

IMIDAZOLONE DERIVATIVES, PREPARATION METHOD THEREOF
AND BIOLOGICAL USE OF SAME

The subject of the invention is imidazolone
5 derivatives. The invention also relates to a method for the
preparation thereof.

It also relates to the biological uses of these
derivatives as kinase inhibitors, in particular for the
treatment of neurodegenerative diseases (especially
10 Alzheimer's disease, Pick's disease and trisomy 21).

The vast majority of human pathological conditions
involve phosphorylation abnormalities, often associated with
abnormalities in regulation of certain protein kinases.

The search for effective inhibitors of these kinases
15 has thus been very active over the past few years.

Using their long experience concerning kinases, CDKs,
GSK-3 and CK1 as a basis for support, the inventors have
focused on the production of inhibitors selective for the
DYRK1A kinase (Dual-specificity Tyrosine-phosphorylation-
20 Regulated Kinase 1 A).

It is an enzyme which autophosphorylates on its
Tyrosine 321 (thereby resulting in its activation) and which
phosphorylates Serine and Threonine residues.

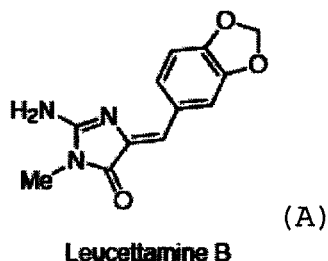
The DYRK1A protein kinase gene is located in a quite
25 specific region of chromosome 21, the "Down's syndrome
critical region", which covers about 20 genes responsible for
the trisomic phenotype. Many arguments support the hypothesis
that even a modest (X 1.5) overexpression of DYRK1A makes an
essential contribution to the abnormal development of the
30 brain observed during trisomy 21. Moreover, DYRK1A also
appears to be highly involved in Alzheimer's disease (which
appears in individuals suffering from trisomy 21
systematically and early after the age of about 40) (Kimura R,

et al., 2006. The DYRK1A gene, encoded in chromosome 21 Down syndrome critical region, bridges between beta-amyloid production and tau phosphorylation in Alzheimer disease. Hum Mol Genet. 16, 15-23; Ferrer I, et al., 2005. Constitutive
5 DyRK1A is abnormally expressed in Alzheimer disease, Down syndrome, Pick disease, and related transgenic models. Neurobiol Dis. 20,392-400).

DYRK1A inhibitors have been sought by virtual screening *in silico* on a structural model of DYRK1A based on the
10 crystalline structure of GSK-3 (Kim et al., Bioorg.Med.Chem.Lett.,2006 Jul.15; 16 (14):3712-6). In this approach, out of the 182 compounds selected, only 11 molecules showed an inhibitory activity with an IC₅₀ ranging from 2.5 to 50 μ M.

15 The studies by the inventors in order to search for, optimize and characterize pharmacological inhibitors of the DYRK1A kinase have led them to discover that imidazolone derivatives corresponding to derivatives or analogs of leucettamine B constitute, in this respect, potent and
20 selective pharmacological inhibitors of the DYRK1A kinase. Hereinafter, the term "compounds" will also be used to denote these derivatives and analogs as a whole.

Leucettamine B is a marine alkaloid extracted from the sponge *Leucetta microraphis*, of formula A



Research development has led the inventors to set up synthesis pathways for obtaining a family of compounds having inhibitory properties of great interest with respect to

DYRK1A, with IC_{50} values of mostly less than 50 μM and even than 10 μM , or even 1 μM .

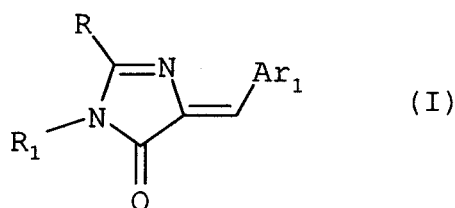
The invention therefore relates to the use, as medicaments, of imidazolone derivatives constituting
5 leucettamine B analogs and derivatives.

It also relates to a process for preparing these compounds.

The invention also relates to the compounds which correspond to novel imidazolone derivatives and to the uses
10 thereof as active ingredients of medicaments.

According to a first aspect, the invention thus relates to the use, for producing medicaments for the treatment of neurodegenerative diseases, of imidazolone derivatives corresponding to formula (I)

15



20 in which:

- R_1 represents H, a linear or branched, optionally substituted, C_1 to C_5 alkyl radical; an aryl group, or a 5- or 6-membered heterocyclic group, the aryl group and the heterocyclic group
25 optionally comprising one or more substituents, which may be identical or different, occupying any positions;
- Ar_1 represents an aryl group with optionally one or more substituents, it being possible for two adjacent substituents to form a 5- or 6-membered
30 ring, this ring being, where appropriate, substituted; or an aromatic heterocycle with optionally one or more substituents and/or

condensed with a 5- or 6-membered aromatic ring, the heteroatom being chosen from N, S and O;

- R represents R_2-S- , R_3-HN- , R_4COHN or Ar_2 , with
 - R_2 = a linear, branched or cyclic C_1-C_5 alkyl radical; a vinyl or vinyl(C_1-C_5)alkyl radical, a nitrile or nitrile(C_1-C_5)alkyl radical, or an aryl or benzyl radical, said radicals being optionally substituted on one or more carbon atoms with one or more groups, which may be identical or different, occupying any positions, it being possible for two adjacent substituents to form a 5- or 6-membered ring, this ring being, where appropriate, substituted,
 - R_3 = the meanings given above and may also represent H;
 - Ar_2 representing a substituted or unsubstituted aryl radical, it being possible for two adjacent substituents to form a 5 or 6-membered ring, this ring being optionally substituted.

The invention also relates to the racemic forms of the above derivatives and also the enantiomeric forms thereof taken individually.

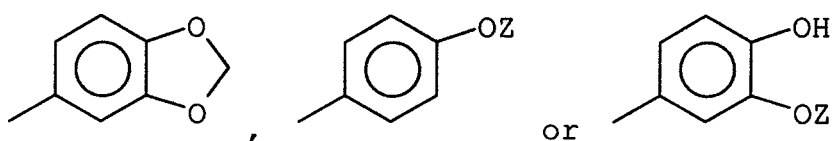
As illustrated by the examples, the above derivatives more especially constitute selective inhibitors of the DYRK1A kinase with IC_{50} values of less than 5 μM , or even less than 1 μM , particularly advantageous derivatives having IC_{50} values of less than 0.1 μM .

