 150-155. Beavo J.A. *et al.* (1994) Molecular Pharmacol. 46, 399-405). The PDE4 enzymes are specific for cAMP.

Non-specific phosphodiesterase inhibitor compounds are known, which inhibit several families of enzymes. This is the case for certain methyl xanthines such as theophylline. These compounds have a low therapeutic index, in particular on account of their action on types of PDE present in cells other than the target cells. Conversely, certain families of PDE can be selectively inhibited by various pharmacological agents: the hydrolysis of cyclic nucleotides is slowed down and their concentration thus increases in only the cells in which the type of PDE that is sensitive to the inhibitor is found.

A specific advantage is shown for the phosphodiesterases 4 (PDE4), which have been identified in many tissues including the central nervous system, the heart, vascular endothelium, vascular smooth muscle and that of the aerial pathways, myeloid lines and lymphoid lines.

An increase in cAMP in the cells involved in inflammation inhibits their activation: inhibition of the synthesis and release of mediators in mastocytes, monocytes, polymorphonuclear eosinophils and basophils, inhibition of chemotaxis and degranulation of

polymorphonuclear neutrophils and eosinophils, inhibition of the proliferation and differentiation of lymphocytes.

Cytokines, in particular TNF and interleukins, produced by various types of leukocytes such as the T lymphocytes and polymorphonuclear eosinophils, play an important role in triggering inflammatory manifestations, in particular in response to stimulation by an allergen in the respiratory pathways.

Moreover, cAMP reduces the tonus of the smooth muscle fibres in the aerial pathways; PDE4 inhibitors bring about bronchorelaxation.

Chronic obstructive pulmonary disease (COPD) is a chronic pathology, of slow evolution, which is characterized by obstruction of the respiratory pathways (associated with an inflammation of the respiratory pathways and an elevated neutrophil count). The impairment in pulmonary function is for the most part irreversible (although improvements are possible by treatment with bronchodilators).

The clinical presentation of chronic obstructive pulmonary disease can vary according to the seriousness of the attack, ranging from a simple, non-incapacitating chronic bronchitis to a highly incapacitating condition of the type with chronic respiratory insufficiency. The main clinical characteristics of patients suffering from chronic obstructive pulmonary disease are chronic bronchitis and/or emphysema (associated with an inflammation of the respiratory pathways and/or an elevated neutrophil count).

In the course of recent years, selective second-generation phosphodiesterase-4 inhibitors have been proposed as agents that are potentially effective in the treatment of chronic obstructive pulmonary disease (see, inter alia, Doherty, *Chemical Biology* 1999, 3:466-473; Mohammed et al., *Anti-inflammatory & Immunodilatory Investigational Drugs* 1999 **1**(1) :1-28 ; Schmidt et al., *Clinical and Experimental Allergy*, **29**, supplement 2, 99-109).

Ariflo, a PDE4 inhibitor which is active via the oral route, has been proposed for the treatment of chronic obstructive pulmonary disease (see, inter alia: Nieman et al., Am J Respir Crit Care Med 1998, **157** :A413 ; Underwood et al., Eur Respir J 1998, **12** :86s ; Compton et al., Am J Respir Crit Care Med 1999, **159** :A522. See also the oral account by Compton given at the meeting of the "European Respiratory Society" held in Madrid on 12 October 1999, as well as that by Torphy and Underwood at the 4th world conference on inflammation, held in Paris from 27 to 30 June 1999. Ariflo is currently under study, in phase III clinical trials, for the treatment of chronic obstructive pulmonary disease.

However, it should be pointed out that Ariflo has a number of drawbacks. Specifically, significant undesirable effects, such as nausea and vomiting, have been reported after administration of a dose of 20 mg as a single intake (see Murdoch et al., Am J Respir Crit Care Med 1998, **157** :A409). The appearance of undesirable effects at such low doses will limit the use of Ariflo and will prevent the use of daily single-dose pharmaceutical forms, thus leading to discomfort for the patient.

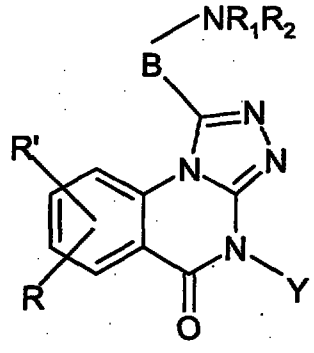
Osteoporosis is a disease characterized by a decrease in bone mass and the loss of skeletal architecture, thus leading to bone fracture. A large number of post-menopausal women suffer from this disease and the number of patients is continuing to grow.

Two different types of bone cell exist: osteoblasts, which participate in the formation of bone; and osteoclasts, which play a role in bone resorption. More particularly, the bone mass results from the sum of the formation of bone by the osteoblasts and the resorption of bone by the osteoclasts. Consequently, molecules which inhibit the bone resorption induced by the osteoclasts are effective in the treatment of osteoporosis. Calcitonin, biphosphonates and, quite probably, oestrogens are agents for combating resorption and are used clinically. Molecules which stimulate the formation of bone by the osteoblasts also constitute agents that are promising in the treatment of osteoporosis (see also Yoshihiro et al. Jpn. J. Pharmacolog. 1999, 79, 477 – 483).

Extensive research has been carried out in recent years to obtain and develop powerful PDE4 inhibitors. This turns out to be difficult due to the fact that many of the potential PDE4 inhibitors are not without activity on the phosphodiesterases of other families.

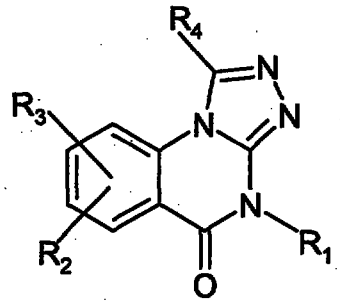
At the present time, the lack of selectivity of PDE4 inhibitors represents a major problem, given the extent of the functions regulated by cAMP. There is thus a need for powerful and selective PDE4 inhibitors, i.e. inhibitors which have no action with respect PDEs belonging to other families.

European patent EP 0076199 describes compounds having the following general formula:



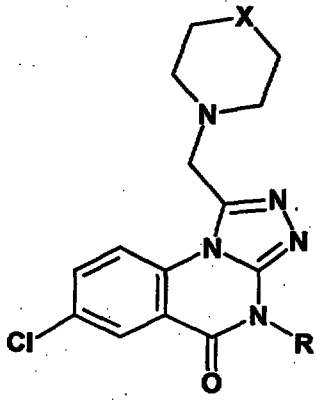
in which R and R', which may be identical or different, represent H, halogen, C_{1-3} alkyl, alkoxy or nitro; Y represents an alkyl, C_{3-8} cycloalkyl, C_{2-4} alkenyl, aryl or aralkyl group and B represents $(CH_2)_n$ with n = 1, 2, 3 or $CH(CH_3)$. These compounds are proposed for use in the treatment of asthma, bronchitis and allergic disorders.

Patent DDR 158 549 describes compounds having the following general formula:



in which R_1 represents H, alkyl or aryl; R_2 and R_3 represent H, alkyl, halogen, OH, SH, O-alkyl or S-alkyl; R_4 represents H, alkyl, haloalkyl, OH, SH, O-alkyl, S-alkyl, SO_2-alkyl, NH_2, SCN, aryl or $(CH_2)_nCOOalkyl$ and n = 0 to 2. These compounds are proposed for use as diuretics and anti-anaphylactic agents.

In J. Prakt. Chem, 1990, 332(5), 629-39, Ram et al. describe compounds having the following formula:

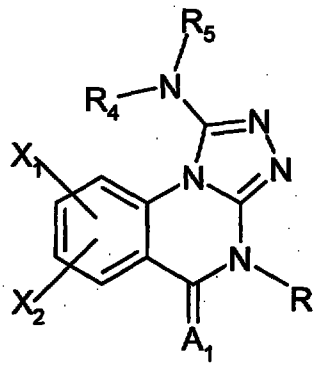


(X) R=CH_3, C_2H_5; X= C, NH, N-CH_3, N-Ar

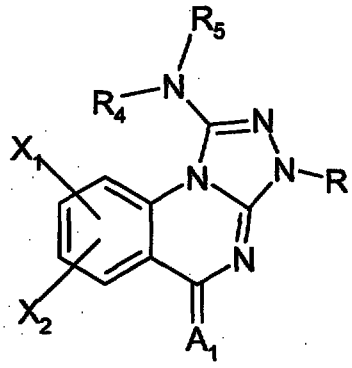
These compounds are proposed for use in treating hypertension.

Summary of the invention

The invention relates to triazolo[4,3-a]quinazolin-5-ones and/or –5-thiones of formula I or II:



I

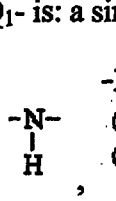
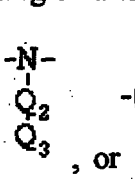
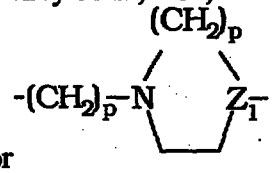


II

I and II being positional isomers of the group R on nitrogen 3 or 4, in which:

- A_1 is O or S ;
- X_1 and X_2, which may be identical or different, represent:
  - hydrogen, hydroxyl, halogen, amino, nitro, mercapto, cyano or carboxyl,
  - lower alkyl, lower alkoxy or $-S(O)_mR_8$ in which m is 0, 1 or 2 and R_8 is a lower alkyl, which are optionally substituted with one or more halogen atoms,
  - $-CO-Q_1-Q_2-Q_3$ in which:

    $-Q_1-$ is: a single-valency bond, -O-,

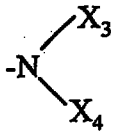
    
    ,
    
    , or
    
    , in which p is an integer which can range from 0 to 3 and Z_1 is CH, N, O or S,

    $-Q_2-$ is:

    a) $-(CH_2)_q-$, q being equal to 0, 1, 2, 3, or 4, or

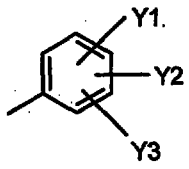
    b) $-(CH_2-CH_2-O)_r-$, r being equal to 2, 3, or 4, and

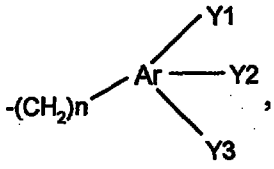
    $-Q_3$ is: -H, -OH, lower alkoxy, $-O-CO-X_3$, $-NHX_3$ or

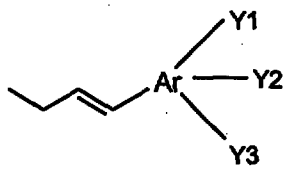
    

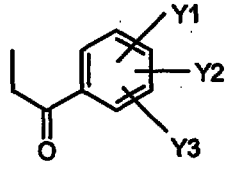
    in which X_3 and X_4, which may be identical or different, represent a lower alkyl group, it being possible for X_3 and X_4 to be linked to form a ring, comprising one or more hetero atoms chosen from O, S and N,
  - $-NH-R_1$ in which R_1 represents a lower alkyl group, optionally substituted with one or more groups chosen from halogen, hydroxyl, cyano, lower alkoxy and $-CO-Q_1-Q_2-Q_3$, or
  - $-NR_2R_3$ in which R_2 and R_3, which may be identical or different, represent a lower alkyl, optionally substituted with one or more hydroxyl, halogen, cyano, lower alkoxy or $-CO-Q_1-Q_2-Q_3$ groups, it being possible for R_2 and R_3 to be linked to form a ring, comprising one or more hetero atoms chosen from O, S and N and optionally bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy and $-CO-Q_1-Q_2-Q_3$;

- R represents:
  - lower alkyl, lower alkenyl, lower alkynyl, arylalkynyl or 2-, 3- or 4-pyridylalkyl

optionally substituted with a lower alkyl, a lower alkoxy, a 



, 

or 

hydroxyl, halo or amino group,

in which:

- n is an integer from 1 to 5,
- Ar is an aromatic ring comprising 5 or 6 atoms including from 0 to 3 hetero atoms chosen from O, S and N,
- Y1, Y2 and Y3, which may be identical or different, represent:
  - hydrogen, hydroxyl, mercapto, amino, nitro, halogen, $-NHR_1$, $-NHR_2R_3$, $-(CH_2)_sCN$ or $-(CH_2)_s$ $CO-Q_1-Q_2-Q_3$ in which s is an integer from 0 to 6 ;
  - lower alkyl, lower alkoxy or $-S(O)_mR_8$ in which m is 0, 1 or 2 and R_8 is a lower alkyl, it being possible for each to be optionally substituted with one or more halogen atoms; and

- R_4 and R_5, represent:

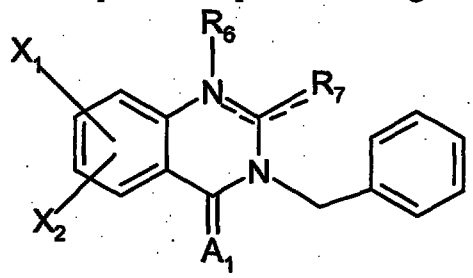
  - lower alkyl when R4 and R5 are identical, or aralkyl, cycloalkyl or cycloalkylalkyl when R_4 and R_5 are different,
  - lower alkyl, it being possible for R_4 and R_5 to be linked to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N and optionally substituted with a lower alkyl, a hydroxyl or a lower alkoxy or bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy, phenylalkyl or $CO-Q_1-Q_2-Q_3$, it also being possible for two of the atoms in the ring thus formed to form part of another ring chosen from phenyl or heteroaryl comprising from 4 to 8 carbon atoms including 1 to 4 hetero atoms;

and optionally the racemic forms and isomeric forms thereof, as well as the pharmaceutically acceptable salts thereof.

The compounds of the present invention are useful as inhibitors, in particular as selective inhibitors, of the phosphodiesterase enzyme, and more particularly the enzyme PDE4.

The invention also relates to compounds used mainly as intermediates in the synthesis of the compounds of formula I or II.

A first series of intermediates comprises compounds having the general formula III below:



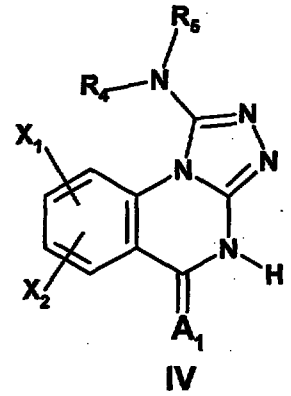
III

in which:

- X_1, X_2 and A_1 are as defined above;
- the dashed lines represent optional double bonds;
- R_6 is hydrogen; and
- R_7 is S or hydrazino;

it being possible for R_7 to be linked to the nitrogen at R_6 to form a ring, particularly a triazole, optionally substituted with a lower thioalkyl, mercapto or halogen group.

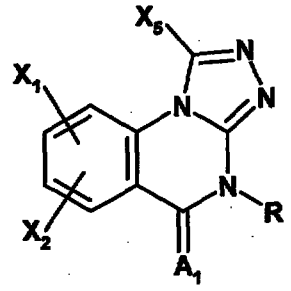
A second series of intermediates comprises compounds having the general formula IV below:



IV

in which X_1, X_2, A_1, R_4 and R_5 are as defined above.

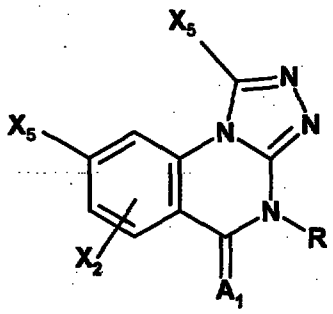
A third series of intermediates comprises the compounds having the general formula V below:



(V)

in which X_1, X_2, A_1 and R are as defined above and X_5 is a halogen, particularly F, Br or Cl, or an $-OCOX_7$, $-OSO_2X_7$ or $-SO_2X_7$ group in which X_7 is a lower alkyl or aryl group.

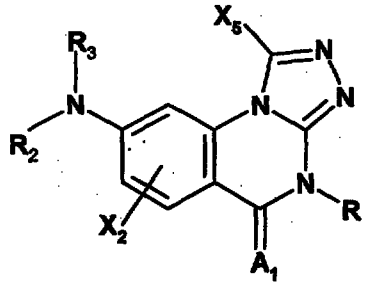
A fourth series of intermediates comprises compounds having the general formula VI below:



(VI)

in which X_2, X_5, A_1 and R are as defined above.

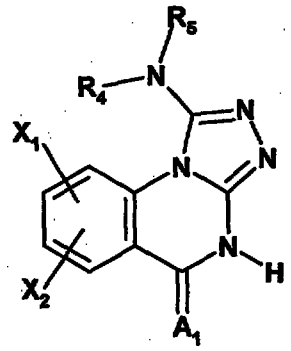
A fifth series of intermediates comprises compounds having the general formula VII below:



(VII)

in which X_2, A_1, R_2 and R_3 are as defined above, X_5 is a halogen, particularly F, Br or Cl, or an $-OCOX_7$, $-OSO_2X_7$ or $-SO_2X_7$ group in which X_7 is a lower alkyl or aryl group.

The invention also relates to a process for manufacturing compounds of formulae I and II. The process is characterized in that it comprises the reaction of a compound of general formula IV:



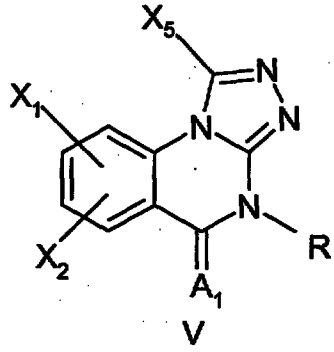
IV

in which X_1, X_2, A_1, R_4 and R_5 are as defined above,
with a compound of general formula

R-X'

in which R is as defined above and X' is a halogen, particularly F, Br or Cl, or an $-OCOX_7$ or $-OSO_2X_7$ group in which X_7 is a lower alkyl or aryl group;
in order to obtain a mixture of compounds of general formulae I and II which are then optionally separated.

The compounds of general formula I can also be prepared by a process characterized in that it comprises the reaction of a compound of general formula V :

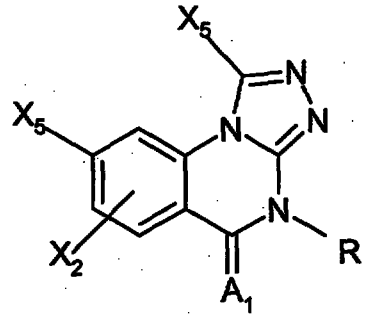


V

in which X_1, X_2, A_1 and R are as defined above and X_5 is a halogen, particularly F, Br or Cl, or an $-OCOX_7$, $-OSO_2X_7$ or $-SO_2X_7$ group in which X_7 is a lower alkyl or aryl group;
with a compound of general formula:

HNR_4R_5

in which R_4 and R_5 are as defined above,
in order to obtain a compound of general formula I.
When X_1 is $-NR_2R_3$ and $-NR_2R_3$ and $-NR_4R_5$ are identical, the compounds of formula I corresponding to this definition can be obtained in particular by reacting a compound of general formula VI:

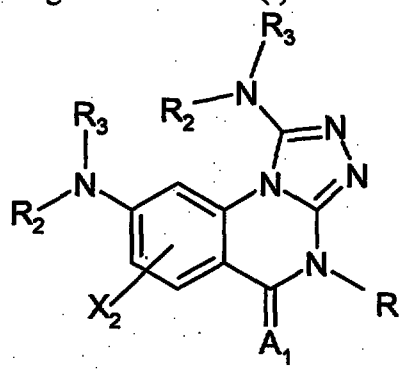


VI

in which X_2, X_5, A_1 and R are as defined above,
with a compound of general formula:

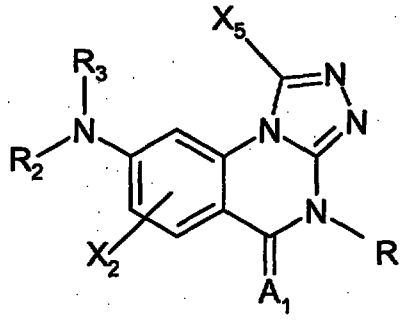
HNR_2R_3

in which R_2 and R_3 are as defined above,
in order to obtain a compound of general formula (I):



I

When X_1 is $-NR_2R_3$ and $-NR_2R_3$ and $-NR_4R_5$ are different, the compounds of formula I corresponding to this definition can also be obtained in particular by reacting a compound of general formula VII:

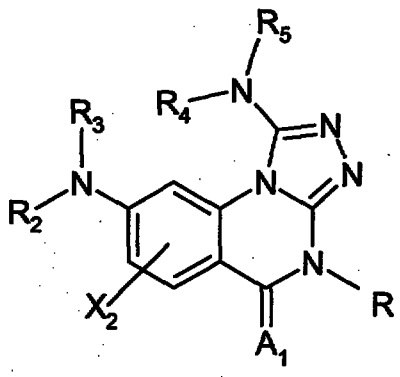


VII

in which X_2, X_5, A_1, R, R_2 and R_3 are as defined above,
with a compound of general formula :

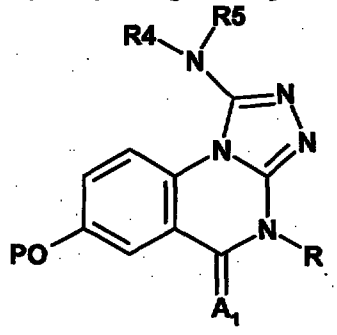
HNR_4R_5

in which R_4 and R_5 are as defined above,
in order to obtain a compound of general formula (I):



I

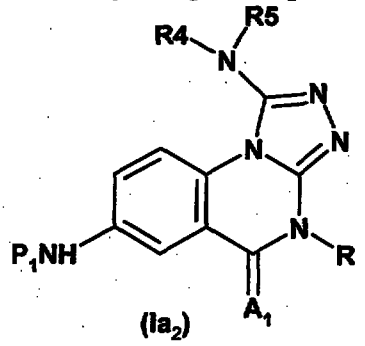
When X_1 is H and X_2 is OH, the compounds of formula I corresponding to this definition can also be obtained in particular by subjecting a compound of general formula Ia_1 :



(Ia_1)

in which A_1, R, R_4 and R_5 are as defined above and P is a protecting group,
to conditions allowing the removal of the protecting group P in order to obtain a compound of general formula I.

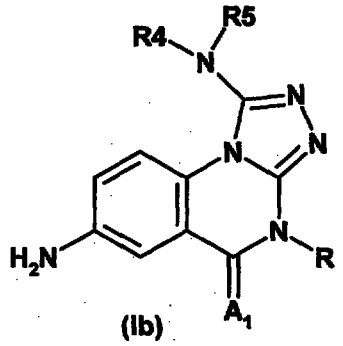
When X_1 is H and X_2 is NH_2, the compounds of formula I corresponding to this definition can also be obtained in particular by subjecting a compound of general formula Ia_2 :



(Ia_2)

in which A_1, R, R_4 and R_5 are as defined above and P_1 is a protecting group,
to conditions allowing the removal of the protecting group P_1 in order to obtain a compound of general formula I.

When X_1 is H and X_2 is NHR_2 in which R_2 is as defined above, the compounds of formula I corresponding to this definition can also be obtained in particular by reacting a compound of general formula Ib :

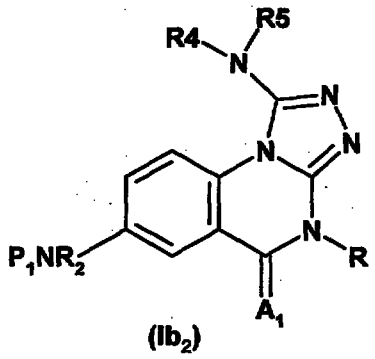


(Ib)

in which A_1, R, R_4 and R_5 are as defined above,

with a compound of formula R_2X_5 in which R_2 and X_5 are as defined above, in order to obtain a compound of general formula I.

Furthermore, when X_1 is H and X_2 is NHR_2 in which R_2 is as defined above, the compounds of formula I corresponding to this definition can also be obtained by subjecting a compound of general formula Ib_2 :

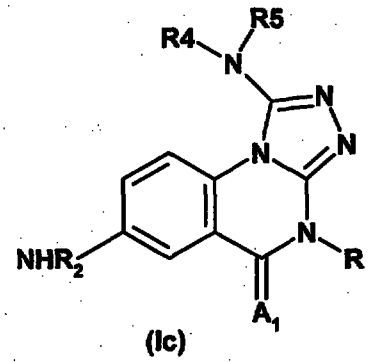


(Ib_2)

in which A_1, R, R_4 and R_5 are as defined above and P_1 is a protecting group,

to conditions allowing the removal of the protecting group, in order to obtain a compound of general formula I.

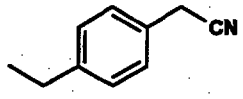
When X_1 is H and X_2 is NR_2R_x in which R_2 is as defined above and R_x represents R_2 or R_3 as defined above, the compounds of formula I corresponding to this definition can also be obtained in particular by reacting a compound of general formula Ic :



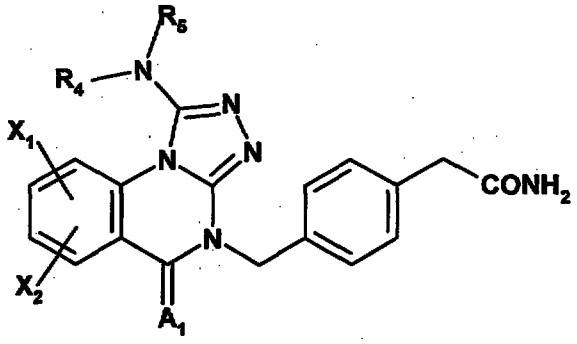
(Ic)

in which A_1, R, R_2, R_4 and R_5 are as defined above,
with a compound of formula R_xX_5 in which R_x and X_5 are as defined above, in order to obtain a compound of general formula I.

When R is



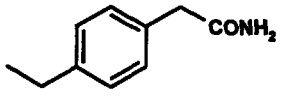
the compounds of formula I corresponding to this definition can also be obtained in particular by dehydrating a compound of general formula Ig :



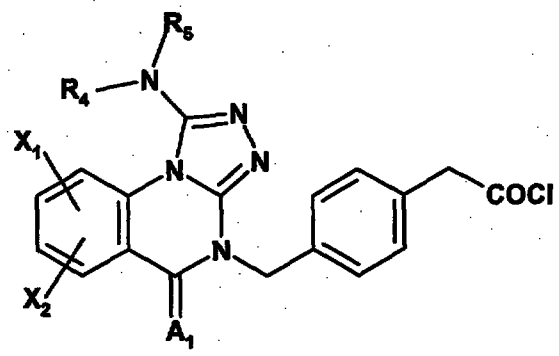
(Ig)

in which X_1, X_2, A_1, R_4 and R_5 are as defined above,
in order to obtain a compound of general formula I.

When R is



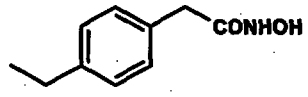
the compounds of formula I corresponding to this definition can also be obtained in particular by reacting a compound of general formula If:



(If)

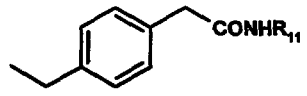
in which X_1, X_2, A_1, R_4 and R_5 are as defined above,
with aqueous ammonia in order to obtain a compound of general formula I.

When R is



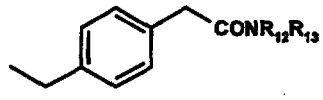
the compounds of formula I corresponding to this definition can also be obtained in particular by reacting a compound of general formula If with hydroxylamine in order to obtain a compound of general formula I.

When R is



the compounds of formula I corresponding to this definition can also be obtained in particular by reacting a compound of general formula If with the compound of formula $R_{11}NH_2$ in which R_{11} has the same meaning as R_2, in order to obtain a compound of general formula I.

When R is



the compounds of formula I corresponding to this definition can also be obtained in particular by reacting a compound of general formula If with the compound of formula $HNR_{12}R_{13}$ in which R_{12} and R_{13} have the same meaning as R_4 and R_5, respectively, in order to obtain a compound of general formula I.

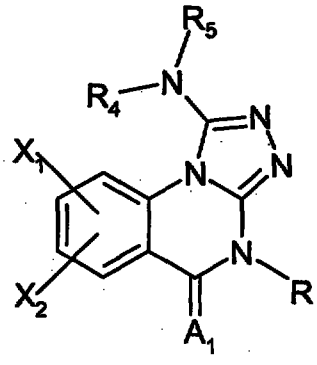
The invention also relates to a pharmaceutical composition comprising a compound of formula I or II and a pharmaceutically acceptable excipient.

The invention also relates to the use of a compound of formula I or II for the preparation of a medicinal product intended for the treatment of a disease or complaint which falls within the domain of a therapy by inhibition of phosphodiesterases, and more particularly of PDE4.

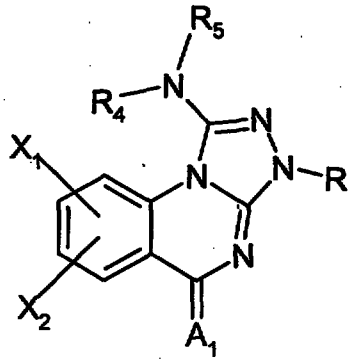
The invention also relates to a method for treating a disease or complaint which falls within the domain of therapy by inhibition of phosphodiesterases, and more particularly of PDE4, the said method comprising the administration to a patient of an effective concentration of a compound of formula I or II.

Detailed description of the invention

The present invention thus relates to the compounds of general formula I or II:



I



II

in which X_1, X_2, A_1, R, R_4 and R_5 are as defined above.

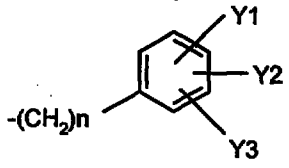
The invention relates particularly to the compounds of general formula I or II, in which:

A_1 represents an oxygen atom;

X_1 represents a hydrogen atom and X_2 is a halogen, amino, lower alkyl, hydroxyl or -NHR_1 group, R1 being as defined above;

R represents :

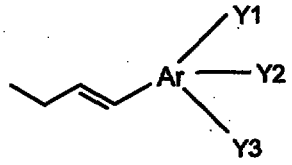
- a lower alkyl, lower alkenyl, arylalkynyl or 2-, 3- or 4-pyridylalkyl group optionally substituted on the pyridine ring with a lower alkyl, a halogen or a hydroxyl;



in which:

- n is an integer from 1 to 3,

- Y1, Y2 and Y3 each represent a hydrogen atom or a lower alkoxy group, more particularly methoxy,
- Y1 and Y2 each represent a hydrogen atom and Y3 represents a lower alkoxy group, an amino, nitro or hydroxyl group, a group $-(CH_2)_sCO-Q_1-Q_2-Q_3$, a group $(CH_2)_s-CN$ in which s, Q_1, Q_2, Q_3 are as defined above, or a lower alkyl group optionally substituted with one or more halogen atoms, the position particularly preferred for the substituent Y3 being position 4, or
- Y1 represents a hydrogen atom and Y2 and Y3, which may be identical or different, represent a hydroxyl, halogen or lower alkoxy group, or



in which :

- Ar is as defined above ;
- Y1, Y2 and Y3 each represent a hydrogen atom, or
- Y1 and Y2 each represent a hydrogen atom and Y3 is lower alkoxy or halogen ;

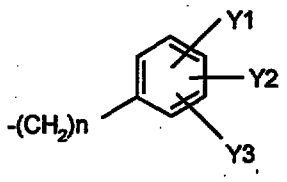
R_4 and R_5 represent :

- lower alkyl when R4 and R5 are identical, aralkyl, cycloalkyl or cycloalkylalkyl when R_4 and R_5 are different,
- lower alkyl, it being possible for R_4 and R_5 to be linked to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N and optionally substituted with a lower alkyl, a hydroxyl or a lower alkoxy or bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy, phenylalkyl or $CO-Q_1-Q_2-Q_3$, it being possible for two of the atoms in the ring thus formed also to form part of another ring chosen from phenyl and heteroaryl comprising from 4 to 8 atoms including 1 to 4 hetero atoms.

The invention relates more particularly to the compounds of general formula I in which :

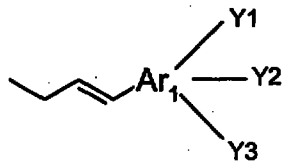
X_1 represents a hydrogen atom,
X_2 represents a halogen, amino, lower alkyl, hydroxyl or $-NHR_1$ group;

R represents :



in which :

- n is an integer from 1 to 3,
- Y1, Y2 and Y3 each represent a hydrogen atom or a lower alkoxy group, more particularly methoxy and in particular 3,4,5-trimethoxy,
- Y1 and Y2 each represent a hydrogen atom and Y3 represents a lower alkoxy, amino, nitro or hydroxyl group, a lower alkyl group optionally substituted with one or more halogen atoms, a group $-(CH_2)_sCO-Q_1-Q_2-Q_3$ in which s is 0 or 1, Q_1 is O, -NH- or a valency bond, Q_2 is $-(CH_2)_q-$, q being equal to 0, 1, 2, 3 or 4 and Q_3 is H, OH or $-NX_3X_4$ in which X_3 and X_4 are as defined above, a group $(CH_2)_s-CN$ in which s is 0 or 1, the position particularly preferred for the substitutent Y3 being position 4, or
- Y1 represents a hydrogen atom and Y2 and Y3, which may be identical or different, represent a hydroxyl, halogen or lower alkoxy group, or



in which :

- Ar_1 is an aromatic ring comprising 6 atoms which can include a nitrogen atom in position 2, 3 or 4 and preferably in position 3 ;
- Y1, Y2 and Y3 each represent a hydrogen atom, or
- Y1 and Y2 each represent a hydrogen atom and Y3 is a lower alkoxy group or a halogen group when Ar_1 does not comprise a nitrogen atom; and

R_4 and R_5, represent :

- lower alkyl when R4 and R5 are identical, aralkyl, cycloalkyl or cycloalkylalkyl when R_4 and R_5 are different,
- lower alkyl, it being possible for R_4 and R_5 to be linked to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N and optionally substituted with a lower alkyl, a hydroxyl or a lower alkoxy or bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy, phenylalkyl or $CO-Q_1-Q_2-Q_3$, it being possible for two of the atoms in the ring thus formed also to form part of another ring chosen from

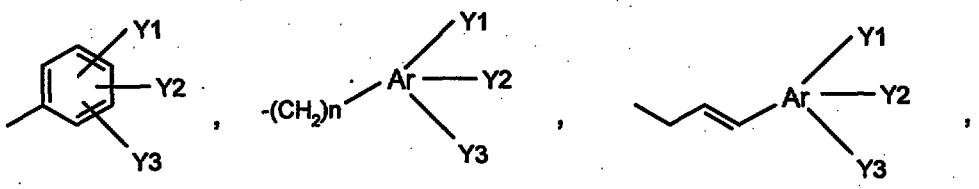
phenyl and heteroaryl comprising from 4 to 8 atoms including 1 to 4 hetero atoms.

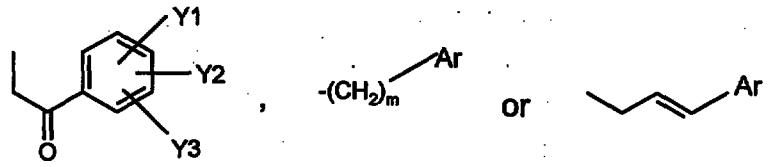
The invention also relates to compounds of general formula I or II in which :

X_1, X_2, A_1, R_4 and R_5 are as defined in the summary of the invention ; and

R represents :

- lower alkynyl, arylalkynyl, 2-, 3- or 4-pyridylalkyl optionally substituted with a lower alkyl, a lower alkoxy, a hydroxyl group or a halogen,





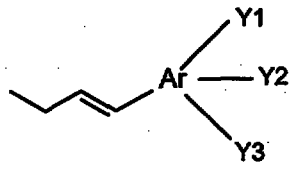
in which :

- n is an integer from 1 to 5 and m is an integer from 3 to 5 ;
- Ar is an aromatic ring comprising 5 or 6 atoms including from 0 to 3 hetero atoms chosen from O, S and N ;
- Y1, Y2 and Y3, which may be identical or different, represent :
  - hydroxyl, mercapto, amino, nitro, halogen, $-(CH_2)_sCO-Q_1-Q_2-Q_3$, $(CH_2)_s-CN$, in which s is an integer from 0 to 6, lower alkyl, lower alkoxy or lower thioalkyl, optionally substituted with one or more halogen atoms.

In another of its embodiments, the present invention relates to compounds of general formula I or II, in which :

X_1, X_2, R_4 and R_5 are as defined in the summary of the invention ; and

R represents :



in which :

- Ar is an aromatic ring comprising 5 or 6 atoms including from 0 to 3 hetero atoms chosen from O, S and N (the aromatic rings comprising 6 atoms, optionally including a nitrogen atom in position 2, 3 or 4, preferably in position 3, being particularly preferred);
- Y1, Y2 and Y3, which may be identical or different, represent :
  - hydrogen, hydroxyl, mercapto, amino, nitro, halogen, cyano, $-(CH_2)_sCO-Q_1-Q_2-Q_3$ in which s is an integer from 0 to 6, lower alkyl, lower alkoxy or lower thioalkyl, optionally substituted with one or more halogen atoms.

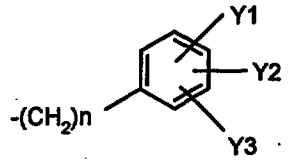
Preferably :

- Y1, Y2 and Y3 each represent a hydrogen atom, or
- Y1 and Y2 each represent a hydrogen atom and Y3 is lower alkoxy or halogen.

In another of its embodiments, the present invention relates to compounds of general formula I or II, in which :

X_1, X_2, A_1, R_4 and R_5 are as defined in the summary of the invention ; and

R represents :



in which :

- n is an integer from 1 to 3 ;
- Y1, Y2 and Y3, which may be identical or different, represent :
  - hydroxyl, mercapto, amino, nitro, halogen, $-(CH_2)_sCO-Q_1-Q_2-Q_3$, $(CH_2)_s-CN$ in which s is an integer from 0 to 6, lower alkyl, lower alkoxy or lower thioalkyl, optionally substituted with one or more halogen atoms.

Preferably :

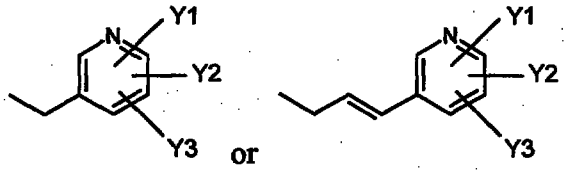
- n is an integer from 1 to 3,

- Y1, Y2 and Y3 each represent a lower alkoxy group, more particularly methoxy and in particular 3,4,5-trimethoxy,
- Y1 and Y2 each represent a hydrogen atom and Y3 represents a lower alkoxy, cyano, amino, nitro or hydroxyl group, a lower alkyl group optionally substituted with one or more halogen atoms or a group $-(CH_2)_sCO-Q_1-Q_2-Q_3$ in which s is 0 or 1, Q_1 is O, -NH- or a valency bond, Q_2 is $-(CH_2)_q-$, q being equal to 0, 1, 2, 3 or 4 and Q_3 is H, OH or $-NX_3X_4$ in which X_3 and X_4 are as defined above, the position particularly preferred for the substitutent Y3 being position 4, or
- Y1 represents a hydrogen atom and Y2 and Y3, which may be identical or different, represent a hydroxyl, halogen or lower alkoxy group.

In another of its embodiments, the present invention relates to compounds of general formula I or II in which:

X_1, X_2, A_1, R_4 and R_5 are as defined in the summary of the invention; and

R represents :



in which :

- Y1, Y2 and Y3, which may be identical or different, represent :
  - hydrogen, hydroxyl, mercapto, amino, nitro, halogen, $-(CH_2)_sCO-Q_1-Q_2-Q_3$, $(CH_2)_s-CN$, in which s is an integer from 0 to 6, lower alkyl, lower alkoxy or lower thioalkyl, optionally substituted with one or more halogen atoms.

Preferably :

- Y1, Y2 and Y3 each represent a hydrogen atom, or
- Y1 and Y2 each represent a hydrogen atom and Y3 is lower alkoxy or halogen.

In another of its embodiments, the present invention relates to compounds of general formula I or II in which :

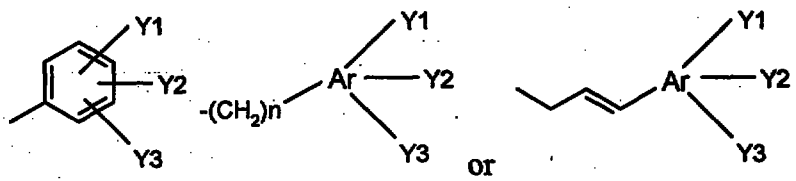
X_1, X_2, A_1, R, R_4 and R_5 are as defined in the summary of the invention ; and :

- when X_1 and X_2 represent hydrogen, R is not alkyl, phenyl, benzyl or allyl,

- when X_1 represents hydrogen and X_2 represents 7-Cl or CH_3, R is not an alkyl ; and
- when X_1 represents hydrogen, X_2 is not 8-Cl.

The invention also relates to a group of compounds of formula I or II which are particularly active as TNFα inhibitors and in which :

- A_1 is O or S ;
- X_1 and X_2, which may be identical or different, represent :
  - hydrogen, hydroxyl, halogen, amino, nitro, mercapto, cyano, carboxyl,
  - lower alkyl, lower alkoxy or $-S(O)_mR_8$ in which m is 0, 1 or 2 and R_8 is a lower alkyl, optionally substituted with one or more halogen atoms.
  - Preferably, X_1 is H and X_2 is halogen, in particular 7-Br, or lower alkyl, in particular 7-CH_3.
- R represents:



in which :

- n is an integer from 1 to 5,
- Ar is an aromatic ring comprising 5 or 6 atoms including from 0 to 3 hetero atoms chosen from O, S and N,
- Y1, Y2 and Y3, which may be identical or different, represent :
  - hydrogen, hydroxyl, mercapto, amino, nitro, halogen, $-(CH_2)_sCO-Q_1-Q_2-Q_3$, $(CH_2)_s-CN$ in which s is an integer from 0 to 6 ;
  - lower alkyl, lower alkoxy or $-S(O)_mR_8$ in which m is 0, 1 or 2 and R_8 is a lower alkyl, optionally substituted with one or more halogen atoms.

The substituents forming the group R which are particularly preferred include cinnamyl, 3-pyridylallyl, para-cyanobenzyl, dimethoxybenzyl and 3-pyridylmethyl.

- R_4 and R_5, which may be identical or different, represent :
  lower alkyl, it being possible for R_4 and R_5 to be linked to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N and optionally bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy, phenylalkyl or $CO-Q_1-Q_2-Q_3$. The substituents forming the group

NR_4R_5 which are particularly preferred include dimethylamino, pyrrolidine and azepanyl.

The compounds which are particularly preferred as TNFα inhibitors include the following molecules :

3	7-Bromo-1-dimethylamino-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
104	1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
94	4-(3,4-Dimethoxybenzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
101	4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile
85	7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
98	7-Methyl-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
79	4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile
91	1-Azepan-1-yl-7-methyl-4-pyrid-3-ylmethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
93	4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile
103	1-Dimethylamino-7-methyl-4-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
46	4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile
35	1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Among the groups defined above, the following substituents are particularly preferred :

- In general, for the groups X_1, X_2, X_3, X_4, R, R_1, R_2, R_3, R_4 and R_5 :
  - halogen : F, Cl, Br, I, preferably Br and Cl,
  - lower alkyl : linear or branched containing from 1 to 6, and preferably from 1 to 3 carbon atoms,

- lower alkoxy : linear or branched containing from 1 to 5 and preferably from 1 to 3 carbon atoms,
- lower alkylthio : linear or branched containing from 1 to 5 and preferably from 1 to 3 carbon atoms,
- lower alkenyl : containing from 3 to 6 and preferably from 3 to 4 carbon atoms, more particularly allyl,
- lower alkynyl : containing from 3 to 9 carbon atoms, more particularly propargyl and phenylpropargyl,
- 2-, 3- or 4-pyridylalkyl in which the alkyl contains from 1 to 5 and preferably from 1 to 3 carbon atoms,
- aryl : containing from 5 to 8 and preferably 5 or 6 atoms,
- aralkyl in which the alkyl contains from 1 to 6 and preferably from 1 to 4 carbon atoms,
- cycloalkyl : containing from 3 to 8 and preferably from 3 to 6 carbon atoms,
- cycloalkylalkyl in which the alkyl contains from 1 to 6 and preferably from 1 to 3 carbon atoms and the cycloalkyl contains from 3 to 8 and preferably from 3 to 6 carbon atoms,
- lower alkyl, lower alkoxy or lower alkylthio optionally substituted with one or more halogen atoms: trisubstituted groups such as $-(CH_2)_p-CF_3$, $-O-(CH_2)_p-CF_3$ or $-S-(CH_2)_p-CF_3$, in which p is an integer from 0 to 3, will be preferred.

- In particular, for the groups X_1 and X_2 :
  - $-NH-R_1$, or $-NR_2R_3$: when the lower alkyl is substituted with one or more groups chosen from halogen, hydroxyl, cyano, lower alkoxy and $CO-Q_1-Q_2-Q_3$, the number of substituents ranges between 1 and 4, preferably between 1 and 2,
  - $-NR_2R_3$: when R_2 and R_3 are linked to form a ring, this ring is characterized in that it preferably comprises :
    - between 1 and 4 and more particularly between 1 and 2 hetero atoms chosen from O, S and N, the cyclic substituents of this type preferably being saturated rings of the type C_mN in which m is an integer from 2 to 7, preferably from 4 to 6, the rings which are particularly preferred being chosen from the group comprising pyrrolidine, piperidine, homopiperidine or cyclooctylamine and
    - between 0 and 4, preferably between 0 and 2, more particularly between 1 and 2 substituents chosen from hydroxyl, keto, lower alkyl, lower alkoxy and $-CO-Q_1-Q_2-Q_3$,
  - the groups X_1 and X_2 are particularly located in positions 7 and 8 of the aromatic ring of the compounds of formulae I and II to which they are linked.

- In particular, for the group R :
  - the substituents Y1, Y2 and Y3 are particularly located in position 3 and/or 4 of the aromatic ring to which they are attached.

- Particularly, for the groups R_4 and R_5 :
  - when R_4 and R_5 are linked to form a ring, this ring is characterized in that it preferably comprises :
    - between 1 and 4 hetero atoms chosen from O, S and N, the cyclic substituents of this type preferably being saturated rings of the type C_mN, m being an integer from 2 to 7, the rings particularly preferred being chosen from the group comprising pyrrolidine, piperidine, homopiperidine and cyclooctylamine, and
    - between 0 and 4 and preferably between 0 and 2 substituents chosen from hydroxyl, keto, lower alkyl, lower alkoxy and $-CO-Q_1-Q_2-Q_3$.

The following compounds are among the preferred compounds of the present invention :

1 1-(Azepan-1-yl)-7-chloro-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

2 1-(azepan-1-yl)-7-chloro-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

3 7-Bromo-1-dimethylamino-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4 7-Bromo-4-pyrid-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

5 7-Bromo-3-pyrid-3-ylmethyl-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

6 1-Azepan-1-yl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7 1-(azepan-1-yl)-7-chloro-4-allyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

8 1-(azepan-1-yl)-7-chloro-4-(4-methylbenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

9 1-(azepan-1-yl)-7-chloro-4-(2-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

10 1-(azepan-1-yl)-7-chloro-4-(3-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

11 1-(azepan-1-yl)-7-chloro-4-(4-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

12 1-(azepan-1-yl)-7-chloro-4-(4-bromobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

13 1-(azepan-1-yl)-7-chloro-4-(4-fluorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

14 1-(azepan-1-yl)-7-chloro-4-(4-(trifluoromethyl)benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

15 1-(azepan-1-yl)-7-chloro-4-(4-cyanobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

16 1-(azepan-1-yl)-7-chloro-4-(2-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

17 1-(azepan-1-yl)-7-chloro-4-(3-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

18 1-(azepan-1-yl)-7-chloro-4-(4-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

19 1-(azepan-1-yl)-7-chloro-4-(3,4-dichlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

20 1-(azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

21 1-(azepan-1-yl)-7-chloro-4-(2-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

22 1-(azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

23 1-(azepan-1-yl)-7-chloro-4-(4-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

24 1-(azepan-1-yl)-7-chloro-4-(2-phenylethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

25 1-(azepan-1-yl)-7-chloro-4-[2-(4-methoxyphenyl)ethyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

26 1-(azepan-1-yl)-7-chloro-4-(3-phenylpropyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

27 1-Azepan-1-yl-7-chloro-4-(2-oxo-2-phenylethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

28 1-(azepan-1-yl)-7-chloro-4-[2-(4-methoxyphenyl)-2-oxoethyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

29 1-(azepan-1-yl)-7-chloro-4-[2-(4-chlorophenyl)-2-oxoethyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

30 5-[(1-(azepan-1-yl)-7-chloro-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl)acetyl]-2-methoxybenzoic acid methyl ester

31 7-Chloro-4-pyrid-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

32 1-(azepan-1-yl)-7-bromo-4-(4-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

33 1-Azepan-1-yl-7-bromo-4-(4-fluorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

34 4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

35 1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

36 1-(azepan-1-yl)-7-bromo-4-(3-pyridinylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

37 1-(azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

38 1-Azepan-1-yl-7-bromo-4-[3-(4-chlorophenyl)-allyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

39 1-Azepan-1-yl-7-bromo-4-[3-(4-methoxyphenyl)-allyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

40 1-Azepan-1-yl-7-bromo-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

41 1-Azepan-1-yl-7-bromo-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

42 7-Bromo-4-(4-methylbenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

43 7-Bromo-4-(4-chlorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

44 7-Bromo-4-(4-fluorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

45 3-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

46 4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

47 4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzoic acid methyl ester

48 7-Bromo-4-(4-nitrobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

49 7-Bromo-4-(4-methoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

50 Acetic acid 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl ester

51 7-Bromo-4-(4-hydroxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

52 7-Bromo-4-(3,4-dimethoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

53 4-Benzo[1,3]dioxol-5-ylmethyl-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

54 7-Bromo-4-(3,5-dimethoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

55 7-Bromo-1-pyrrolidin-1-yl-4-(3,4,5-trimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

56 [4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid

57 1-(pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

58 7-Bromo-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

59 7-Bromo-4-[(E)-3-(4-chlorophenyl)-allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

60 7-Bromo-4-[3-(4-methoxyphenyl)-allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

61 7-Bromo-4-(3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

62 7-Bromo-4-((E)-3-pyrid-4-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

63 7-Bromo-4-(1H-imidazol-4-ylmethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

64 7-Bromo-4-(3,5-dimethylisoxazol-4-ylmethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

65 7-Bromo-4-cyclopentylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

66 7-Bromo-4-butyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

67 7-Bromo-1-pyrrolidin-1-yl-4-(2,2,2-trifluoroethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

68 7-Bromo-4-(2-hydroxyethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

69 7-Bromo-4-(2-diethylaminoethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

70 7-Bromo-4-prop-2-ynyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

71 7-Bromo-4-(2-phenoxyethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

72 7-Bromo-4-(2-phenylsulphenylethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

73 (7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl)phenylacetic acid methyl ester

74 4-(7-Bromo-5-oxo-1-piperid-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

75 7-Bromo-4-(3,4-dimethoxybenzyl)-1-piperid-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

76 1-(piperid-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

77 7-Bromo-4-(3-pyrid-3-ylallyl)-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

78 Bromo-dimethylamino-(4-methylbenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

79 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

80 7-Bromo-1-dimethylamino-4-(4-hydroxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

81 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzoic acid methyl ester

82 [4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid

83 [4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetonitrile

84 7-Bromo-1-dimethylamino-4-pyrid-3-ylmethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

85 7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

86 7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

87 7-Bromo-1-dimethylamino-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

88 7-Bromo-1-dimethylamino-4-prop-2-ynyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

89 7-Bromo-1-dimethylamino-4-(3-phenyl-prop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

90 (7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl)phenylacetic acid methyl ester

91 1-Azepan-1-yl-7-methyl-4-pyrid-3-ylmethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

92 1-Azepan-1-yl-7-methyl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

93 4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

94 4-(3,4-Dimethoxybenzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

95 4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzoic acid methyl ester

96 [4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid

97 7-Methyl-4-pyrid-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

98 7-Methyl-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

99 [4-(7-Methyl-5-oxo-1-thiomorpholin-4-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid

100 7-Methyl-4-(3-pyrid-3-ylallyl)-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

101 4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

102 [4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid

103 1-Dimethylamino-7-methyl-4-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

104 1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

105 1-Dimethylamino-7-methyl-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

106 1-(azepan-1-yl)-8-methyl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

107 4-(4-Cyanobenzyl)-1-dimethylamino-5-oxo-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile

108 7-Hydroxy-4-((E)-3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

109 1-(azepan-1-yl)-3-(3-phenylallyl)- 3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

110 3-Allyl-1-azepan-1-yl-7-chloro-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

111 1-(azepan-1-yl)-7-chloro-3-benzyl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

112 1-Azepan-1-yl-7-chloro-3-(4-methylbenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

113 1-(azepan-1-yl)-7-chloro-3-(2-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

114 1-(azepan-1-yl)-7-chloro-3-(3-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

115 1-(azepan-1-yl)-7-chloro-3-(4-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

116 1-(azepan-1-yl)-7-chloro-3-(4-bromobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

117 1-(azepan-1-yl)-7-chloro-3-(4-fluorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

118 1-(azepan-1-yl)-7-chloro-3-(4-(trifluoromethyl)benzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

119 1-(azepan-1-yl)-7-chloro-3-(4-cyanobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

120 1-(azepan-1-yl)-7-chloro-3-(2-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

121 1-(azepan-1-yl)-7-chloro-3-(3-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

122 1-(azepan-1-yl)-7-chloro-3-(4-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

123 1-(azepan-1-yl)-7-chloro-3-(3,4-dichlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

124 1-(azepan-1-yl)-7-chloro-3-(3,4-dimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

125 1-(azepan-1-yl)-7-chloro-3-(2-pyridylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

126 1-(azepan-1-yl)-7-chloro-3-(3-pyridylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

127 1-(azepan-1-yl)-7-chloro-3-(2-phenylethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

128 1-(azepan-1-yl)-7-chloro-3-[2-(4-methoxyphenyl)ethyl]-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

129 1-(azepan-1-yl)-7-chloro-3-(3-phenylpropyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

130 1-Azepan-1-yl-7-chloro-3-(2-oxo-2-phenylethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

131 1-(azepan-1-yl)-7-chloro-3-[2-(4-methoxyphenyl)-2-oxoethyl]-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

132 1-(azepan-1-yl)-7-chloro-3-[2-(4-chlorophenyl)-2-oxoethyl]-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

133 5-[(1-(azepan-1-yl)-7-chloro-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl)acetyl]-2-methoxybenzoic acid methyl ester

134 1-(azepan-1-yl)-7-bromo-3-(4-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

135 1-(azepan-1-yl)-7-bromo-3-(4-fluorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

136 4-(1-(azepan-1-yl)-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)benzonitrile

137 1-(azepan-1-yl)-7-bromo-3-(3,4-dimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

138 [4-(7-Bromo-5-oxo-1-perhydro-azepin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)phenyl]acetic acid

139 1-(azepan-1-yl)-7-bromo-3-(pyrid-3-ylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

140 1-Azepan-1-yl-7-bromo-3-((E)-3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

141 7-Bromo-3-((E)-3-phenylallyl)-1-piperid-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

142 7-bromo-3-(4-chlorobenzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

143 7-bromo-3-(4-fluorobenzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

144 4-(7-bromo-5-oxo-1-(pyrrolidin-1-yl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)benzonitrile

145 4-(7-bromo-5-oxo-1-(pyrrolidin-1-yl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)benzoic acid methyl ester

146 7-Bromo-3-(4-methoxybenzyl)-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

147 Acetic acid 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)phenyl ester

148 7-Bromo-1-dimethylamino-3-(4-hydroxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

149 3-(benzo[1,3]dioxol-5-ylmethyl)-7-bromo-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

150 7-bromo-3-(3,5-dimethoxybenzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo-[4,3-a]quinazolin-5-one

151 7-bromo-1-(pyrrolidin-1-yl)-3-(3,4,5-trimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

152 7-Bromo-3-(1H-imidazol-4-ylmethyl)-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

153 7-bromo-3-(n-butyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

154 (7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl)phenylacetic acid methyl ester

155 7-Bromo-1-dimethylamino-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

156 (7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl)phenylacetic acid methyl ester

157 1-(azepan-1-yl)-7-methyl-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

158 7-methyl-3-(3-phenylallyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

159 1-(azepan-1-yl)-3,8-dimethyl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

160 1-Azepan-1-yl-8-methyl-3-((E)-3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

161 7-hydroxy-3-(3-phenylallyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

162 1,8-bis(azepan-1-yl)-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

163 1-(azepan-1-yl)-4-benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

164 4-benzyl-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

165 4-Benzyl-7-bromo-1-(butyl-methyl-amino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

166 4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

167 7-chloro-1-dibutylamino-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

168 7-chloro-4-methyl-1-(piperid-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

169 7-Chloro-4-methyl-1-(4-methyl-piperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

170 7-Chloro-4-methyl-1-(1,8,8-trimethyl-3-azabicyclo[3.2.1]oct-3-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

171 1-(azepan-1-yl)-7-chloro-4-phenyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

172 1-(azepan-1-yl)-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

173 4-benzyl-7-chloro-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

174 4-benzyl-7-chloro-1-(piperid-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

175 1-(azepan-1-yl)-8-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

176 1-(azepan-1-yl)-4-benzyl-8-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

177 1-(azepan-1-yl)-7-bromo-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

178 4-benzyl-7-bromo-1-(piperid-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

179 4-Benzyl-7-bromo-1-dimethylamino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

180 4-Benzyl-7-bromo-1-morpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

181 4-Benzyl-7-bromo-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

182 4-Benzyl-7-bromo-1-(4-methylpiperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

183 4-Benzyl-7-bromo-1-(4-phenylpiperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

184 4-Benzyl-1-(4-benzylpiperazin-1-yl)-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

185 4-Benzyl-7-bromo-1-(3,6-dihydro-2H-pyrid-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

186 4-Benzyl-7-bromo-1-(2,5-dihydropyrrol-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

187 4-Benzyl-7-bromo-1-(3-hydroxypyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

188 4-Benzyl-7-bromo-1-methylamino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

189 4-Benzyl-7-iodo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

190 1-Azepan-1-yl-4-benzyl-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

191 4-Benzyl-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

192 4-Benzyl-1-dimethylamino-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

193 4-Benzyl-7-methyl-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

194 1-Azepan-1-yl-4-benzyl-8-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

195 1-Azepan-1-yl-4-benzyl-7-methoxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

196 4-Benzyl-7-methoxy-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

197 4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile

198 1-Azepan-1-yl-4-benzyl-7-nitro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

199 1-(azepan-1-yl)-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

200 1-(azepan-1-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

201 1-(azepan-1-yl)-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

202 1-(azepan-1-yl)-6-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

203 1-(azepan-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

204 1-(azepan-1-yl)-7-chloro-4-ethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

205 7-chloro-4-methyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

206 7-chloro-4-methyl-1-(morpholin-4-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

207 1-(azocan-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

208 7-chloro-1-(3,4-dihydro-2H-quinolin-1-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

209 7-chloro-1-(3,4-dihydro-1H-isoquinolin-2-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

210 1-(4-benzylpiperid-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

211 7-chloro-4-methyl-1-(1,3,3-trimethyl-6-azabicyclo[3,2,1]oct-6-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

212 1-(azepan-1-yl)-7-fluoro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

213 1-(azepan-1-yl)-7-iodo-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

214 1-(azepan-1-yl)-7-methoxy-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

215 4-Benzyl-7-bromo-1-(ethylmethylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

216 4-Benzyl-1-diethylamino-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

217 4-Benzyl-7-bromo-1-pyrrol-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

218 4-(4-Aminobenzyl)-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

219 4-Benzyl-7-hydroxy-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

220 4-(7-Hydroxy-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

221 N-(4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazolin-7-yl)acetamide

222 N-[5-Oxo-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazolin-7-yl]acetamide

223 7-Amino-4-((E)-3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

224 7-Amino-1-azepan-1-yl-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

225 7-Amino-4-benzyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

226 4-(7-Amino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

227 7-Amino-4-((E)-3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

228 4-(7-Amino-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

229 7-Amino-1-dimethylamino-4-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

230 4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

231 4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

232 4-Benzyl-8-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

233 4-Benzyl-7-ethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

234 4-Benzyl-7-isopropylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

235 N-(4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazolin-7-yl)methanesulphonamide

236 4-Benzyl-7-dimethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

237 4-Benzyl-1-dimethylamino-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile

238 4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazoline-7-carboxylic acid

239 [4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid methyl ester

240 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]-N-methylacetamide

241 2-[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetamide

242 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]-N,N-dimethylacetamide

243 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]-N-hydroxyacetamide

244 4-(1-Dimethylamino-7-methyl-5-thioxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

245 4-(7-Bromo-1-dimethylamino-5-thioxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

246 1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

247 4-benzyl-7-(N,N-dimethylsulphonylamino)-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo[4,3-a]quinazolin-5-one

Among the compounds mentioned above, the following compounds are preferred :

1	1-(Azepan-1-yl)-7-chloro-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
3	7-Bromo-1-dimethylamino-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
11	1-(azepan-1-yl)-7-chloro-4-(4-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
13	1-(azepan-1-yl)-7-chloro-4-(4-fluorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
20	1-(azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
22	1-(azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
32	1-(azepan-1-yl)-7-bromo-4-(4-chlorophenylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
34	4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile
35	1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
37	1-(azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
40	1-Azepan-1-yl-7-bromo-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
41	1-Azepan-1-yl-7-bromo-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
42	7-Bromo-4-(4-methylbenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
43	7-Bromo-4-(4-chlorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
44	7-Bromo-4-(4-fluorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
46	4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile
47	4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzoic acid methyl ester

48 7-Bromo-4-(4-nitrobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

49 7-Bromo-4-(4-methoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

50 Acetic acid 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl ester

51 7-Bromo-4-(4-hydroxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

52 7-Bromo-4-(3,4-dimethoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

57 1-(pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

59 7-Bromo-4-[(E)-3-(4-chlorophenyl)allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

60 7-Bromo-4-[3-(4-methoxyphenyl)allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

61 7-Bromo-4-(3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

62 7-Bromo-4-((E)-3-pyrid-4-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

75 7-Bromo-4-(3,4-dimethoxybenzyl)-1-piperid-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

76 1-(piperid-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

78 7-Bromo-1-dimethylamino-4-(4-methylbenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

79 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

80 7-Bromo-1-dimethylamino-4-(4-hydroxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

81 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzoic acid methyl ester

83 [4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetonitrile

85	7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
89	7-Bromo-1-dimethylamino-4-(3-phenyl-prop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
92	1-Azepan-1-yl-7-methyl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
94	4-(3,4-Dimethoxybenzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
96	[4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid
98	7-Methyl-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
102	[4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid
103	1-Dimethylamino-7-methyl-4-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
104	1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
138	[4-(7-Bromo-5-oxo-1-perhydroazepin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)phenyl]acetic acid
164	4-benzyl-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
186	4-Benzyl-7-bromo-1-(2,5-dihydropyrrol-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
189	4-Benzyl-7-iodo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
190	1-Azepan-1-yl-4-benzyl-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
218	4-(4-Aminobenzyl)-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
223	7-Amino-4-((E)-3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
224	7-Amino-1-azepan-1-yl-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

227 7-Amino-4-((E)-3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

229 7-Amino-1-dimethylamino-4-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

230 4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

231 4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

232 4-Benzyl-8-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

233 4-Benzyl-7-ethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

234 4-Benzyl-7-isopropylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

239 [4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid methyl ester

240 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]-N-methylacetamide

241 2-[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetamide

242 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]-N,N-dimethylacetamide

243 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]-N-hydroxyacetamide

246 1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

Among the compounds mentioned above, the following compounds are particularly preferred :

3 7-Bromo-1-dimethylamino-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

20 1-(azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

22 1-(azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

34 4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

35 1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

37 1-(azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

40 1-Azepan-1-yl-7-bromo-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

41 1-Azepan-1-yl-7-bromo-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

42 7-Bromo-4-(4-methylbenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

43 7-Bromo-4-(4-chlorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

52 7-Bromo-4-(3,4-dimethoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

57 1-(pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

61 7-Bromo-4-(3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

76 1-(piperid-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

79 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

81 4-(Bromo-dimethylaminooxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzoic acid methyl ester

85 7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

89 7-Bromo-1-dimethylamino-4-(3-phenylprop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

92 1-Azepan-1-yl-7-methyl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

94	4-(3,4-Dimethoxybenzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
98	7-Methyl-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
223	7-Amino-4-((E)-3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
227	7-Amino-4-((E)-3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
230	4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
231	4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile
239	[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid methyl ester
240	2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]-N-methyacetamide
242	2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]-N,N-dimethylacetamide
246	1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

The invention also relates to the pharmaceutically acceptable salts of the compounds of formula I or II. A review of the pharmaceutically acceptable salts will be found in J. Pharm. Sci., 1977, 66, 1-19. However, the expression "pharmacologically acceptable salt of a compound of formula I or II containing a basic function" means the addition salts of the compounds of formula I or II which are formed from non-toxic inorganic or organic acids such as, for example, the hydrobromic, hydrochloric, sulphuric, phosphoric, nitric, acetic, succinic, tartaric, citric, maleic, hydroxymaleic, benzoic, fumaric, toluenesulphonic and isethionic acid salts and the like. The various quaternary ammonium salts of derivatives I or II are also included in this catetory of compounds of the invention. Also, the expression "pharmacologically acceptable salt of a compound of formula I or II containing an acidic function" means the usual salts of the compounds of formula I or II which are formed from non-toxic inorganic or organic bases such as, for example, alkali metal and alkaline-earth metal (sodium, potassium, magnesium and calcium) hydroxides, amines

(dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like) or quaternary ammonium hydroxides such as tetramethylammonium hydroxide.

As mentioned previously, the compounds of formulae I and II of the present invention are inhibitors of the enzyme phosphodiesterase and particularly of the enzyme phosphodiesterase 4 (PDE4).

In this respect, their use is recommended in the treatment of conditions or complaints which fall within the domain of a treatment by inhibition of PDE4. By way of example, the use of the compounds of the present invention may be recommended in the treatment of septicaemia, multiple organ failure syndrome, asthma, chronic bronchitis, emphysema, chronic obstructive pulmonary disease (or COPD), allergic rhinitis, atopic dermatitis, pulmonary hypertension, cardiac or pulmonary insufficiency, congestive cardiac insufficiency, psoriasis, inflammatory conditions of the digestive system such as haemorrhagic rectocolitis and Crohn's disease, conditions associated with a high level of TNF-α such as acute respiratory distress syndrome in adults and acute pancreatitis, rheumatoid arthritis, osteoporosis, multiple sclerosis and depression.
The PDE4 inhibitors of the present invention can also be used for the treatment of acute pulmonary attack, ischaemia-induced neuronal damage, diabetes and chronic lymphoid leukaemia, and to attenuate the development of phenomena of tolerance or dependency on morphine. The compounds of the invention can also contribute towards reducing the losses of behavioural memory as observed, for example, in patients suffering from Alzheimer's disease.
The use of the compounds of the present invention may also be envisaged in the field of urology, more particularly in the treatment of complaints of the prostate such as benign hypertrophy of the prostate or for the prevention of premature labour, for example by inhibiting the onset of contractions before term, preferably by the action of a PDE4 inhibitor on the myometrium.

Structure-activity analysis of the compounds of formulae I and II

Without wishing to be bound by a definitive theory, the inventors are of the opinion that the structural parameters mentioned below can be considered in order to guide a person skilled in the art in the choice of the combination of substituents which, beyond the preferred compounds described in the present application, may allow not only an optimization of the inhibitory activity of PDE4, but also better optimization of important additional parameters such as the solubility, the bioavailability and the toxicity of the compounds envisaged.

Firstly, the inventors are of the opinion that the catalytic site of the enzyme PDE4 is large enough to accommodate overall a fairly wide range of structural changes in the substituents of the compounds of the invention which may be linked to this site. In this regard, the inventors consider that the compounds of the present invention probably have the capacity of interacting with at least three separate points of the catalytic site of the isoenzyme PDE4. A first point of interaction is thought to be the aromatic ring comprising the substituents X_1 and X_2. A second point of interaction is quite probably the substituent R while the third point of interaction is probably the group NR_4R_5. The potential functionality of each of these binding points is proposed below.

However, it is important to point out here that the points of interaction listed above are not necessarily given in increasing or decreasing order of importance as regards their effect on the inhibitory activity of the compounds of the invention. In fact, it appears possible that each of these points of interaction participates differently in the overall pharmacological properties of these compounds.

The first point of interaction listed above is thought to be the aromatic nucleus comprising the substituents X_1 and X_2. This aromatic nucleus is thought to participate in the binding of the compounds of the invention to the catalytic site of the enzyme PDE4, and it appears to be possible to modulate this binding by the choice of the substituents X_1 and X_2.

The experiments carried out hitherto by the inventors tend to show that the substituents X_1 and X_2 currently preferred are those for which X_1 is hydrogen and X_2 is chosen from halogen, more particularly Br and Cl, methyl, hydroxyl, amino and alkylamino. It is thus observed that among the preferred substituents of X_2, both electron-donating groups (e.g. methyl) and electron-withdrawing groups (e.g. Br, Cl) are found. It thus appears unlikely that X_2 can be chosen solely as a function of the electronic properties of the recommended substituent. The inventors are of the opinion that the important selection criteria firstly concern the position of the substituent on the aromatic nucleus, and then certain parameters such as the steric bulk of the substituent or the presence of a proton-donating or proton-accepting atom.

However, it appears to be accepted that the position of the substituents X_1 and X_2 on the aromatic nucleus can have an influence on the final activity of the compounds of the invention. By way of example, compounds comprising a substituent other than hydrogen in position 7 are generally more active than the same compounds comprising this substituent in position 8. It thus appears probable that the choice and position of the substituents X_1

and X_2 makes it possible to shift the aromatic nucleus inside a cavity of the catalytic site of PDE4 and consequently modulate the inhibitory activity of the compounds of the invention. Furthermore, it appears that the compounds comprising a substituent in position 7 are more selective for the subtype PDE4 with respect to the other isoenzymes PDE5, PDE3 and PDE1 than compounds comprising a substituent in position 8. The latter compounds have PDE4-inhibiting activity (although weaker), but they appear to be less selective with respect to the other isoenzymes. However, it also appears clear that although X_1 and X_2 can be chosen from a considerable number of substituents, better tolerance as regards this choice will be obtained if the substituent R is well targeted.

The second point of interaction of the compounds of the present invention with the enzyme PDE4 is thought to be substituent R. The inventors believe that it is quite probably the most important point of attachment of the molecule to the enzyme. In fact, it appears likely that this second point of interaction is in a vast cavity inside the catalytic site of PDE4. It is thus of fundamental importance for the substituent R to be able to attach to the catalytic site. However, the choice of groups included in the definition of R given above appears to demonstrate a certain flexibility as regards the attachment of R to this second binding site. In other words, it would appear to be possible to obtain inhibitory activity of PDE4 with compounds possessing substituents R that are structurally quite different. By way of example, it will be preferred to use a substituent comprising an aromatic nucleus, which is itself preferably substituted, and separated from the main heterocycle by a chain comprising between 1 and 4 atoms, in particular carbon atoms, the said substituent having a relatively variable orientation in space. This observation appears to open the way to the possibility of more subtly modulating the overall properties of the compounds of the invention.

The inventors are in fact of the opinion that although the substituent R quite probably remains a deciding factor in the PDE4-inhibiting activity of the compounds of the invention, it is probably possible to vary it and thus to act on important additional pharmacological parameters without substantially impairing this inhibitory activity. By way of example, compounds respectively comprising a $-CH_2CH = CH-C_6H_5$ or a substituted benzyl group, preferably substituted in position 4 (the other substituents being identical for the two compounds), in the substituent R have a PDE4-inhibiting activity of the same order of magnitude.

The third site of interaction of the compounds of the invention with PDE4 is quite probably the group $-NR_4R_5$. The inventors are of the opinion that this is probably a much more specific binding site than the two sites described above, although the displacement of the

substituent R in the enzymatic cavity can, however, have an influence on the specificity of this third site. The compounds of the invention having the best inhibitory activities are those for which R_4 and R_5, which each represent a lower alkyl, are linked to form a ring, preferably a ring containing between 5 and 8 carbon atoms, more particularly a ring containing 5 or 7 carbon atoms. The margin for manoeuvre of a person skilled in the art as regards the variation of this groups thus appears to be more limited.

In summary, the experiments carried out by the inventors with the compounds of the present invention appear to show that the size of the catalytic site of PDE4 is large enough to accommodate several structural changes in the three binding sites described above. However, the greatest margin for manoeuvre nonetheless appears to be in the variation of the substitutent R.

Pharmaceutical formulation of the compounds of the invention

The compounds of the invention are administered in the form of compositions that are suitable for the nature and seriousness of the complaint to be treated. The daily dosage in man is usually between 2 mg and 1 g of product which can be absorbed in one or more intakes. The compositions are prepared by methods that are common to those skilled in the art and generally comprise 0.5% to 60% by weight of active principle (compound of formula I) and 40% to 99.5% by weight of pharmaceutically suitable vehicle.
The compositions of the present invention are thus prepared in forms that are compatible with the desired route of administration. For example, the following pharmaceutical forms may be envisaged, although the list given below is not limiting :

1) Forms for oral administration :
Drinkable solutions, suspensions, sachets of powder for drinkable solution, sachets of powder for drinkable suspension, gel capsules, gastro-resistant gel capsules, sustained-release forms, emulsions, HPMR wafer capsules or gel capsules, lyophilizates to be melted under the tongue.

2) Forms for parenteral administration :
Intravenous route :
Aqueous solutions, water/co-solvent solutions, solutions using one or more solubilizing agents, colloidal suspensions, emulsions, nanoparticulate suspensions which can be used for the injection of sustained-release forms, dispersed forms and liposomes

Subcutaneous/intramuscular route :

In addition to the forms which can be used intravenously and which can also be used for the subcutaneous and intramuscular routes, other types of form such as suspensions, dispersed forms, sustained-release gels and sustained-release implants, can also be used.

3) Forms for topical administration :

Among the topical forms most commonly used are creams, gels (aqueous phases gelled with polymers), patches, which are dressings to be stuck directly on the skin and which can be used to treat dermatitides without percutaneous penetration of the active substance, sprays, emulsions and solutions.

4) Forms for pulmonary administration :

Included in this category are forms such as solutions for aerosols, powders for inhalers and other appropriate forms.

5) Forms for nasal administration :

This especially concerns solutions for nose drops.

6) Forms for rectal administration :

Mention will be made, inter alia, of suppositories and gels.

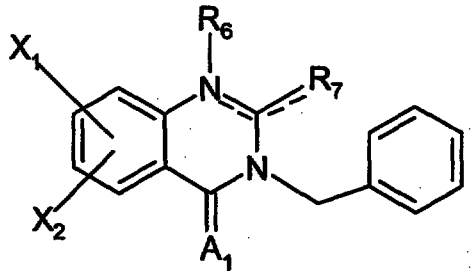
It may be envisaged to use forms allowing the administration of ophthalmic solutions or allowing the vaginal administration of the active principle.

Another important category of pharmaceutical form which can be used in the context of the present invention concerns forms for improving the solubility of the active principle. By way of example, it may be envisaged to use aqueous solutions of cyclodextrin, and more particularly forms comprising hydroxypropyl beta-cyclodextrin. A detailed review of this type of pharmaceutical form is presented in the article published under the reference *Journal of Pharmaceutical Sciences, 1142-1169, 85 (11), 1996*, and incorporated by way of reference in the present application.

The various pharmaceutical forms recommended above are described in detail in the book « Pharmacie galénique [Pharmaceutical pharmacy]» by A. LEHIR *(published by Masson, 1992 (6th edition)*, which is incorporated by way of reference in the present application.

Intermediate compounds

The present invention also relates to the intermediate compounds of general formula III :



III

in which X_1, X_2, A_1, R_6 and R_7 are as defined above.

The invention relates particularly to the intermediate compounds of general formula III in which :

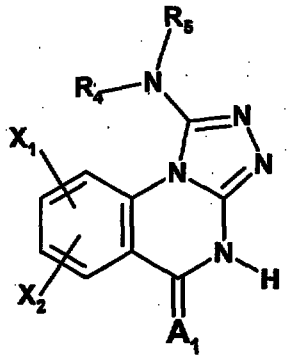
X_1 and X_2 are as defined above, and
R_7 is linked to the nitrogen at R_6 to form a triazole, substituted in position 1 with a Br, Cl, mercapto or lower thioalkyl, preferably CH_3-S, group.

The following substituents are particularly preferred among the groups defined above :
- In general, for the groups X_1, X_2, R_6 and R_7 :
  - halogen : F, Cl, Br, I, preferably Br and Cl,
  - lower alkyl : linear or branched containing from 1 to 6 and preferably from 1 to 3 carbon atoms,
  - lower alkoxy : lineair or branched comprising from 1 to 5 and preferably from 1 to 3 carbon atoms,
  - lower thioalkyl : linear or branched comprising from 1 to 5 and preferably from 1 to 3 carbon atoms.

- In particular, for the groups X_1 and X_2 :
  X_1 and X_2 are particularly located in positions 6 and 7 of the main quinazolinone ring.

- In particular, for the groups R_6 and R_7 :
  when R_7 is linked to the nitrogen at R_6 to form a ring, the ring formed is preferably a triazole, substituted in position 1 with a Br, Cl, mercapto or lower thioalkyl, preferably CH_3-S-, group.

A second series of intermediates comprises compounds having the general formula IV below :



IV

in which X_1, X_2, A_1, R_4 and R_5 are as defined above.

For the above groups, the following substituents are particularly preferred :

- In general, for the groups X_1, X_2, R_4 and R_5 :
  - halogen : F, Cl, Br, I, preferably Br and Cl,
  - lower alkyl : linear or branched containing from 1 to 6 and preferably from 1 to 3 carbon atoms,
  - lower alkoxy : linear or branched containing from 1 to 5 and preferably from 1 to 3 carbon atoms ,
  - lower alkyl, it being possible for R_4 and R_5 to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N and optionally bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy, phenylalkyl or $CO\text{-}Q_1\text{-}Q_2\text{-}Q_3$, it being possible for two of the atoms in the ring thus formed also to form part of another ring chosen from phenyl and heteroaryl containing from 4 to 8 atoms including 1 to 4 hetero atoms.