In formula (I) above, "aryl" represents phenyl or naphthyl and "heterocycle" represents a 5- or 6-membered ring with N, O and/or S as heteroatom(s). The substituents of R_1 , Ar_1 , Ar_2 and R are chosen from: OH, OZ, COH, COZ, COOH, COOZ, NH_2 , $NHalk.$, $N(alk.)_2$, $NHCOOH$, $NHCOOZ$, Z representing a linear or branched C_1-C_5 alkyl, aryl, benzyl, substituted benzyl or

aryl, or benzodioxolyl radical, one or more halogens and/or a CCl_3 group, and alk. representing a $\text{C}_1\text{-C}_3$ alkyl radical.

The invention relates more especially, for use as medicaments, to imidazalone derivatives having an IC_{50} of less than 5 μM and corresponding to formula I above in which:

- R_1 represents a $\text{C}_1\text{-C}_3$ alkyl radical or a hydrogen atom, and/or an aryl radical,
- Ar_1 is chosen from



- R represents
 - an $\text{R}_2\text{-S-}$ group, R_2 then being chosen from radicals of $\text{T}_1\text{-(CH}_2)_n$ type, with $n = 0, 1, 2$ or 3 and T_1 representing one of the following radicals: methyl, vinyl, alkyl, alkynyl, nitrile, cycloalkyl, which may be C_3 or C_4 , Z-O , Z-CO , with $\text{Z} = \text{C}_1\text{-C}_3$ alkyl, or hal, hal representing F, Cl, Br or I or a CCl_3 group,

or

- an $\text{R}_3\text{-NH-}$ group, R_3 then being chosen from radicals of $\text{T}_2\text{-(CH}_2)_n$ type, with $n = 0, 1$ or 2 , and T_2 representing one of the following radicals: methyl, vinyl, ZO , ZO-CONH- , -CH-(OZ)_2 , ZCO , with $\text{Z} = \text{H}$ or linear or branched $\text{C}_1\text{-C}_4$ alkyl, NH_2 , C_3 cycloalkyl, aryl, or substituted aryl, or $\text{R}_2 = \text{H}$,

or

- an $\text{R}_4\text{-CONH-}$ group, R_4 then being a branched $\text{C}_3\text{-C}_5$ alkyl radical,

or

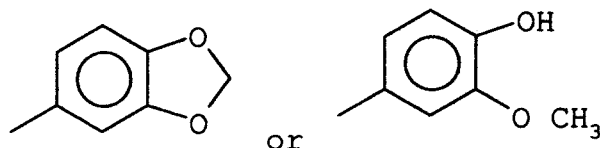
- $\text{R} = \text{Ar}_2$, Ar_2 being chosen from a phenyl, substituted phenyl or benzodioxolyl radical.

30

Preferably, the invention relates, for use as

medicaments, to imidazolone derivatives having an IC_{50} of less than 1 μM and corresponding to formula I in which:

- R_1 represents H or CH_3
- Ar_1 represents the radical



- R_2 represents

- an R_2-S- group, R_2 then being chosen from radicals of $T_1-(CH_2)_n$ type, with T_1 = a methyl, alkynyl, nitrile, hal, CH_3O , cyclopropyl or cyclobutyl radical, $n = 0, 1, 2$ or 3, "hal" representing a halogen atom or a CCl_3 group,

or

- an R_3-HN- group, R_3 then being chosen from radicals of $T_2-(CH_2)_n$ type, with T_2 = C_3 alkyl, OH, cyclopropyl, phenyl, phenyl substituted with OH, OCH_3 , $COOH$ and OH, CH_2OH , $C(CH_3, OH)$, CH_2-CH_2OH , CH_2-COOH or benzodioxolyl, or $R_3 = H$, $n = 0, 1$ or 2,

or

- an Ar_2 group chosen from a para-hydroxyphenyl or benzodioxolyl group.

In one preferred group of imidazolone derivatives of formula (I),

- R represents R^2S , R^3HN , or Ar^2 ;
- R^1 represents H or a linear or branched C_1-C_5 alkyl radical;
- R^2 represents H or a linear or branched C_1-C_5 alkyl radical, where appropriate substituted with one or more

OH, C₁-C₅ alkoxy, (CH₂)_n-OH or (CH₂)_n-COOH radicals; or represents a cyclic radical, where appropriate of the -(CH₂)_n- cycloalkyl type, the cycloalkyl radical having 3 to 5 members and n=1-5, the cyclic radical being, where
 5 appropriate, substituted with a C₁-C₅ alkyl; or represents a (C₁-C₅)alkylenenitrile; (C₁-C₅)alkylenevinyl; or C₁-C₅ alkynyl radical;

- 10 • R³ represents a linear or branched C₁-C₅ alkyl radical, where appropriate substituted with one or more C₁-C₅ alkoxy, OH, or COOH radicals; or represents a cyclic radical, where appropriate of the -(CH₂)_n- cycloalkyl type; or represents a phenyl radical, where appropriate substituted with one or more -OH, (CH₂)_n-OH; alkoxy or
 15 COOH; or a benzodioxolyl radical; or represents a cyclic radical, where appropriate of the -(CH₂)_n-cycloalkyl type, the cycloalkyl radical having 3 to 5 members, and n=1-5; or NH₂;

- 20 • Ar¹ represents a benzodioxolyl radical;
- Ar² represents a benzodioxolyl or phenyl radical, the latter being, where appropriate, substituted with one or more -OH or alkoxy.