- In particular, for the groups X_1 and X_2 :

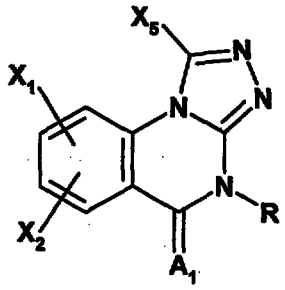
  X_1 and X_2 are particularly located in positions 6 and 7 of the main quinazolinone ring.

- In particular, for the groups R_4 and R_5 :

  R_4 and R_5 are lower alkyl, it being possible for R_4 and R_5 to be linked to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N, substituted with one or more groups chosen from hydroxyl, keto, lower alkyl and lower alkoxy. The substituents forming the

group NR_4R_5 which are particularly preferred include pyrrolidine, 3-hydroxypyrrolidine, thiamorpholine, dimethylamino, azepanyl and piperidyl.

A third series of intermediates comprises compounds having the general formula V below :



(V)

in which X_1, X_2, X_5, A_1 and R are as defined above.

The following substituents are particularly preferred for the above groups :

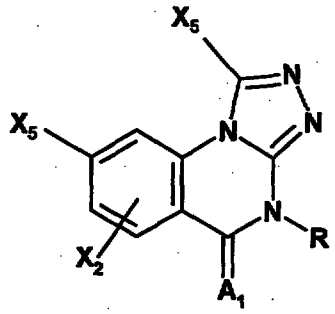
- In general, for the groups X_1, X_2 et X_5 :
  - halogen : F, Cl, Br, I, preferably Br and Cl,
  - lower alkyl : linear or branched containing from 1 to 6 and preferably from 1 to 3 carbon atoms,
  - lower alkoxy : linear or branched containing from 1 to 5 and preferably from 1 to 3 carbon atoms.

- In particular, for the groups X_1 and X_2 :

  X_1 and X_2 are particularly located in positions 6 and 7 of the main quinazolinone ring.

- In particular, for the group X_5 : X_5 is F, Br or Cl.

A fourth series of intermediates comprises compounds having the general formula VI below :



(VI)

in which X_2, X_5, A_1 and R are as defined above.

The following substituents are particularly preferred for the above groups :

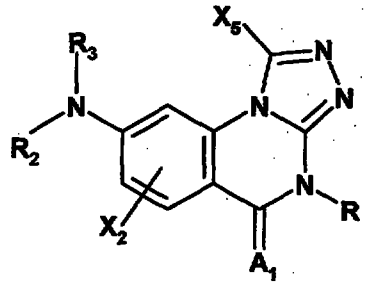
- In general, for the groups X_2 and X_5 :
  - halogen : F, Cl, Br, I, preferably Br and Cl,
  - lower alkyl : linear or branched containing from 1 to 6 and preferably from 1 to 3 carbon atoms,
  - lower alkoxy : linear or branched containing from 1 to 5 and preferably from 1 to 3 carbon atoms.

- In particular, for the group X_2 :

X_2 is particularly located in position 7 of the main quinazolinone ring.

- In particular, for the group X_5 : X_5 is F, Br or Cl.

A fifth series of intermediates comprises compounds having the general formula VII below :



(VII)

in which X_2, X_5 A_1, R_2 and R_3 are as defined above.

The following substituents are particularly preferred for the above groups :

- In general, for the groups X_2, X_5, R_2 and R_3 :
  - halogen : F, Cl, Br, I, preferably Br and Cl,
  - lower alkyl : linear or branched containing from 1 to 6 and preferably from 1 to 3 carbon atoms,
  - lower alkoxy : linear or branched containing from 1 to 5 and preferably from 1 to 3 carbon atoms,
  - hydrogen, lower alkyl, optionally substituted with one or more hydroxyl, halogen, cyano, lower alkoxy or $-CO-Q_1-Q_2-Q_3$ groups, if being possible for R_2 and R_3 to be linked to form a ring comprising one or more hetero atoms chosen from O, S and N and optionally bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy and $-CO-Q_1-Q_2-Q_3$.

- In particular, for the group X_2 :

X_2 is particularly located in position 7 of the main quinazolinone ring.

- In particular, for the group X_5 : X_5 is F, Br or Cl.

- In particular, for the groups R_2 and R_3 :

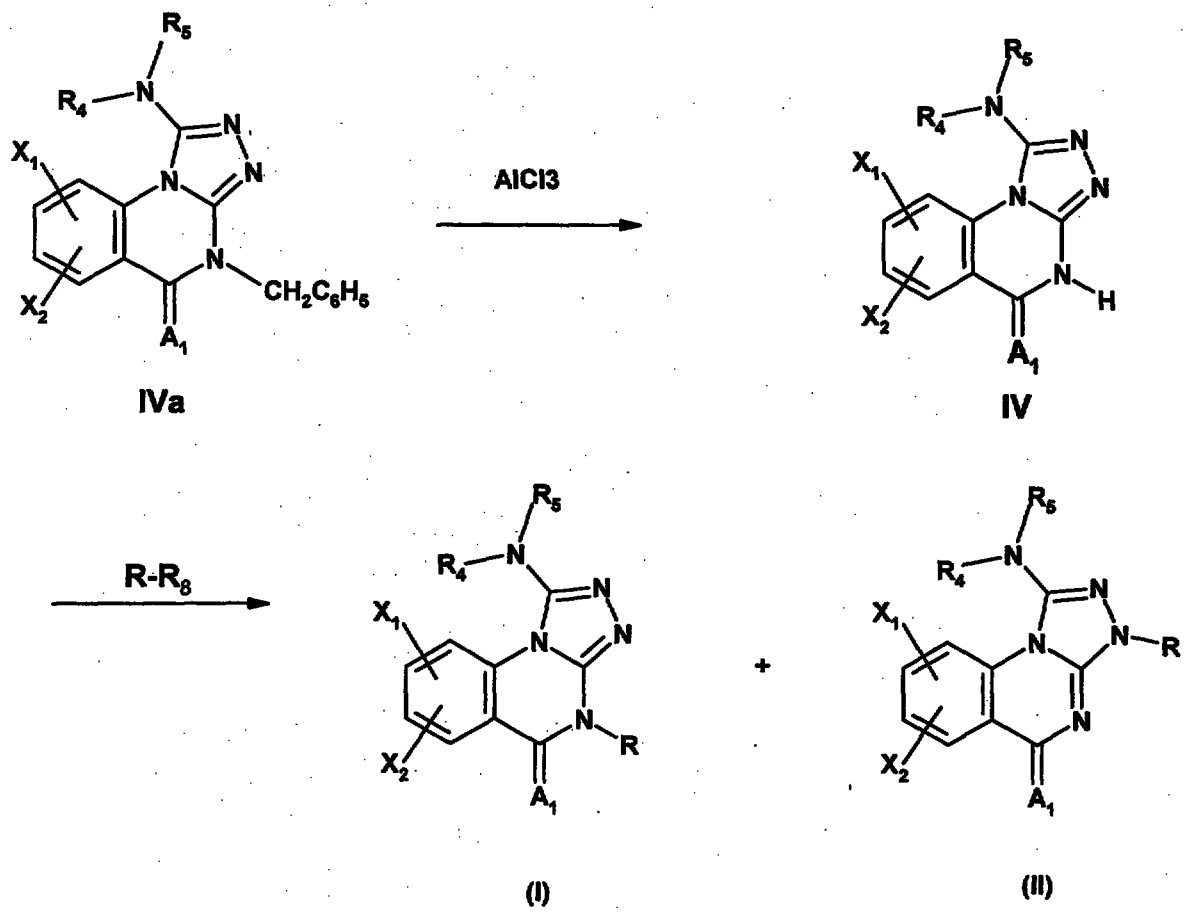
R_2 and R_3, which may be identical or different, are hydrogen or lower alkyl or R_2 and R_3 are linked to form a ring comprising one or more hetero atoms chosen from O, S and N and optionally substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy and $-CO-Q_1-Q_2-Q_3$. Among the embodiments particularly preferred for the substituents NR_2R_3 are azepanyl, pyrrolidine, NH_2 and $NHCH_3$ groups.

Processes for synthesizing the compounds of formulae I and II

A) The compounds of the present invention can be obtained by carrying out several synthetic processes. A number of these synthetic processes are described below.

The compounds of the present invention can firstly be obtained in a convergent manner by the method represented in Scheme 1.

SCHEME 1



in which X_1, X_2, A_1, R, R_4 and R_5 are as defined above and R_8 represents Cl, Br, OSO_2CH_3, OSO_2CF_3 or OSO_2Ar.

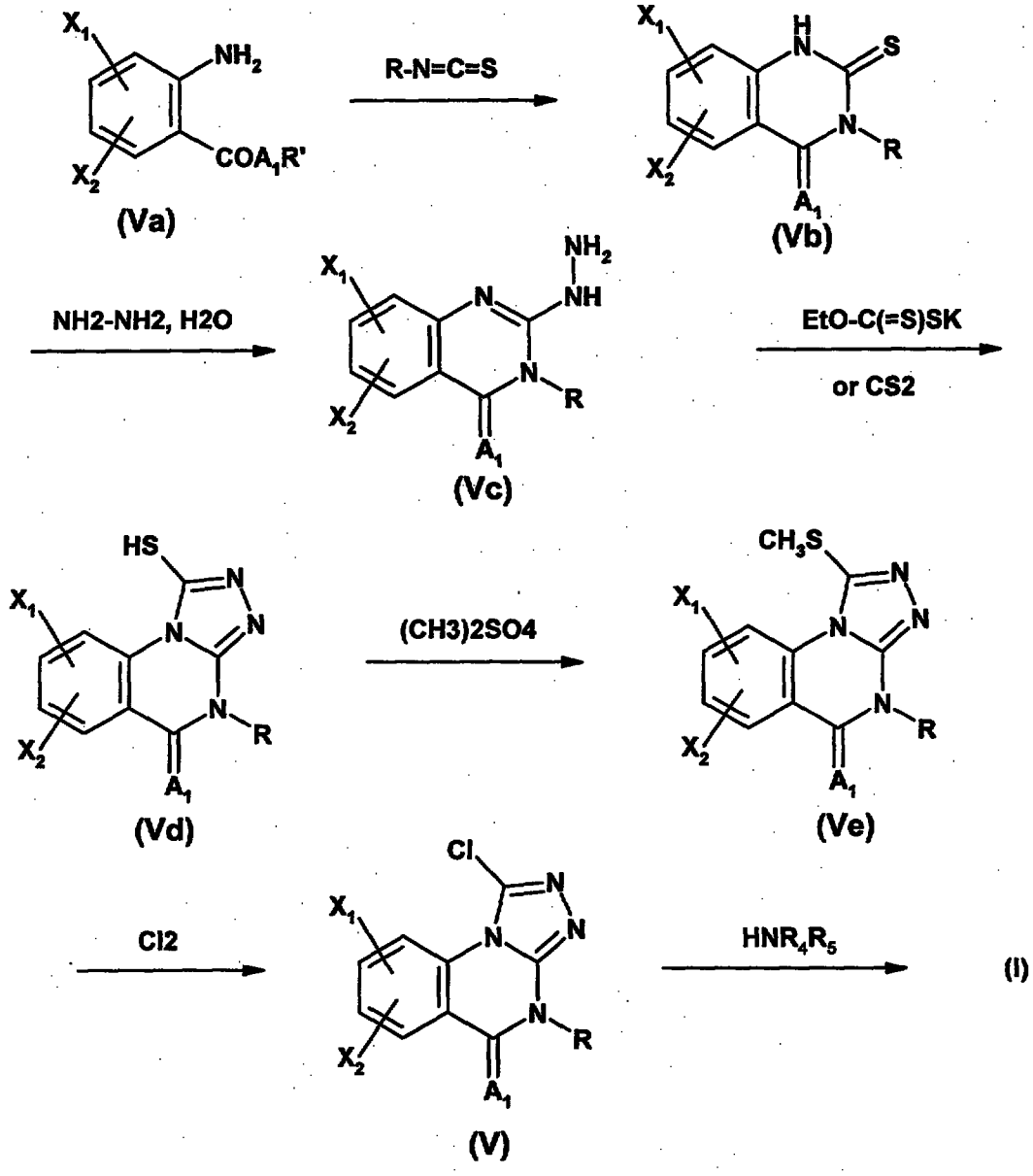
4-Benzyl-1-aminotriazolo[4,3-a]quinazolin-5-one and/or –5-thione (IVa) is treated with aluminium trichloride in an aromatic solvent such as benzene or toluene to give the corresponding N-debenzylated compound (IV). This is then treated with a halide or a sulphonate chosen as a function of the desired substituent R under basic conditions ; for example sodium hydride in a solvent such as 1,2-dimethoxyethane (DME) or caesium carbonate in dimethylformamide, to give the 1-aminotriazolo[4,3-a]quinazolin-5-ones of formulae (I) and (II).

In fact, as a function of the basic conditions used, the alkylation is not particularly regioselective in certain cases. A mixture of N_4 and N_3 regioisomers, (I) and (II), respectively, is thus obtained.

The 2 compounds are generally separated by conventional chromatographic techniques.

B) Another example of a synthetic method used to construct the suitably substituted triazolo[4,3-a]quinazolin-5-one and/or –5-thione unit of formula (I) is illustrated in Scheme 2 :

SCHEME 2



in which X_1, X_2, A_1, R, R_4, and R_5 are as defined above, and

R' represents a linear or branched lower alkyl group containing from 1 to 6 and preferably from 1 to 3 carbon atoms.

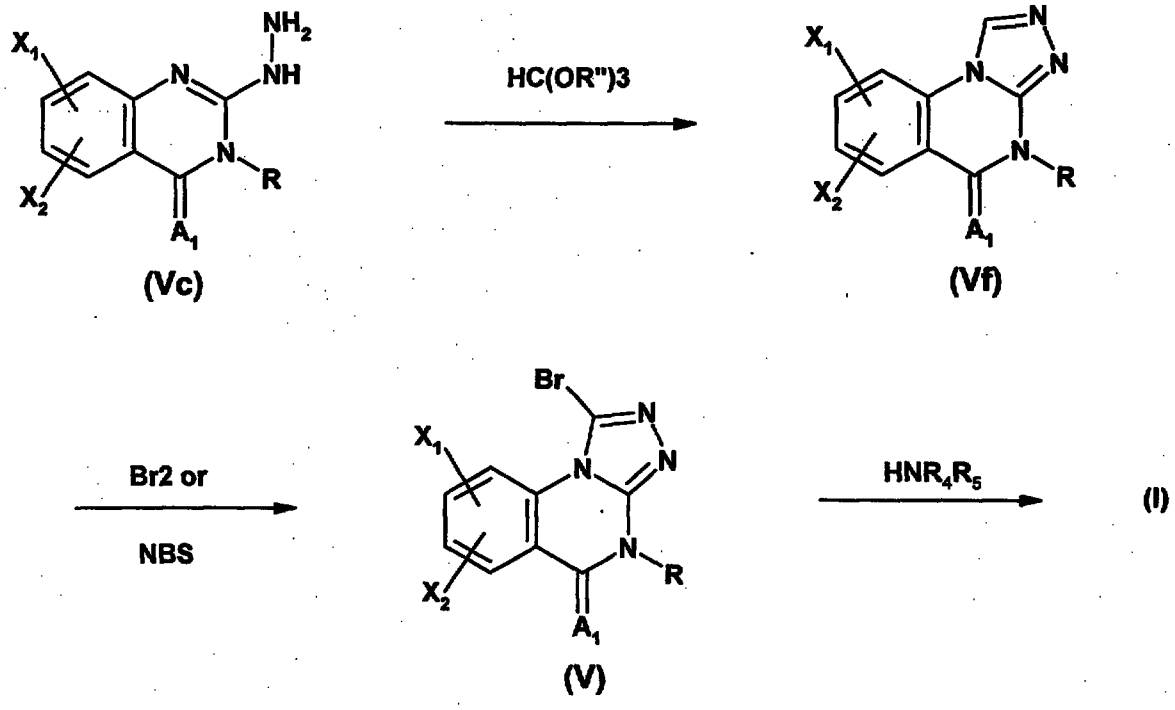
An anthranilic acid or ester suitably substituted on the aromatic ring (Va) is first converted into the corresponding 2-thioquinazolin-4-one (Vb) and/or –4-thione by cyclization using an alkyl, aryl or aralkyl isothiocyanate, in a solvent such as acetic acid or pyridine.

The thioquinazolin-4-one and/or –4-thione (Vb) is treated with hydrazine hydrate to give the 2-hydrazinoquinazolin-4-one and/or –4-thione (Vc) which is in turn cyclized into the 1-mercaptotriazolo[4,3-a]quinazolin-5-one and/or –5-thione (Vd) by the action of potassium xanthogenate or other reagents such as CS_2.

By the action of an alkylating agent such as dimethyl sulphate, the thiol (VI) is converted into the 1-methylthio derivative (Ve) which is then converted, by means of chlorine, into the 1-chlorotriazolo[4,3-a]quinazolin-5-one and/or –5-thione (V).

The latter compound is treated with a primary or secondary amine to finally give the 1-aminotriazolo[4,3-a]quinazolin-5-one of formule (I).

C) Another advantageous method in certain cases is represented in Scheme 3.



SCHEME 3

in which X_1, X_2, A_1, R, R_4 and R_5 are as defined above, and

R" represents a linear or branched lower alkyl containing from 1 to 6 and preferably from 1 to 3 carbon atoms, such as CH_3 or C_2H_5.

The 2-hydrazinoquinazolin-4-one and/or –4-thione (Vc), obtained from an anthranilate in 2 steps (as illustrated in Scheme 2), is cyclized by means of an alkyl orthoformate, in acidic medium, into the triazolo[4,3-a]quinazolin-5-one and/or –5-thione (Vf).

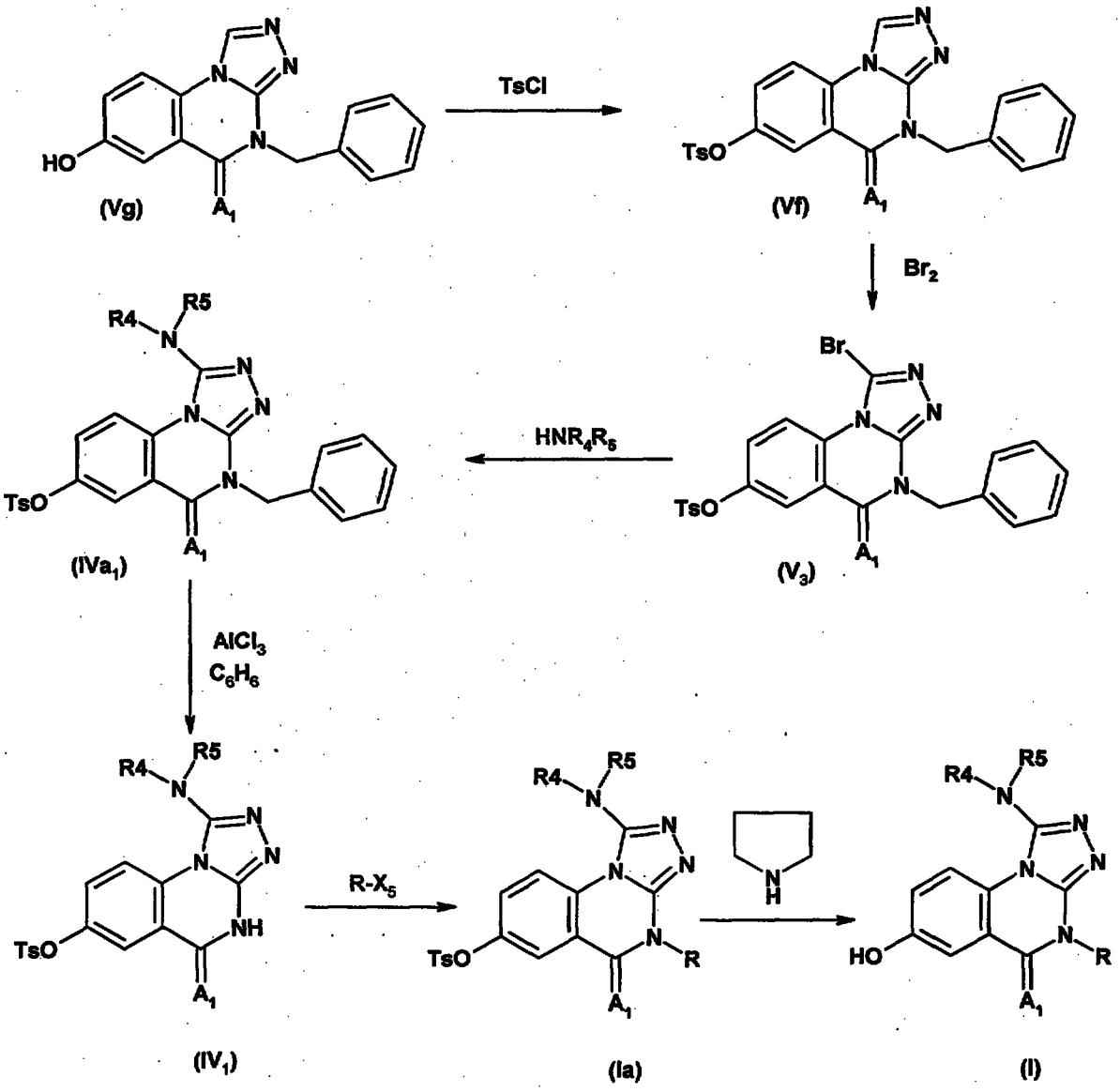
This is then brominated with bromine or N-bromosuccinimide (NBS) to give the 1-bromotriazolo[4,3-a]quinazolin-5-one and/or –5-thione (V).

This bromo derivative is finally treated with an ethanolic solution of a primary or secondary amine to give the 1-aminotriazolo[4,3-a]quinazolin-5-one and/or -5-thione of formula (I).

D) When X_1 is H and X_2 represents a reactive phenolic OH function, this group should generally be protected during the last steps in the synthesis of the compounds (I). By way of example, Scheme 4 shows the synthesis of such a compound hydroxylated in position 7. 4-Benzyl-7-hydroxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or –5-thione (Vg), obtained by a method represented in Scheme 3, is treated with a compound allowing the insertion of an oxygen-protecting group (P) onto the OH function. A person skilled in the art may select the appropriate protecting group without difficulty. The protecting group can be chosen, inter alia, from trimethylsilyl, methoxymethyl, tolylsulphonyl, methylsulphonyl (mesyl) and methoxyethoxymethyl (MEM). By way of example, the compound (Vg) is treated with tosyl chloride, in a solvent such as methylene chloride, in the presence of a base or an amine such as triethylamine, to give the corresponding O-tosyl phenol (Vf). This compound is treated with bromine to give 4-benzyl-1-bromo-7-(4-tolylsulphonyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or –5-thione (V_3), which reacts with an amine HNR_4R_5 at reflux, preferably in the presence of a base such as sodium bicarbonate, in a solvent such as dimethylformamide, to give 1-amino-4-benzyl-7-(4-tolylsulphonyl)–4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or –5-thione (IVa_1).

The benzyl group in position 4 can then be replaced with another group R, for example by debenzylating the compound (IVa_1) obtained above by means of aluminium chloride in a solvent such as benzene, and then alkylating the intermediate obtained (IV_1) by treatment with a halide or a sulphonate R-X_5, under basic conditions, to give the 1-amino-7-(4-tolylsulphonyl)–4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or –5-thione (Ia) which are variously substituted in position 4. These are preferably detosylated into the 7-hydroxy derivatives (I), for example by heating for a few hours in pyrrolidine.

SCHEME 4



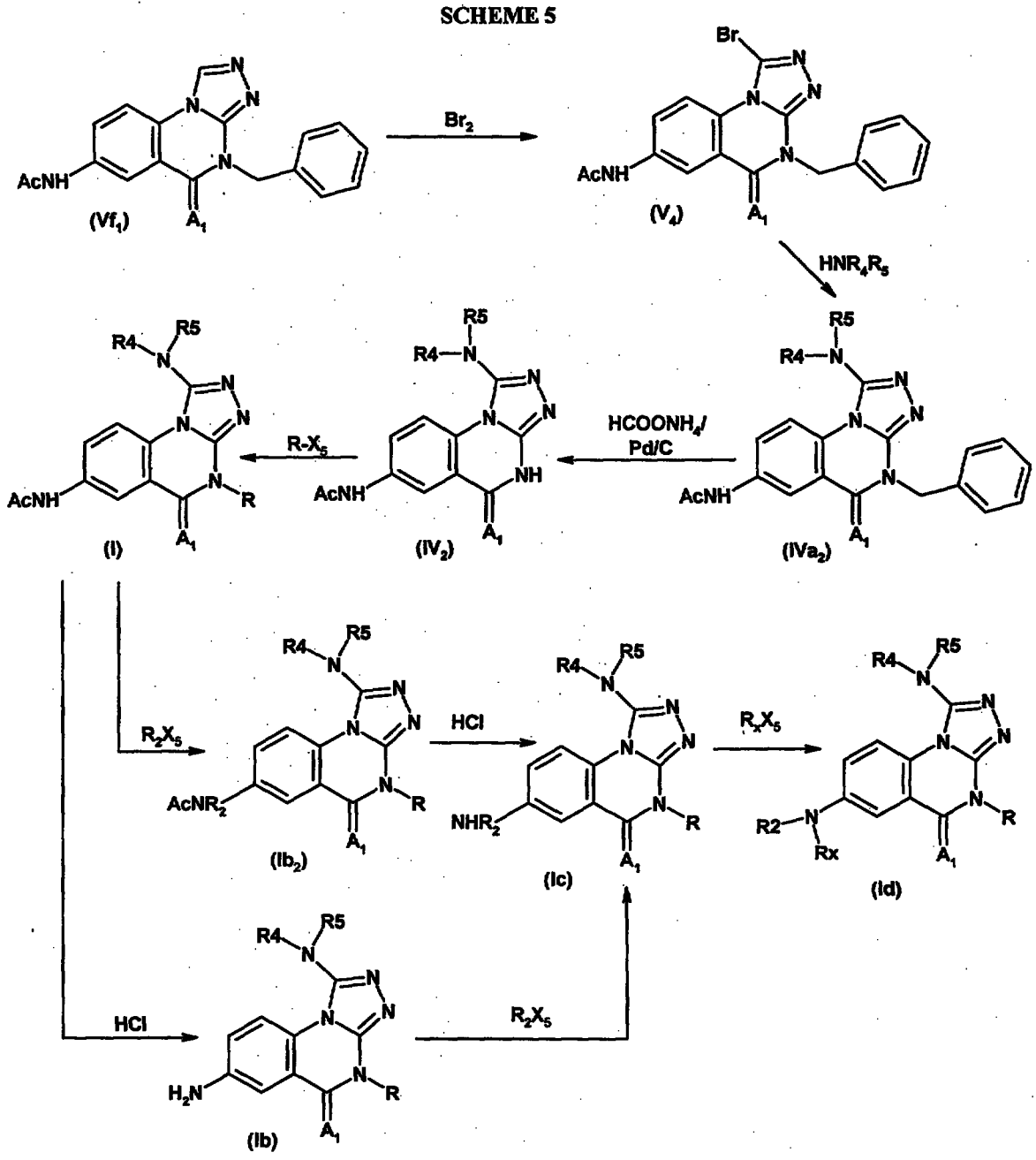
in which A_1, R_4 and R_5 are as defined above.

E) When X1 represents H and X2 represents a reactive anilino function : NH2, NHR2 or NR_2R_x (R2 as defined above and R_x represents R_2 or R_3 as defined above), the amino group NH2 should generally be protected during the last steps in the synthesis of the compounds (I). By way of example, Scheme 5 shows the synthesis of such a compound aminated in position 7. 7-Acetamido-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or –5-thione (Vf_1), obtained by a method represented in Scheme 3, is treated with bromine to give 7-acetamido-4-benzyl-1-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or –5-thione (V_4). This compound is reacted with an amine HNR_4R_5 at reflux, preferably in the presence of a base such as sodium bicarbonate, in a solvent such as dimethylformamide, to give 7-acetamido-1-amino-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or –5-

thione (IVa_2). In the example described above, the protecting group (P_1) for the NH function is an acetyl group. However, a person skilled in the art can select another protecting group, for example methylsulphonyl, tolylsulphonyl or phthalimido.

In this case, the benzyl group in position 4 can be replaced with another group R, for example by debenzylating the compound (IVa_2) obtained above, using ammonium formate and palladium-on-charcoal, in a solvent such as tetrahydrofuran, and then alkylating the intermediate obtained (IV_2) by treatment with a halide or a sulphonate R-X_5, under basic conditions, to give the 7-acetamido-1-amino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or –5-thione (I) variously substituted in position 4. These can be N-deacetylated into final compounds (Ib) bearing an NH2 function in position 7, by conventional methods such as, for example, heating to reflux in an aqueous hydrochloric acid solution. These compounds can in turn be treated, depending on the case, with a reagent R2-X_5 (R2 and X_5 having the meaning given above) to give an N-monosubstituted final compound (Ic), which can itself then be treated with a reagent R_xX_5 to give an N,N-disubstituted final compound (1d). It is also possible to treat the 7-acetamido-1-amino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or –5-thione (I) which are variously substituted in position 4, firstly with a reagent R_2X_5 to give the compound ($1b_2$) which is then N-deacetylated to give the compound (Ic).

SCHEME 5

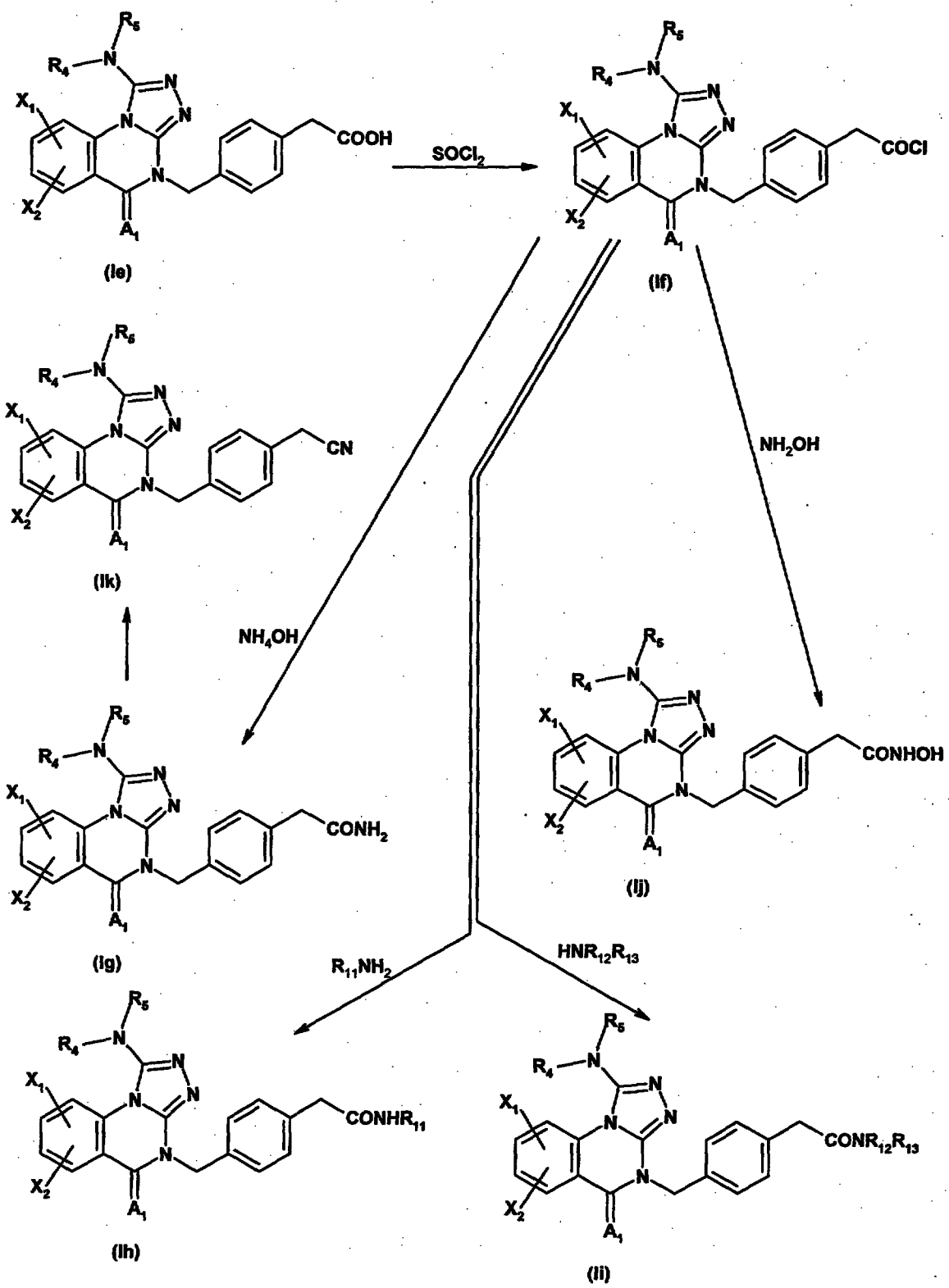


F) When the substituent R in position 4 of the compounds (I) represents a 4-(carboxymethyl)benzyl group, it may be advantageous to convert the carboxylic acid function into an ester, amide, nitrile or hydroxamic acid derivative. For this, the methods represented in Scheme 6 may be applied to an acid of general formula (Id). This is converted into an acid chloride (Ie) which is directly coupled either with aqueous ammonia to give a primary amide (If), or with a primary or secondary amine to give, respectively, a secondary amide (Ih) or tertiary amide (Ii) (in these structures, R11 has the same meaning as R2, and R12 and R13 have the same meanings as R4 and R5, respectively).

Hydroxamic acid (Ij) can be obtained by reacting the acid chloride (Ie) with hydroxylamine. The primary amide (If) can also be dehydrated by conventional methods that are known per se, such as, for example, using phosphorus pentoxide, to give the corresponding nitrile (Ig).

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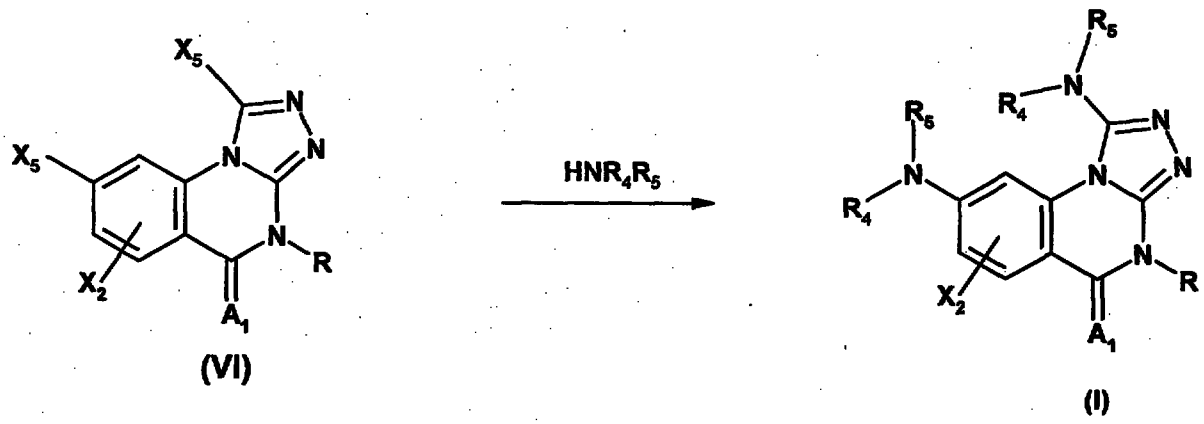
SCHEME 6



in which X_1, X_2, A_1, R_4 and R_5 are as defined above.

G) The compounds of structure (I) in which X_1 or X_2 represents an amino group NR_2R_3 in position 8 which is identical to the group NR_4R_5, can also be obtained by heating the corresponding 1-bromo intermediate (VI ; X_5 = hal) in the presence of an excess of amine HNR_4R_5, without solvent or in a solvent such as dimethylformamide, as illustrated in Scheme 7.

SCHEME 7

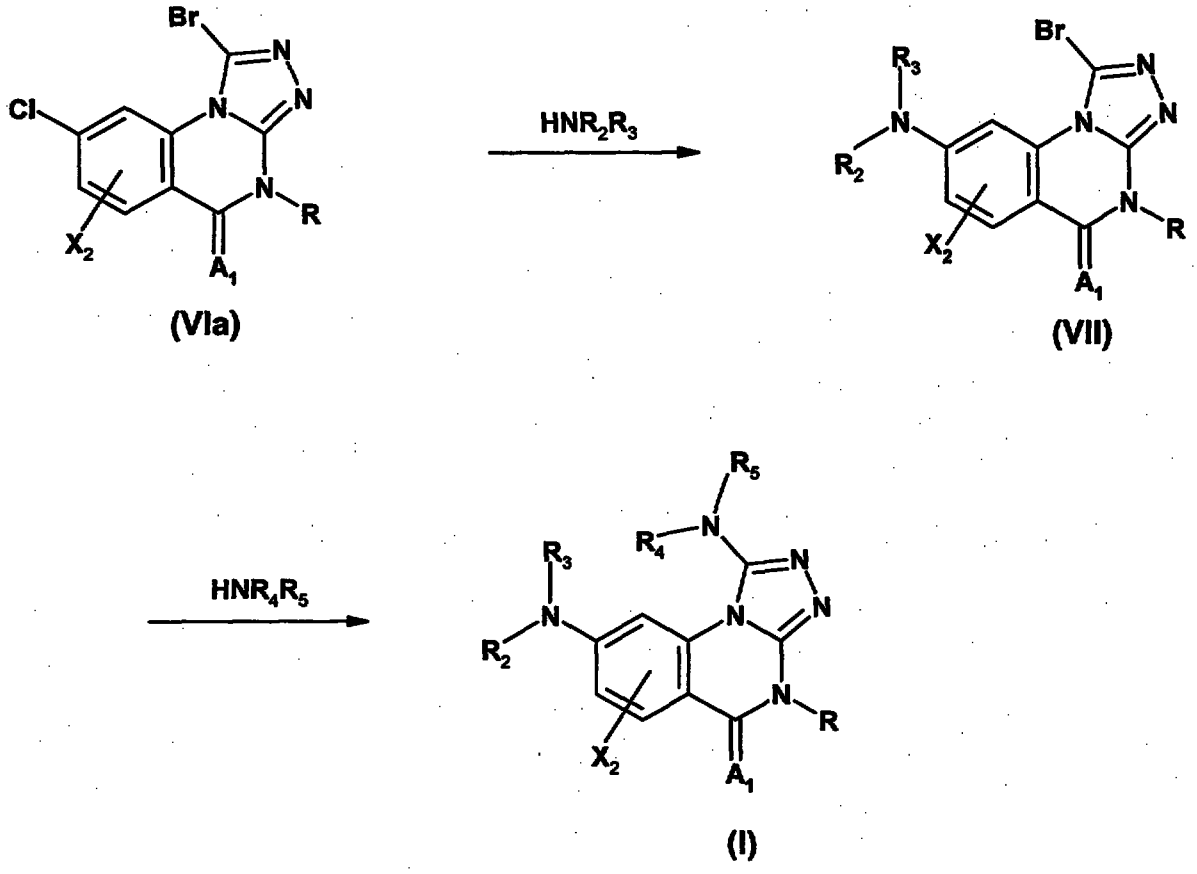


in which X_2, X_5, A_1, R, R_4 and R_5 are as defined above.