25 In another preferred group of imidazolone derivatives of formula (I),

- R represents R²S, R³HN, or Ar²;
- R¹ represents H or a linear or branched C₁-C₅ alkyl radical;
- 30 • R² represents a linear or branched C₁-C₅ alkyl radical, where appropriate substituted with one or more OH, C₁-C₅

alkoxy or $(\text{CH}_2)_n\text{-OH}$ radicals; or represents a cyclic radical, where appropriate of the $-(\text{CH}_2)_n\text{-cycloalkyl}$ type, the cycloalkyl radical having 3 to 5 members, and $n=1-5$; or represents a $(\text{C}_1\text{-C}_5)\text{alkylenenitrile}$ radical or a
 5 $(\text{C}_1\text{-C}_5)\text{alkylenevinyl}$ radical;

- R^3 represents a phenyl radical, where appropriate substituted with one or more $-\text{OH}$, $(\text{CH}_2)_n\text{-OH}$; alkoxy; or a benzodioxolyl radical; or represents a cyclic radical,
 10 where appropriate of the $-(\text{CH}_2)_n\text{-cycloalkyl}$ type, the cycloalkyl radical having 3 to 5 members, and $n=1-5$; or NH_2 ;
- Ar^1 represents a benzodioxolyl radical;
- 15 • Ar^2 represents a benzodioxolyl or phenyl radical, the latter being, where appropriate, substituted with one or more $-\text{OH}$.

Particularly advantageously, the imidazolone
 20 derivatives used according to the invention are chosen from the following compounds in which, in formula (I),

$\text{R} = \text{R}_2\text{S}$

- 25 $\text{R}_2 = \text{CH}_2\text{C}\equiv\text{CH}$; $\text{R}_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$
- $\text{R}_2 = \text{CH}_2\text{C}\equiv\text{N}$; $\text{R}_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$
- $\text{R}_2 = \text{CH}_2\text{CH}_2\text{Cl}$; $\text{R}_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$
- $\text{R}_2 = \text{CH}_3$; $\text{R}_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$
- $\text{R}_2 = \text{CH}_2\text{CH}_3$; $\text{R}_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$
- 30 $\text{R}_2 = \text{CH}_2\text{CH}_2\text{CH}_3$; $\text{R}_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$
- $\text{R}_2 = \text{CH}(\text{CH}_3)_2$; $\text{R}_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$
- $\text{R}_2 = \text{CH}_2\text{C}\equiv\text{N}$; $\text{R}_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_2 = \text{CH}_2(\text{CH}_2)_2\text{CH}_3$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_2 = \text{CH}_2\text{CH}_2\text{OCH}_3$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_2 = \text{CH}_2\text{T}_1$ with $\text{T}_1 = \text{cyclopropyl}$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

5 $R_2 = \text{CH}_2\text{T}_1$ with $\text{T}_1 = \text{cyclobutyl}$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$\text{R} = \text{R}_3\text{NH}$

10 $R_3 = \text{CH}_2\text{CH}_3$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = \text{CH}_2\text{CH}_2\text{OH}$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = \text{CH}_2\text{T}_1$ with $\text{T}_1 = \text{cyclopropyl}$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = \text{CH}_2\text{CH}_3$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

15 $R_3 = o\text{-HO-C}_6\text{H}_4$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = \text{C}_6\text{H}_5$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = p\text{-HO-C}_6\text{H}_4$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = p\text{-HO-m-HO}_2\text{C-C}_6\text{H}_3$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = p\text{-m-OCH}_2\text{O-C}_6\text{H}_3$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

20 $R_3 = p\text{-CH}_3\text{-C}_6\text{H}_4$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = \text{HOCH}_2\text{CHOHCH}_2$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = p\text{-m-OCH}_2\text{CH}_2\text{O-C}_6\text{H}_3$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = p\text{-CH}_3\text{O-C}_6\text{H}_4$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = m\text{-HOCH}_2\text{-C}_6\text{H}_4$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

25 $R_3 = m\text{-HOCH(CH}_3\text{)-C}_6\text{H}_4$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = p\text{-HOCH}_2\text{CH}_2\text{-C}_6\text{H}_4$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = p\text{-HO}_2\text{CCH}_2\text{O-C}_6\text{H}_4$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = \text{CH}_2\text{CH}_2\text{CH}_3$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = \text{CH}_2\text{T}_1$ with $\text{T}_1 = \text{cyclopropyl}$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-}$

30 benzodioxol-5-yl

$R_3 = \text{C}_6\text{H}_5$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = p\text{-HO-C}_6\text{H}_4$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = \text{H}$; $R_1 = \text{H}$; $\text{Ar}_1 = p\text{-HO-m-MeO-C}_6\text{H}_3$

R = Ar₂

Ar₂ = p-HO-C₆H₄; R₁ = Me; Ar₁ = 1,3-benzodioxol-5-yl

5 Ar₂ = p-m-OCH₂O-C₆H₃; R₁ = Me; Ar₁ = 1,3-benzodioxol-5-yl

According to another aspect, the invention relates to novel imidazolone derivatives.

In fact, with the exclusion of the derivatives mentioned hereinafter, the derivatives of formula I above are
10 new derivatives and, in this respect, are part of the field of the invention.

The invention thus relates, as novel products, to imidazolone derivatives, characterized in that they correspond to formula I of claim 1, with the exclusion of the derivatives in which:

15 R = R₂S and

- Ar₁ = 1,3-benzodioxol-5-yl; R₁ = CH₃ and R₂ = CH₃, CH₃CH₂, CH₂ = CH-CH₂, CH ≡ C-CH₂, CH₃-CH₂-OCO-CH₂, C₆H₄-CH₂

- Ar₁ = p, m-OCH₃; R₁ = CH₃ and R₂ = CH₃CH₂

- Ar₁ = m, m'-OCH₃ C₆H₄; R₁ = CH₃ and R₂ = CH₃CH₂

20 • Ar₁ = 1,3-benzodioxol-5-yl; R₁ = n-butyl; R₂ = CH₃, CH₃-CH₂, CH₂=CH-CH₂, CH≡CH₂, C₆H₄-CH₂, p NO₂-C₆H₄-CH₂, CH₃CH₂OCO-CH₂

- Ar₁ = 1,3-bromobenzodioxol-5-yl; R₁ = n butyl; R₂ = CH₃-CH₂

25 • Ar₁ = m, p OCH₃-C₆H₄; R₁ = n butyl; R₂ = CH₃CH₂

- Ar₁ = 1,3-benzodioxol-5-yl; R₁ = CH₃; R₂ = C₆H₅ or p-OHC₆H₄

R = R₃HN and

- Ar₁ = 1,3-benzodioxol-5-yl; R₁ = CH₃; R₂ = H, CH₃-(CH₂)₂, CH₃-(CH₂)₃, p COOH-C₆H₄CH₂

30 • Ar₁ = 1,3-benzodioxol-5-yl; R₁ = CH₃-(CH₂)₃; R₂ = CH₃-(CH₂)₂ or CH₃-(CH₂)₃

- Ar₁ = 1,3-benzodioxol-5-yl; R₁ = C₆H₅, R₂ = CH₃-(CH₂)₂

- $Ar_1 = p\text{ OH, } m\text{-OCH}_3\text{-C}_6\text{H}_4 \text{ or } m, p\text{ OH-C}_6\text{H}_4$; $R_1 = \text{H}$; $R_2 = \text{H}$.