However, it is preferable, for this type of reaction, to avoid substituents R comprising a halogen group which is liable to react competitively with the reagent HNR_4R_5.

H) When the 2 amino groups NR_2R_3 and NR_4R_5 are different, a slightly modified synthetic route is indicated in Scheme 8.

SCHEME 8



in which X_2, A_1, R, R_2, R_3, R_4 and R_5 are as defined above. The amino substituent NR_2R_3 is in position 8.

A 1-bromo-8-chlorotriazolo[4,3-a]quinazolin-5-one and/or –5-thione (VIa) suitably substituted at 4, and prepared as above by bromination of the derivative which is unsubstituted at 1, is treated with a light excess of amine HNR_2R_3, in a solvent such as dimethylformamide, to give the intermediate (VII).
This intermediate is in turn heated in an excess of amine HNR_4R_5, in a solvent such as dimethylformamide, to give the compound (I).

Surprisingly, the inventors have found that the reactivity of the halogen atom in position 8 is much higher than the reactivity of the other halogen atom of the intermediate. This therefore allows a first selective reaction on this halogen in position 8, which can be followed by a reaction on the second halogen. The example above illustrates the use of chlorine in position 8. However, it is possible to use other halogens such as bromine and fluorine, the latter proving to be particularly reactive.

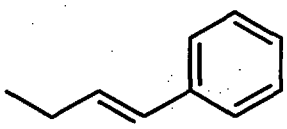
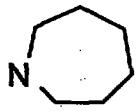
Examples

A. Compounds of the type (I) and (II)

Examples 1 and 2

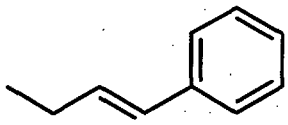
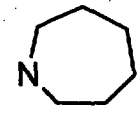
METHOD A : 1-Azepanyl-7-chloro-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Ex. 1)

(I): $X_1 = 7 - Cl$; $X_2 = H$;

R=  ; NR_4R_5=  and

1-Azepanyl-7-chloro-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Ex. 2)

(II) : $X_1 = 7 - Cl$; $X_2 = H$;

R=  ; NR_4R_5=  and

2.5 g (7.87 mmol) of 1-azepanyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one suspended in 35 ml of 1,2-dimethoxyethane are placed in a reactor protected from moisture, and then stirred.

240 mg of a 75% sodium hydride suspension (representing 7.90 mmol of NaH) are then added, under inert atmosphere.

The mixture is heated at 60°C with stirring for 6 hours.

1.56 g (7.90 mmol) of cinammyl bromide are then added portionwise.

The mixture obtained is then heated at 60°C for 20 hours with stirring.

After cooling, the suspension is poured into 200 ml of ice-cold water.

The mixture is extracted 3 times with ethyl acetate; the combined organic phases are washed with saturated aqueous sodium chloride solution and dried over sodium sulphate, and the solvent is then evaporated off under vacuum.

3.5 g of a crude mixture of the 2 regioisomers is obtained (theory : 3.4 g).

The 2 isomers are separated by flash chromatography on a column of silica, eluting with a 99 methylene chloride / 1 methanol mixture.

The following are obtained, in order of elution :

1) 0.58 g of the compound of Example 1

Yield = 17%

m.p. (Tottoli) = 125°C

TLC (98 CH_2Cl_2 / 2 CH_3OH) = 0.60

^{1}H NMR δ (ppm) $CDCl_3$: 1.7 – 2.0 (m, 8H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (d, 2H) ; 6.45 (dt, 1H) ; 6.9 (d, 1H) ; 7.15 – 7.3 (m, 3H) ; 7.35 (d, 2H) ; 7.75 (d, 1H) ; 8.35 (s, 1H) ; 8.4 (d, 1H).

2) 2.1 g of the compound of Example 2

Yield = 61.5%

m.p. (Tottoli) = 188°C

TLC (98 CH_2Cl_2 / 2 CH_3OH) : Rf = 0.35.

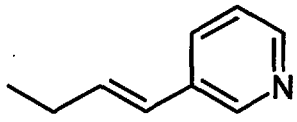
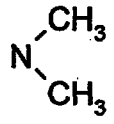
^{1}H NMR δ (ppm) $CDCl_3$:

1.7 – 2.0 (m, 8H) ; 3.4 (m, 4H) ; 4.9 (d, 2H) ; 6.35 (dt, 1 H) ; 6.75 (d, 1H); 7.2 – 7.45 (m, 5H) ; 7.65 (d, 1H) ; 8.2 (d, 1H) ; 8.45 (s, 1H)

Example 3 :

METHOD B : 7-Bromo-1-(N,N-dimethylamino)-4-[3-(3-pyridyl)allyl]-4H-[1,2,4]triazolo-[4,3-a]quinazolin-5-one (Ex. 3)

(I): X_1 = 7 – Br ; X_2 = H ;

R=  ; NR4R5= 

7.4 g (0.024 mol) of 7-bromo-1-(N,N-dimethylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one dissolved in 200 ml of 1,2-dimethoxyethane are placed in a reactor equipped with a magnetic stirrer and a condenser, and are then stirred. 17.0g (0.052 mol) of caesium carbonate are added and the mixture is then stirred at room temperature for 15 minutes. 4.5 g (0.024 mol) of 3-(3-pyridyl)allyl chloride hydrochloride are then added portionwise, after which the mixture is heated at 70°C with stirring for 3 hours. The solvent is evaporated off under vacuum and the residue is then suspended in 300 ml of ice-cold water. After repeated extractions with ethyl acetate, the combined organic phases are washed with saturated aqueous sodium chloride solution and dried over sodium sulphate, and the solvent is then evaporated off under vacuum.

The residue is chromatographed on a column of silica, eluting with a 98 CH_2Cl_2/2 CH_3OH/0.2 NH_4OH mixture. 6.3g of TLC-pure isomer (I) are recovered. This product is recrystallized from 20 ml of isopropanol to give 5.3 g of the compound of Example 3 :

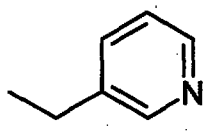
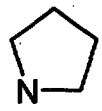
Yield = 52%

^{1}H NMR δ (ppm) $CDCl_3$: 2.95 (s, 6H) ; 5.1 (d, 2H) ; 6.45 (dt, 1H) ; 6.8 (d, 1H) ; 7.15 (m, 1H) ; 7.65 (d, 1H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.4 – 8.6 (m, 3H).

Examples 4 and 5 :

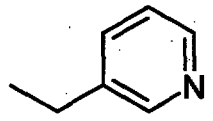
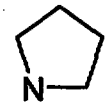
METHOD C : 7-Bromo-1-(pyrrolidin-1-yl)-4-[(3-pyridyl)methyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Ex. 4)

(I): $X_1 = 7 - Br$; $X_2 = H$;

R=  ; NR4R5= 

7-Bromo-1-(pyrrolidin-1-yl)-3-[(3-pyridyl)methyl]-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Ex. 5)

(II) : X1 = 7-Br ; X2 = H ;

R=  ; NR4R5= 

2.0g (0.006 mol) of 1-(pyrrolidin-1-yl)-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one dissolved in 125 ml of dimethyl sulphoxide (DMSO) are placed in a reactor protected from moisture, equipped with a stirring system, followed by addition of 1.0g (0.018 mol) of finely ground potassium hydroxide. The mixture is stirred at room temperature for 1 h 30 min, until a slightly cloudy solution is obtained. 0.82 g (0.005 mol) of 3-picolyl chloride hydrochloride is then added in a single portion, after which stirring is continued at room temperature for 4 hours.

The mixture obtained is poured into ice-cold water and the resulting suspension is extracted three times with ethyl acetate. The combined organic extracts are washed with saturated NaCl solution and dried over Na_2SO_4 and then concentrated under vacuum. 2.0 g of a crude mixture of the 2 regioisomers are obtained, which are separated by chromatography on a column of silica, eluting with a 98 CH_2Cl_2/2 CH_3OH/0.4 NH_4OH mixture.

The following are obtained, in the order of elution :

1) 1.2 g of the major product, which is recrystallized from methanol to give, after drying under vacuum, 1.1 g of the compound of Example 4

Yield = 57%

m.p. (Tottoli) = 206-207°C

TLC (97 CH_2Cl_2 / 3 CH_3OH /0.3 NH_4OH) : Rf = 0.30

^1H NMR δ (ppm) $CDCl_3$: 1.95 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 5.45 (s, 2H) ; 7.2 – 7.3 (dd, 1H) ; 7.85 (d, 1H) ; 8.0 (d, 1H) ; 8.2 (d, 1H) ; 8.45 – 8.55 (m, 2H) ; 8.9 (s, 1H).

2) 0.25 g of the minor product, which is recrystallized from methanol to give, after drying under vacuum, 0.17 g of the compound of Example 5.

Yield = 12%

m.p. (Tottoli) = 261-262°C

TLC (97 CH_2Cl_2 / 3 CH_3OH / 0.3 NH_4OH) : Rf = 0.20

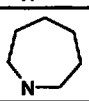
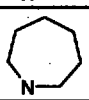
^1H NMR δ (ppm) $CDCl_3$: 1.9 – 2.05 (m, 4H) ; 3.2 – 3.4 (m, 4H) ; 5.25 (s, 2H) ; 7.1 – 7.2 (m, 1H) ; 7.7 (d, 1H) ; 7.8 (d, 1H) ; 7.9 (d, 1H) ; 8.45 – 8.60 (m, 2H) ; 8.65 (s, 1H).

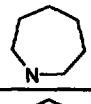
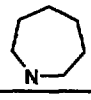
The compounds (I) of Examples 6 to 108 and the compounds (II) of Examples 109 to 162, in which $X_2 = H_1$, are prepared according to the process of Example 1 :

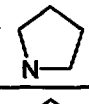
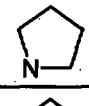
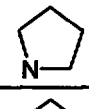
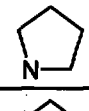
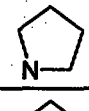
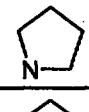
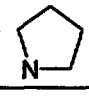
Compounds (I) : Table 1

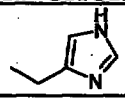
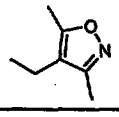
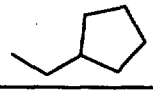
Compounds (II) : Table 2

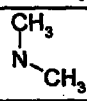
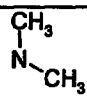
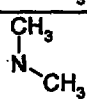
TABLE 1

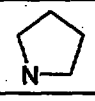
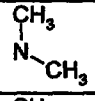
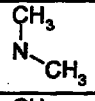
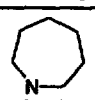
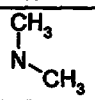
Compound No.	X1	R	NR4R5	Yield (%)	m.p. (°C)	Method
6	H	(E) C6H5CH=CHCH2		11	144	A
7	7-Cl	CH2=CHCH2		9	-	A
8	7-Cl	4-CH3C6H4CH2		16	163	A
9	7-Cl	2-ClC6H4CH2		6	160-162	A
10	7-Cl	3-ClC6H4CH2		35	157	A
11	7-Cl	4-ClC6H4CH2		20	166	A
12	7-Cl	4-BrC6H4CH2		25	104-110	A
13	7-Cl	4-FC6H4CH2		48	150	A
14	7-Cl	4-CF3C6H4CH2		22	138	A
15	7-Cl	4-CNC6H4CH2		49	165-168	A
16	7-Cl	2-(CH3O)C6H4CH2		6	98-100	A
17	7-Cl	3-(CH3O)C6H4CH2		22	138	A
18	7-Cl	4-(CH3O)C6H4CH2		26	138	A

Compound No.	X1	R	NR4R5	Yield (%)	m.p. (°C)	Method
19	7-Cl	3,4-Cl2C6H3CH2		19	-	A
20	7-Cl	3,4-(CH3O)2C6H3CH2		41	172	A
21	7-Cl	(2-pyridyl)CH2		16	152	A
22	7-Cl	(3-pyridyl)CH2		29	155	A
23	7-Cl	(4-pyridyl)CH2		64	137	A
24	7-Cl	C6H5CH2CH2		5	105	A
25	7-Cl	4-(CH3O)C6H4(CH2)2		12	136	A
26	7-Cl	C6H5(CH2)3		17	-	A
27	7-Cl	C6H5C(=O)CH2		26.5	105-107	A
28	7-Cl	4-(CH3O)C6H4C(=O)		30	191	A
29	7-Cl	4-ClC6H4C(=O)CH2		36	190	A
30	7-Cl	4-(CH3O)-3-(COOCH3)-		18	140	A
31	7-Cl	(3-pyridyl)-CH2		39	176	C
32	7-Br	4-ClC6H4CH2		8	179	A
33	7-Br	4-FC6H4CH2		21	158	A
34	7-Br	4-CNC6H4CH2		21	190	A
35	7-Br	3,4-(CH3O)2C6H3CH2		23.5	185	A
36	7-Br	(3-pyridyl)-CH2		4	180	C

Compound No.	X1	R	NR4R5	Yield (%)	m.p. (°C)	Method
37	7-Br	(E) C6H5CH=CHCH2		64	155	B
38	7-Br	(E) 4-Cl-C6H4CH=CHCH2		25	176	B
39	7-Br	(E) 4-(CH30)C6H4CH=C		30	129	B
40	7-Br	(E) (3-pyridyl)CH=CHCH2		12	185	B
41	7-Br	(E) (4-pyridyl)CH=CHCH2		39	216	B
42	7-Br	4-CH3C6H4CH2		53	215	B
43	7-Br	4-ClC6H4CH2		12	105	A
44	7-Br	4-FC6H4CH2		42	166	A
45	7-Br	3-CNC6H4CH2		52	206	B
46	7-Br	4-CNC6H4CH2		19	116	A
47	7-Br	4-(COOCH3)C6H4CH		54	205	A
48	7-Br	4-NO2C6H4CH2		52	200	B
49	7-Br	4-(CH3O)C6H4CH2		39	169	B
50	7-Br	4-(OCOCH3)C6H4CH		21	195	B
51	7-Br	4-OHC6H4CH2		13	288	B
52	7-Br	3,4-(CH3O)2C6H3CH2		15	151	A
53	7-Br	3,4-(OCH2O)C6H3CH2		21	194	A
54	7-Br	3,5-(CH3O)2C6H3CH2		31	-	A

Compound No.	X1	R	NR4R5	Yield (%)	m.p. (°C)	Method
55	7-Br	3,4,5-(CH3O)3C6H2CH2		35	141-143	A
56	7-Br	4-(CH2COOH)C6H4C		17	260	B
57	7-Br	(E) C6H5CH=CHCH2		57	152-155	A
58	7-Br	(Z) C6H5CH=CHCH2		24	110	B
59	7-Br	(E) (4-ClC6H4)-CH=CHCH2		45	187	B
60	7-Br	(E) (4-CH3O)C6H4CH=CH		32	171	B
61	7-Br	(E) (3-pyridyl)-CH=CHCH2		10	102	B
62	7-Br	(E) (4-pyridyl)-CH=CHCH2		38	167	B
63	7-Br			4	290(dec)	B
64	7-Br			60	221	B
65	7-Br			32	155	B
66	7-Br	n-butyl		39	135	B
67	7-Br	CH2CF3		14	202	B
68	7-Br	CH2CH2OH		25	240	B
69	7-Br	CH2CH2N(C2H5)2		50	215 (HCl)	C
70	7-Br			36	204	B
71	7-Br	CH2CH2OC6H5		25	171	B
72	7-Br	CH2CH2SC6H5		20	122	B

Compound No.	X1	R	NR4R5	Yield (%)	m.p. (°C)	Method
73	7-Br	CH(C6H5)COOCH3		14	184	B
74	7-Br	4-CNC6H4CH2		72	200	B
75	7-Br	3,4-(CH3O)2C6H3CH2		67	178	B
76	7-Br	(E) C6H5CH=CHCH2		8	-	A
77	7-Br	(E) (3-pyridyl)CH=CHCH2		48	177	B
78	7-Br	4-CH3C6H4CH2		56	223	B
79	7-Br	4-CNC6H4CH2		56	207	B
80	7-Br	4-OHC6H4CH2		15	284	B
81	7-Br	4-(COOCH3)C6H4CH		35	197	B
82	7-Br	4-(CH2COOH)C6H4C		8	246	B
83	7-Br	4-(CH2CN)C6H4CH2		<1	230	B
84	7-Br	(3-pyridyl)-CH2		28	142	B
85	7-Br	(E) C6H5CH=CHCH2		63	171	B
86	7-Br	(Z) C6H5CH=CHCH2		28	167	B
87	7-Br	(E) (4-pyridyl)-CH=CHCH2		48	115	B
88	7-Br			<1	234	B
89	7-Br	C6H5C≡CCH2		15	159	B
90	7-Br	CH(C6H5)COOCH3		18	243	B

Compound No.	X1	R	NR4R5	Yield (%)	m.p. (°C)	Method
91	7-CH3	(3-pyridyl)-CH2		64	175	C
92	7-CH3	(E) C6H5CH=CHCH2		16	195	A
93	7-CH3	4-CNC6H4CH2		84	166	B
94	7-CH3	3,4-(CH3O)2C6H3CH2		52	184	B
95	7-CH3	4-(COOCH3)C6H4CH		44	230	B
96	7-CH3	4-(CH2COOH)C6H4C		21	262	B
97	7-CH3	(3-pyridyl)-CH2		10	139	C
98	7-CH3	(E) C6H5CH=CHCH2		17	173	A
99	7-CH3	4-(CH2COOH)C6H4C		10	-	B
100	7-CH3	(E) (3-pyridyl)CH=CHCH2		51	230	B
101	7-CH3	4-CNC6H4CH2		73	201	B
102	7-CH3	4-(CH2COOH)C6H4C		3	-	B
103	7-CH3	(E) C6H5CH=CHCH2		50	171	B
104	7-CH3	(E) (3-pyridyl)CH=CHCH2		53	155	B
105	7-CH3	(E) (4-pyridyl)-CH=CHCH2		66	119	B
106	8-CH3	(E) C6H5CH=CHCH2		52	-	A
107	7-CN	4-CNC6H4CH2		43	147-149	B
108	7-OH	(E) C6H5CH=CHCH2		3	295(dec)	A

- **Compound 6** :

^{1}H NMR δ (ppm) : 1.7 – 1.85 (m, 8H) ; 3.3 – 3.4 (m, 4H) ; 4.95 (d, 2H) ; 6.4 – 6.5 (dt, 1H) ; 6.7 – 6.75 (d, 1H) ; 7.25 (t, 1H) ; 7.3 (t, 2H) ; 7.45 (d, 2H) ; 7.6 (t, 1H) ; 7.95 (t, 1H) ; 8.25 (d, 1H) ; 8.4 (d, 1H)

Solvent : DMSO

- **Compound 7** :

^{1}H NMR δ (ppm) : 1.5 – 1.9 (m, 8H) ; 3.3 (m, 4H) ; 4.8 (d, 2H) ; 5.2 (d, 1H) ; 5.4 (d, 1H) ; 5.95 (m, 1H) ; 7.65 (d, 1H) ; 8.25 (s, 1H) ; 8.3 (d, 1H)

Solvent : $CDCl_3$

- **Compound 8** :

^{1}H NMR δ (ppm): 1.7 – 2.0 (m, 8H) ; 2.3 (s, 3H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.1 (d, 2H) ; 7.6 (d, 2H) ; 7.7 (d, 1H) ; 8.35 (m, 2H)

Solvent : $CDCl_3$

- **Compound 9** :

^{1}H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.6 (s, 2H) ; 7.05 – 7.25 (m, 3H) ; 7.4 (d, 1H) ; 7.75 (d, 1H) ; 8.35 (s, 1H) ; 8.45 (d, 1H)

Solvent : $CDCl_3$

- **Compound 10** :

^{1}H NMR δ (ppm) : 1.6 – 2.0 (m, 8H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.2 (m, 2H) ; 7.55 (s, 1H) ; 7.65 (s, 1H) ; 7.7 (d, 1H) ; 8.35 (m, 2H)

Solvent : $CDCl_3$

- **Compound 11** :

^{1}H NMR δ (ppm) : 1.65 – 1.9 (m, 8H) ; 3.3 (m, 4H) ; 5.35 (s, 2H) ; 7.2 (d, 2H) ; 7.55 (d, 2H) ; 7.65 (d, 1H) ; 8.25 (m, 2H)

Solvent : $CDCl_3$

- **Compound 12** :

^{1}H NMR δ (ppm) : 1.7 – 2 (m, 8H) ; 3.4 (m, 4H) ; 5.4 (s, 2H) ; 7.4 (d, 2H) ; 7.55 (d, 2H) ; 7.7 (d, 1H) ; 8.3 (s, 1H) ; 8.35 (d, 1H)

Solvent : $CDCl_3$

- **Compound 13** :
^{1}H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.4 (s, 2H) ; 7.0 (m, 2H) ; 7.7 (m, 3H) ; 8.35 (m, 2H)
Solvent : $CDCl_3$

- **Compound 14** :
^{1}H NMR δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.5 (s, 2H) ; 7.55 (d, 2H) ; 7.7 (d, 1H) ; 7.8 (d, 2H) ; 8.3 – 8.45 (m, 2H)
Solvent : $CDCl_3$

- **Compound 15** :
^{1}H NMR δ (ppm) : 1.65 – 2 (m, 8H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.55 (d, 2H) ; 7.7 – 7.85 (m, 3H) ; 8.25 – 8.45 (m, 2H)
Solvent : $CDCl_3$

- **Compound 16** :
^{1}H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 5.5 (s, 2H) ; 6.8 (t, 1H) ; 6.9 (d, 1H) ; 7.1 (d, 1H) ; 7.2 (t, 1H) ; 8.35 (s, 1H) ; 8.4 (d, 1H)
Solvent : $CDCl_3$

- **Compound 17** :
^{1}H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.8 (s, 3H) ; 5.5 (s, 2H) ; 6.8 (m, 1H) ; 7.25 (m, 3H) ; 7.75 (d, 1H) ; 8.4 (m, 2H)
Solvent : $CDCl_3$

- **Compound 18** :
^{1}H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.75 (s, 3H) ; 5.4 (s, 2H) ; 6.85 (d, 2H) ; 7.7 (m, 3H) ; 8.35 (m, 2H)
Solvent : $CDCl_3$

- **Compound 19** :
^{1}H NMR δ (ppm) : 1.7 – 2.0 (m, 8H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.3 (d, 1H) ; 7.5 (d, 1H) ; 7.75 (m, 2H) ; 8.3 (s, 1H) ; 8.35 (d, 1H)
Solvent : $CDCl_3$

- **Compound 20** :
^{1}H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.85 (s, 3H) ; 3.90 (s, 3H) ; 5.4 (s, 2H) ; 6.75 (d, 1H) ; 7.35 (m,2H) ; 7.7 (d, 1H) ; 8.35 (m, 2H)

Solvent : $CDCl_3$

- **Compound 21** :

^1H NMR δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.6 (s, 2H) ; 7.15 (m, 1H) ; 7.4 (d, 1H) ; 7.6 (m, 1H) ; 7.75 (d, 1H) ; 8.35 (s, 1H) ; 8.4 (d, 1H) ; 8.45 (m, 1H)

Solvent : $CDCl_3$

- **Compound 22** :

^1H NMR δ (ppm) : 1.6 – 1.95 (m, 8H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.2 (m, 1H) ; 7.7 (d, 1H) ; 8.0 (m, 1H) ; 8.3 (m, 2H) ; 8.5 (m, 1H) ; 8.9 (s, 1H)

Solvent : $CDCl_3$

- **Compound 23** :

^1H NMR δ (ppm) : 1.6 – 1.9 (m, 8H) ; 3.3 (m, 4H) ; 5.35 (s, 2H) ; 7.4 (d, 2H) ; 7.65 (d, 1H) ; 8.25 (s, 1H) ; 8.3 (d, 1H) ; 8.45 (d, 2H)

Solvent : $CDCl_3$

- **Compound 24** :

^1H NMR δ (ppm) : 1.7 – 2.1 (m, 8H) ; 3.15 (t, 2H) ; 3.4 (m, 4H) ; 4.5 (t, 2H) ; 7.2-7.45 (m, 5H) ; 7.7 (d, 1H) ; 8.35 (s, 1H) ; 8.35 (s, 1H) ; 8.4 (d, 1H)

Solvent : $CDCl_3$

- **Compound 25** :

^1H NMR δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.05 (t, 2H) ; 3.4 (m, 4H) ; 3.8 (s, 3H) ; 4.45 (t, 2H) ; 6.85 (d, 2H) ; 7.25 (d, 2H) ; 7.7 (d, 1H) ; 8.3 (s, 1H) ; 8.4 (d, 1H)

Solvent : $CDCl_3$

- **Compound 26** :

^1H NMR δ (ppm) : 1.7 – 2.0 (m, 8H) ; 2.2 (qn, 2H) ; 2.75 (t, 2H) ; 3.35 (m, 4H) ; 4.35 (t, 2H) ; 7.0 – 7.2 (m, 5H) ; 7.7 (d, 1H) ; 8.3 (s, 1H) ; 8.35 (d, 1 H)

Solvent : $CDCl_3$

- **Compound 27** :

^1H NMR δ (ppm) : 1.65-1.85(m,8H) ; 3.35(m,4H) ; 5.7(s,2H) ; 7.6(t,2H) ; 7.75(t,1H) ; 8.05(d,1H) ; 8.15(m,3H) ; 8.4(d,1H)

Solvent : DMSO

- **Compound 28** :
^{1}H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 5.7 (s, 2H) ; 7.0 (d, 2H) ; 7.8 (d, 1H) ; 8.05 (d, 2H) ; 8.35 (s, 1H) ; 8.45 (d, 1 H)
Solvent : $CDCl_3$

- **Compound 29** :
^{1}H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.7 (s, 2H) ; 7.45 (d, 2H) ; 7.8 (d, 1H) ; 8 (d, 2H) ; 8.3 (s, 1H) ; 8.4 (d, 1H)
Solvent : $CDCl_3$

- **Compound 30** :
^{1}H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 4 (s, 3H) ; 5.7 (s, 2H) ; 7.1 (d, 1H) ; 7.8 (d, 1H) ; 8.2 (d, 1 H) ; 8.35 (s, 1H) ; 8.45 (s, 1H) ; 8.5 (s, 1H)
Solvent : $CDCl_3$

- **Compound 31** :
^{1}H NMR δ (ppm) : 2.0 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 5.45 (s, 2H) ; 7.2 - 7.3 (dd, 1H) ; 7.75 (d, 1H) ; 8.05 (d, 1H) ; 8.25 (d, 1H) ; 8.35 (s, 1 H) ; 8.55 (d, 1H) ; 8.9 (s, 1H)
Solvent : $CDCl_3$

- **Compound 32** :
^{1}H NMR δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.25 (d, 2H) ; 7.75 (d, 2H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.45 (s, 1H)
Solvent : $CDCl_3$

- **Compound 33** :
^{1}H NMR δ (ppm) : 1.7 – 2.0 (m, 8H) ; 3.3 – 3.45 (m, 4H) ; 5.4 (s, 2H) ; 6.9 – 7.0 (m, 2H) ; 7.65 - 7.75 (m, 2H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)
Solvent : $CDCl_3$

- **Compound 34** :
^{1}H NMR δ (ppm) : 1.8 – 2 (m, 8H) ; 3.35 – 3.5 (m, 4H) ; 5.5 (s, 2H) ; 7.6 (dd, 2H) ; 7.8 (dd,2H) ; 7.9 (m, 1H) ; 8.3 (dd, 1H) ; 8.5 (d, 1H)
Solvent : $CHCl_3$

- **Compound 35** :
^{1}H NMR δ (ppm) : 1.7 – 2 (m, 8H) ; 3.3 – 3.45 (m, 4H) ; 3.8 (s, 3H) ; 3.85 (s, 3H) ; 5.4 (s, 2H) ; 6.8 (d, 1H) ; 7.25 – 7.35 (m, 2H) ; 7.8 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 36** :

^1H NMR δ (ppm) : 1.8 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.25 (m, 1H) ; 7.9 (d, 1H) ; 8.1 (d, 1H) ; 8.35 (d, 1H) ; 8.5 (m, 2H) ; 8.95 (s, 1H)

Solvent : $CDCl_3$

- **Compound 37** :

^1H NMR δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.05 (d, 2H) ; 6.45 (dt, 1H) ; 6.9 (d, 1H) ; 7.15 – 7.3 (m, 3H) ; 7.35 (d, 2H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 38** :

^1H NMR δ (ppm) : 1.7 – 2 (m, 8H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (d, 2H) ; 6.35 – 6.45 (m, 1H) ; 6.75 – 6.85 (d, 1H) ; 7.2 – 7.35 (m, 4H) ; 7.85 (m, 1H) ; 8.3 (m, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 39** :

^1H NMR δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.3 – 3.45 (m, 4H) ; 3.75 (s, 3H) ; 5.05 (m, 2H) ; 6.25 – 6.35 (m, 1H) ; 6.8 (m, 3H) ; 7.3 (m, 2H) ; 7.85 (m, 1H) ; 8.3 (m, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 40** :

^1H NMR δ (ppm) : 1.7 – 2 (m, 8H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (d, 2H) ; 6.45 – 6.55 (m, 1H) ; 6.85 (d, 1H) ; 7.2 (m, 1H) ; 7.65 (m, 1H) ; 7.9 (m, 1H) ; 8.35 (d, 1H) ; 8.45 (m, 1H) ; 8.5 (d, 1H) ; 8.6 (d, 1H)

Solvent : $CDCl_3$

- **Compound 41** :

^1H NMR δ (ppm) : 1.7 – 2 (m, 8H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (d, 2H) ; 6.55 – 6.7 (m, 1H) ; 6.8 (d, 1H) ; 7.2 (d, 2H) ; 7.9 (m, 1H) ; 8.3 (d, 1H) ; 8.5 (m, 3H)

Solvent : $CDCl_3$

- **Compound 42** :

^1H NMR δ (ppm) : 2 - 2.1 (m, 4H) ; 2.3 (s, 3H) ; 3.3 – 3.45 (m, 4H) ; 5.4 (s, 2H) ; 7.1 (d, 2H) ; 7.6 (d, 2H) ; 7.8 (d, 1H) ; 8.1 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 43** :

^1H NMR δ (ppm) : 1.9 – 2.05 (m, 4H) ; 3.25 – 3.4 (m, 4H) ; 5.35 (s, 2H) ; 7.2 (d, 2H) ; 7.6 (d, 2H) ; 7.8 (d, 1H) ; 8.1 (d, 1H) ; 8.4 (s, 1H)

Solvent : $CDCl_3$

- **Compound 44** :

^1H NMR δ (ppm) : 2.0 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 5.4 (s, 2H) ; 6.9 – 7.0 (m, 2H) ; 7.6 – 7.7 (m, 2H) ; 7.85 (d, 1H) ; 8.1 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 45** :

^1H NMR δ (ppm) : 2 – 2.15 (m, 4H) ; 3.35 – 3.5 (m, 4H) ; 5.45 (s, 2H) ; 7.45 (t, 1H) ; 7.55 (d, 1H) ; 7.85 – 8.0 (m, 3H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 46** :

^1H NMR δ (ppm) : 1.95 – 2.1 (m, 4H) ; 3.35 – 3.5 (m, 4H) ; 5.45 (s, 2H) ; 7.6 (d, 2H) ; 7.8 (d, 2H) ; 7.9 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 47** :

^1H NMR δ (ppm) : 2 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 3.9 (s, 3H) ; 5.5 (s, 2H) ; 7.7 (d, 2H) ; 7.9 (d, 1H) ; 8.0 (d, 2H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 48** :

^1H NMR δ (ppm) : 2 – 2.15 (m, 4H) ; 3.3 – 3.45 (m, 4H) ; 5.5 (s, 2H) ; 7.75 - 7.9 (m, 3H) ; 8.1 – 8.2 (m, 3H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 49** :

^1H NMR δ (ppm) : 2 – 2.15 (m, 4H) ; 3.35 – 3.5 (m, 4H) ; 3.75 (s, 3H) ; 5.4 (s, 2H) ; 6.8 (d, 2H) ; 7.65 (d, 2H) ; 7.8 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 50** :

^1H NMR δ (ppm) : 2 – 2.15 (m, 4H) ; 2.25 (s, 3H) ; 3.35 – 3.45 (m, 4H) ; 5.45 (s, 2H) ; 7.0 (d, 2H) ; 7.75 (d, 2H) ; 7.85 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 51** :

^1H NMR δ (ppm) : 1.9 – 2.1 (m, 4H) ; 3.2 – 3.45 (m, 4H) ; 5.2 (s, 2H) ; 6.7 (d, 2H) ; 7.35 (d, 2H) ; 8 (d, 1H) ; 8.2 (d, 1H) ; 8.3 (s, 1H) ; 9.25 (s, 1H)

Solvent : $CDCl_3$

- **Compound 52** :

^1H NMR δ (ppm) : 2.0 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 3.85 (s, 3H) ; 3.9 (s, 3H) ; 5.4 (s, 2H) ; 6.8 (d, 1H) ; 7.2 – 7.35 (m, 2H) ; 7.8 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 53** :

^1H NMR δ (ppm) : 2.0 – 2.1 (m, 4H) ; 3.3 – 3.4 (m, 4H) ; 5.35 (s, 2H) ; 5.9 (s, 2H) ; 6.7 (d, 1H) ; 7.15 – 7.3 (m, 2H) ; 7.85 (d, 1H) ; 8.1 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

Compound 54 :

^1H NMR δ (ppm) : 2 – 2.1 (m, 4H) ; 3.35 – 3.4 (m, 4H) ; 3.75 (s, 6H) ; 5.4 (s, 2H) ; 6.35 (s, 1H) ; 6.8 (s, 2H) ; 7.85 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 55** :

^1H NMR δ (ppm) : 2 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 3.8 (s, 3H) ; 3.85 (s, 6H) ; 5.4 (s, 2H) ; 7 (s, 2H) ; 7.85 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 56** :

^1H NMR δ (ppm) : 1.95 - 2.1 (m, 4H) ; 3.25 – 3.45 (m, 4H) ; 3.55 (s, 2H) ; 5.4 (s, 2H) ; 7.25 (d, 2H) ; 7.35 (d, 2H) ; 8.15 (d, 1H) ; 8.2 (d, 1H) ; 8.35 (s, 1H) ; 12.2 – 12.5 (m, 1H)

Solvent : $CDCl_3$

- **Compound 57** :
^{1}H NMR δ (ppm) : 2.1 (m, 4H) ; 3.4 (m, 4H) ; 5.05 (d, 2H) ; 6.4 (dt, 1H) ; 6.9 (d, 1H) ; 7.15 – 7.3 (m, 3H) ; 7.35 (d, 2H) ; 7.9 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)
Solvent : $CDCl_3$

- **Compound 58** :
^{1}H NMR δ (ppm) : 2.0 – 2.15 (m, 4H) ; 3.35 – 3.5 (m, 4H) ; 5.2 (d, 2H) ; 5.7 – 5.8 (m, 1H) ; 6.7 (d, 1H) ; 7.2 – 7.45 (m, 5H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.6 (s, 1H)
Solvent : $CDCl_3$

- **Compound 59** :
^{1}H NMR δ (ppm) : 2.05 (m, 4H) ; 3.4 (m, 4H) ; 5 (d, 2H) ; 6.4 (m, 1H) ; 6.85 (d, 1H) ; 7.15 – 7.3 (m, 4H) ; 7.85 (m, 1H) ; 8.15 (d, 1H) ; 8.45 (s, 1H)
Solvent : $CDCl_3$

- **Compound 60** :
^{1}H NMR δ (ppm) : 1.95 – 2.10 (m, 4H) ; 3.4 (m, 4H) ; 3.75 (s, 3H) ; 4.95 (m, 2H) ; 6.25 – 6.35 (m, 1H) ; 6.75 – 6.9 (m, 3H) ; 7.2 – 7.3 (m, 2H) ; 7.85 (m, 1H) ; 8.15 (m, 1H) ; 8.45 (m, 1H)
Solvent : $CDCl_3$

- **Compound 61** :
^{1}H NMR δ (ppm) : 1.95 – 2.15 (m, 4H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (m, 2H) ; 6.45 – 6.55 (m, 1H) ; 6.75 – 6.9 (d, 1H) ; 7.2 (m, 1H) ; 7.6 – 7.7 (m, 1H) ; 7.85 – 7.95 (m, 1H) ; 8.15 (m, 1H) ; 8.4 (m, 1H) ; 8.5 (m, 1H) ; 8.6 (m, 1H)
Solvent : $CDCl_3$

- **Compound 62** :
^{1}H NMR δ (ppm) : 1.9 – 2.05 (m, 4H) ; 3.3 – 3.45 (m, 4H) ; 5.05 (d, 2H) ; 6.55 – 6.7 (m, 1H) ; 6.8 (d, 1H) ; 7.25 (m, 2H) ; 7.9 (m, 1H) ; 8.2 (m, 1H) ; 8.45 - 8.55 (m, 3H)
Solvent : $CDCl_3$

- **Compound 63** :
^{1}H NMR δ (ppm) : 1.8 – 1.9 (m, 2H) ; 3.25 (m, 2H) ; 5.1 (s, 2H) ; 6.9 (s, 1H) ; 7.4 (s, 1H) ; 8 (d, 1H) ; 8.1 (d, 1H) ; 8.2 (s, 1H) ; 11.8 (m, 1H)

Solvent : DMSO

- **Compound 64** :
^{1}H NMR δ (ppm) : 2.05 – 2.15 (m, 4H) ; 2.4 (s, 3H) ; 2.6 (s, 3H) ; 3.4 (m, 4H) ; 5.2 (s, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.4 (s, 1H)
Solvent : $CDCl_3$

- **Compound 65** :
^{1}H NMR δ (ppm) : 1.25 – 1.75 (m, 8H) ; 1.9 – 2.05 (m, 4H) ; 2.5 – 2.7 (m, 1H) ; 3.3 – 3.4 (m, 4H) ; 4.2 (d, 2H) ; 7.8 (d, 1H) ; 8.1 (d, 1H) ; 8.45 (s, 1H)
Solvent : $CDCl_3$

- **Compound 66** :
^{1}H NMR δ (ppm) : 1 (t, 3H) ; 1.4 – 1.55 (m, 2H) ; 1.8 – 1.9 (m, 2H) ; 2.0 – 2.1 (m, 4H) ; 3.4 – 3.5 (m, 4H) ; 4.3 (t, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)
Solvent : $CDCl_3$

- **Compound 67** :
^{1}H NMR δ (ppm) : 2 – 2.15 (m, 4H) ; 3.35 – 3.5 (m, 4H) ; 5.0 (q, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.55 (s, 1H)
Solvent : $CDCl_3$

- **Compound 68** :
^{1}H NMR δ (ppm) : 2 (m, 4H) ; 3.15 (m, 1H) ; 3.3 (m, 4H) ; 4.05 (m, 2H) ; 4.5 (m, 2H) ; 7.08 (m, 1H) ; 8.15 (m, 1H) ; 8.4 (s, 1H)
Solvent : $CDCl_3$

- **Compound 69** :
^{1}H NMR δ (ppm) : 1.1 (t, 6H) ; 2.0 – 2.1 (m, 4H) ; 2.65 (q, 4H) ; 2.9 (t, 2H) ; 3.35 – 3.45 (m, 4H) ; 4.4 (t, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)
Solvent : $CDCl_3$

- **Compound 70** :
^{1}H NMR δ (ppm) : 2 – 2.15 (m, 4H) ; 2.3 (s, 1H) ; 3.35 – 3.5 (m, 4H) ; 5.1 (s, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)
Solvent : $CDCl_3$

- **Compound 71 :**
^{1}H NMR δ (ppm) : 2.1 (m, 4H) ; 3.4 (m, 4H) ; 4.45 (m, 2H) ; 4.75 (m, 2H) ; 6.9 (m, 3H) ; 7.2 – 7.3 (m, 2H) ; 7.9 (m, 1H) ; 8.2 (m, 1H) ; 8.5 (s, 1H)
Solvent : $CDCl_3$

- **Compound 72 :**
^{1}H NMR δ (ppm) : 2.1 (m, 4H) ; 3.45 (m, 6H) ; 4.6 (m, 2H) ; 7.1 (m, 1H) ; 7.2 (m, 2H) ; 7.4 (m, 2H) ; 7.85 (m, 1H) ; 8.1 (m, 1H) ; 8.45 (s, 1H)
Solvent : $CDCl_3$

- **Compound 73 :**
^{1}H NMR δ (ppm) : 1.9 - 2.05 (m, 4H) ; 3.3 - 3.4 (m, 4H) ; 3.08 (s, 3H) ; 6.7 (s, 1H) ; 7.2 – 7.35 (m, 3H) ; 7.7 – 7.85 (m, 3H) ; 8.1 (d, 1H) ; 8.4 (s, 1H)
Solvent : $CDCl_3$

- **Compound 74 :**
^{1}H NMR δ (ppm) : 1.4 – 1.6 (m, 1H) ; 1.7 - 2 (m, 5H) ; 3 – 3.1 (m, 2H) ; 3.3 – 3.4 (m, 2H) ; 5.5 (s, 2H) ; 7.6 (d, 2H) ; 7.8 (d, 2H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)
Solvent : $CDCl_3$

- **Compound 75 :**
^{1}H NMR δ (ppm) : 1.4 (m, 1H) ; 1.7 – 1.95 (m, 5H) ; 3 – 3.1 (m, 2H) ; 3.3 – 3.4 (m, 2H) ; 3.8 (s, 3H) ; 3.9 (s, 3H) ; 5.4 (s, 2H) ; 6.8 (d, 1H) ; 7.25 – 7.35 (m, 2H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.40 (s, 1H)
Solvent : $CDCl_3$

- **Compound 76 :**
^{1}H NMR δ (ppm) : 1.35 – 2.1 (m, 6H) ; 3.05 (t, 2H) ; 3.35 (m, 2H) ; 5.1 (d, 2H) ; 6.5 (dt, 1H) ; 6.9 (d, 1H) ; 7.1 – 7.5 (m, 5H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.55 (s, 1H)
Solvent : $CDCl_3$

- **Compound 77 :**
^{1}H NMR δ (ppm) : 2.9 (m, 4H) ; 3.45 (m, 2H) ; 3.6 (m, 2H) ; 5.1 (m, 2H) ; 6.5 (m, 1H) ; 6.85 (d, 1H) ; 7.2 (m, 1H) ; 7.65 (m, 1H) ; 7.9 (m, 1H) ; 8.25 (m, 1H) ; 8.45 (m, 1H) ; 8.5 (m, 1H) ; 8.55 (s, 1H)
Solvent : $CDCl_3$

- **Compound 78 :**

^{1}H NMR δ (ppm) : 2.3 (s, 3H) ; 2.9 (s, 6H) ; 5.4 (s, 2H) ; 7.1 (d, 2H) ; 7.6 (d, 2H) ; 7.85 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 79 :**

^{1}H NMR δ (ppm) : 2.95 (s, 6H) ; 5.45 (s, 2H) ; 7.55 (d, 2H) ; 7.75 (d, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 80 :**

^{1}H NMR δ (ppm) : 2.85 (s, 6H) ; 5.2 (s, 2H) ; 6.7 (d, 2H) ; 7.3 (d, 2H) ; 8 (d, 1H) ; 8.2 – 8.3 (m, 2H) ; 9.3 (s, 1H)

Solvent : $CDCl_3$

- **Compound 81 :**

^{1}H NMR δ (ppm) : 2.9 (s, 6H) ; 3.9 (s, 3H) ; 5.45 (s, 2H) ; 7.7 (m, 2H) ; 7.85 (m, 1H) ; 7.9 (m, 2H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 82 :**

^{1}H NMR δ (ppm) : 2.85 (s, 6H) ; 3.6 (s, 2H) ; 5.35 (s, 2H) ; 7.25 (d, 2H) ; 7.5 (d, 2H) ; 8.15 (d, 1H) ; 8.3 (d, 1H) ; 8.35 (s, 1H) ; 12.2 – 12.45 (m, 1H)

Solvent : DMSO

- **Compound 83 :**

^{1}H NMR δ (ppm) : 2.9 (s, 6H) ; 3.7 (s, 2H) ; 5.45 (s, 2H) ; 7.25 (m, 2H) ; 7.7 (m, 2H) ; 7.85 (m, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 84 :**

^{1}H NMR δ (ppm) : 2.9 (s, 6H) ; 5.5 (s, 2H) ; 7.25 (m, 1H) ; 7.85 (m, 1H) ; 8.05 (m, 1H) ; 8.25 (d, 1H) ; 8.5 (m, 2H) ; 8.9 (s, 1H)

Solvent : $CDCl_3$

- **Compound 85 :**

^{1}H NMR δ (ppm) : 2.9 (s, 6H) ; 5.05 (d, 2H) ; 6.4 – 6.55 (dt, 1H) ; 6.9 (d, 1H) ; 7.2 – 7.4 (m, 5H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.55 (s, 1H)

Solvent : $CDCl_3$

- **Compound 86 :**

^1H NMR δ (ppm) : 2.95 (s, 6H) ; 5.29 (d, 2H) ; 5.7 – 5.8 (m, 1H) ; 6.7 (d, 1H) ; 7.2 – 7.45 (m, 5H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 87 :**

^1H NMR δ (ppm) : 2.9 (s, 6H) ; 5.05 (d, 2H) ; 6.55 – 6.7 (m, 1H) ; 6.85 (d, 1H) ; 7.2 (m, 2H) ; 7.85 (m, 1H) ; 8.25 (d, 1H) ; 8.5 (m, 3H)

Solvent : $CDCl_3$

- **Compound 88 :**

^1H NMR δ (ppm) : 2.8 (s, 6H) ; 3.2 (s, 1H) ; 4.9 (s, 2H) ; 8.1 (m, 1H) ; 8.2 (d, 1H) ; 8.3 (s, 1H)

Solvent : DMSO

- **Compound 89 :**

^1H NMR δ (ppm) : 2.9 (s, 6H) ; 5.2 (s, 2H) ; 7.2 (m, 3H) ; 7.4 (m, 2H) ; 7.85 (m, 1H) ; 8.2 (d, 1H) ; 8.55 (s, 1H)

Solvent : $CDCl_3$

- **Compound 90 :**

^1H NMR δ (ppm) : 2.95 (s, 6H) ; 3.85 (s, 3H) ; 6.8 (s, 1H) ; 7.3 – 7.4 (m, 3H) ; 7.75 – 7.9 (m, 3H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 91 :**

^1H NMR δ (ppm) : 1.75 – 1.9 (m, 8H) ; 2.5 (s, 3H) ; 3.4 – 3.5 (m, 4H) ; 5.5 (s, 2H) ; 7.2 – 7.3 (dd, 1H) ; 7.6 – 7.65 (d, 1H) ; 8.05 – 8.01 (d, 1H) ; 8.2 (s, 1H) ; 8.3 – 8.35 (d, 1H) ; 8.55 (d, 1H) ; 8.95 (s, 1H)

Solvent : $CDCl_3$

- **Compound 92:**

^1H NMR δ (ppm) : 1.75 – 2 (m, 8H) ; 2.5 (s, 3H) ; 3.4 – 3.5 (m, 4H) ; 5.1 (d, 1H) ; 5.4 – 5.55 (dt, 1H) ; 6.9 – 7 (d, 1H) ; 7.2 – 7.3 (m, 4H) ; 7.4 (d, 2H) ; 7.6 (d, 1H) ; 8.2 (s, 1H) ; 8.3 (d, 1H)

Solvent : $CDCl_3$

- **Compound 93 :**

^1H NMR δ (ppm) : 2 – 2.1 (m, 4H) ; 2.5 (s, 3H) ; 3.3 – 3.4 (m, 4H) ; 5.5 (s, 2H) ; 7.6 (m, 3H) ; 7.8 (d, 2H) ; 8.1 - 8.2 (m, 2H)
Solvent : $CDCl_3$

- **Compound 94 :**

^1H NMR δ (ppm) : 2 – 2.1 (m, 4H) ; 2.5 (s, 3H) ; 3.4 – 3.5 (m, 4H) ; 3.8 (s, 3H) ; 3.9 (s, 3H) ; 5.4 (s, 2H) ; 6.8 (d, 1H) ; 7.3 - 7.4 (m, 2H) ; 7.5 (d, 1H) ; 8.1 – 8.2 (m, 2H)
Solvent : $CDCl_3$

- **Compound 95 :**

^1H NMR δ (ppm) : 2.1 – 2.2 (m, 4H) ; 2.5 (s, 3H) ; 3.4 – 3.5 (m, 4H) ; 3.9 (s, 3H) ; 5.5 (s, 2H) ; 7.6 (m, 1H) ; 7.7 (m, 2H) ; 7.95 - 8 (m, 2H) ; 8.1 – 8.2 (m, 2H)
Solvent : $CDCl_3$

- **Compound 96 :**

^1H NMR δ (ppm) : 2 (m, 4H) ; 2.5 (s, 3H) ; 3.3 – 3.4 (m, 4H) ; 3.6 (s, 2H) ; 5.3 (s, 2H) ; 7.3 (m, 2H) ; 7.45 (m, 2H) ; 7.8 (m, 2H) ; 8.1 (s, 1H) ; 8.2 (d, 2H) ; 12.4 (m, 1H)
Solvent : DMSO

- **Compound 97 :**

^1H NMR δ (ppm) : 1.95 (m, 4H) ; 2.5 (s, 3H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.35 (dd, 1H) ; 7.55 (d, 1H) ; 8.05 (s, 1H) ; 8.15 (d, 1H) ; 8.5 (d, 1H) ; 8.7 (s, 1H)
Solvent : DMSO

- **Compound 98 :**

^1H NMR δ (ppm) : 2 – 2.1 (m, 4H) ; 2.45 (s, 3H) ; 3.3 – 3.45 (m, 4H) ; 5.05 (d, 2H) ; 6.4 – 6.5 (dt, 1H) ; 6.85 – 6.95 (d, 1H) ; 7.1 – 7.45 (m, 5H) ; 7.6 (d, 1H) ; 8.1 – 8.2 (m, 2H)
Solvent : $CDCl_3$

- **Compound 99 :**

^1H NMR δ (ppm) : 2.4 – 3.75 (m, 13H) ; 5.35 (s, 2H) ; 7.1 – 7.5 (m, 4H) ; 7.8 (d, 1H) ; 8.1 (s, 1H) ; 8.25 (d, 1H)
Solvent : DMSO

- **Compound 100** :

^{1}H NMR δ (ppm) : 2.5 (s, 3H) ; 2.9 (m, 4H) ; 3.45 (m, 2H) ; 3.65 (m, 2H) ; 5.1 (m, 2H) ; 6.5 (m, 1H) ; 6.85 (d, 1H) ; 7.2 (m, 1H) ; 7.6 (m, 1H) ; 7.7 (m, 1H) ; 8.2 (m, 2H) ; 8.45 (d, 1H) ; 8.6 (1s, 1H)

Solvent : $CDCl_3$

- **Compound 101** :

^{1}H NMR δ (ppm) : 2.5 (s, 3H) ; 2.95 (s, 6H) ; 5.5 (s, 2H) ; 7.6 (m, 3H) ; 7.8 (m, 2H) ; 8.15 –8.25 (m, 2H)

Solvent : $CDCl_3$

- **Compound 102** :

^{1}H NMR δ (ppm) : 2.2 (s, 3H) ; 2.6 (s, 6H) ; 3.25 (s, 2H) ; 5.1 (s, 2H) ; 7 (m, 2H) ; 7.15 (m, 2H) ; 7.5 (m, 1H) ; 7.8 (s, 1H) ; 8 (d, 1H) ; 12 (m, 1H)

Solvent : DMSO

- **Compound 103** :

^{1}H NMR δ (ppm) : 2.5 (s, 3H) ; 3 (s, 6H) ; 5.1 (d, 2H) ; 6.4 – 6.5 (dt, 1H) ; 6.9 (d, 1H) ; 7.15 – 7.4 (m, 6H) ; 7.6 (d, 1H) ; 8.2 (m, 1H)

Solvent : $CDCl_3$

- **Compound 104** :

^{1}H NMR δ (ppm) : 2.5 (s, 3H) ; 2.95 (s, 6H) ; 5.1 (d, 2H) ; 6.45 – 6.55 (dt, 1H) ; 6.8 – 6.85 (d, 1H) ; 7.2 (m, 1H) ; 7.6 (dd, 1H) ; 7.7 (dd, 1H) ; 8.2 – 8.25 (m, 2H) ; 8.4 (d, 1H) ; 8.6 (s, 1H)

Solvent : $CDCl_3$

- **Compound 105** :

^{1}H NMR δ (ppm) : 2.5 (s, 3H) ; 2.95 (s, 6H) ; 5.1 (d, 2H) ; 6.6 – 6.7 (dt, 1H) ; 6.8 (d, 1H) ; 7.2 (d, 2H) ; 7.6 (d, 1H) ; 8.2 – 8.25 (dd, 2H) ; 8.5 (d, 2H)

Solvent : $CDCl_3$

- **Compound 106** :

^{1}H NMR δ (ppm) : 1.7 - 2 (m, 8H) ; 2.55 (m, 3H) ; 3.35 – 3.6 (m, 4H) ; 5.1 (d, 2H) ; 6.45 (dt, 1H) ; 6.85 (d, 1H) ; 7.1 – 7.45 (m, 6H) ; 8.25 (m, 2H)

Solvent : $CDCl_3$

- **Compound 107** :

^{1}H NMR δ (ppm) : 2.9 (d, 6H) ; 5.5 (s, 2H) ; 7.6 (m, 2H) ; 7.7 (m, 2H) ; 8.0 (m, 1H) ; 8.4 (m, 1H) ; 8.7 (s, 1H)

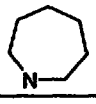
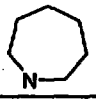
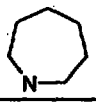
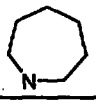
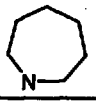
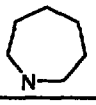
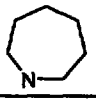
Solvent : $CDCl_3$

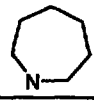
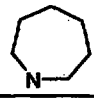
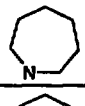
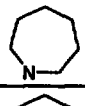
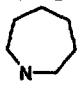
- **Compound 108** :

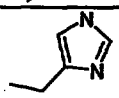
^{1}H NMR δ (ppm) : 1.9 (m, 4H) ; 3.25 (m, 4H) ; 6.85 (d, 2H) ; 6.3 – 6.4 (dt, 1H) ; 6.6 – 6.7 (d, 1H) ; 7.15 – 7.3 (m, 4H) ; 7.35 – 7.4 (d, 2H) ; 7.5 (s, 1H) ; 8.05 (d, 1H) ; 10.1 (m, 1H),

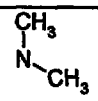
Solvent : DMSO

TABLE 2

Compound No.	X1	R	NR4R5	Yield (%)	m.p. (°C)	Method
109	H	(E) C6H5CH=CHCH2		28	176	A
110	7-Cl	CH2=CHCH2		24	173	A
111	7-Cl	C6H5CH2		58	148	A
112	7-Cl	4-CH3C6H4CH2		50	182	A
113	7-Cl	2-ClC6H4CH2		77	228	A
114	7-Cl	3-ClC6H4CH2		31	166	A
115	7-Cl	4-ClC6H4CH2		60	245	A
116	7-Cl	4-BrC6H4CH2		38	244	A
117	7-Cl	4-FC6H4CH2		42.5	224	A
118	7-Cl	4-CF3C6H4CH2		39	232	A
119	7-Cl	4-CNC6H4CH2		46	> 260	A
120	7-Cl	2-(OCH3)C6H4CH2		57	184	A

Compound No.	X1	R	NR4R5	Yield (%)	m.p. (°C)	Method
121	7-Cl	3-(OCH3)C6H4CH2		46	163	A
122	7-Cl	4-(OCH3)C6H4CH2		32.5	164-165	A
123	7-Cl	3,4-Cl2C6H3CH2		60	212	A
124	7-Cl	3,4-(OCH3)2C6H3CH2		39	153	A
125	7-Cl	(2-pyridyl)CH2		9	153	A
126	7-Cl	(3-pyridyl)CH2		8	184	C
127	7-Cl	C6H5CH2CH2		7	196	A
128	7-Cl	4(CH3O)C6H4(CH2)2		61	196	A
129	7-Cl	C6H5(CH2)3		36	130	A
130	7-Cl	C6H5C(=O)CH2		38.5	230-232	A
131	7-Cl	4(CH3O)C6H4C(=O)CH2		42	238	A
132	7-Cl	4-ClC6H4C(=O)CH2		59	238	A
133	7-Cl	4(CH3O)-3-(COOCH3)-		30	136	A
134	7-Br	4-ClC6H4CH2		57	247	A
135	7-Br	4-FC6H4CH2		54	216	A
136	7-Br	4-CNC6H4CH2		53	293	A
137	7-Br	3,4-(CH3O)2C6H3CH2		61	174	A
138	7-Br	4-(CH2COOH)C6H4C		1	269	B

Compound No.	X1	R	NR4R5	Yield (%)	m.p. (°C)	Method
139	7-Br	(3-pyridyl)CH2		4	192	C
140	7-Br	(E) C6H5CH=CHCH2		70	198	A
141	7-Br	(Z) C6H5CH=CHCH2		57	187	A
142	7-Br	4-ClC6H4CH2		18	185	A
143	7-Br	4-FC6H4CH2		16	233	A
144	7-Br	4-CNC6H4CH2		52	222	A
145	7-Br	4-(COOCH3)C6H4CH		31	193	A
146	7-Br	4-(CH3O)C6H4CH2		14	164	B
147	7-Br	4-(OCOCH3)C6H4CH		24	199	B
148	7-Br	4-OHC6H4CH2		15	283	B
149	7-Br	3,4-(OCH2O)C6H4CH2		57	234	A
150	7-Br	3,5-(CH3O)2C6H4CH2		21	168	A
151	7-Br	3,4,5-(CH3O)3C6H2CH2		21	199-201	A
152	7-Br			4	-	B
153	7-Br	n-butyl		13	130	B
154	7-Br	CH(C6H5)COOCH3		55	187	A
155	7-Br	(E) C6H5CH=CHCH2		10	206	B

Compound No.	X1	R	NR4R5	Yield (%)	m.p. (°C)	Method
156	7-Br	CH(C6H5)COOCH3		32	83	B
157	7-CH3	(E) C6H5CH=CHCH2		43	193	A
158	7-CH3	(E) C6H5CH=CHCH2		35	225	A
159	8-CH3	CH3		70	-	A
160	8-CH3	(E) C6H5CH=CHCH2		18	-	A
161	7-OH	(E) C6H5CH=CHCH2		10	255	A
162	7- 	(E) C6H5CH=CHCH2		28	-	A

Compound 109 :

^{1}H NMR δ (ppm) : 1.7 – 1.85 (m, 8H) ; 3.3 – 3.45 (m, 4H) ; 5.85 (d, 2H) ; 6.35 – 6.45 (dt, 1H) ; 6.65 – 6.75 (d, 1H) ; 7.25 (t, 1H) ; 7.35 (t, 1H) ; 7.45 (d, 1H) ; 7.6 (t, 1H) ; 7.85 (t, 1H) ; 8.2 (d, 1H) ; 8.3 (d, 1H)

Solvent : $CDCl_3$

- **Compound 110 :**

^{1}H NMR δ (ppm) : 1.65 – 1.95 (m, 8H) ; 3.35 (m, 4H) ; 4.8 (d, 2H) ; 5.25 – 5.4 (m, 2H) ; 5.9 – 6.1 (m, 1H) ; 7.55 – 8.4 (m, 3H)

Solvent : $CDCl_3$

- **Compound 111 :**

^{1}H NMR δ (ppm): 1.7 – 1.9 (m, 8H) ; 3.35 (m, 4H) ; 5.25 (s, 2H) ; 7.2 – 7.4 (m, 3H) ; 7.45 (d, 2H) ; 7.6 (d, 1H) ; 8.15 (d, 1H) ; 8.4 (s, 1H)

Solvent : $CDCl_3$

- **Compound 112 :**

^{1}H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 2.3 (s, 3H) ; 3.35 (m, 4H) ; 5.25 (s, 2H) ; 7.1 – 8.45 (m, 7H)

Solvent : $CDCl_3$

- Compound 113 :

^1H NMR δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.15 – 7.3 (m, 3H) ; 7.4 (d, 1H) ; 7.65 (d, 1H) ; 8.2 (d, 1H) ; 8.45 (s, 1H)

Solvent : $CDCl_3$

- Compound 114 :

^1H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 3.4 (m, 4H) ; 5.25 (s, 2H) ; 7.2 – 7.4 (m, 3H) ; 7.45 (s, 1H) ; 7.6 (d, 1H) ; 8.15 (d, 1H) ; 8.45 (s, 1H)

Solvent : $CDCl_3$

- Compound 115 :

^1H NMR δ (ppm) : 1.65 – 1.85 (m, 8H) ; 3.3 (m, 4H) ; 5.15 (s, 2H) ; 7.25 (d, 2H) ; 7.35 (d, 2H) ; 7.55 (d, 1H) ; 8.05 (d, 1H) ; 8.3 (s, 1H)

Solvent : $CDCl_3$

- Compound 116 :

^1H NMR δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.35 (m, 4H) ; 5.25 (d, 2H) ; 7.35 (d, 2H) ; 7.45 (d, 2H) ; 7.6 (d, 1H) ; 8.1 (d, 1H) ; 8.4 (s, 1H)

Solvent : $CDCl_3$

- Compound 117 :

^1H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 3.35 (m, 4H) ; 5.35 (s, 2H) ; 7.5 – 7.7 (m, 5H) ; 8.15 (d, 1H) ; 8.4 (s, 1H)

Solvent : $CDCl_3$

- Compound 118 :

^1H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 3.4 (m, 4H) ; 5.35 (s, 2H) ; 7.5 – 7.7 (m, 5H) ; 8.1 (d, 1H) ; 8.4 (s, 1H)

Solvent : $CDCl_3$

- Compound 119 :

^1H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 5.35 (s, 2H) ; 6.9 (m, 2H) ; 7.2 (d, 1H) ; 7.3 (t, 1H) ; 7.6 (d, 1H) ; 8.2 (d, 1H) ; 8.4 (s, 1H)

Solvent : $CDCl_3$

- **Compound 120** :
^{1}H NMR δ (ppm) : 1.7 – 2.0 (m, 8H) ; 3.35 (m, 4H) ; 3.75 (s, 3H) ; 5.4 (s, 2H) ; 6.8 (m, 1H) ; 7.15 – 7.3 (m, 3H) ; 7.7 (d, 1H) ; 8.35 (m, 2H)
Solvent : $CDCl_3$

- **Compound 121** :
^{1}H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 3.35 (m, 4H) ; 3.8 (s, 3H) ; 5.2 (s, 2H) ; 6.85 (d, 2H) ; 7.45 (d, 2H) ; 7.65 (d, 1H) ; 8.15 (d, 1H) ; 8.45 (s, 1H)
Solvent : $CDCl_3$

- **Compound 122** :
1.7 – 1.9 (m, 8H) ; 3.4 (m, 4H) ; 5.2 (s, 2H) ; 7.3 (d, 1H) ; 7.4 (d, 1H) ; 7.5 (s, 1H) ; 7.6 (d, 1H) ; 8.15 (d, 1H) ; 8.4 (s, 1H)
Solvent : $CDCl_3$

- **Compound 123** :
^{1}H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 3.4 (m, 4H) ; 3.85 (s, 3H) ; 3.90 (s, 3H) ; 5.2 (s, 2H) ; 6.85 (d, 1H) ; 7.1 (m, 2H) ; 7.65 (d, 1H) 8.2 (d, 1H) ; 8.45 (s, 1H)
Solvent : $CDCl_3$

- **Compound 124** :
^{1}H NMR δ (ppm) : 1.65 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.2 (m, 1H) ; 7.3 (d, 1H) ; 7.65 (m, 2H) ; 8.2 (d, 1H) ; 8.4 (s, 1H) ; 8.55 (d, 1H)
Solvent : $CDCl_3$

- **Compound 125** :
^{1}H NMR δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.3 (s, 2H) ; 7.25 (m, 1H) ; 7.6 (d, 1H) ; 7.85 (d, 1H) ; 8.15 (d, 1H) ; 8.45 (s, 1H) ; 8.6 (d, 1H) ; 8.75 (s, 1H)
Solvent : $CDCl_3$

- **Compound 126** :
^{1}H NMR δ (ppm) : 1.55 – 1.9 (m, 8H) ; 3.1 (t, 2H) ; 3.25 (m, 4H) ; 4.25 (t, 2H) ; 7.05 – 7.25 (m,5H) ; 7.55 (d, 1H) ; 8.1 (d, 1H) ; 8.35 (s, 1H)
Solvent : $CDCl_3$

- **Compound 127** :
^{1}H NMR δ (ppm) : 1.75 – 1.9 (m, 8H) ; 3.15 (t, 2H) ; 3.35 (m, 4H) ; 3.75 (s, 3H) ; 4.35 (t, 2H) ; 6.8 (d, 2H) ; 7.15 (d, 2H) ; 7.6 (d, 1H) ; 8.15 (d, 1H) ; 8.4 (s, 1H)
Solvent : $CDCl_3$

- **Compound 128** :
^{1}H NMR δ (ppm) : 1.7 – 1.95 (m, 8H) ; 2.2 (m, 2H) ; 2.7 (t, 2H) ; 3.35 (m, 4H) ; 4.2 (t, 2H) ; 7 – 7.3 (m, 5H) ; 7.65 (d, 1H) ; 8.1 (d, 1H) ; 8.45 (s, 1H)
Solvent : $CDCl_3$

- **Compound 129** :
^{1}H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 5.6 (s, 2H) ; 7.0 (d, 2H) ; 7.7 (d, 1H) ; 8 (d, 2H) ; 8.25 (d, 1H) ; 8.45 (s, 1H)
Solvent : $CDCl_3$

- **Compound 130** :
^{1}H NMR δ (ppm) : 1.6-1.9(m,8H) ; 3.4(m,4H) ; 5.8(s,2H) ; 7.6(t,2H) ; 7.75(t,1H) ; 7.95(d,1H) ; 8.1(m,3H) ; 8.3(d,1H)
Solvent : DMSO

- **Compound 131** :
^{1}H NMR δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.55 (s, 2H) ; 7.45 (d, 2H) ; 7.65 (d, 1H) ; 7.9 (d, 2H) ; 8.2 (d, 1H) ; 8.4 (s, 1 H)
Solvent : $CDCl_3$

- **Compound 132** :
^{1}H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 4.0 (s, 3H) ; 5.6 (s, 2H) ; 7.1 (d, 1H) ; 7.7 (d, 1H) ; 8.1 (d, 1H) ; 8.2 (d, 1 H) ; 8.4 (m, 2H)
Solvent : $CDCl_3$

- **Compound 133** :
^{1}H NMR δ (ppm) : 1.75 – 1.9 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 4.0 (s, 3H) ; 5.6 (s, 2H) ; 7.1 (m, 1H) ; 7.7 (m, 1H) ; 8.15 –8.45 (m, 4H)
Solvent : $CDCl_3$

- **Compound 134**:
^{1}H NMR δ (ppm) : 1.75 – 1.9 (m, 8H) ; 3.35 (m, 4H) ; 5.25 (s, 2H) ; 7.25 - 8.6 (m, 7 H)

Solvent : $CDCl_3$

- **Compound 135** :

^1H NMR δ (ppm) : 1.65 – 1.95 (m, 8H) ; 3.3 – 3.45 (m, 4H) ; 5.25 (s, 2H) ; 6.95 – 7.1 (m, 2H) ; 7.4 – 7.55 (m, 2H) ; 7.8 (d, 1H) ; 8.1 (d, 1H) ; 8.6 (s, 1H)

Solvent : $CDCl_3$

- **Compound 136** :

^1H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.3 – 3.45 (m, 4H) ; 5.3 (s, 2H) ; 7.5 – 7.7 (m, 4H) ; 7.8 (m, 1H) ; 8.1 (dd, 1H) ; 8.6 (s, 1H)

Solvent : $CDCl_3$

- **Compound 137** :

^1H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 3.25 – 3.4 (m, 4H) ; 3.8 (s, 3H) ; 3.82 (s, 3H) ; 5.2 (s, 2H) ; 6.8 (d, 1H) ; 7.05 – 7.1 (m, 2H) ; 7.75 (d, 1H) ; 8.05 (d, 1H) ; 8.6 (s, 1H)

Solvent : $CDCl_3$

- **Compound 138** :

^1H NMR δ (ppm) : 1.6 – 1.85 (m, 8H) ; 3.2 - 3.4 (bs, 4H) ; 3.55 (s, 2H) ; 5.2 (s, 2H) ; 7.2 (m, 2H) ; 7.3 (m, 2H) ; 8 (m, 1H) ; 8.2 (m, 1H) ; 8.25 (s, 1H) ; 12.3 (bs, 1H)

Solvent : DMSO

- **Compound 139** :

^1H NMR δ (ppm) : 1.75 – 1.9 (m, 8H) ; 3.4 (m, 4H) ; 5.35 (s, 2H) ; 7.3 (m, 1H) ; 7.8 (d, 1H) ; 7.9 (d, 1H) ; 8.1 (d, 1H) ; 8.65 (m, 2H) ; 8.8 (s, 1H)

Solvent : $CDCl_3$

- **Compound 140** :

^1H NMR δ (ppm) : 1.8 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 4.9 (d, 2H) ; 6.35 (m, 1H) ; 6.75 (d, 1H) ; 7.25 – 7.45 (m, 5H) ; 7.8 – 8.65 (m, 3H)

Solvent : $CDCl_3$

- **Compound 141** :

^1H NMR δ (ppm) : 1.35 – 2.05 (m, 6H) ; 2.95 (t, 2H) ; 3.4 (d, 2H) ; 4.9 (d, 2H) ; 6.35 (dt, 1H) ; 6.75 (d, 1H) ; 7.25 – 7.45 (m, 5H) ; 7.85 (d, 1H) ; 8.15 (d, 1H) ; 8.65 (s, 1H)

Solvent : $CDCl_3$

- **Compound 142** :
^{1}H NMR δ (ppm) : 2 – 2.1 (m, 4H) ; 3.3 - 3.4 (m, 4H) ; 5.25 (s, 2H) ; 7.25 (d, 2H) ; 7.4 (d, 2H) ; 7.75 (d, 1H) ; 7.95 (d, 1H) ; 8.55 (s, 1H)
Solvent : $CDCl_3$

- **Compound 143** :
^{1}H NMR δ (ppm) : 1.95 – 2.1 (m, 4H) ; 3.3 - 3.45 (m, 4H) ; 5.2 (s, 2H) ; 6.95 – 7.1 (m, 2H) ; 7.35 – 7.5 (m, 2H) ; 7.75 (d, 1H) ; 7.95 (d, 1H) ; 8.6 (s, 1H)
Solvent : $CDCl_3$

- **Compound 144** :
^{1}H NMR δ (ppm) : 2 – 2.15 (m, 4H) ; 3.3 - 3.45 (m, 4H) ; 5.3 (s, 2H) ; 7.55 – 7.7 (m, 4H) ; 7.8 – 7.9 (d, 1H) ; 8.0 (d, 1H) ; 8.6 (s, 1H)
Solvent : $CDCl_3$

- **Compound 145** :
^{1}H NMR δ (ppm) : 2 – 2.1 (m, 4H) ; 3.3 - 3.4 (m, 4H) ; 3.9 (s, 3H) ; 5.3 (s, 2H) ; 7.5 (d, 2H) ; 7.8 (d, 1H) ; 7.9 – 8.05 (m, 3H) ; 8.6 (s, 1H)
Solvent : $CDCl_3$

- **Compound 146** :
^{1}H NMR δ (ppm) : 2 – 2.1 (m, 4H) ; 3.3 - 3.4 (m, 4H) ; 3.8 (s, 3H) ; 5.2 (s, 2H) ; 6.9 (d, 2 H) ; 7.45 (d, 2H) ; 7.8 (d, 1H) ; 7.95 (d, 1H) ; 8.6 (s, 1H)
Solvent : $CDCl_3$

- **Compound 147** :
^{1}H NMR δ (ppm) : 2 – 2.1 (m, 4H) ; 2.3 (s, 3H) ; 3.3 – 3.4 (m, 4H) ; 5.25 (s, 2H) ; 7.05 (d, 2H) ; 7.5 (d, 2H) ; 7.8 (d, 1H) ; 8.0 (d, 1H) ; 8.6 (s, 1H)
Solvent : $CDCl_3$

- **Compound 148** :
^{1}H NMR δ (ppm) : 2.7 (s, 6H) ; 5 (s, 2H) ; 6.6 (d, 2H) ; 7.1 (d, 2H) ; 7.9 (d, 1H) ; 8.0 (d, 1H) ; 8.1 (s, 1H) ; 9.35 (s, 1H)
Solvent : $CDCl_3$

- **Compound 149** :
^{1}H NMR δ (ppm) : 2 – 2.15 (m, 4H) ; 3.3 - 3.45 (m, 4H) ; 5.15 (s, 2H) ; 5.9 (s, 2H) ; 6.75 (d, 1H) ; 6.9 – 7.0 (m, 2H) ; 7.8 (d, 1H) ; 7.9 (d, 1H) ; 8.6 (s, 1H)

Solvent : $CDCl_3$

- **Compound 150** :

^1H NMR δ (ppm) : 2.0 – 2.1 (m, 4H) ; 3.3 - 3.4 (m, 4H) ; 3.75 (s, 6H) ; 5.2 (s, 2H) ; 6.4 (s, 1H) ; 6.65 (s, 2H) ; 7.8 (d, 1H) ; 7.95 (d, 1H) ; 8.65 (s, 1H)

Solvent : $CDCl_3$

- **Compound 151** :

^1H NMR δ (ppm) : 2.0 – 2.1 (m, 4H) ; 3.3 - 3.4 (m, 4H) ; 3.85 (s, 3H) ; 3.9 (s, 6H) ; 5.2 (s, 2H) ; 6.8 (s, 2H) ; 7.8 (d, 1H) ; 7.95 (d, 1H) ; 8.65 (s, 1H)

Solvent : $CDCl_3$

- **Compound 152** :

^1H NMR δ (ppm) : 2 (m, 4H) ; 3.35 (m, 4H) ; 5.2 (s, 2H) ; 7.15 (s, 1H) ; 7.6 (s, 1H) ; 8 – 8.15 (m, 2H) ; 8.3 (s, 1H) ; 12 (m, 1H)

Solvent : DMSO

- **Compound 153** :

^1H NMR δ (ppm) : 0.95 (t, 3H) ; 1.35 – 1.5 (m, 2H) ; 1.8 – 1.9 (m, 2H) ; 2.0 – 2.1 (m, 4H) ; 3.4 - 3.5 (m, 4H) ; 4.1 (t, 2H) ; 7.8 (d, 1H) ; 8.0 (d, 1H) ; 8.6 (s, 1H)

Solvent : $CDCl_3$

- **Compound 154** :

^1H NMR δ (ppm) : 2.45 – 2.55 (m, 4H) ; 3.25 - 3.4 (m, 4H) ; 3.7 (s, 3H) ; 6.6 (s, 1H) ; 7.35 – 7.50 (m, 3H) ; 7.55 (d, 2H) ; 8 – 8.1 (m, 2H) ; 8.3 (s, 1H)

Solvent : DMSO

- **Compound 155** :

^1H NMR δ (ppm) : 2.9 (s, 6H) ; 4.8 (d, 2H) ; 6.2 – 6.3 (dt, 1H) ; 6.7 (d, 1H) ; 7.1 – 7.35 (m, 5H) ; 7.75 (d, 1H) ; 8.0 (d, 1H) ; 8.6 (s, 1H)

Solvent : $CDCl_3$

- **Compound 156** :

^1H NMR δ (ppm) : 2.9 (s, 6H) ; 3.8 (s, 3H) ; 6.6 (s, 1H) ; 7.35 – 7.45 (m, 3H) ; 7.55 (d, 2H) ; 7.8 (d, 1H) ; 8 (d, 1H) : 8.6 (s, 1H)

Solvent : $CDCl_3$

- **Compound 157** :

^{1}H NMR δ (ppm) : 1.8 – 1.95 (m, 8H) ; 2.5 (s, 3H) ; 3.4 – 3.5 (m, 4H) ; 4.9 (d, 2H) ; 6.3 – 6.45 (dt, 1H) ; 6.7 – 6.8 (d, 1H) ; 7.2 – 7.3 (m, 3H) ; 7.35 (d, 2H) ; 7.55 (d, 2H) ; 8.1 (d, 1H) ; 8.3 (s, 1H)

Solvent : $CDCl_3$

- **Compound 158** :

^{1}H NMR δ (ppm) : 2.1 (m, 4H) ; 2.5 (s, 3H) ; 3.4 (m, 4H) ; 4.9 (d, 2H) ; 6.3 – 6.45 (dt, 1H) ; 6.7 – 6.8 (d, 1H) ; 7.2 – 7.4 (m, 5H) ; 7.5 (m, 1H) ; 8 (d, 1H) ; 8.3 (d, 1H)

Solvent : $CDCl_3$

- **Compound 159** :

^{1}H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 2.45 (s, 3H) ; 3.25 – 3.35 (m, 4H) ; 3.65 (s, 3H) ; 7.2 – 7.3 (m, 2H) ; 8 (m, 1H) ; 8.2 - 8.3 (m, 1H)

Solvent : $CDCl_3$

- **Compound 160** :

^{1}H NMR δ (ppm) : 1.8 – 2 (m, 8H) ; 2.55 (s, 3H) ; 3.3 - 3.5 (m, 4H) ; 4.9 (m, 2H) ; 6.3 – 6.4 (m, 1H) ; 6.7 – 6.8 (d, 1H) ; 7.2 – 7.4 (m, 6H) ; 8.1 (s, 1H) ; 8.35 (m, 1H)

Solvent : $CDCl_3$

- **Compound 161** :

^{1}H NMR δ (ppm) : 2 (m, 4H) ; 3.4 (m, 4H) ; 4.8 (d, 2H) ; 6.35 – 6.4 (dt, 1H) ; 6.7 (d, 1H) ; 7.2 – 7.4 (m, 4H) ; 7.45 (d, 2H) ; 7.55 (s, 1H) ; 8 (d, 1H) ; 10 (m, 1H)

Solvent : $CDCl_3$

- **Compound 162** :

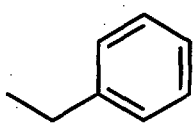
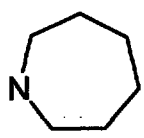
^{1}H NMR δ (ppm) : 1.5 – 2.1 (m, 16H) ; 3.3 - 3.7 (m, 8H) ; 4.9 (d, 2H) ; 6.3 – 6.4 (dt, 1H) ; 6.7 – 6.8 (d, 1H) ; 6.8– 6.9 (d, 1H) ; 7.2 – 7.5 (m, 6H) ; 8.25 (d, 1H)

Solvent : $CDCl_3$

Example 163

METHOD A : 1-Azepanyl-4-benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

(I) : X1 = 7-Br ; X2 = H ;

R =  ; NR4R5 = 

4.0 g (10.7 mmol) of 4-benzyl-1,7-dibromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (prepared by the method of Example 256) suspended in 25 ml of hexamethyleneimine are placed in a 50 ml round-bottomed flask protected from moisture.