These novel derivatives, in the use thereof as medicaments, are also part of the invention.

The invention therefore relates to pharmaceutical compositions comprising a therapeutically effective amount of the derivatives of formula (I) defined above.

As shown by the IC_{50} values reported in the examples, the compounds defined above constitute potent inhibitors of the DYRK1A kinase and, in this respect, are useful both as pharmacological tools for fundamental research and as therapeutic agents for the treatment of neurodegenerative diseases, in particular Alzheimer's disease and other tau pathologies, Pick's disease and trisomy 21.

The derivatives of formula I or the novel derivatives according to the invention in fact constitute tools for studying the functions of DYRK1A in various cell models, and the consequences of the expression thereof and of an abnormal activity. They constitute active ingredients of medicaments for countering the effects of the overexpression/abnormal activation of DYRK1A in the pathological conditions above.

During the production of medicaments, the active ingredients, used in therapeutically effective amounts, are mixed with the carriers that are pharmaceutically acceptable for the method of administration selected.

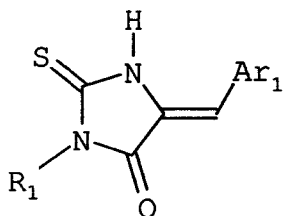
Thus for oral administration, the medicaments are prepared in the form of gel capsules, tablets, sugar-coated tablets, capsules, pills, drops, and the like. Such medicaments may contain from 1 to 100 mg of active ingredient per unit.

For injectable (intravenous, subcutaneous, intramuscular) administration, the medicaments are in the form of sterile or sterilizable solutions. The doses per unit intake may range from 1 to 50 mg of active ingredient. The

daily dosage is chosen so as to obtain a final concentration of at most 100 μ M of imidazolone analog or derivative in the blood of the patient treated.

According to yet another aspect, the present invention also relates to a method for synthesizing the imidazolone derivatives of formula I defined above.

This method is characterized in that it comprises the use of an arylidene thiohydantoin derivative corresponding to formula 3



(3)

in which:

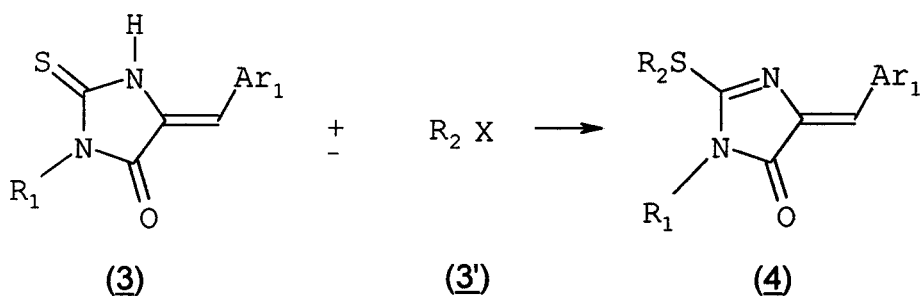
R_1 , R_2 and Ar_1 are as defined above.

According to one embodiment aimed at preparing the imidazolone derivatives of formula I in which $R = R_2S$, the method of the invention comprises reacting a thiohydantoin derivative 3 with a halogenated derivative 3' of formula



with $X = Cl, Br$ or I

under conditions which make it possible to obtain an imidazolone derivative 4, according to scheme 4 below:

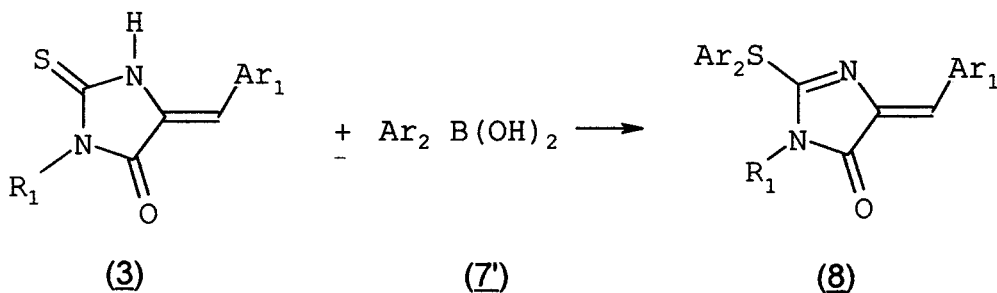


Advantageously, the reaction between the compounds 3 and 3' is carried out in an organic solvent, at a temperature of from 70 to 100°C, in particular of 80°C, in the presence of carbonate.

In order to more particularly obtain derivatives of formula (I) in which R₂ is an aryl radical, the method of the invention comprises reacting the thiohydantoin derivative 3 with an arylboronic acid 7' of formula



under conditions which give the derivatives of formula 8, according to scheme 1':

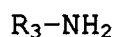


Satisfactory conditions correspond to a reaction, under microwave, of thioxohydantoin with boronic acid in the presence of Cu(AcO)₂, (with Ac = acetyl) and of phenanthroline in an organic solvent such as dichloroethane.

The mixture is irradiated for from 50 to 100 min, in particular from 60 to 90 min, at 70-90°C, in particular 80°C, with a maximum power of approximately 300 Watts.