The mixture is then refluxed with stirring for 16 hours.

After cooling, the solution obtained is concentrated under vacuum to give 4.8 g of residue which is purified by flash chromatography on a column of silica, eluting with a 99.6 CH_2Cl_2/ 0.4 CH_3OH mixture.

The TLC-pure fractions are combined and evaporated to dryness and the product obtained (4.0 g) is recrystallized from ethanol.

3.2 g of the compound of Example 163 are obtained in the form of crystals.

Yield = 66%.

m.p. (Tottoli) = 175° C

TLC (99 CH_2Cl_2 /1 CH_3OH) : Rf = 0.40

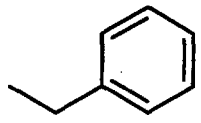
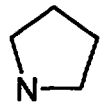
^1H NMR δ (ppm) $CDCl_3$:

1.7 – 1.85 (m, 8H) ; 3.3 (m, 4H) ; 5.3 (s, 2H) ; 7.2 – 7.35 (m, 3H) ; 7.45 –d, 2H) ; 8.0 (d, 1H) ; 8.15 (s, 1H) ; 8.4 (d, 1H)

Example 164

METHOD B : 1-(Pyrrolidin-1-yl)-4-benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a] quinazolin-5-one.

(I) : X1 = 7-Br ; X2 = H ;

R =  ; NR4R5 = 

37.0 g (85 mmol) of 4-benzyl-1,7-dibromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one dissolved in 750 ml of dimethylformamide (DMF) are placed in a reactor protected from moisture and 14.3 g (340 mmol) of sodium bicarbonate are added, followed by 12.1 g (340 mmol) of pyrrolidine.

The mixture is then refluxed with stirring for 6 hours.

After cooling, the solvent is evaporated off under vacuum, the residue obtained is taken up in a water/ethyl acetate mixture and the insoluble material therein is triturated and then filtered and dried: 18.3g of a TLC-pure first crop of the compound of Example 164 are thus obtained.

The aqueous and organic phases are separated and the ethyl acetate phase is washed with water and dried over Na_2SO_4. After concentrating the solvent under vacuum, 14.2 g of a second crop of the compound of Example 164, which is also TLC-pure, are obtained.

Yield (of crude product) = 90% ; the product is used for the next step without further purification.

A sample of 0.35 g is recrystallized from methanol to give 0.32 g of the pure compound in the form of crystals.

m.p. (Tottoli) = 173°C

TLC (99 CH_2Cl_2/1 CH_3OH) = 0.35

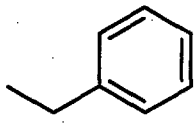
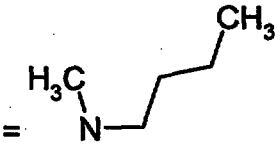
^1H NMR δ (ppm) : 2.1 (m, 4H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.3 (m, 3H) ; 7.65 (d, 2H) ; 7.85 (d, 1H) ; 8.15 (d, 1H) ; 8.45 (s, 1H)

Solvent : $CDCl_3$

Example 165

METHOD C : 1-[N-(n-butyl)-N-methylamino]-4-benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

(I) : X1 = 7-Br ; X2 = H

R =  ; NR4R5 = 

2.5 g (5.75 mmol) of 4-benzyl-1,7-dibromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one suspended in 30 ml of ethanol are placed in a reactor under pressure. 5.0g of n-butylmethylamine (57.5 mmol) are added, the reactor is closed hermetically and it is then heated on an oil bath at 160°C for 8 hours. After cooling and leaving to stand for 2 days, the residual oil (2.8 g) is chromatographed on a column of silica, eluting with a 99.5 CH_2Cl_2 / 0.5 CH_3OH mixture. 1.8 g of the compound of Example 165 are obtained.

Yield = 70%.

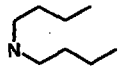
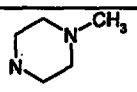
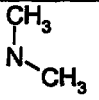
TLC (98.5 CH_2Cl_2/1.5 CH_3OH) : Rf = 0.45

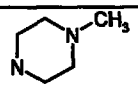
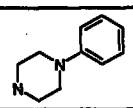
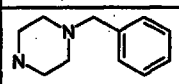
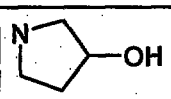
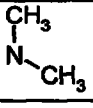
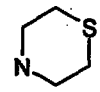
^1H NMR δ (ppm) : 0.9 (t, 3H) ; 1.25 – 1.4 (m, 2H) ; 1.55 – 1.7 (m, 2H) ; 2.85 (s, 3H) ; 2.9 – 3.5 (m, 2H) ; 5.5 (s, 2H) ; 7.2 – 7.35 (m, 3H) ; 7.7 (d, 2H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

The compounds (I) of Examples 166 to 198 (Table 3) are prepared according to one of the methods A, B and C described in Examples 163 to 165.

TABLE 3

Compound No.	X1	R	NR4R5	Yield (%)	m.p. (°C)	Method
166	H	C6H5CH2		70	167	B
167	7-Cl	CH3		17	112	A
168	7-Cl	CH3		35	192	A
169	7-Cl	CH3		50	180-182	A
170	7-Cl	CH3		60	185	A
171	7-Cl	C6H5		5	179	A
172	7-Cl	C6H5CH2		88	162	A
173	7-Cl	C6H5CH2		78	163	B
174	7-Cl	C6H5CH2		68	178	B
175	8-Cl	CH3		11	179	A
176	8-Cl	C6H5CH2		1	-	B
177	7-Br	CH3		72	174	A
178	7-Br	C6H5CH2		67	183-185	A
179	7-Br	C6H5CH2		53	171	B
180	7-Br	C6H5CH2		50	189	B

Compound No.	X1	R	NR4R5	Yield (%)	m.p. (°C)	Method
181	7-Br	C6H5CH2		49	235	B
182	7-Br	C6H5CH2		60	230	B
183	7-Br	C6H5CH2		51	238	B
184	7-Br	C6H5CH2		50	226	B
185	7-Br	C6H5CH2		82	172	B
186	7-Br	C6H5CH2		85	210	B
187	7-Br	C6H5CH2		79	176	B
188	7-Br	C6H5CH2	NHCH3	52	238	C
189	7-I	C6H5CH2		100	184	B
190	7-CH3	C6H5CH2		90	183	B
191	7-CH3	C6H5CH2		60	189	B
192	7-CH3	C6H5CH2		75	186	B
193	7-CH3	C6H5CH2		78	265	B
194	8-CH3	C6H5CH2		50	202	A
195	7-OCH3	C6H5CH2		42	153	B
196	7-OCH3	C6H5CH2		65	154	B
197	7-CN	C6H5CH2		77	219	B

Compound No.	X1	R	NR4R5	Yield (%)	m.p. (°C)	Method
198	7-NO2	C6H5CH2		32	206	A

- **Compound 166** :

^{1}H NMR δ (ppm) : 2 (m, 4H) ; 3.3 (m, 4H) ; 5.35 (s, 2H) ; 7.2 – 7.3 (m, 3H) ; 7.4 (d, 2H) ; 7.6 (t, 1H) ; 7.9 (t, 1H) ; 8.2 (m, 2H)
Solvent : DMSO

- **Compound 167** :

^{1}H NMR δ (ppm) : 0.8 (m, 6H) ; 1.15 – 1.25 (m, 4H) ; 1.35 – 1.55 (m, 4H) ; 3 (m, 2H) ; 3.2 (m, 2H) ; 3.7 (s, 3H) ; 7.65 (m, 1H) ; 8.3 (m, 1H) ; 8.45 (m, 1H)
Solvent : $CDCl_3$

- **Compound 168 :**

^{1}H NMR δ (ppm) : 1.3-1.9 (m, 6H) ; 2.9 (t, 2H) ; 3.3 (m, 2H) ; 3.5 (s, 3H) ; 8.0 (d, 1H) ; 8.1 (d, 1H) ; 8.3 (d, 1H)
Solvent : $CDCl_3$

- **Compound 170 :**

1H NMR δ (ppm) : 0.7 (s, 3H) ; 0.8 (s, 3H) ; 1.0 (s, 3H) ; 1.5-1.9 (m, 5H) ; 2.55 (d, 1H) ; 2.85 (d, 1H) ; 3.15 (m, 4H) ; 3.4 (m, 4H) ; 7.9 (d, 1 H) ; 8.0 (s, 1H) ; 8.4 (m, 1H)
Solvent : DMSO

- **Compound 171** :

^{1}H NMR δ (ppm) : 1.7 – 1.8 (m, 8H) ; 3.3 (m, 4H(+H_2O) ; 7.45 – 7.6 (m, 5H) ; 8.05 (m, 1H) ; 8.15 (s, 1H) ; 8.45 (d, 1H)
Solvent : DMSO

- **Compound 172** :

^{1}H NMR δ (ppm) : 1.7 – 1.85 (m, 8H) ; 3.3 (s, 4H) ; 5.3 (s, 2H) ; 7.25 – 7.5 (m, 5H) ; 8.0 (m, 1H) ; 8.15 (d, 1H) ; 8.4 (d, 1H)
Solvent : DMSO

- **Compound 173** :
^{1}H NMR δ (ppm) : 2.05 (m, 4H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.2 – 7.35 (m, 3H) ; 7.65 – 7.75 (m, 3H) ; 8.2 (dd, 1H) ; 8.35 (s, 1H)
Solvent : $CDCl_3$

- **Compound 174** :
^{1}H NMR δ (ppm) : 1.4 – 1.6 (m, 1H) ; 1.7 - 2 (m, 4H) ; 3 - 3.15 (m, 2H) ; 3.3 – 3.45 (m, 2H) ; 5.45 (s, 2H) ; 7.25 – 7.35 (m, 3H) ; 7.7 – 7.8 (m, 3H) ; 8.3 – 8.4 (m, 2H)
Solvent : $CDCl_3$

- **Compound 175** :
^{1}H NMR δ (ppm) : 1.85 – 1.95 (m, 4H) ; 3.4 (m, 4H + H_2O) ; 3.65 (s, 3H) ; 7.7 (d, 1H) ; 8.3 (d, 1H) ; 8.55 (s, 1H)
Solvent : DMSO

- **Compound 176** :
^{1}H NMR δ (ppm) : 1.8 – 2 (m, 8H) ; 3.3 – 3.5 (m, 4H) ; 5.4 (s, 2H) ; 7.2 – 7.35 (m, 3H) ; 7.4 – 7.45 (m, 2H) ; 7.65 – 7.7 (m, 2H) ; 8.25 –8.3 (m, 2H) ; 8.6 (s, 1H)
Solvent : $CDCl_3$

- **Compound 177** :
^{1}H NMR δ (ppm) : 1.7 – 1.85 (m, 8H) ; 3.4 (m, 4H) ; 3.7 (s, 3H) ; 7.75 (m, 1H) ; 8.25 (m, 1H) ; 8.4 (m, 1H)
Solvent : $CDCl_3$

- **Compound 178** :
^{1}H NMR δ (ppm) : 1.35 – 1.95 (m, 6H) ; 3.05 (t, 2H) ; 3.35 (d, 2H) ; 5.45 (s, 2H) ; 7.3 (m, 3H) ; 7.75 (d, 2H) ; 7.95 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)
Solvent : $CDCl_3$

- **Compound 179** :
^{1}H NMR δ (ppm) : 2.9 (s, 6H) ; 5.5 (s, 2H) ; 7.25 – 7.35 (m, 3H) ; 7.7 (d, 2H) ; 7.85 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)
Solvent : $CDCl_3$

- **Compound 180** :
^{1}H NMR δ (ppm) : 3.2 – 3.4 (m, 4H) ; 3.75 – 3.9 (m, 2H) ; 3.9 – 4.1 (m, 2H) ; 5.5 (s, 2H) ; 7.2 – 7.35 (m, 3H) ; 7.7 (d, 2H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 181** :
^1H NMR δ (ppm) : 2.8 – 3.0 (m, 4H) ; 3.35 – 3.5 (m, 2H) ; 3.5 – 3.7 (m, 2H) ; 5.45 (s, 2H) ; 7.2 – 7.35 (m, 3H) ; 7.7 (d, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)
Solvent : $CDCl_3$

- **Compound 182** :
^1H NMR δ (ppm) : 2.3 – 2.45 (m, 5H) ; 2.9 – 3.0 (m, 2H) ; 3.25 – 3.35 (m, 4H) ; 5.5 (s, 2H) ; 7.2 – 7.35 (m, 3H) ; 7.7 (d, 2H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.5 (s, 1H)
Solvent : $CDCl_3$

- **Compound 183** :
^1H NMR δ (ppm) : 3.0 – 3.2 (m, 2H) ; 3.35 – 3.5 (m, 4H) ; 3.6 – 3.75 (m, 2H) ; 5.5 (s, 2H) ; 6.9 – 7.05 (m, 3H) ; 7.2 – 7.35 (m, 5H) ; 7.7 (d, 2H) ; 7.85 (d, 1H) ; 8.3 (d, 1H) ; 8.55 (s, 1H)
Solvent : $CDCl_3$

- **Compound 184** :
^1H NMR δ (ppm) : 2.4 (m, 2H) ; 3 (m, 2H) ; 3.3 (m, 4H) ; 5.5 (s, 2H) ; 7.3 (m, 8H) ; 7.7 (m, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)
Solvent : $CDCl_3$

- **Compound 185** :
^1H NMR δ (ppm) : 2.2 – 2.65 (m, 2H) ; 3.2 – 3.9 (m, 4H) ; 5.45 (s, 2H) ; 5.8 – 5.9 (m, 1H) ; 5.9 – 6.0 (m, 1H) ; 7.2 – 7.35 (m, 3H) ; 7.7 (d, 2H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.5 (s, 1H)
Solvent : $CDCl_3$

- **Compound 186** :
^1H NMR δ (ppm) : 4.3 (s, 4H) ; 5.5 (s, 2H) ; 5.95 (s, 2H) ; 7.25 – 7.4 (m, 3H) ; 7.7 (d, 2H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.5 (s, 1H)
Solvent : $CDCl_3$

- **Compound 187** :
^1H NMR δ (ppm) : 2 - 2.1 (m, 1H) ; 2.3 – 2.4 (m, 1H) ; 3.2 – 3.6 (m, 5H) ; 4.6 – 4.7 (m, 1H) ; 5.45 (s, 2H) ; 7.2 – 7.3 (m, 3H) ; 7.65 (d, 1H) ; 7.85 (d, 1H) ; 8.3 (d, 2H) ; 8.5 (s, 1H)
Solvent : $CDCl_3$

- **Compound 188** :

^{1}H NMR δ (ppm) : 3.05 (s, 3H) ; 3.9 – 4.0 (m, 1H) ; 5.35 (s, 2H) ; 7.15 – 7.25 (m, 3H) ; 7.6 (d, 2H) ; 7.7 (d, 1H) ; 7.95 (d, 1H) ; 8.4 (s, 1H)

Solvent : $CDCl_3$

- **Compound 189** :

^{1}H NMR δ (ppm) : 2 (m, 4H) ; 3.4 (m, 4H) ; 5.3 (s, 2H) ; 7.3 (m, 3H) ; 7.4 (m, 2H) ; 8.0 (m, 1H) ; 8.2 (m, 1H) ; 8.5 (m, 1H)

Solvent : DMSO

- **Compound 190** :

^{1}H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 2.45 (s, 3H) ; 3.35 – 3.45 (m, 4H) ; 5.45 (s, 2H) ; 7.2 – 7.35 (m, 3H) ; 7.45 (dd, 1H) ; 7.7 (dd, 2H) ; 8.15 (s, 1H) ; 8.3 (d, 1H)

Solvent : $CDCl_3$

- **Compound 191** :

^{1}H NMR δ (ppm) : 2 (m, 4H) ; 2.5 (s, 3H) ; 3.3 (m, 4H) ; 5.3 (s, 2H) ; 7.2 – 7.55 (m, 5H) ; 7.7 (d, 1H) ; 8 (s, 1H) ; 8.15 (d, 1H)

Solvent : $CDCl_3$

- **Compound 192** :

^{1}H NMR δ (ppm) : 2.45 (s, 3H) ; 2.9 (s, 6H) ; 5.45 (s, 2H) ; 7.2 – 7.3 (m, 3H) ; 7.45 (d, 1H) ; 7.7 (d, 2H) ; 8.2 (d, 2H)

Solvent : $CDCl_3$

- **Compound 193** :

^{1}H NMR δ (ppm) : 2.5 (s, 3H) ; 2.8 – 3.05 (m, 4H) ; 3.35 – 3.75 (m, 4H) ; 5.5 (s, 2H) ; 7.15 – 7.4 (m, 3H) ; 7.6 (d, 1H) ; 7.7 (d, 2H) ; 8.1 – 8.25 (m, 2H)

Solvent : $CDCl_3$

- **Compound 194** :

^{1}H NMR δ (ppm) : 1.8 – 1.95 (m, 8H) ; 2.55 (s, 3H) ; 3.4 (m, 4H) ; 5.4 (s, 2H) ; 7.25 – 7.35 (m, 4H) ; 7.7 (m, 2H) ; 8.25 (m, 2H)

Solvent : $CDCl_3$

- **Compound 195** :

^{1}H NMR δ (ppm) : 1.8 – 1.95 (m, 8H) ; 3.35 – 3.40 (m, 4H) ; 3.9 (s, 3H) ; 5.4 (s, 2H) ; 7.25 – 7.35 (m, 4H) ; 7.7 (dd, 2H) ; 7.8 (d, 1H) ; 8.35 (d, 1H)

Solvent : $CDCl_3$

- **Compound 196** :

^{1}H NMR δ (ppm) : 2 (m, 4H) ; 3.35 (m, 4H) ; 3.9 (s, 3H) ; 5.35 (s, 2H) ; 7.25 – 7.35 (m, 3H) ; 7.45 (d, 2H) ; 7.55 (d, 1H) ; 7.7 (s, 1H) ; 8.2 (d, 1H)

Solvent : DMSO

- **Compound 197** :

^{1}H NMR δ (ppm) : 2.4 (m, 4H) ; 3.2 (m, 4H) ; 5.2 (s, 2H) ; 7.1 – 7.25 (m, 3H) ; 7.35 (m, 2H) ; 8.25 (m, 2H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

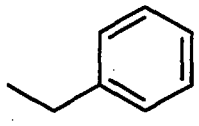
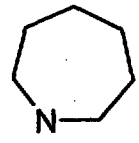
- **Compound 198** :

^{1}H NMR δ (ppm) : 1.7 – 1.85 (m, 8H) ; 3.3 (s, 4H + H_2O) ; 5.35 (s, 2H) ; 7.3 (m, 3H) ; 7.5 (m, 2H) ; 8.55 (d, 1H) ; 8.75 (d, 1H) ; 8.9 (s, 1H)

Solvent : DMSO

Example 199 : 1-Azepanyl-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

(I) ; X1 = 7-Cl ; X2 = H

R =  ; NR4R5 = 

0.44 g (1.27 mmol) of 4-benzyl-1,7-dichloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Example 254) suspended in 2.5 ml of hexamethyleneimine is placed in a 50 ml round-bottomed flask fitted with a stirrer and a condenser. The mixture is refluxed for 16 hours with stirring. The brown solution obtained is then left to stand at room temperature until it has cooled completely; it is poured into a mixture of water and methylene chloride, the mixture is stirred and the 2 phases are separated by settling. The organic phase is washed twice with water, dried over Na_2SO_4 and then evaporated under vacuum to give 0.59 g of a solid brown residue.

This product is chromatographed on a column of silica, eluting with a 99.5 CH_2Cl_2 / 0.5 CH_3OH mixture.

After combining and evaporating the TLC-pure fractions, 0.46 g of the compound of Example 199 is obtained. This product is recrystallized from ethanol to give 0.4 g of colourless crystals.

Yield = 77%

m.p. (Tottoli) = 162°C

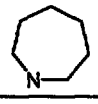
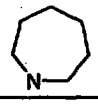
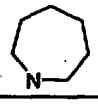
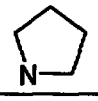
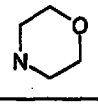
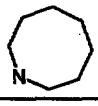
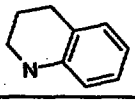
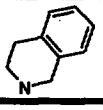
TLC (98.5 CH_2Cl_2 / 1.5 CH_3OH) : Rf = 0.35

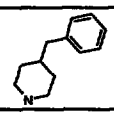
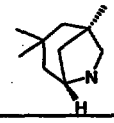
^1H NMR δ (ppm) : 1.7 – 1.85 (m, 8H) ; 3.3 (s, 4H) ; 5.3 (s, 2H) ; 7.25 – 7.5 (m, 5H) ; 8.0 (m, 1H) ; 8.15 (d, 1H) ; 8.4 (d, 1H)

Solvent : DMSO

Compounds (I) of Examples 200 to 214 (Table 4) are prepared according to the process of Example 199.

TABLE 4

Compound No.	X1	R	NR4R5	Yield (%)	m.p. (°C)	Method
200	H	CH3		40	199 – 203	A
201	H	C6H5CH2		66	157	A
202	6-Cl	CH3		8.5	> 275	A
203	7-Cl	CH3		77	145	A
204	7-Cl	CH3CH2		11	98-100	A
205	7-Cl	CH3		50	203-205	A
206	7-Cl	CH3		25	232	A
207	7-Cl	CH3		25	123-125	A
208	7-Cl	CH3		15	204	A
209	7-Cl	CH3		30	272	A

Compound No.	X1	R	NR4R5	Yield (%)	m.p. (°C)	Method
210	7-Cl	CH3		25	180	A
211	7-Cl	CH3		25	165	A
212	7-F	CH3		13	136	A
213	7-I	CH3		47	206	A
214	7-OCH3	CH3		34	203	A

- **Compound 200** :

^{1}H NMR δ (ppm) : 1.75-1.9 (m, 8H) ; 3.4 (m, 4H) ; 3.6 (s, 3H) ; 7.6 (t, 1H) ; 8 (t, 1H) ; 8.25 (d, 1H) ; 8.4 (d, 1H)

Solvent : DMSO

- **Compound 201** :

^{1}H NMR δ (ppm) : 1.7 - 1.85 (m, 8H) ; 3.3 (m, 4H) ; 5.3 (s, 2H) ; 7.2 - 7.35 (m, 3H) ; 7.45 (d, 2H) ; 7.6 (t, 1H) ; 7.95 (t, 1H) ; 8.2 (d, 1H) ; 8.4 (d, 1H)

Solvent : DMSO

- **Compound 202** :

^{1}H NMR δ (ppm) : 1.5 - 1.8 (m, 8H) ; 3.4 (m, 4H) ; 3.5 (s,3H) ; 7.05 (d, 1H) ; 7.5 (t, 1H) ; 8.4 (d, 1H)

Solvent : DMSO

- **Compound 203** :

^{1}H NMR δ (ppm) : 1.7 - 1.85 (m, 8H) ; 3.3 (m, 4H) ; 3.5 (s, 3H) ; 7.95 (d, 1H) ; 8.1 (s, 1H) ; 8.35 (d, 1H)

Solvent : DMSO

- **Compound 204** :

^{1}H NMR δ (ppm) : 1.3 (t, 3H) ; 1.7 - 1.9 (m, 8H) ; 3.3 (m, 4H) ; 4.15 (q, 2H) ; 7.95 (d, 1H) ; 8.1 (s, 1H) ; 8.35 (d, 1H)

Solvent : DMSO

- **Compound 205** :
^{1}H NMR δ (ppm) : 2.0 (m, 4H) ; 3.35 (m, 4H) ; 3.75 (s, 3H) ; 7.65 (d, 1H) ; 8.15 (d, 1H) ; 8.3 (s, 1H)
Solvent : CDCl3

- **Compound 206** :
^{1}H NMR δ (ppm) : 3.1 - 3.35 (m, 4H) ; 3.65 (s, 3H) ; 3.85 (m, 2H) ; 4.0 (m, 2H) ; 7.75 (d, 1H) ; 8.35 (m, 2H)
Solvent : $CDCl_3$

- **Compound 207** :
^{1}H NMR δ (ppm) : 1.8 (m, 10H) ; 3.4 (m, 4H) ; 3.75 (s, 3H) ; 7.75 (d, 1H) ; 8.35 (s, 1H) ; 8.4 (d, 1H)
Solvent : $CDCl_3$

- **Compound 208** :
^{1}H NMR δ (ppm) : 2.1 (m, 2H) ; 2.8 - 3.1 (m, 2H) ; 3.65 (m,1H) ; 3.75 (s,3H) ; 3.9 (m,1H) ; 6.15 (d,1H) ; 6.75 (t, 1H) ; 6.85 (t,1H) ; 7.1 (d, 1H) ; 7.5 (d, 1H) ; 7.85 (d,1H) ; 8.3 (s, 1H)
Solvent : $CDCl_3$

- **Compound 209** :
^{1}H NMR δ (ppm) : 2.9 (m, 1H) ; 3.2 (m, 1H) ; 3.4 (m, 1H) ; 3.6 (m, 1H) ; 3.7 (s, 3H) ; 4.3 (d, 1H) ; 4.45 (d, 1H) ; 7.05 (d, 1H) ; 7.2 (m, 3H) ; 7.6 (d, 1H) ; 8.2 (d, 1H) ; 8.3 (s, 1H)
Solvent : $CDCl_3$

- **Compound 210** :
^{1}H NMR δ (ppm) : 1.4 (m, 2H) ; 1.7 (m, 3H) ; 2.6 (d, 2H) ; 2.9 - 3.15 (m, 2H) ; 3.3-3.5 (m, 2H) ; 3.65 (s, 3H) ; 7.0-7.35 (m, 5H) ; 7.7 (d, 1H) ; 8.3 (m, 2H)
Solvent : $CDCl_3$

- **Compound 211** :
^{1}H NMR δ (ppm) : 1 (s, 3H) ; 1.1 (s, 3H) ; 1.25-1.4 (m, 5H) ; 1.45 (d, 1H) ; 1.6 (m, 2H) ; 1.9 (d,1H) ; 2.05 (m, 1H) ; 3.35 (d,1H) ; 3.45 (d, 1H) ; 3.7 (s, 3H) ; 4 (m, 1H) ; 7.65 (d, 1H) ; 8.3 (s, 1H) ; 8.6 (d, 1H)
Solvent : $CDCl_3$

- **Compound 212** :

^{1}H NMR δ (ppm) : 1.7 – 1.8 (m, 8H) ; 3.3 (m, 4H (+H_2O)) ; 3.5 (s, 3H) ; 7.8 (m, 1H) ; 7.9 (m, 1H) ; 8.4 (m,1H)

Solvent : DMSO

- **Compound 213** :

^{1}H NMR δ (ppm) : 1.7 - 1.9 (m, 8H) ; 3.3 (m, 4H) ; 3.7 (s, 3H) ; 8.0 (d, 1H) ; 8.1 (d, 1H) ; 8.65 (s,1H)

Solvent : $CDCl_3$

- **Compound 214** :

^{1}H NMR δ (ppm) : 1.7 - 1.85 (m, 8H) ; 3.3 (s, 4H) ; 3.5 (s, 3H) ; 3.9 (s, 3H) ; 7.5 (d, 1H) ; 7.6 (s,1H) ; 8.3 (d, 1H)

Solvent : $CDCl_3$

Example 215 : 4-Benzyl-7-bromo-1-(N-ethyl-N-methylamino)-4H-[1,2,4]triazolo[4,3-a] quinazolin-5-one.

0.3 g (0.8 mmol) of 4-benzyl-7-bromo-1-(N-methylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (compound of Example 188) is dissolved in 5 ml of DMF. 0.135 g (0.85 mmol) of methyl iodide and 0.13 g (0.93 mmol) of potassium carbonate are added. The mixture obtained is stirred at room temperature overnight and then heated at 100°C for 6 hours. After cooling, the solvent is evaporated off under vacuum and the residue is taken up in water and ethyl acetate. The organic phase is separated out by settling, washed with saturated sodium chloride solution, dried over Na_2SO_4 and evaporated under vacuum. 0.3 g of crude product is obtained, which is purified by chromatography on a column of silica, eluting with a 99 CH_2Cl_2 / 1 CH_3OH mixture. The fractions containing the desired product are combined and concentrated under vacuum, and the residue is then recrystallized from methanol to give 0.05 g of pure compound of Example 215.

Yield = 22%

m.p. (Tottoli) = 148°C

TLC (98.5 CH_2Cl_2 / 1.5 CH_3OH) : Rf = 0.45

^{1}H NMR δ (ppm) : 1.25 (t, 3H) ; 2.9 (s, 3H) ; 3.2 – 3.4 (m, 2H) ; 5.45 (s, 2H) ; 7.2 – 7.35 (m, 3H) ; 7.7 (d, 2H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

Example 216 : 4-Benzyl-1-(N,N-diethyl)-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

2.3g (5.87 mmol) of 4-benzyl-7-methyl-1-(thiamorpholin-4-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (compound of Example 193) are suspended in 250 ml of ethanol. A catalytic amount of Raney nickel is added and the mixture is refluxed for 24 hours with stirring. The catalyst is removed by filtration through Celite and the alcoholic solution is concentrated under vacuum: 1.6 g of crude product are obtained, which product is purified by chromatography on a column of silica, eluting with CH_2Cl_2 and a methanol gradient from 99.5/0.5 to give 0.9 g of TLC-pure product. A sample is recrystallized from ethanol for the determination of the physical constants.

Yield = 42%

m.p. (Tottoli) = 154°C

TLC (99 CH_2Cl_2 / 1 CH_3OH) : Rf = 0.35

^1H NMR δ (ppm) : 1 - 1.3 (m, 6H) ; 2.4 (s, 3H) ; 2.9 – 3.45 (m, 4H) ; 5.4 (s, 2H) ; 7.1 – 7.3 (m, 3H) ; 7.45 (d, 1H) ; 7.6 (d, 2H) ; 8.15 (s, 1H) ; 8.3 (d, 1H)

Solvent : CDCl3

Example 217 : 4-Benzyl-7-bromo-1-(pyrrol-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

0.7g (1.8 mmol) of 1-amino-4-benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (intermediate compound 10 of Example 271) suspended in 5 ml of acetic acid is placed in a 25 ml round-bottomed flask. 0.25g (1.9 mmol) of 2,5-dimethoxytetrahydrofuran is added and the mixture is then refluxed for 1 hour. After cooling and evaporation of the acetic acid under vacuum, 0.8 g of a highly coloured solid is obtained, which is purified by chromatography on a column of silica, eluting with a CH_2Cl_2 / CH_3OH mixture (99.4/0.6 then 99/1). The solid obtained from the pure fractions is recrystallized from ethanol to give 0.45 g of the compound of example 217.

Yield = 55%

m.p. (Tottoli) = 214°C

TLC (99 CH_2Cl_2 / 1 CH_3OH) : Rf = 0.5

^1H NMR δ (ppm) : 5.55 (s, 2H) ; 5.8 (d, 1H) ; 6.5 (s, 2H) ; 6.9 (s, 2H) ; 7.25 – 7.4 (m, 3H) ; 7.7 (d, 1H) ; 7.75 (d, 2H) ; 8.55 (s, 1H)

Solvent : $CDCl_3$

Example 218 : 4-(4-Aminobenzyl)-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

0.45g (0.96 mmol) of 7-bromo-4-(4-nitrobenzyl)-1-(pyrrol-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (compound of Example 48) in 10 ml of ethanol is loaded into a 50 ml round-bottomed flask. 1.08g (24 mmol) of stannous chloride dihydrate are added and the mixture is then heated at 70°C for 30 minutes with stirring. After cooling, the mixture is poured into ice-cold water. It is extracted several times with ethyl acetate with a small amount of $CHCl_3$, the organic phase is washed with saturated sodium chloride solution, dried over Na_2SO_4 then concentrated under vacuum. The solid residue obtained (0.35 g) is washed with methanol (50 ml) to give 0.25 g of TLC-pure product.
Yield = 83%
m.p. (Tottoli) = 263°C
TLC (98 CH_2Cl_2 / 2 CH_3OH) : Rf = 0.25
^1H NMR δ (ppm) : 1.9 - 2.05 (m, 4H) ; 3.3 – 3.4 (m, 4H) ; 5 (s, 2H) ; 5.1 (s, 2H) ; 6.5 (d, 2H) ; 7.2 (d, 2H) ; 8.1 (d, 1H) ; 8.2 (d, 1H) ; 8.3 (s, 1H)
Solvent : DMSO

Example 219 : 4-(Benzyl)-7-hydroxy-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a] quinazolin-5-one.

Example 219-1/ 4-Benzyl-7-(4-tolylsulphonyloxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.
1.46g (5 mmol) of 4-benzyl-7-hydroxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (intermediate obtained by the method of Example 255) in 15 ml of dry methylene chloride are loaded into a reactor equipped with a stirring system. 0.95 g (5 mmol) of tosyl chloride is added, after which 1 ml (7.5 mmol) of triethylamine is added over 5 minutes with stirring, the reaction being slightly exothermic. After stirring at room temperature for a further 2 hours, the organic solution obtained is washed with water and dried over Na_2SO_4 to give, after evaporation of the solvent, a coloured amorphous residue which is purified by chromatography on a column of silica, eluting with ethyl acetate. 1.9 g of TLC-pure product are obtained. This product is used for the next step without further purification.
Yield = 85%

2/ Example 219-2/ 4-Benzyl-1-bromo-7-(4-tolylsulphonyloxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

0.4g of this compound is obtained from 0.45 g of 4-benzyl-7-(4-tolylsulphonyloxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Example 219-1) by the bromination method described in Example 256.

Yield = 76%

3/ Example 219-3/ 4-Benzyl-1-(pyrrolidin-1-yl)-7-(4-tolylsulphonyloxy)-4H-[1,2,4]-triazolo[4,3-a]quinazolin-5-one and 4-benzyl-7-hydroxy-1-(pyrrolidin-1-yl)-4H-[1,2,4]-triazolo[4,3-a]quinazolin-5-one.

0.83 g of bromo derivative obtained in Example 219-2 is treated with pyrrolidine, under the conditions of Example 164. After treatment, 1.0 g of a crude mixture of 2 major compounds is obtained, which compounds are separated by chromatography on a column of silica, eluting with a 98 CH_2Cl_2 / 2 CH_3OH mixture. The fractions containing the first pure product are combined and concentrated to give 0.375 g of 4-benzyl-1-(pyrrolidin-1-yl)-7-(4-tolylsulphonyloxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

Yield = 45%

The fractions containing the second pure product are combined and evaporated under vacuum to give 0.12g of 4-benzyl-7-hydroxy-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

Yield = 15%

m.p. (Tottoli) = 287°C

^{1}H NMR δ (ppm) : 1.95 (m, 4H) ; 3.3 (m, 4H) ; 7.3 (s, 2H) ; 7.2 – 7.6 (m, 7H) ; 8.1 (d, 1H) ; 10.2 (s, 1H)

Solvent : DMSO

Example 220 : 4-(4-Cyanobenzyl)-7-hydroxy-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

1/ Example 220-1/ 1-(Pyrrolidin-1-yl)-7-(4-tolylsulphonyloxy)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

1.3 g of this compound are obtained from 2.4 g of 4-benzyl-1-(pyrrolidin-1-yl)-7-(4-tolylsulphonyloxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Example 219-3) by the debenzylation method described in Example 263.

Yield = 68%

2/ Example 220-2/ 4-(4-Cyanobenzyl)-1-(pyrrolidin-1-yl)-7-(4-tolylsulphonyloxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

0.48 g of this compound is obtained from 0.66 g of 1-(pyrrolidin-1-yl)-7-(4-tolylsulphonyloxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Example 220-1) by the N-alkylation method described in Example 3.

Yield = 52%

3/ Example 220-3/ 4-(4-Cyanobenzyl)-7-hydroxy-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo-[4,3-a]quinazolin-5-one.

0.3 g (0.55 mmol) of 4-(4-cyanobenzyl)-1-(pyrrolidin-1-yl)-7-(4-tolylsulphonyloxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (described in Example 220-2) is dissolved in 1 ml of dry DMF. 0.27 ml of pyrrolidine (2.75 mmol) is added and the mixture is then heated at 140°C for 6 hours with stirring. The solvent is evaporated off under vacuum and the residue is taken up in a mixture of ethyl acetate / aqueous N hydrochloric acid solution. The insoluble material is separated out by filtration, washed with water to neutral pH and dried under vacuum; 0.13 g of crude product is obtained, which is crystallized from 5 ml of ethanol, filtered and dried to give 0.085 g of pure product.

Yield = 40%

m.p. (Tottoli) = 305°C

^{1}H NMR δ (ppm) : 2 (m, 4H) ; 3.3 (m, 4H) ; 5.35 (s, 2H) ; 7.35 (d, 1H) ; 7.6 – 7.7 (m, 3H) ; 7.8 (d, 2H) ; 8.1 (d, 1H) ; 10.2 (s, 1H)

Solvent : DMSO

Example 221 : 7-Acetamido-4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

1/ Example 221-1/ 7-Acetamido-4-benzyl-1-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

0.45 g of this compound is obtained from 0.5 g of 7-acetamido-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one by the bromination method described in Example 256.

Yield = 72%

2/ Example 221-2/ 7-Acetamido-4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

8.7 g (21 mmol) of the bromo derivative obtained in Example 221-1 are treated with 3.7 ml (42 mmol) of pyrrolidine and 3.54 g (42 mmol) of sodium bicarbonate in 80 ml of DMF, under the conditions of Example 164. After treatment, 8.0 g of crude product are obtained,

which product is purified by chromatography on a column of silica, eluting with a 98 CH_2Cl_2 / 2 CH_3OH mixture. The fractions containing the pure product are combined and concentrated and the residue is then crystallized from ethanol to give 6.6 g of 7-acetamido-4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

Yield = 78 %

m.p. (Tottoli) = 265°C

^{1}H NMR δ (ppm) : 2 – 2.1 (m, 4H) ; 2.25 (s, 3H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.2 – 7.3 (m, 3H) ; 7.6 (d, 2H) ; 8.1 (s, 1H) ; 8.2 (m, 2H) ; 8.4 (d, 1H)

Solvent : $CDCl_3$

Example 222 : 7-Acetamido-4-[(E)-3-phenylallyl]-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo-[4,3-a]quinazolin-5-one.

Starting with 1.2 g (3.0 mmol) of 7-acetamido-4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (described in Example 221), debenzylated to 7-acetamido-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one by the method with palladium/C described in Example 257 and then treated directly with 0.59 g of cinnamyl bromide in the presence of 0.98 g of caesium carbonate in 15 ml of DMF, according to the method described in Example 3, and after purification by chromatography on a column of silica and recrystallization from ethanol, 0.4 g of the pure compound of Example 222 is obtained.

Yield = 31%.

m.p. (Tottoli) = 248° C

TLC (95 CH_2Cl_2 / 5 CH_3OH) : Rf = 0.30

^{1}H NMR δ (ppm) $CDCl_3$:

2.0-2.1 (m,4H) ; 2.25 (s, 3H) ; 3.45 (m, 4H) ; 5 (d, 2H) ; 6.35-6.4 (dt, 1H) ; 6.8 (d, 1H) ; 7.15-7.35 (m, 5H) ; 8.1 (s, 1H) ; 8.2-8.3 (m, 2H) ; 8.4 (m, 1H)

Example 223 : 7-Amino-4-[(E)-3-phenylallyl]-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

0.2 g (0.46 mmol) of 7-acetamido-4-[(E)-3-phenylallyl]-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (described in Example 222) in 5 ml of a 6N hydrochloric acid solution is placed in a 20 ml round-bottomed flask and refluxed for 15 minutes with stirring. After cooling, the solution obtained is basified with sodium hydroxide solution and extracted 3 times with methylene chloride. The combined organic phases are washed with saturated NaCl solution, dried (Na_2SO_4) and then evaporated under

vacuum. The crude product (0.12 g) is recrystallized from ethanol to give 0.08 g of the pure compound of Example 223.

Yield = 44%

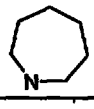
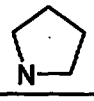
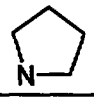
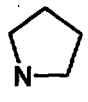
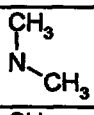
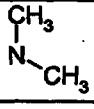
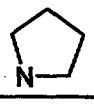
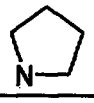
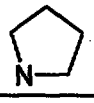
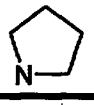
m.p. (Tottoli) = 199°C

^{1}H NMR δ (ppm) $CDCl_3$:

2.1 (m, 4H) ; 3.4 (m, 4H) ; 4.0 (m, 2H) ; 5.1 (d, 2H) ; 6.5-6.6 (dt, 1H) ; 6.85 (d, 1H) ; 7.0-7.3 (m, 3H) ; 7.6 (m, 1H) ; 7.7 (m, 1H) ; 8.1 (m, 1H) ; 8.45 (s, 1H) ; 8.6 (s, 1H).

The compounds of general formula (I) of Examples 224 to 233 in Table 5 are prepared by the method of Example 223.

TABLE 5

Compound No.	X1	R	NR4R5	Yield (%)	m.p. (°C)
224	7-NH2	C6H5CH2		40	240 (dec)
225	7-NH2	C6H5CH2		60	230
226	7-NH2	4-CNC6H4CH2		67	152
227	7-NH2	(E) (3-pyridyl)-CH=CHCH2		70	201
228	7-NH2	4-CNC6H4CH2		68	163
229	7-NH2	(E) C6H5CH=CHCH2		67	198
230	7-CH3NH	C6H5CH2		58	171
231	7-CH3NH	4-CNC6H4CH2		91	270
232	8-CH3NH	C6H5CH2		76	-
233	7-C2H5NH	C6H5CH2		67	225

- Compound 224 :

^{1}H NMR δ (ppm) : 1.8 – 1.9 (m, 8H) ; 3.4 – 3.45 (m, 4H) ; 4 (s, 2H) ; 5.4 (s, 2H) ; 7 (m, 1H) ; 7.25 – 7.35 (m, 3H) ; 7.55 (s, 1H) ; 7.65 – 7.80 (m, 2H) ; 8.15 – 8.2 (m, 1H)

Solvent : $CDCl_3$

- Compound 225 :

^{1}H NMR δ (ppm) : 2.1 (m, 4H) ; 3.4 (m, 4H) ; 4 (s, 2H) ; 5.45 (s, 2H) ; 7 (d, 1H) ; 7.2 – 7.35 (m, 3H) ; 7.6 (s, 1H) ; 7.7 – 7.8 (d, 2H) ; 8 – 8.1 (d, 1H)

Solvent : $CDCl_3$

- Compound 226 :

^{1}H NMR δ (ppm) : 2 - 2.1 (m, 4H) ; 3.35 - 3.45 (m, 4H) ; 4.05 (s, 2H) ; 8.5 (s, 2H) ; 7.05 (m, 1H) ; 7.4 – 7.5 (m, 3H) ; 7.8 (s, 1H) ; 8.05 (d, 1H)

Solvent : $CDCl_3$

- Compound 227 :

^{1}H NMR δ (ppm) : 2.1 (m, 4H) ; 3.4 (m, 4H) ; 4 (m, 2H) ; 5.1 (d, 2H) ; 6.4 – 6.5 (dt, 1H) ; 6.9 (d, 1H) ; 7.05 (m, 1H) ; 7.2 – 7.3 (m, 2H) ; 7.35 (d, 2H) ; 7.6 (s, 1H) ; 8.1 (d, 1H)

Solvent : $CDCl_3$

- Compound 228 :

^{1}H NMR δ (ppm) : 2.8 (s, 6H) ; 5.4 (s, 2H) ; 5.7 (m, 2H) ; 7.10 – 7.15 (m, 1H) ; 7.4 (s, 1H) ; 7.6 (d, 2H) ; 7.8 (d, 2H) ; 8.05 (d, 1H)

Solvent : DMSO

- Compound 229 :

^{1}H NMR δ (ppm) : 2.9 (s, 6H) ; 4.95 (d, 2H) ; 5.75 (m, 2H) ; 6.45 – 6.5 (dt, 1H) ; 6.7 – 6.8 (d, 1H) ; 7.2 (m, 1H) ; 7.25 – 7.4 (m, 6H) ; 8.1 (d, 1H)

Solvent : DMSO

- Compound 230 :

^{1}H NMR δ (ppm) : 2.1 (m, 4H) ; 2.95 (s, 3H) ; 3.4 (m, 4H) ; 4.1 (m, 1H) ; 5.4 (s, 2H) ; 6.95 (d, 1H) ; 7.3 (m, 3H) ; 7.45 (s, 1H) ; 7.75 (dd, 2H) ; 8.1 (d, 1H)

Solvent : $CDCl_3$

- Compound 231 :

^{1}H NMR δ (ppm) : 2.1 (m, 4H) ; 2.9 (s, 3H) ; 3.4 (m, 4H) ; 5.5 (s, 2H) ; 7 (m, 1H) ; 7.45 (s, 1H) ; 7.6 (m, 2H) ; 7.8 (m, 2H) ; 8.1 (d, 1H)

Solvent : $CDCl_3$

- **Compound 232 :**

^1H NMR δ (ppm) : 1.9 - 2 (m, 4H) ; 2.85 (d, 3H) ; 3.3 (m, 4H) ; 5.3 (s, 2H) ; 6.7 (d, 1H) ; 7.2 (q, 1H) ; 7.25 – 7.45 (m, 6H) ; 7.9 (d, 1H)

Solvent : DMSO

- **Compound 233 :**

^1H NMR δ (ppm) : 1.3 (t, 3H) ; 2.1 (m, 4H) ; 3.25 (m, 2H) ; 3.4 (m, 4H) ; 3.9 (m, 1H) ; 5.45 (s, 2H) ; 7 (m, 1H) ; 7.2 – 7.3 (m, 3H) ; 7.45 (s, 1H) ; 7.7 (m, 2H) ; 8.1 (d, 1H)

Solvent : $CDCl_3$

Example 234 : 4-Benzyl-7-(N-isopropylamino)-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

0.31 g (0.86 mmol) of 7-amino-4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (described in Example 225) suspended in 10 ml of methylene chloride is placed in a 20 ml round-bottomed flask. 0.14 ml (1.9 mmol) of acetone, 0.115 ml (1.9 mmol) of pure acetic acid and then 0.546 g (2.6 mmol) of sodium triacetoxyborohydride are added. The mixture is stirred at room temperature under a nitrogen atmosphere for 48 hours. The solvent is evaporated off under vacuum and the residue is taken up in ethyl acetate. The organic phase is washed with sodium bicarbonate solution and then with saturated NaCl solution. After drying (Na_2SO_4) and removal of the solvent under vacuum, 0.3 g of crude product is obtained, which is purified by chromatography on a column of silica, eluting with a 98 CH_2Cl_2 / 2 CH_3OH mixture to give 0.2 g of the TLC-pure compound of Example 234.

Yield = 58%

m.p. (Tottoli) = 208°C [EtOH]

^1H NMR δ (ppm) : 1.2 (m, 6H) ; 2.05 (m, 4H) ; 3.4 (m, 4H) ; 3.7 - 3.85 (m, 2H) ; 5.5 (s, 2H) ; 6.9 (m, 1H) ; 7.2 – 7.3 (m, 3H) ; 7.4 (s, 1H) ; 7.7 (m, 2H) ; 8.1 (m, 1H)

Solvent : $CDCl_3$

Example 235: 4-Benzyl-7-methylsulphonylamino-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo-[4,3-a]quinazolin-5-one and **Example 247** : 4-benzyl-7-(N,N-dimethylsulphonylamino)-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

0.55 g (1.5 mmol) of 7-amino-4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (described in Example 225) suspended in 10 ml of methylene chloride is placed in a 20 ml round-bottomed flask. 0.42 ml (3.0 mmol) of triethylamine is added, followed by 0.24 ml (3.0 mmol) of methanesulphonyl chloride. The solution obtained is

stirred at room temperature for 24 hours. After cooling, the solution obtained is washed with water, dried (Na_2SO_4) and then evaporated under vacuum. The crude mixture of the 2 compounds obtained (0.85 g) is chromatographed on a column of silica, eluting with a 99 CH_2Cl_2 / 1 CH_3OH / 0.1 NH_4OH mixture. The fractions containing the first product by order of elution are combined and evaporated under vacuum to give 0.65 g of 4-benzyl-7-(N,N-dimethylsulphonylamino)-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

m.p. (Tottoli) = 221°C

^{1}H NMR δ (ppm) DMSO : 2.2 – 2.3 (m, 4H) ; 2.9 (s, 3H) ; 3.15 (m, 4H) ; 5.15 (s, 2H) ; 7.1 – 7.2 (m, 3H) ; 7.25 (m, 2H) ; 7.5 – 7.6 (d, 1H) ; 7.85 (s, 1H) ; 8.05 – 8.1 (d, 1H) ; 10.05 (s, 1H)

The fractions containing the second product by order of elution are treated in a similar manner to give 0.15 g of 4-benzyl-7-methylsulphonylamino-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

Yield = 23%

m.p. (Tottoli) = 283°C [EtOH]

^{1}H NMR δ (ppm) DMSO : 2 (m, 4H) ; 3.45 (m, 4H) ; 3.5 (s, 3H) ; 5.45 (s, 2H) ; 7.3 (m, 3H) ; 7.7 (m, 3H) ; 6.35 (m, 2H)

Example 236 : 7-(N,N-Dimethylamino)-4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo-[4,3-a]quinazolin-5-one.

0.75g (2.05 mmol) of 7-amino-4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (described in Example 225) suspended in 0.8 ml of formic acid and 0.8 ml of formaldehyde are placed in a round-bottomed flask. The mixture is heated at 100°C for 1 hour with stirring. After cooling, the solution obtained is poured into ice-cold water and the suspension is extracted several times with ethyl acetate; the combined organic phases are washed with saturated aqueous sodium chloride solution, dried over Na_2SO_4 and the concentrated under vacuum.

The crude product obtained (0.8 g) is purified by chromatography on a column of silica, eluting with a 98 methylene chloride / 2 methanol mixture. 0.23 g of the TLC-pure product of Example 236 is obtained.

Yield = 29%

m.p. (Tottoli) = 194°C [EtOH]

TLC (97 CH_2Cl_2 / 3 CH_3OH) : Rf = 0.65

^{1}H NMR δ (ppm) : 2.1 (m, 4H) ; 3.05 (s, 6H) ; 3.45 (m, 4H) ; 5.45 (s, 2H) ; 7.1 (m, 1H) ; 7.3 (m, 3H) ; 7.6 (d, 1H) ; 7.75 (m, 2H) ; 8.1 (d, 1H)

Solvent : $CDCl_3$

Example 237 : 4-Benzyl-7-cyano-1-(N,N-dimethylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

10.8 g (27.1 mmol) of 4-benzyl-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Example 164) in 100 ml of N-methylpyrrolidinone (NMP) are introduced into a 500 ml round-bottomed flask fitted with a stirring system, a condenser and a nitrogen inlet. 4.4 g (49 mmol) of cuprous cyanide are added and the mixture is then heated for 12 hours under nitrogen with stirring. The solvent is removed by evaporation under vacuum; the residue is stirred in a mixture of methylene chloride and 2N aqeuous ammonia, the insoluble material is removed by filtration and the phases are then separated by settling. The organic phase is washed with saturated NaCl solution, dried (Na_2SO_4) and evaporated to give 24.0 g of crude product. This product is purified by chromatography on a column of silica, eluting with a 65 ethyl acetate / 35 cyclohexane mixture. The TLC-pure fractions are combined and evaporated under vacuum: 8.4 g of the compound of Example 237 are obtained.

Yield = 90%.

m.p. (Tottoli) = 212-214°C

^{1}H NMR δ (ppm) : 2.9 (s, 6H) ; 5.3 (s, 2H) ; 7.3 (m, 3H) ; 7.5 (m, 2H) ; 8.4 (m, 1H) ; 8.5 (m, 1H) ; 8.6 (m, 1H)

Solvent : DMSO

Example 238 : 4-Benzyl-7-carboxy-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

5.0 g (13.5 mmol) of 4-benzyl-7-cyano-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one suspended in 100 ml of 16 N hydrochloric acid solution are placed in a 250 ml round-bottomed flask and the mixture is then refluxed for 3 hours with stirring.

After cooling, the precipitate is filtered off, washed several times with water, dried and purified by chromatography on a column of silica, eluting with a 97 CH_2Cl_2 / 3 CH_3OH mixture to give 2.3 g of the TLC-pure compound of Example 238.

Yield = 44%

m.p. (Tottoli) = 335-337°C

^{1}H NMR δ (ppm) : 1.9 (s, 4H) ; 3.4 (s, 4H) ; 5.3 (s, 2H) ; 7.3 (m, 3H) ; 7.4 (m, 2H) ; 8.2 (m, 1H) ; 8.4 (m, 1H) ; 8.7 (s, 1H)

Solvent : DMSO

Example 239 : 7-Bromo-4-[(4-methoxycarbonylmethyl)benzyl]-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

0.8 g (1.65 mmol) of 7-bromo-4-[(4-carboxymethyl)benzyl]-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Example 56) and 0.25 g of potassium carbonate are suspended in 10 ml of DMF. 0.26 g (1.82 mmol) of methyl iodide is added and the mixture is then heated at 80°C for 2 hours with stirring. The solvent is evaporated off under vacuum and the residue is taken up in water which is extracted 3 times with ethyl acetate; the combined organic phases are washed with saturated sodium chloride solution, dried over Na_2SO_4 and the solvent is then evaporated off under vacuum to give 0.7 g of crude product.

This product is purified by chromatography on a column of silica, eluting with a 99 CH_2Cl_2 / 1 CH_3OH mixture. 0.5 g of TLC-pure product is obtained.

Yield = 61%

m.p. (Tottoli) = 161-162°C [C_2H_5OH]

^1H NMR δ (ppm) : 2 - 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 3.6 (s, 2H) ; 3.7 (s, 3H) ; 5.45 (s, 2H) ; 7.2 (d, 2H) ; 7.65 (d, 2H) ; 7.85 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent : CDCl3

Example 240 : 7-Bromo-4-[(4-(N-methylcarbamoyl)methyl)benzyl]-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

240-1/ 7-Bromo-4-[(4-chloroformylmethyl)benzyl]-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo-[4,3-a]quinazolin-5-one.

0.85 g (1.76 mmol) of 7-bromo-4-[(4-carboxymethyl)benzyl]-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Example XX) is placed in 85 ml of dry chloroform. The mixture is stirred under a stream of nitrogen, followed by addition of 0.42 g (3.52 mmol) of thionyl chloride while maintaining the temperature below +5°C. After 1 h 30 min, the reaction is virtually complete and the acid chloride precipitates out in the form of crystals. This solution is used for the next step without further purification.

240-2/ 7-Bromo-4-[(4-(N-methylcarbamoyl)methyl)benzyl]-1-(pyrrolidin-1-yl)-4H-[1,2,4]-triazolo[4,3-a]quinazolin-5-one.

The solution obtained in Example 240-1 is added slowly, while maintaining the temperature < +5°C, to a solution, cooled to 0°C, of 0.6 g (8.8 mmol) of methylamine hydrochloride and 1.06 g of triethylamine in 85 ml of acetone. Stirring is then continued at 0°C for 15 minutes, after which the solution obtained is concentrated under vacuum. The residue is dissolved in methylene chloride, the organic phase is washed twice with water, dried over Na_2SO_4, the solvent is evaporated off under vacuum and 1.0 g of crude product is thus recovered. This product is chromatographed on a column of silica, eluting with a

96 CH_2Cl_2 / 4 CH_3OH mixture to give 0.4 g which is recrystallized from ethanol . After drying, 0.27 g of pure compound is obtained.

Yield = 31%

m.p. (Tottoli) = 240°C

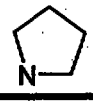
TLC (92CH_2Cl_2 / 8CH_3OH) : Rf = 0,5

^{1}H NMR δ (ppm) : 1.95 - 2.1 (m, 4H) ; 2.7 (d, 3H) ; 3.35 – 3.45 (m, 4H) ; 3.5 (s, 2H) ; 5.3 – 5.5 (m, 3H) ; 7.15 (d, 2H) ; 7.65 (d, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : CDCl3

The compounds (I) of Examples 241 to 243 (Table 6) are prepared according to the process of Example 240.

TABLE 6

Compound No.	R	NR4R5	Yield (%)	m.p. (°C)
241	4-(NH2COCH2)C6H4CH		38	268
242	4-(Me2NCOCH2)C6H4C		74	202
243	4-(HONHCOCH2)C6H4C		47	229

- **Compound 241 :**

^{1}H NMR δ (ppm) : 2.7 (s, 6H) ; 3.2 (s, 2H) ; 5.1 (s, 2H) ; 6.7 (s, 1H) ; 7.05 (d, 2H) ; 7.2 (m, 3H) ; 7.95 (m, 1H) ; 8.05 (d, 1H) ; 8.15 (s, 1H)

Solvent : DMSO

- **Compound 242 :**

^{1}H NMR δ (ppm) : 2 - 2.15 (m, 4H) ; 2.9 (s, 3H) ; 2.95 (s, 3H) ; 3.35 – 3.45 (m, 4H) ; 3.7 (s, 2H) ; 5.45 (s, 2H) ; 7.15 (d, 2H) ; 7.65 (d, 2H) ; 7.85 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 243 :**

^{1}H NMR δ (ppm) : 1.95 - 2.1 (m, 4H) ; 3.3 (s, 2H) ; 3.3 – 3.4 (m, 4H) ; 5.3 (s, 2H) ; 7.25 (d, 2H) ; 7.45 (d, 2H) ; 8.15 (d, 1H) ; 8.25 (d, 1H) ; 8.35 (s, 1H) ; 8.8 (s, 1H) ; 10.7 (s, 1H)

Solvent : DMSO

Example 244 : 7-Methyl-4-(4-cyanobenzyl-1-(N,N-dimethylamino)-4H-[1,2,4]triazolo-[4,3-a]quinazolin-5-thione.

244-1/ 7-Methyl-1-(N,N-dimethylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-thione.

1.0g (4.1 mmol) of 7-methyl-1-(N,N-dimethylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one in 70 ml of toluene is placed in a three-necked round-bottomed flask equipped with a stirring system, a condenser and a nitrogen-introduction system, and 3.3 g (8.2 mmol) of Lawesson's reagent are added in a single portion. The mixture is refluxed for 24 hours with stirring. After cooling, 30 ml of 5% hydrochloric acid solution are added and the mixture is then poured into 250 ml of methanol with stirring. 250 ml of cyclohexane are added and the insoluble material is removed by filtration. The acidic methanolic phase is separated out by settling and concentrated under vacuum, and the residue is taken up in ice and triturated therein several times. The insoluble material recovered in the form of a lacquer is dissolved in 10 ml of isopropanol; starting with the solution obtained, stirred for 30 minutes, the yellow crystals which precipitated are filtered off, washed with isopropanol and then with ether and dried under vacuum. 0.98 g of product is obtained, which is used for the next step without further purification.

Yield = 80 %

244-2/ 4-(4-Cyanobenzyl)-1-(N,N-dimethylamino)-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-thione.

Starting with 0.5 g (1.93 mmol of 7-methyl-1-(N,N-dimethylamino)-4H-[1,2,4]-triazolo[4,3-a]quinazolin-5-thione (Example 244-2), using method B described in Example 3, and after recrystallization from ethanol, 0.29 g of the compound of Example 244 is obtained.

Yield = 40%

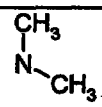
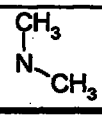
m.p. (Tottoli) = 236°C

^{1}H NMR δ (ppm) : 2.9(s,6H) ; 3.7(s,2H) ; 5.45(s,2H) ; 7.25(m,2H) ; 7.7(m,2H) ; 7.85(m,1H) ; 8.2(d,1H) ; 8.5(s,1H)

Solvent : $CDCl_3$

Compounds (I) of Examples 245 and 246 (Table 7) are prepared according to the process of Example 244.

TABLE 7

Compound No.	X1	R	NR4R5	Yield (%)	m.p. (°C)
245	7-Br	4-CNC6H4CH2		13	276
246	7-CH3	(E) (pyrid-3-yl)-CH=CHCH2		26	133

- **Compound 245 :**

^{1}H NMR δ (ppm) : 2.9 (s, 6H) ; 4.7 (s, 2H) ; 7.65 (d, 2H) ; 7.75 (d, 2H) ; 8.1 (m, 2H) ; 8.4 (d, 1H)

Solvent : DMSO

- **Compound 246 :**

^{1}H NMR δ (ppm) : 2.5 (s, 3H) ; 3.0 (s, 6H) ; 4.25 (d, 2H) ; 6.45 (dt, 1H) ; 6.75 (d, 1H) ; 7.2 (m, 1H) ; 7.6 (d, 1H) ; 7.7 (d, 1H) ; 7.9 (s, 1H) ; 8.4 (m, 2H) ; 8.6 (bs, 1H)

Solvent : $CDCl_3$

B. Intermediate compounds

Particularly preferred embodiments of the intermediate compounds of the present invention can be prepared according to the examples which follow. However, a person skilled in the art may easily modify the procedures described below as a function of the desired intermediate.

Example 250

Intermediate 1 :

1,2,3,4-Tetrahydro-3-benzyl-6-bromo-4-oxo-2-thiaquinazoline from 5-bromoanthranilic acid.

150 g (694 mmol) of 5-bromo-2-aminobenzoic acid suspended in 1.5 l of acetic acid are placed in a reactor fitted with a stirrer, a condenser and a dropping funnel.

The mixture is heated to reflux with stirring, and 92 ml (103 g; 694 mmol) of benzyl isothiocyanate are then added slowly and uniformly via the dropping funnel.

After the end of the addition, the mixture is refluxed for a further 6 hours with stirring; during this period, dissolution takes place gradually.

After cooling to room temperature, the solid which has precipitated is filtered off and washed with acetic acid.

The product obtained is dried under vacuum to 60°C to give 125.2 g of the TLC-pure expected compound (elution solvent : 99.2 CH_2Cl_2 / 0.8 CH_3OH ; Rf = 0.9)
Yield = 52%
The ^1H NMR and ^{13}C NMR spectra are compatible with the expected structure.

Example 251

Intermediate 2 :

3,4-Dihydro-3-benzyl-6-bromo-2-hydrazinoquinazolin-4-one.

125.2 g (360 mmol) of 1,2,3,4-tetrahydro-3-benzyl-6-bromo-4-oxo-2-thiaquinazoline (Intermediate 1) suspended in 3.5 l of ethanol are placed in a reactor fitted with a stirrer and a condenser.
167.6 g (3.348 mmol) of hydrazine hydrate are added with stirring.
The suspension obtained is refluxed for 18 hours, during which dissolution takes place gradually.
After cooling to room temperature, about half of the solvent is evaporated off under vacuum and the residual solution obtained is left to stand in a bath of ice for 1 hour.
After filtering off the precipitate, washing with cold ethanol and then drying under vacuum at 60°C, 89.7 g of the TLC-pure expected compound are obtained (elution solvent : 99 CH_2Cl_2 / 1 CH_3OH ; Rf = 0.1)
Yield = 72%
The ^1H NMR and ^{13}C NMR spectra are compatible with the expected structure.

Example 252

Intermediate 3 :

4-Benzyl-7-chloro-1-mercapto-4H-[1,2,4]triazolo[4, 3-a]quinazolin–5-one

47.7 g (158 mmol) of 3,4-dihydro-3-benzyl-6-chloro-2-hydrazinoquinazolin-4-one (prepared in a similar manner to that of Intermediate 2) dissolved in 600 ml de pyridine are placed in a reactor fitted with a stirrer and a condenser.
25.3 g (158 mmol) of potassium xanthogenate are then added portionwise and the solution obtained is refluxed for 7 hours with stirring, during which a solid gradually precipitates out.
After leaving to stand at room temperature overnight, the precipitate is separated out by filtration and then redissolved in 1.5 litres of water.
The solution obtained is neutralized with acetic acid and the precipitate formed is then filtered off, washed with water to neutral pH and dried.

54.0 g of crude product are obtained, which product is used for the next step without further purification.
Yield ≈ 100%

Example 253
Intermediate 4 :
4-Benzyl-7-chloro-1-methylthio-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

A solution of 6.72 g of sodium hydroxide in 1200 ml of water is placed in a reactor fitted with a stirrer and dropping funnel, followed by addition of 57.0 g (166 mmol) of 4-benzyl-7-chloro-1-mercaptotriazolo[4,3-a]quinazolin-5-one (Intermediate 3).
15.74 ml (166 mmol) of dimethyl sulphate are added with stirring at room temperature, over a period of 30 minutes. Stirring is continued for 7 hours.
After leaving to stand at room temperature overnight, the precipitate is filtered off, washed with water and then dried under vacuum.
51.2 g of crude solid are obtained, which product is used for the next step without further purification.
Yield = 100%

Example 254
Intermediate 5 : 4-Benzyl-1,7-dichloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.
51.0 g (143 mmol) of 4-benzyl-7-chloro-1-methylthiotriazolo[4,3-a]quinazolin-5-one (Intermediate 4) in a mixture of 1.5 l of chloroform and 0.9 l of water are placed in a reactor fitted with a stirrer, a dip tube and a condenser.
The mixture is cooled to 0°C with stirring, and a stream of chlorine is then bubbled through for 2 hours, while keeping the temperature below 10°C.
Introduction of chlorine is then stopped, the mixture is allowed to return to room temperature and stirring is then continued for 2 hours.
The 2 phases are separated by settling and the chloroform phase is dried over Na_2SO_4 and concentrated under vacuum.
50.9 g of crude solid residue are obtained. This product is suspended in 400 ml of ethanol and the heterogeneous mixture is stirred for 30 minutes. The insoluble material is filtered off, washed with ethanol and dried at 50°C under vacuum to give 46.5 g of the TLC-pure expected compound (elution solvent : 99 CH_2Cl_2 / 1 CH_3OH ; Rf = 0.50)
Yield = 94%
The proton and ^{13}C NMR spectra are compatible with the expected structure.

Example 255

Intermediate 6 : 4-Benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

89.7 g (260 mmol) of 3,4-dihydro-3-benzyl-6-bromo-2-hydrazinoquinazolin-4-one (Intermediate 2) suspended in 2.9 l of dry chloroform are placed in a 6 litre reactor fitted with a stirrer.

The suspension is cooled to 0°C on an ice bath, with stirring, followed by addition of 216 ml (192.5 g ; 1299 mmol) of triethyl orthoformate, which results in a slight rise in temperature (to 6°C).

8.2 ml of concentrated sulphuric acid are added in a single portion, while keeping the temperature below 5°C. The mixture is then stirred for 15 min at a temperature below 5°C and the ice bath is then removed; stirring is continued for a further 4 hours, during which a solid gradually precipitates out.

1.5 l of water and 0.7 l of chloroform are added, with stirring until completely distributed between the 2 phases, and the aqueous phase is then neutralized to pH 7 with sodium bicarbonate.

The organic phase is separated out by settling, washed with saturated NaCl solution, dried (Na_2SO_4) and evaporated under vacuum to give 91.3 g of the TLC-pure expected compound (elution solvent : 97 CH_2Cl_2 / 3 CH_3OH / 0.3 NH_4OH ; Rf = 0.5).

Yield = 99%

m.p. (Tottoli) = 237°C

The ^1H NMR and ^{13}C NMR spectra are compatible with the expected structure.

Example 256

Intermediate 7 :

4-Benzyl-1,7-dibromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

35 g (98.5 mmol) of 4-benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Intermediate 6) suspended in 630 ml of chloroform and 11 ml of pyridine are placed in a 3 litre reactor equipped with a stirrer, a condenser and a dropping funnel.

16.4 ml (320 mmol) of bromine are then added at room temperature with stirring, over a period of 30 minutes.

After the end of the addition, stirring is continued at room temperature for 1 hour ;

the reaction medium is then partitioned between1 l of water and 1.5 l of chloroform and the heterogeneous mixture is stirred for 15 min.

The insoluble material is spin-filtered, washed with water to neutral pH and then triturated from ethanol.

Under drying under vacuum, at 50°C, a first fraction of 8.2 g of the TLC-pure expected compound is obtained (elution solvent : 99 CH_2Cl_2 / 1 CH_3OH ; Rf = 0.6).

After separation of the chloroform phase, washing with sodium bicarbonate solution and then with water, drying (Na_2SO_4), evaporation of the solvent under vacuum and then trituration of the residue from ethanol, filtration and drying of the solid at 50°C, 33.1 g of a second fraction of the expected compound, which is equivalent to the preceding fraction by TLC, are obtained.

Total yield (for the 2 fractions) = 96%

The ^1H NMR spectrum is compatible with the expected structure.

Example 257

Intermediate 8 : 1-Azepanyl-4H-[1,2,4] triazolo[4,3-a] quinazolin-5-one

1.0 g (2.68 mmol) of 1-azepanyl-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one is dissolved in 60 ml of tetrahydrofuran in a 150 ml round-bottomed flask equipped with a stirrer and a condenser.

2.0 g of ammonium formate are added, followed by 1.5 g of activated 10% palladium-on-charcoal.

The mixture is stirred and heated at the reflux point of the solvent for 5 hours.

After cooling, the suspension is filtered and the solvent is then evaporated off under vacuum to give 0.55 g of residual solid.

This product is chromatographed on a column of silica, eluting with a 97 CH_2Cl_2 / 3 CH_3OH 3 mixture; the TLC-pure fractions are combined and concentrated under vacuum to give 0.42 g of solid residue.

Yield = 55%

m.p. (Tottoli) = 222 – 224°C

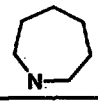
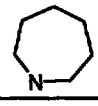
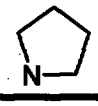
TLC (95CH_2Cl_2 / 5CH_3OH) : Rf = 0.4

^1H NMR δ (ppm) : 1.65-1.85 (m, 8H) ; 3.25 (m, 4H) ; 7.5 (t,1H) ; 7.9 (t, 1H) ; 8.15 (d, 1H) ; 8.3 (d,1H) ; 12.6 (m, 1H)

Solvent : DMSO

The compounds (I ; R = H) of Examples 258 to 262 (Table 8) are prepared according to the process of Example 257.

TABLE 8

Compound No.	X1	NR4R5	Yield (%)	m.p. (°C)
258	7-Br		96	>290
259	8-CH3		64	-
260	8- 		75	-
261	7-Br		89	>300
262	7-Br		90.5	>300

Example 263

Intermediate 9 : 1-Azepanyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

10.0 g of 1-azepanyl-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (24.5 mmol) and then 19.6 g (147 mmol) of dry aluminium chloride are suspended in 200 ml of anhydrous benzene.

The suspension is stirred and heated at 50°C in the absence of moisture.

After 1 hour 30 minutes, the reaction mixture is allowed to cool, ice is added and this mixture is then stirred vigorously for 30 minutes.

The precipitate obtained is spin-filtered, washed with water to neutrality and dried at 50°C to give 7.5 g of TLC-pure solid.

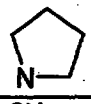
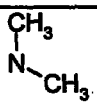
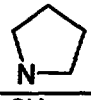
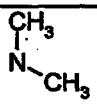
Yield = 96%

m.p. (Tottoli) : >300°C

TLC (95 CH_2Cl_2 / 5 CH_3OH) : Rf = 0.35

^1H NMR δ (ppm) : 1.65-1.9 (m, 8H) ; 3.3 (m, 4H) ; 7.95 (d, 1H) ; 8.05 (s, 1H) ; 8.3 (d, 1H) ; 12.8 (m,1H)

TABLE 9

Compound No.	X1	NR4R5	m.p. (°C)
264	H		283
265	7-CH3		298
266	7-CH3		>300
267	7-CH3		-
268	7-OH		295
269	7-CN		>300
270	7-CN		-

Example 271

Intermediate 10 : 1-Amino-4-benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

5.0g (14.5 mmol) of 3,4-dihydro-3-benzyl-6-bromo-2-hydrazinoquinazolin-4-one (prepared according to Example XX) suspended in 150 ml of dry methanol are placed in a 500 ml reactor fitted with a stirring system, a condenser equipped with a potassium hydroxide guard tube, a dip thermometer and a nitrogen inlet. 1.62g (15.3 mmol) of cyanogen bromide are added and the heterogeneous mixture is stirred for 1 hour at room temperature and then refluxed for 5 hours. After cooling, saturated aqueous sodium bicarbonate solution is added dropwise, with vigorous stirring, to pH 8. The insoluble solid is filtered off, washed several times with water and dried under vacuum to give 4.9 g of crude product.

This product is triturated from 100 ml of methanol and the insoluble fraction is separated out by filtration, washed with methanol and dried under vacuum. 4.6g of TLC-pure product are obtained. The ^{1}H NMR and ^{13}C NMR spectra are compatible with the expected structure.

Yield = 86.5%

m.p. (Tottoli) = 287°C
TLC (95 CH_2Cl_2 / 5 CH_3OH 5) : Rf = 0.5

Evaluation of the *in vitro* activity of the preferred compounds of the invention

Inhibition of phosphodiesterase

The capacity of the compounds of formula (I) of the invention to inhibit cyclic nucleotide phosphodiesterases is evaluated by measuring their IC_{50} (concentration required to inhibit 50% of the enzymatic activity).

The type 4 phosphodiesterases are obtained from a cytosolic preparation extracted from a cell line U937 of human origin according to the method adapted from T.J. Torphy et al., 1992, J.Pharm.Exp. Ther. 263 : 1195-1205.

The other types of phosphodiesterase are obtained from partial purification by FPLC on a Mono Q column (anion exchange column) according to a method adapted from **Lavan B. E., Lakey T., Houslay M. D.** Biochemical Pharmacology, 1989, 38(22), 4123-4136., and **Silver P.J** et al., 1988, Eur.J. Pharmacol. 150 : 85-94, either from cell lines of human origin for PDE1 (TPH1 monocyte line) and PDE5 (MCF7 line obtained from an adenocarcinoma), or from dog aorta for PDE3, or, for human PDE3A, from cloning genes in SF21 insect cells into baculoviruses, according to the method adapted from Luckow, V. A. et al., 1991 in Recombinant DNA Technology&Applications., eds. Prokop, Bajpai, R.K.&Ho,C.S., pp 97-152.

The measurement of the enzymatic activity of the various types of PDE, and in particular the PDEs 4, is carried out according to a method adapted from W.J. Thompson et al. 1979, Advances in Cyclic Nucleotide Research, Vol. 10 : 69-92, ed. G. Brooker et al. Raven Press, NY.

For the determination of the IC_{50}, the enzymatic activity is measured in the presence of the inhibitor over a range of concentrations from 0.1 µM to 100 µM.

The table which follows illustrates the inhibitory activity of PDE4 on an enzyme preparation obtained from the U937 line.

Compound No.	IC_{50} (µM)	Compound No.	IC_{50} (µM)	Compound No.	IC_{50} (µM)
1	**0.054**	**59**	**0.090**	**190**	**0.19**
3	**0.079**	**60**	**0.050**	**218**	**0.048**
11	**0.080**	**61**	**0.011**	**223**	**0.012**
13	**0.060**	**62**	**0.053**	**224**	**0.075**

Compound No.	IC_{50} (μM)	Compound No.	IC_{50} (μM)	Compound No.	IC_{50} (μM)
20	0.04	75	0.078	227	0.028
22	0.41	76	0.070	229	0.080
32	0.053	78	0.038	230	0.002
34	0.056	79	0.14	231	0.00027
35	0.020	80	0.073	233	0.18
37	0.015	81	0.016	234	2.69
40	0.014	83	0.012	239	0.005
41	0.018	85	0.041	240	0.013
42	0.024	89	0.027	242	0.011
43	0.030	92	0.030	243	0.028
44	0.090	94	0.029	246	0.041
46	0.090	96	0.058		
47	0.050	98	0.029		
48	0.025	102	0.060		
49	0.080	103	0.039		
50	0.035	104	0.077		
51	0.027	164	0.090		
52	0.030	186	0.090		
57	0.014	189	0.078		

Examination of the results in the above table shows that the preferred products of the invention tested in the trial inhibit the enzyme PDE4 *in vitro* effectively.

Inhibition of the production of TNFα by human leukocytes stimulated by lipopolysaccharide

The aim of this test is to evaluate the capacity of the compounds of the invention to inhibit the production of TNFα (tumor necrosis factor-α) by human leukocytes in the presence of a high concentration of human serum (75%). The reason for this is that it is found that many compounds having the capacity to inhibit phosphodiesterase 4 in enzymatic or cell tests no longer have this capacity when the test is carried out in human blood. The test described here is based on the use of human leukocytes cultured in 75% human serum. It has previously been documented that these conditions mimic the situation observed when the assay of TNFα is carried out in human blood.

The test compounds are dissolved at 20 mM (occasionally 6 mM) in DMSO. 100 µl of DMSO are distributed in 7 wells of a 96-well microplate (wells B to H). 150 µl of the solution of compounds are placed in the wells of line A. 50 µl are then sequentially transferred 7 times. 20 µl of these serial dilutions of compounds are sequentially transferred twice into wells containing 180 µl of RPMI 1640 (Gibco). 50 µl of these dilutions are then transferred into wells into which the cells will be added.

Each test comprises a series of eight wells without LPS (100% inhibition), eight wells with LPS (0% inhibition) and a series of dilutions of Rolipram in order to be able to compare the tests with each other and thus evaluate their variability.

An ampule of leukocytes is thawed on a water bath (37°C), its contents are transferred into a 15 ml tube containing 10 ml of RPMI supplemented with 5% human serum (RPMI-5% HS). The cells are sedimented (800 × g, 6 minutes, 4°C), taken up in 10 ml of the same medium and counted by dilution in a solution of Trypan blue. After centrifugation (800 × g, 6 minutes, 4°C), the cells are taken up at a proportion of 2×10^6/ml in human serum.