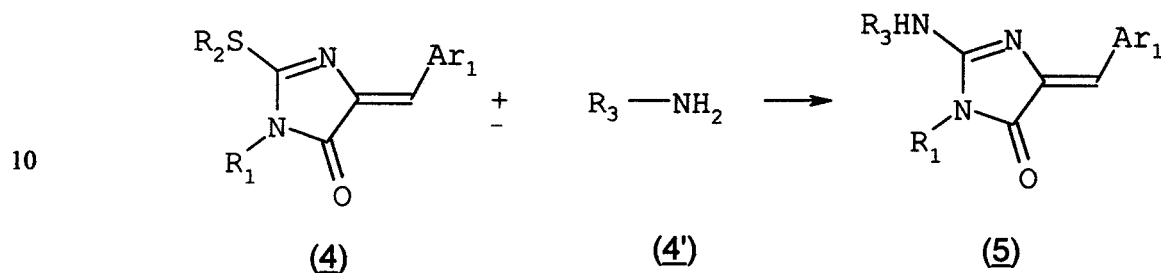
According to one embodiment aimed at preparing the imidazolone derivatives of formula I in which R = R₃ HN, the method of the invention comprises:

- either reacting an imidazolone derivative as defined above 4 with an amine 4' of formula

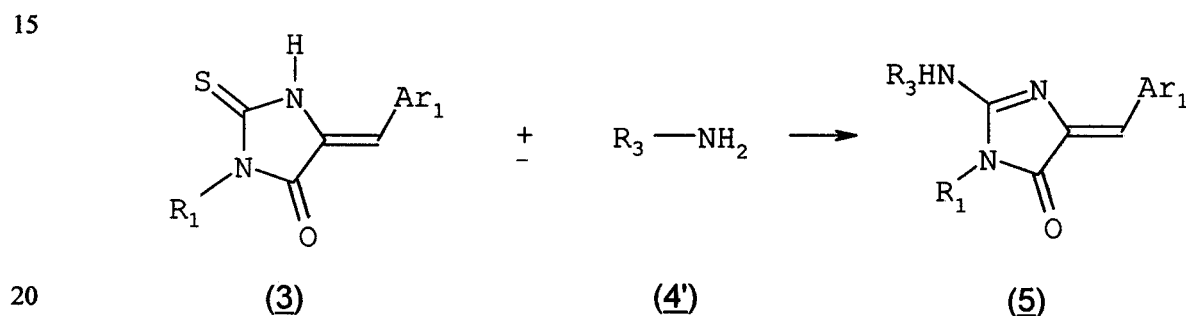


(4')

under conditions which make it possible to obtain the
 5 imidazolone derivative 5 of formula and according to scheme 2
 below:



- or reacting a hydantoin derivative 3 as defined
 above with an amine 4', according to scheme 3 below:

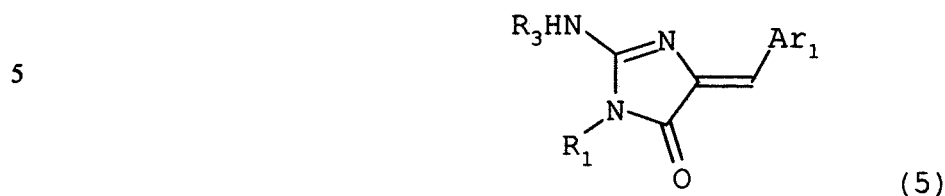


Preferably, the reaction according to scheme 3 is
 carried out in an oil bath and a microwave. In the procedure
 with the oil bath, the reaction mixture is heated to a
 25 temperature below the boiling point of the amine. When the
 procedure is carried out under microwave, the mixture is
 advantageously irradiated for from 10 to 100 minutes at an
 appropriate temperature and power.

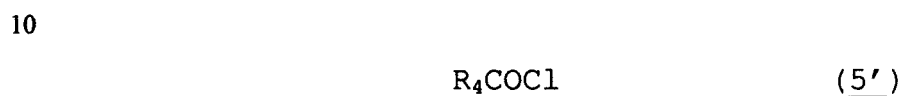
The reaction according to scheme 3 is advantageously
 30 carried out in a solvent such as methanol in the presence of
 hydroperoxide.

According to one embodiment aimed at preparing the
 imidazolone derivatives of formula I in which $R = R_4 COHN$, the

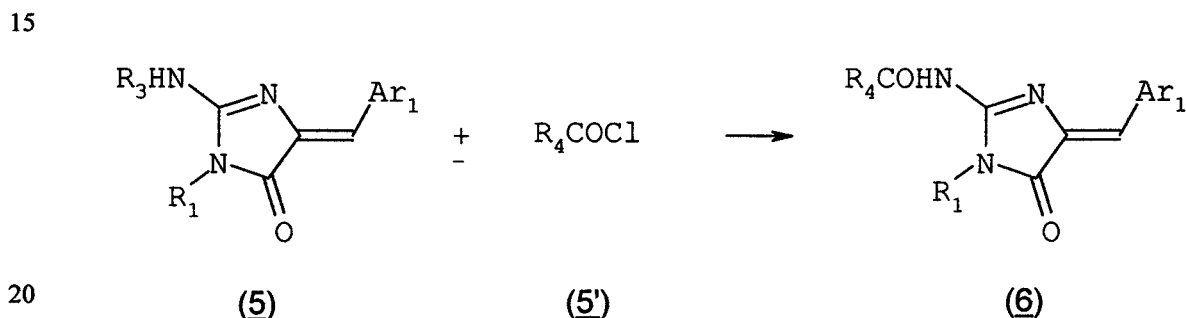
method of the invention comprises reacting an imidazolone derivative 5 of formula



with an acid chloride 5' of formula



under conditions which make it possible to obtain an imidazolone derivative 6, according to scheme 4 below:



The substituents in these various formulae are as defined above.

Appropriate conditions for carrying out the reaction between these derivatives comprise the addition of triethylamine, and then of the acid chloride (5') to a solution, in an organic solvent such as THF, of the imidazolone derivative 5.

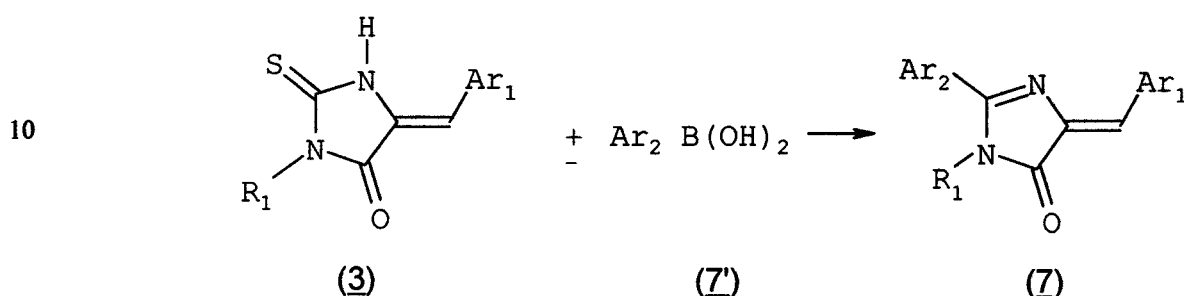
This reaction is advantageously carried out at a temperature of the order of 20 to 25°C.