100 µl of cells are added to 50 µl of the various dilutions of compounds. The plates are then incubated for 30 minutes at 37°C, after which 50 µl of a 4 µg/ml solution of LPS prepared in human serum are added. The plates are incubated overnight at 37°C.

After incubation for 15-18 hours, 90 µl of culture supernatant are removed and transferred into round-bottomed microplate wells. The presence of TNFα is then evaluated by ELISA (Pharmingen), using 50 µl of supernatant. The protocol described by the manufacturer is applied rigorously.

The results obtained for some of the preferred compounds of the present invention are illustrated in the table which follows.

Compound	Inhibition (human leukocytes) IC_{50} µM
3	3.4
104	8.1
94	6.3
101	8.6
85	6.8
98	-
79	5.2
91	-
93	4.3
103	10.7
46	-
35	-

Evaluation of the *in vivo* activity of the compounds of the invention

***in vivo* TNFα model in Wistar rats**

TNFα is a cytokine which plays a central role in the mechanisms of inflammation. Its production can be induced by an injection of lipopolysaccharide (LPS). It has been shown that the increase in intracellular cAMP, produced in particular by PDE4 inhibitors, decreases the production of TNFα in *in vitro* and *in vivo* models. Thus, what is involved here is to quantify *in vivo* the anti-inflammatory potential of the compounds of the invention, administered orally (p.o.), by measuring the inhibition of the production of TNFα in the plasma of rats, these rats having received an intraperitoneal (i.p.) injection of lipopolysaccharide (LPS). For the treatment with the compounds of the invention or the vehicle, the latter are administered orally to male Wistar rats, 30 min before the injection of LPS. The rats are sacrificed 90 min after the stimulation with LPS, the blood is collected over EDTA and the concentration of TNFα is measured in each sample of plasma. The results obtained for some of the compounds of the present invention are given in the table below.

Compound	% inhibition at 10 mg/kg
3	- 98 %
104	- 94 %
94	- 87 %
101	- 80 %
85	- 77 %
98	- 75 %
79	- 72 %
91	- 70 %
93	- 67 %
103	- 64 %
46	- 58 %
35	- 51 %

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Prabhakar, U., Lipshutz, D., O'Leary Barthus, J., Slivjak, J., Smith III E. F., Lee, J. C. and Esser K. M. (1994). Characterization of cAMP-dependent inhibition of LPS-induced TNFa production by rolipram, a specific phosphodiesterase IV (PDE IV) inhibitor. Int. J. Immunopharmacol., 16 (10), 805-816.

Model of eosinophilia in rats

The studies carried out using this experimental model are designed to evaluate the inhibitory action of the compounds of the invention on the afflux in inflammatory cells and in particular of eosinophils in the lumen of the tracheobronchal tree of rats. Eosinophils play a major role in the physiopathology of asthma in man by releasing into the pulmonary parenchyma pro-inflammatory mediators such as leukotrienes, specific proteins and

enzymes (ECP, EPO, MBP) and cytokines. The massive recruitment of this cell type in the aerial pathways of asthmatics leads to a gradual degradation of the pulmonary tissue, explaining the bronchial hyperreactivity, the chronic aspect of the condition and the exacerbations in the absence of treatment. This model uses Brown Norway rats, which have the particular feature of producing, like atopic patients, levels of immunoglobulin E (IgE) in reponse to sensitization with an antigen. The protocol used involves two sensitizations with ovalbumin with an interval of fourteen days, followed by a challenge seven days later with an ovalbumin aerosol. 48 hours after the antigenic challenge, the animals undergo bronchoalveolar lavage under anaesthesia in order to collect the infiltrate of inflammatory cells in the lungs. These cells are then counted and differentiated according to the morphological criteria. The products of the invention are adminstered orally, 1 hour before the antigenic challenge. Most of the preferred compounds of the present invention tested in this model also demonstrated excellent activity.

References

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Model of neutrophilia in mice

The studies carried out using this experimental protocol are designed to evaluate the modulatory action of the compounds of the invention on the afflux of pro-inflammatory cells (early phase) in the lumen of the tracheobronchal tree of mice. This cell afflux follows a stimulation mimicking a bacterial infection (bacterial lipopolysaccharide or LPS). This inflammatory early stage is the result of a combination of events, the main ones being the synthesis and release of stimulatory factors (TNFαi) and chemotactic factors (IL-8ii), the increase in vascular permeability in the tracheobronchal microcirculation and the infiltration of polymorphonuclear neutrophils concomitant with the exudation of the plasma proteins into the pulmonary tissues.

This pathological process is found in chronic obstructive pulmonary disease, in which the neutrophils, in concert with the macrophages, play a key role in establishing the amplification of the recruitment of the neutrophils themselves, but also in the destructuring of the pulmonary tissues (decline in the pulmonary functions), the hypersecretion of tracheobronchial mucus (engorgement of the aerial pathways), the tissue inflammation (release of inflammatory mediators and free radicals) and the increase in the basal tonus of the pulmonary smooth muscle fibres (chronic difficulty in breathing). Some of the compounds of the examples showed activity in this model.

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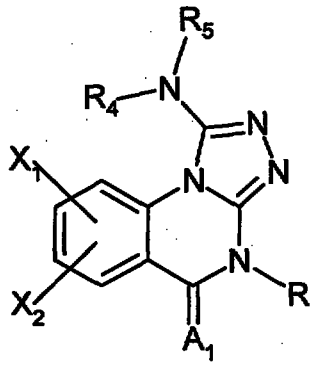
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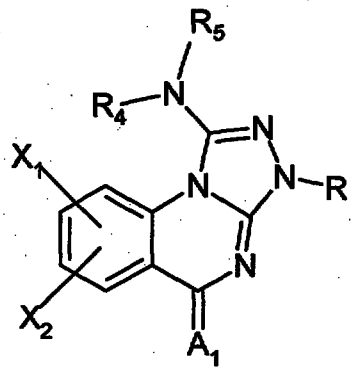
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Claims

1. Triazolo[4,3-a]quinazolin-5-ones and/or –5-thiones of formula I or II:



I

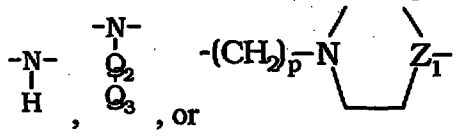


II

I and II being positional isomers of the group R on nitrogens 3 or 4, in which:

- A_1 is O or S;
- X_1 and X_2, which may be identical or different, represent:
  - hydrogen, hydroxyl, halogen, amino, nitro, mercapto, cyano, carboxyl,
  - lower alkyl, lower alkoxy or $-S(O)_mR_8$ in which m is 0, 1 or 2 and R_8 is a lower alkyl, which are optionally substituted with one or more halogen atoms,
  - $-CO-Q_1-Q_2-Q_3$ in which:

$-Q_1-$ is: a single valency bond, -O-,



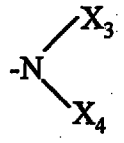
, in which p is an integer which can range from 0 to 3, and Z_1 is CH, N, O or S,

$-Q_2-$ is:

a) $-(CH_2)_q-$, q being equal to 0, 1, 2, 3, or 4, or

b) $-(CH_2-CH_2-O)_r-$, r being equal to 2, 3 or 4, and

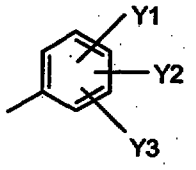
$-Q_3$ is: -H, -OH, lower alkoxy, -O-CO- X_3 $-NHX_3$ or

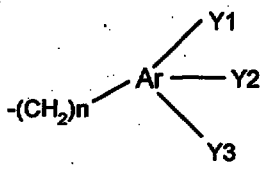


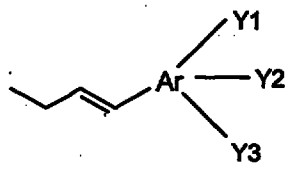
in which X_3 and X_4, which may be identical or different, represent a lower alkyl group, it being possible for X_3 and X_4 to be linked to form a ring, comprising one or more hetero atoms chosen from O, S and N,

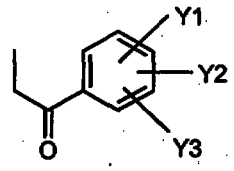
- -NH-R_1 in which R_1 represents a lower alkyl group, optionally substituted with one or more groups chosen from halogen, hydroxyl, cyano, lower alkoxy and -CO-Q_1-Q_2-Q_3, or
- -NR_2R_3 in which R_2 and R_3, which may be identical or different, represent a lower alkyl, optionally substituted with one or more hydroxyl, halogen, cyano, lower alkoxy or -CO-Q_1-Q_2-Q_3 groups, it being possible for R_2 and R_3 to be linked to form a ring, comprising one or more hetero atoms chosen from O, S and N and optionally bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy and -CO-Q_1-Q_2-Q_3;

- R represents:
  - lower alkyl, lower alkenyl, lower alkynyl, arylalkynyl, 2-, 3- or 4-pyridylalkyl optionally substituted with a lower alkyl, lower alkoxy,



,


,


or


hydroxyl, halogen or amino group,

in which:

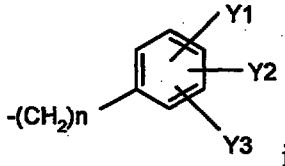
- n is an integer from 1 to 5,
- Ar is an aromatic ring comprising 5 or 6 atoms including from 0 to 3 hereto atoms chosen from O, S and N,
- Y1, Y2 and Y3, which may be identical or different, represent:
  - hydrogen, hydroxyl, mercapto, amino, nitro, halogen, NHR_1, NR_2R_3, -$(CH_2)_s$-CN, or -$(CH_2)_s$CO-Q_1-Q_2-Q_3 in which s is an integer from 0 to 6;
  - lower alkyl, lower alkoxy or -$S(O)_mR_8$ in which case m is 0, 1 or 2 and R_8 is a lower alkyl, it being possible for each to be optionally substituted with one or more halogen atoms; and

- R_4 and R_5, represent:

- lower alkyl when R4 and R5 are identical, aralkyl, cycloalkyl or cycloalkyl-alkyl, when R_4 and R_5 are different,
- lower alkyl, it being possible for R_4 and R_5 to be linked to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N and optionally substituted with a lower alkyl, a hydroxyl or a lower alkoxy or bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy, phenylalkyl and $CO\text{-}Q_1\text{-}Q_2\text{-}Q_3$, it also being possible for two of the atoms in the ring thus formed to form part of another ring chosen from phenyl and heteroaryl comprising from 4 to 8 atoms including 1 to 4 hetero atoms;

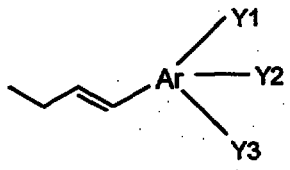
optionally the racemic forms thereof and the isomers thereof, as well as the pharmaceutically acceptable salts thereof.

2. Triazolo[4,3-a]quinazolin-5-ones and/or –5-thiones according to Claim 1, in which:
A_1 represents an oxygen atom;
X_1 represents a hydrogen atom and X_2 is a halogen, amino, lower alkyl, hydroxyl or $-NHR_1$ group, R_1 being as defined above,
R represents:
- a lower alkyl, lower alkenyl, arylalkynyl, 2-, 3- or 4-pyridylalkyl group optionally substituted on the pyridine nucleus with a lower alkyl, a halogen or a hydroxyl;



in which:

- n is an integer from 1 to 3,
- Y1, Y2 and Y3 each represent a hydrogen atom or a lower alkoxy group, more particularly methoxy,
- Y1 and Y2 each represent a hydrogen atom and Y3 represents a lower alkoxy group, an amino group, NHR_1, NR_2R_3, nitro, hydroxyl, a group $-(CH_2)_sCO\text{-}Q_1\text{-}Q_2\text{-}Q_3$, a group $(CH_2)_s\text{-}CN$ in which s, Q_1, Q_2, and Q_3 are as defined above, or a lower alkyl group optionally substituted with one or more halogen atoms, the position which is particularly preferred for the substituent Y3 being position 4, or
- Y1 represents a hydrogen atom and Y2 and Y3, which may be identical or different, represent a hydroxyl, halogen or lower alkoxy group, or



in which:

- Ar is as defined above;
- Y1, Y2 and Y3 each represent a hydrogen atom, or
- Y1 and Y2 each represent a hydrogen atom and Y3 is lower alkoxy or halogen;

R_4 and R_5 represent:

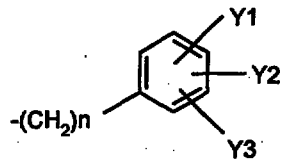
- lower alkyl when R4 and R5 are identical, aralkyl, cycloalkyl or cycloalkylalkyl when R_4 and R_5 are different,

lower alkyl, it being possible for R_4 and R_5 to be linked to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N and optionally substituted with a lower alkyl, a hydroxyl or a lower alkoxy or bridged with lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy, phenylalkyl and $CO\text{-}Q_1\text{-}Q_2\text{-}Q_3$, it being possible for two of the atoms of the ring thus formed also to form part of another ring chosen from phenyl and heteroaryl comprising from 4 to 8 atoms including 1 to 4 hetero atoms.

3. Triazolo[4,3-a]quinazolin-5-ones and/or –5-thiones according to Claim 1 or 2, in which:

X_1 represents a hydrogen atom,
X_2 represents a halogen, amino, lower alkyl, hydroxyl or $-NHR_1$ group;

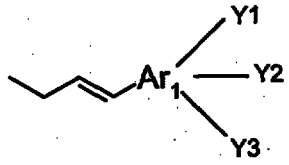
R represents:



in which:

- n is an integer from 1 to 3,
- Y1, Y2 and Y3 each represent a hydrogen atom or a lower alkoxy group, more particularly methoxy and in particular 3, 4, 5-trimethoxy,

- Y1 and Y2 each represent a hydrogen atom and Y3 represents a lower alkoxy, amino, NHR_1, NR_2R_3, nitro, or hydroxyl group, a lower alkyl group optionally substituted with one or more halogen atoms, a group $-(CH_2)_sCO-Q_1-Q_2-Q_3$ in which s is 0 or 1, Q_1 is O, -NH- or a valency bond, Q_2 is $-(CH_2)_q-$, q being equal to 0, 1, 2, 3 or 4 and Q_3 is H, OH or $-NX_3X_4$ in which X_3 and X_4 are as defined above, a group $(CH_2)_s-CN$ in which s is 0 or 1, the position particularly preferred for the substituent Y3 being position 4, or
- Y1 represents a hydrogen atom and Y2 and Y3, which may be identical or different, represent a hydroxyl, halogen or lower alkoxy group; or



in which:

- Ar_1 is an aromatic ring comprising 6 atoms which can include a nitrogen atom in position 2, 3 or 4 and preferably in position 3;
- Y1, Y2 and Y3 each represent a hydrogen atom, or
- Y1 and Y2 each represent a hydrogen atom and Y3 is a lower alkoxy group or a halogen group when Ar_1 does not comprise a nitrogen atom; and

R_4 and R_5, represent:

- lower alkyl, when R4 and R5 are identical, aralkyl, cycloalkyl or cycloalkylalkyl when R_4 and R_5 are different,
- lower alkyl, it being possible for R_4 and R_5 to be linked to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N and optionally substituted with a lower alkyl, a hydroxyl or a lower alkoxy or bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy, phenylalkyl and $CO-Q_1-Q_2-Q_3$, it being possible for two of the atoms of the ring thus formed also to form part of another ring chosen from phenyl and heteroaryl comprising from 4 to 8 atoms including 1 to 4 hetero atoms.

4. Triazolo[4,3-a]quinazolin-5-ones and/or –5-thiones according to any one of Claims 1 to 3, in which:

- the halogen group is chosen from F, Cl, Br and I,

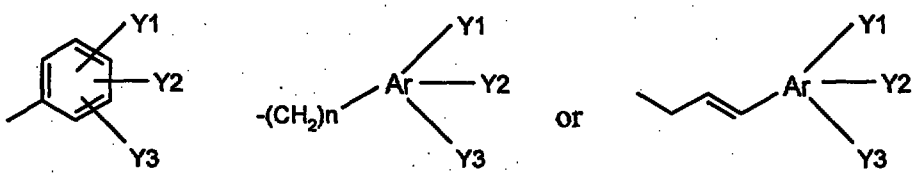
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- the lower alkyl group is a linear or branched group containing from 1 to 6 carbon atoms,
- the lower alkoxy group is a linear or branched group containing from 1 to 5 carbon atoms,
- the lower alkylthio group is a linear or branched group containing from 1 to 5 carbon atoms,
- the lower alkenyl group contains from 3 to 6 carbon atoms,
- the lower alkynyl group contains from 3 to 6 carbon atoms,
- the 2-, 3- or 4-pyridylalkyl group comprises an alkyl containing 1 to 5 carbon atoms,
- the aryl group contains from 5 to 8 carbon atoms,
- the aralkyl group comprises an alkyl containing from 1 to 6 carbon atoms,
- the cycloalkyl group contains from 3 to 8 carbon atoms,
- the cycloalkylalkyl group comprises an alkyl containing from 1 to 6 carbon atoms,
- the lower alkyl, lower alkoxy or lower alkylthio groups substituted with one or more halogen atoms are chosen from the groups $-(CH_2)_p-CF_3$, $-O-(CH_2)_p-CF_3$ and $-S-(CH_2)_p-CF_3$, in which p is an integer from 0 to 3.

5. Triazolo[4,3-a]quinazolin-5-ones and/or –5-thiones according to Claim 1, in which:

- A_1 is O or S;
- X_1 and X_2, which may be identical or different, represent:
  - hydrogen, hydroxyl, halogen, amino, nitro, mercapto, cyano, carboxyl,
  - lower alkyl, lower alkoxy or $-S(O)_mR_8$ in which m is 0, 1 or 2 and R_8 is a lower alkyl, which are optionally substituted with one or more halogen atoms;

- R represents:



in which:

- n is an integer from 1 to 5,
- Ar is an aromatic ring comprising 5 or 6 atoms including from 0 to 3 hetero atoms chosen from O, S and N

- Y1, Y2 and Y3, which may be identical or different, represent:

  - hydrogen, hydroxyl, mercapto, amino, NHR_1, NR_2R_3, nitro, halogen, $-(CH_2)_sCO-Q_1-Q_2-Q_3$, or $-(CH_2)_s-CN$ in which s is an integer from 0 to 6;
  - lower alkyl, lower alkoxy or $-S(O)_mR_8$ in which m is 0, 1 or 2 and R_8 is a lower alkyl, it being possible for each to be optionally substituted with one or more halogen atoms;

- R_4 and R_5, which may be identical or different, represent:

lower alkyl, it being possible for R_4 and R_5 to be linked to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N and optionally bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy, phenylalkyl and $CO-Q_1-Q_2-Q_3$.

6. Triazolo[4,3-a]quinazolin-5-ones and/or –5-thiones according to Claim 5, chosen from the group comprising:

7-Bromo-1-dimethylamino-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(3,4-Dimethoxybenzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)benzonitrile

7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Methyl-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)benzonitrile

1-Azepan-1-yl-7-methyl-4-pyrid-3-ylmethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)benzonitrile

Dimethylamino-methyl-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)benzonitrile

1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7. Triazolo[4,3-a]quinazolin-5-ones and/or –5-thiones according to Claim 1, 2, 3 or 4, chosen from the group comprising:

1-(Azepan-1-yl)-7-chloro-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-pyrid-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-3-pyrid-3-ylmethyl-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-allyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(4-methylbenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(2-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

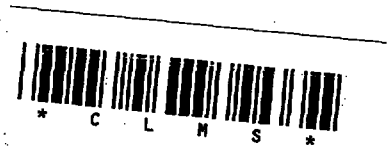
1-(Azepan-1-yl)-7-chloro-4-(4-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(4-bromobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(4-fluorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(4-(trifluoromethyl)benzyl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(4-cyanobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one



1-(Azepan-1-yl)-7-chloro-4-(2-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(4-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3,4-dichlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(2-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(4-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(2-phenylethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-[2-(4-methoxyphenyl)ethyl]-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3-phenylpropyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-chloro-4-(2-oxo-2-phenylethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-[2-(4-methoxyphenyl)-2-oxoethyl]-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-[2-(4-chlorophenyl)-2-oxoethyl]-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

5-[(1-(Azepan-1-yl)-7-chloro-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl)acetyl]-2-methoxybenzoic acid methyl ester

7-Chloro-4-pyrid-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-bromo-4-(4-chlorophenylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-(4-fluorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-bromo-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-[3-(4-chlorophenyl)allyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-[3-(4-methoxyphenyl)allyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-methylbenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-chlorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-fluorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

3-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

Methyl 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzoate

7-Bromo-4-(4-nitrobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-methoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Phenyl 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)acetate

7-Bromo-4-(4-hydroxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3,4-dimethoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzo[1,3]dioxol-5-ylmethyl-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-Bromo-4-(3,5-dimethoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-pyrrolidin-1-yl-4-(3,4,5-trimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]acetic acid

1-(Pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-[(E)-3-(4-chlorophenyl)allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-Bromo-4-[3-(4-methoxyphenyl)allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-Bromo-4-(3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-((E)-3-pyrid-4-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(1H-imidazol-4-ylmethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-Bromo-4-(3,5-dimethylisoxazol-4-ylmethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-Bromo-4-cyclopentylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-butyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

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7-Bromo-1-pyrrolidin-1-yl-4-(2,2,2-trifluoroethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(2-hydroxyethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(2-diethylaminoethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-prop-2-ynyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(2-phenoxyethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(2-phenylsulphenylethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

Methyl (7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl)-phenylacetate

4-(7-Bromo-5-oxo-1-piperid-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

7-Bromo-4-(3,4-dimethoxybenzyl)-1-piperid-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Piperid-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3-pyrid-3-ylallyl)-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(4-methylbenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

7-Bromo-1-dimethylamino-4-(4-hydroxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Methyl 4-(7-bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)benzoate

[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]acetic acid

[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]acetonitrile

7-Bromo-1-dimethylamino-4-(pyrid-3-ylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-prop-2-ynyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(3-phenylprop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Methyl 4-(7-bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl)-phenylacetate

1-Azepan-1-yl-7-methyl-4-pyrid-3-ylmethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-methyl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

4-(3,4-Dimethoxybenzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Methyl 4-(7-methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)benzoate

[4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]acetic acid

7-Methyl-4-pyrid-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Methyl-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

[4-(7-Methyl-5-oxo-1-thiomorpholin-4-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)phenyl]acetic acid

7-Methyl-4-(3-pyrid-3-ylallyl)-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

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4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

[4-(Dimethylaminomethyl-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]-acetic acid

1-Dimethylamino-7-methyl-4-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Dimethylamino-7-methyl-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-8-methyl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

(4-Cyanobenzyl)dimethylaminooxo-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile

7-Hydroxy-4-((E)-3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

3-Allyl-1-azepan-1-yl-7-chloro-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-benzyl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-chloro-3-(4-methylbenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(2-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(3-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(4-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(4-bromobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(4-fluorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(4-(trifluoromethyl)benzyl)-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(4-cyanobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(2-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(3-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(4-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(3,4-dichlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(3,4-dimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(2-pyridylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(3-pyridylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(2-phenylethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-[2-(4-methoxyphenyl)ethyl]-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(3-phenylpropyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-chloro-3-(2-oxo-2-phenylethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-[2-(4-methoxyphenyl)-2-oxoethyl]-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-[2-(4-chlorophenyl)-2-oxoethyl]-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

Methyl 5-[(1-(azepan-1-yl)-7-chloro-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl)-acetyl]-2-methoxybenzoate

1-(Azepan-1-yl)-7-bromo-3-(4-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one



1-(Azepan-1-yl)-7-bromo-3-(4-fluorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(1-(Azepan-1-yl)-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)-benzonitrile

1-(Azepan-1-yl)-7-bromo-3-(3,4-dimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

[4-(7-Bromo-5-oxo-1-perhydroazepin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl-methyl)phenyl]acetic acid

1-(Azepan-1-yl)-7-bromo-3-(pyrid-3-ylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-3-((E)-3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-3-((E)-3-phenylallyl)-1-piperid-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-3-(4-chlorobenzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-3-(4-fluorobenzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-5-oxo-1-(pyrrolidin-1-yl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)-benzonitrile

Methyl 4-(7-bromo-5-oxo-1-(pyrrolidin-1-yl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl-methyl)benzoate

7-Bromo-3-(4-methoxybenzyl)-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Phenyl 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl-methyl)acetate

7-Bromo-1-dimethylamino-3-(4-hydroxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

3-(Benzo[1,3]dioxol-5-ylmethyl)-7-bromo-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-Bromo-3-(3,5-dimethoxybenzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-(pyrrolidin-1-yl)-3-(3,4,5-trimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one



7-Bromo-3-(1H-imidazol-4-ylmethyl)-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-Bromo-3-(n-butyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Methyl (7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl)-phenylacetate

7-Bromo-1-dimethylamino-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Methyl 4-(7-bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl)-phenylacetate

1-(Azepan-1-yl)-7-methyl-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Methyl-3-(3-phenylallyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-3,8-dimethyl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-8-methyl-3-((E)-3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Hydroxy-3-(3-phenylallyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1,8-Bis(azepan-1-yl)-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-4-benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(butylmethylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Chloro-1-dibutylamino-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Chloro-4-methyl-1-(piperid-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

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7-Chloro-4-methyl-1-(4-methylpiperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Chloro-4-methyl-1-(1,8,8-trimethyl-3-azabicyclo[3.2.1]oct-3-yl)-4H-[1,2,4]triazolo-[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-phenyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-chloro-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-chloro-1-(piperid-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-8-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-4-benzyl-8-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-bromo-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(piperid-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-dimethylamino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-morpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(4-methylpiperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(4-phenylpiperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-1-(4-benzylpiperazin-1-yl)-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(3,6-dihydro-2H-pyrid-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(2,5-dihydropyrrol-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(3-hydroxypyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-methylamino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-iodo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-4-benzyl-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-1-dimethylamino-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-methyl-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-4-benzyl-8-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-4-benzyl-7-methoxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-methoxy-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile

1-Azepan-1-yl-4-benzyl-7-nitro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-6-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one



1-(Azepan-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-ethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Chloro-4-methyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Chloro-4-methyl-1-(morpholin-4-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azocan-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Chloro-1-(3,4-dihydro-2H-quinolin-1-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Chloro-1-(3,4-dihydro-1H-isoquinolin-2-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(4-Benzylpiperid-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Chloro-4-methyl-1-(1,3,3-trimethyl-6-azabicyclo[3,2,1]oct-6-yl)-4H-[1,2,4]triazolo-[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-fluoro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-iodo-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-methoxy-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(ethylmethylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-1-diethylamino-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-pyrrol-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(4-Aminobenzyl)-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-hydroxy-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

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4-(7-Hydroxy-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

N-(4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazolin-7-yl)-acetamide

N-[5-Oxo-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazolin-7-yl]acetamide

7-Amino-4-((E)-3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-1-azepan-1-yl-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-4-benzyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Amino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

7-Amino-4-((E)-3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(Aminodimethylaminooxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

7-Amino-1-dimethylamino-4-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)benzonitrile

4-Benzyl-8-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-ethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-isopropylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

N-(4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazolin-7-yl)-methanesulphonamide

4-Benzyl-7-dimethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

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4-Benzyl-1-dimethylamino-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile

4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazoline-7-carboxylic acid

Methyl [4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)phenyl]acetate

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-methylacetamide

2-[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]acetamide

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N,N-dimethylacetamide

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-hydroxyacetamide

4-(1-Dimethylamino-7-methyl-5-thioxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

4-(7-Bromo-1-dimethylamino-5-thioxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

4-Benzyl-7-(N,N-dimethylsulphonylamino)-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a]-quinazolin-5-one

8. Triazolo[4,3-a]quinazolin-5-ones and/or –5-thiones according to any one of Claims 1 to 4, chosen from the group comprising:

1-(Azepan-1-yl)-7-chloro-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(4-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(4-fluorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-bromo-4-(4-chlorophenylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-methylbenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-chlorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-fluorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

Methyl 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)benzoate

7-Bromo-4-(4-nitrobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-methoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Phenyl 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)acetate

7-Bromo-4-(4-hydroxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one



7-Bromo-4-(3,4-dimethoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-[(E)-3-(4-chlorophenyl)allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-Bromo-4-[3-(4-methoxyphenyl)allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-Bromo-4-(3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-((E)-3-pyrid-4-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3,4-dimethoxybenzyl)-1-piperid-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Piperid-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(4-methylbenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

7-Bromo-1-dimethylamino-4-(4-hydroxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Methyl 4-(bromo-dimethylamino-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoate

[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]acetonitrile

7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(3-phenylprop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-methyl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(3,4-Dimethoxybenzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

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[4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]acetic acid

7-Methyl-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

[4-(Dimethylaminomethyloxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid

1-Dimethylamino-7-methyl-4-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

[4-(7-Bromo-5-oxo-1-perhydroazepin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl-methyl)phenyl]acetic acid

4-Benzyl-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(2,5-dihydropyrrol-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-iodo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-4-benzyl-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(4-Aminobenzyl)-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-4-((E)-3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-1-azepan-1-yl-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-4-((E)-3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-1-dimethylamino-4-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

4-Benzyl-8-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-ethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-isopropylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Methyl [4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)phenyl]acetate

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-methylacetamide

2-[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]acetamide

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N,N-dimethylacetamide

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-hydroxyacetamide

1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

9. Triazolo[4,3-a]quinazolin-5-ones and/or –5-thiones according to any one of Claims 1 to 4, chosen from the group comprising:

Bromo-dimethylamino-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-methylbenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-chlorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3,4-dimethoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Piperid-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

Methyl 4-(Bromodimethylaminooxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoate

7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(3-phenylprop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-methyl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(3,4-Dimethoxybenzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Methyl-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-4-((E)-3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-4-((E)-3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)benzonitrile

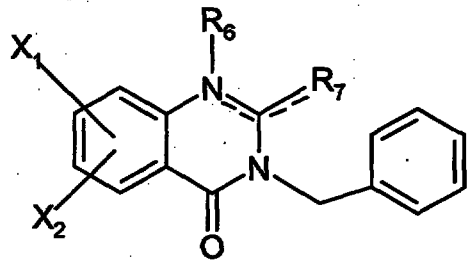
Methyl [4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)phenyl]acetate

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-methylacetamide

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N,N-dimethylacetamide

1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

10. Intermediate compounds of general formula III:



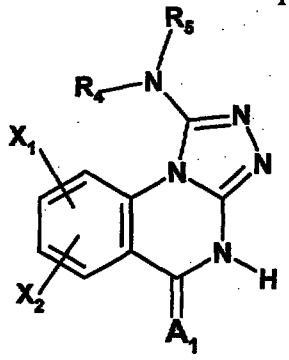
III

in which:

- X_1, X_2 and A_1 are as defined in Claim 1;
- the dashed lines represent optional double bonds;
- R_6 is hydrogen; and
- R_7 is S or hydrazino;

it being possible for R_7 to be linked to the nitrogen at R_6 to form a ring, particularly a triazole, optionally substituted with a lower thioalkyl, mercapto or halogen group.

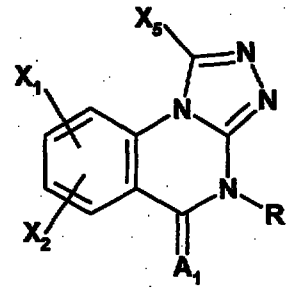
11. Intermediate compounds of general formula IV:



IV

in which X_1, X_2, A_1, R_4 and R_5 are as defined in Claim 1.

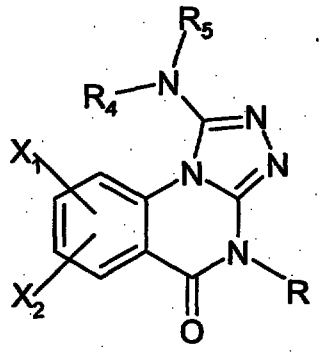
12. Intermediate compounds of general formula V:



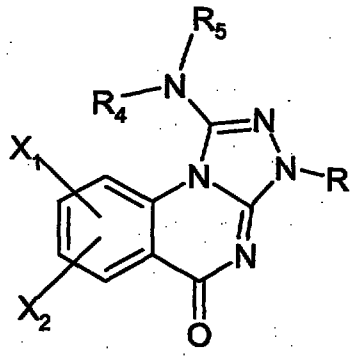
(V)

in which X_1, X_2, A_1 and R are as defined in Claim 1 and X_5 is a halogen, particularly F, Br or Cl, $-OCOX_7$, $-OSO_2X_7$ or $-SO_2X_7$ group in which X_7 is a lower alkyl or aryl group.

13. Process for manufacturing the compounds of general formulae I and II:



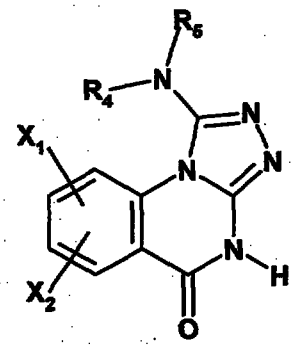
I



II

in which X_1, X_2, R, R_4 and R_5 are as defined in Claim 1,

the said process being characterized in that it comprises the reaction of a compound of general formula IV:



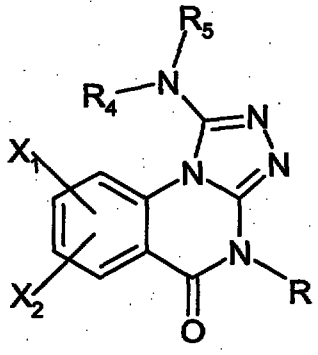
IV

in which X_1, X_2, R_4 and R_5 are as defined in Claim 1,
with a compound of general formula

R-X'

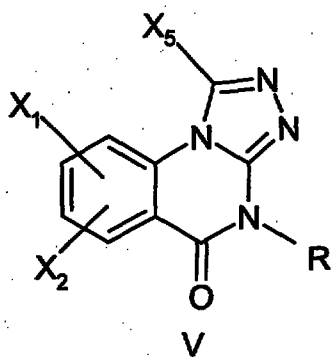
in which R is as defined above and X' is a halogen, particularly F, Br or Cl, $-OCOX_7$ or $-OSO_2X_7$ group in which X_7 is a lower alkyl or aryl group;
to give a mixture of the compounds of general formulae I and II, which are then optionally separated.

14. Process for manufacturing the compounds of general formula I:



I

in which X_1, X_2, R, R_4 and R_5 are as defined in Claim 1,
the said process being characterized in that it comprises the reaction of a compound of general formula V:



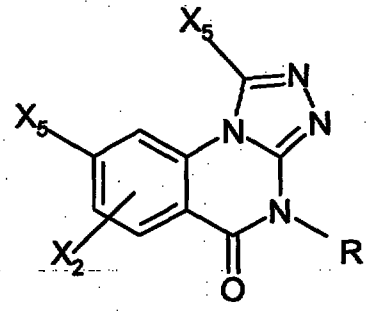
V

in which X_1, X_2 and R are as defined in Claim 1 and X_5 is a halogen, particularly F, Br or Cl, $-OCOX_7$, $-OSO_2X_7$ or $-SO_2X_7$ group in which X_7 is a lower alkyl or aryl group;
with a compound of general formula:

$$HNR_4R_5$$

in which R_4 and R_5 are as defined in Claim 1,
to give a compound of general formula I.

15. Process according to Claim 14, characterized in that when X_1 is $-NR_2R_3$ and $-NR_2R_3$ and $-NR_4R_5$ are identical, the compounds of formula I are obtained by reacting a compound of general formula VI:

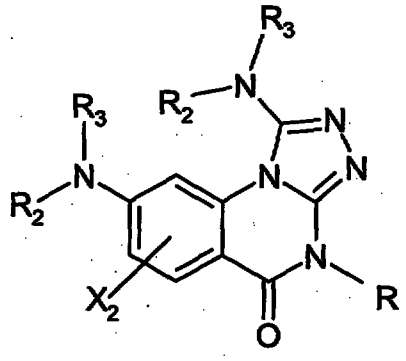


VI

in which X_2, X_5 and R are as defined in Claim 20,
with a compound of general formula:

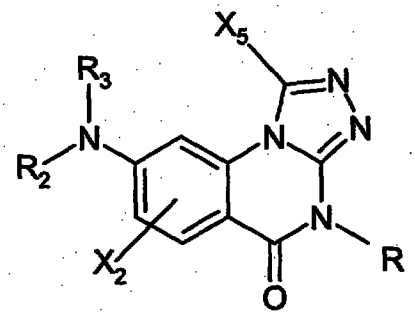
$$HNR_2R_3$$

in which R_2 and R_3 are as defined in Claim 20,
to give a compound of general formula (I):



I

16. Process according to Claim 14, characterized in that when X_1 is $-NR_2R_3$ and $-NR_2R_3$ and $-NR_4R_5$ are different, the compounds of formula I are obtained by reacting a compound of general formula VII:

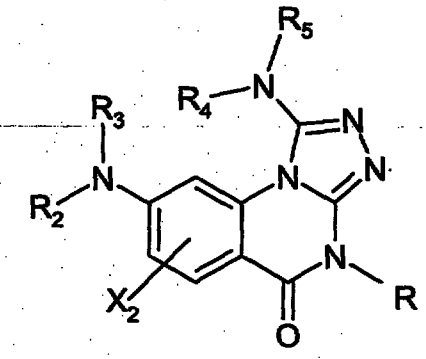


VII

in which X_2, X_5, R, R_2 and R_3 are as defined in Claim 20,
with a compound of general formula:

HNR_4R_5

in which R_4 and R_5 are as defined in Claim 20,
to give a compound of general formula (I):



I

17. Pharmaceutical composition comprising a compound according to any one of Claims 1 to 9 and a pharmaceutically acceptable excipient .

18. Use of a compound according to any one of Claims 1 to 9 for the preparation of a medicinal product intended for treating a condition or complaint involving a treatment by inhibition of phosphodiesterases, and more particularly of PDE4.

19. Use according to Claim 18, characterized in that the condition is asthma.

20. Use according to Claim 18, characterized in that the condition is chronic bronchitis or acute pulmonary attack.

21. Use according to Claim 18, characterized in that the condition is atopic dermatitis.

22. Use according to Claim 18, characterized in that the condition is pulmonary hypertension.

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23. Use according to Claim 18, characterized in that the condition is cardiac or pulmonary insufficiency.

24. Use according to Claim 18, characterized in that the condition is psoriasis.

25. Use according to Claim 18, characterized in that the condition is an inflammatory condition of the digestive system such as haemorrhagic rectocolitis or Crohn's disease.

26. Use according to Claim 18, characterized in that the condition is diabetes or a condition associated with a high level of TNF-α, such as acute respiratory distress syndrome or acute pancreatitis.

27. Use according to Claim 18, characterized in that the condition is benign hypertrophy of the prostate.

28. Use according to Claim 18, characterized in that the condition is chosen from rheumatoid arthritis and multiple sclerosis.

29. Use according to Claim 18, characterized in that the condition is chosen from depression, ischaemia-mediated neuronal attack and partial cerebral ischaemia.

30. Use according to Claim 18, characterized in that the condition is cancer, more particularly malignant tumours or chronic lymphoid leukaemia.

31. Use of a compound according to any one of Claims 1 to 9 to attenuate the development of tolerance or morphine-dependency phenomena.

32. Use of a compound according to any one of Claims 1 to 9 to reduce behavioural memory losses.

33. Use of a compound according to any one of Claims 1 to 9 to prevent premature labour.

34. Use according to Claim 18, characterized in that the condition is septicaemia or multiple organ failure syndrome.