In order to prepare the imidazolone derivatives of formula I in which $R = Ar_2$, the method of the invention comprises reacting a thiohydantoin derivative of formula 3

with a boronic acid 7'

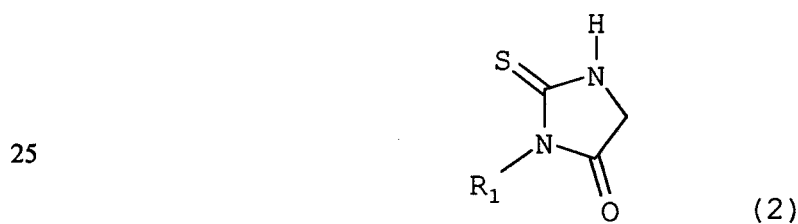


under conditions which make it possible to obtain an imidazolone derivative 7, according to scheme 5 below:

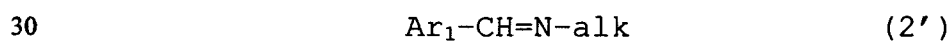


This reaction is advantageously carried out in the presence of a catalyst such as Pd(PPh₃)₄ and of CuTC (Copper Thiophene Carboxylate) in an anhydrous organic solvent such as anhydrous THF. This reaction is advantageously carried out at a temperature of the order of 55 to 65°C.

More particularly preferably, the thiohydantoin derivative 3 is obtained by reacting a thiohydantoin derivative of formula 2

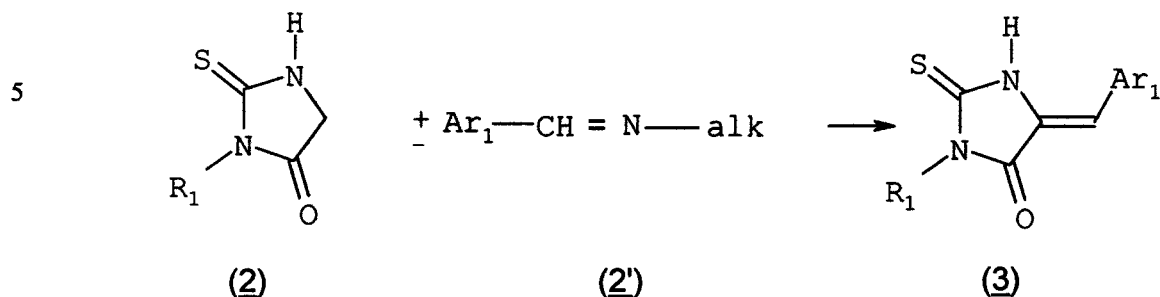


with an aldimine derivative of formula 2'



the substituents being as defined above and "alk" representing a C₃-C₅ alkyl radical, according to scheme 6

below:



10 Advantageously, the reaction is carried out in an oil bath or under microwave.

In the oil bath procedure, the reactants are added to an organic solvent and the reaction mixture is brought to reflux. A viscous oil which crystallizes rapidly is recovered
15 after filtration and purified if desired.

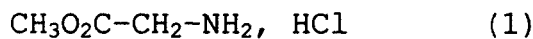
Among the appropriate organic solvents, mention will be made of acetonitrile.

In the microwave procedure, the mixture of thiohydantoin of formula 2 and of aldimine of formula 2' is
20 placed in the microwave reactor, inserted into a microwave oven, where the mixture is irradiated, and then, at the end of the reaction and after a return to ambient temperature, the reaction product is recovered.

Appropriate conditions comprise a treatment of
25 approximately 1 h at 70 - 100°C, in particular 80°C, with a maximum power of 80 - 100 Watts, more especially of 90 Watts.

The aldimine 2' is obtained, for example, starting from an aldehyde 2'' Ar₁-CH=O and from propylamine 2''' CH₃-(CH₂)₂-NH₂. This reaction is advantageously carried out in a
30 microwave reactor at a power of 300 Watts for example at 20-80°C, in particular 25 to 60°C, for 2 to 5 minutes, in particular 3 minutes, and then at 60-80°C at a reduced power of the order of 10 to 30%, in particular 20%.

The thiohydantoin derivative 2 is preferably obtained by reacting methyl glycinate hydrochloride 1



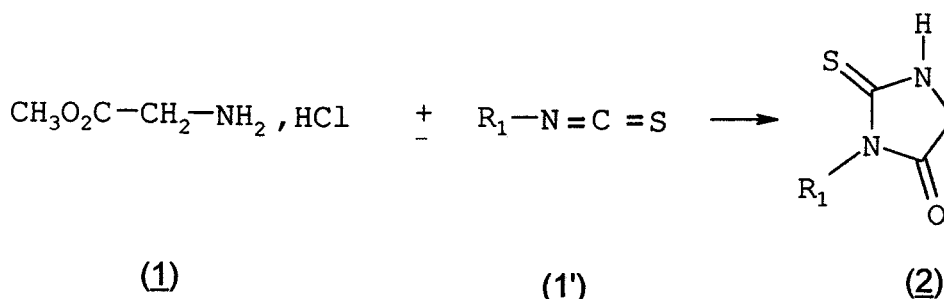
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with an isothiocyanate 1' of formula



10 according to scheme 7 below:

15



Satisfactory reaction conditions comprise reacting 1 and 1' in the presence of triethylamine, in a solvent such as
20 ether, at reflux.

The intermediate compounds in these various operational stages are novel and, in this respect, are also part of the field of the invention.

Other characteristics and advantages of the invention
25 are given in the following exemplary embodiments of the invention relating to the synthesis of the imidazolone derivatives according to the invention.

By way of illustration, the experimental conditions for the reactions denoted A to H, summarized in figure 1, are
30 reported in the experimental section which follows.

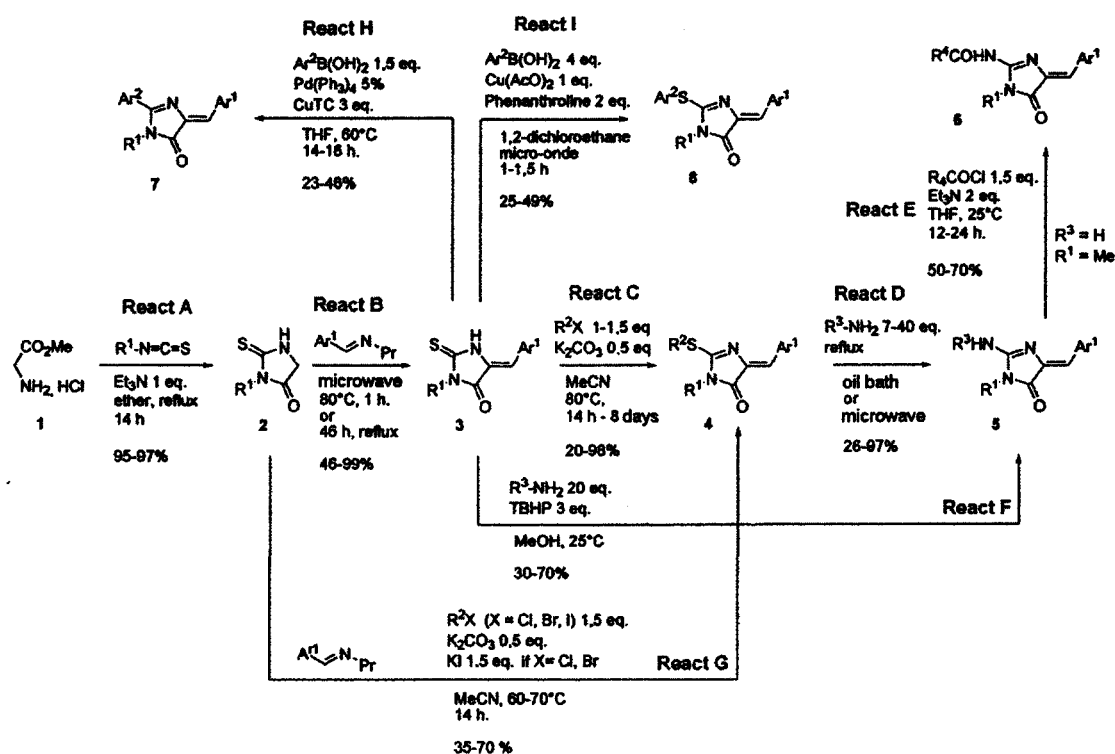
The IC₅₀ values in μM with respect to DYRK1A of compounds according to the invention are subsequently given in table 2 in the section relating to the assay of the DYRD1A

kinase activity.

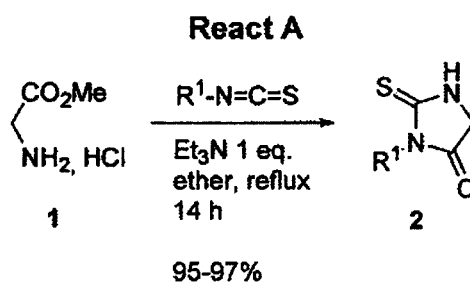
Experimental section

5

Table 1



REACTION A:



- 10 General procedure: A mixture constituted of 7 mmol of isothiocyanate ($R^1N=C=S$), 7 mmol (0.88 g) of methyl glycinate hydrochloride **1**, and 7 mmol (0.97 ml) of triethylamine in 15 ml of ether is heated for 14 hours at the reflux of the

solvent with vigorous magnetic stirring. After cooling of the reaction medium to ambient temperature, the solvent is eliminated under reduced pressure on a rotary evaporator. The triethylamine hydrochloride is eliminated by precipitation from ethyl acetate. After filtration through sintered glass with No. 4 porosity, the filtrate is concentrated on a rotary evaporator under reduced pressure and the expected product **2** is obtained. The latter is subsequently used without further purification.

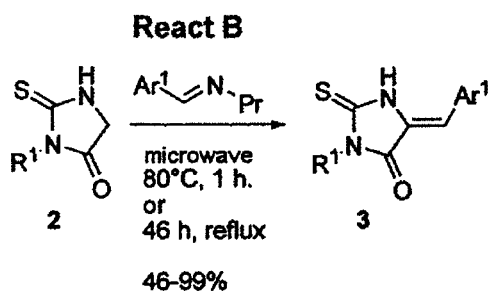
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Example of compound **2**:

3-methyl-2-thioxoimidazolidin-4-one ($R^1 = \text{Me}$)

Yield = 95%, mp = 170-172°C. ^1H NMR (200 MHz, CDCl_3 , TMS) δ : 3.27 (s, 3H, NCH_3); 4.11 (s, 2H, $-\text{CH}_2-$); 7.64 (broad s, 1H, NH). ^{13}C NMR (75 MHz, CDCl_3 , TMS) δ : 27.6 (NCH_3); 48.6 ($-\text{CH}_2-$); 171.6 ($\text{C}=\text{O}$); 185.4 ($\text{C}=\text{S}$).

REACTION B:



General oil bath procedure: Dichloromethane (20 ml), 6.9 mmol of thiohydantoin **2**, and then 6.9 mmol of freshly distilled aldimine(*) are successively added to a round-bottomed flask equipped with a magnetic bar. The reaction mixture is subsequently brought to the reflux of dichloromethane and the reaction is monitored by thin layer chromatography on silica 60 F 254 (Merck). When the reaction is complete, the reaction medium is cooled to ambient temperature, and is then dried

over anhydrous MgSO_4 . After filtration through pleated paper, the filtrate solvent is eliminated by evaporation under reduced pressure and a viscous oil which crystallizes rapidly at ambient temperature is obtained. The purification is carried out either by recrystallization from pentane or, optionally, by chromatography on silica gel 60F 254 (Merck) with an appropriate solvent.

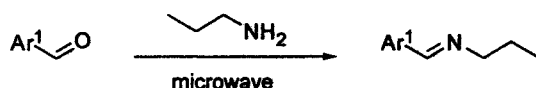
General microwave procedure: A mixture constituted of 10 mmol of thiohydantoin **2** and 10 mmol (1 equivalent) of aldimine(*) is placed in a cylindrical microwave reactor ($\varnothing = 4$ cm). The reactor is then inserted into a Synthewave 402 microwave oven (trademark Prolabo, Merck-Eurolab group) fitted with a blade stirrer system. The mixture is irradiated for one hour at 80°C (3-minute hold) with a maximum power of 90 Watts (Prolabo microwave). After a return to ambient temperature, the reaction mixture is then concentrated on a rotary evaporator. A solution of a chloroform/pentane mixture (1/2) is added to the evaporation residue. After trituration of this mixture, the insoluble solid is filtered through sintered glass with a No. 4 porosity and then dried under reduced pressure.

Example of compound 3:

(5Z)-5-(1,3-Benzodioxol-5-ylmethylene)-3-methyl-2-

thioxoimidazolidin-4-one ($\text{Ar}^1 = 1,3\text{-benzodioxol-5-yl}$, $R^1 = \text{Me}$):

Yield = 87%. Yellow powder, mp = $253\text{--}255^\circ\text{C}$. ^1H NMR (300 MHz, DMSO-d_6) δ = 3.18 (s, 3H, NCH_3); 6.09 (s, 2H, OCH_2O); 6.54 (s, 1H, C=CH); 6.96 (d, 1H, $J = 8.1$ Hz, H-5); 7.27 (d, 1H, $J = 8.1$ Hz, H-6); 7.45 (s, 1H, H-2); 12.22 (bs, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 27.6 (NCH_3); 102.1 (OCH_2O); 109.1 (C-5); 109.8 (C-2); 113.7 (C=CH); 125.1 (C=CH); 126.9 (C-6); 126.9 (C-1); 148.4 (C-4); 149.0 (C-3); 164.6 (C=O); 179.0 (C=S). HRMS, m/z : 262.0409 (calculated for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_3\text{S}$: 262.0412).

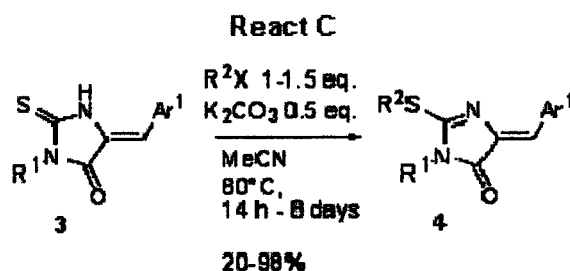


(*) General procedure for the synthesis of aldimines: 20 mmol of aldehyde and 40 mmol (3.28 ml) of propylamine are successively weighed out into a quartz reactor. This reaction medium is heated in the Synthewave 402 microwave reactor ($P_{\text{max.}} = 300 \text{ W}$, trademark Prolabo, Merck-Eurolab group) according to the following programming (from 25 to 60°C for 3 minutes then at 60°C for 30 minutes with a power of 20%). The excess propylamine is eliminated on a rotary evaporator under partial vacuum and then the evaporation residue (solid state) is solubilized in dichloromethane (10 ml/g of product); the organic solution is then dried over MgSO_4 , and filtered through filter paper. The filtrate is concentrated on a rotary evaporator under reduced pressure.

Aldimine example:

N-[(1,3)-benzodioxol-5-ylmethylene]-*N*-propylamine ($\text{Ar}^1 = 1,3\text{-benzodioxol-5-yl}$):

Yield = 97%. Yellow powder. ^1H NMR (200 MHz, CDCl_3) δ : 0.90 (t, 3H, $J = 7.3 \text{ Hz}$, $\text{NCH}_2\text{CH}_2\text{CH}_3$); 1.64 (st, 2H, $J = 7.2 \text{ Hz}$, $\text{NCH}_2\text{CH}_2\text{CH}_3$); 3.47 (t, 2H, $J = 6.9 \text{ Hz}$, $\text{NCH}_2\text{CH}_2\text{CH}_3$); 5.90 (s, 2H, OCH_2O); 6.71 (d, 1H, $J = 7.9 \text{ Hz}$, H-5); 7.02 (dd, 1H, $J = 1.3$; 7.9 Hz, H-6); 7.37 (d, 1H, $J = 1.4 \text{ Hz}$, H-2); 8.10 (s, 1H, N=CH). ^{13}C NMR (75 MHz, CDCl_3) δ : 12.2 (CH_3); 24.5 (CH_2CH_3); 63.7 (NCH_2); 101.8 (OCH_2O); 107.0 (C-3); 108.4 (C-6); 124.5 (C-2); 131.6 (C-1); 148.6 (C-5); 150.0 (C-4); 160.3 (N=CH).

REACTION C:

General procedure: The 5-arylidene thiohydantoin **3** (3.1 mmol, 1 eq.), 20 ml of acetonitrile, the halogenated derivative R^2X with $X = Cl, Br$ or I (3.1 mmol, 1 eq.) and 0.21 g of K_2CO_3 (1.5 mmol, 0.5 eq.) are successively added to a round-bottomed flask. The reaction mixture is heated at $80^\circ C$ for 14 hours with vigorous magnetic stirring. After cooling to ambient temperature, the acetonitrile is eliminated on a rotary evaporator under reduced pressure. 20 ml of ether are added to the crude reaction medium. After filtration of the insoluble inorganic products, under a partial vacuum, through sintered glass with a no. 4 porosity, the filtrate is dried over magnesium sulfate and then filtered through pleated paper. The filtrate solvent is eliminated on a rotary evaporator under reduced pressure and the expected imidazolone **4** is obtained in the form of a powder.

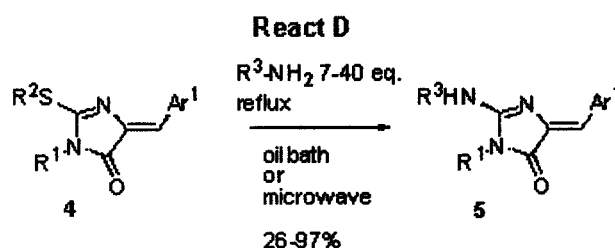
Example of compound 4:

20 [(Z)-(4-Benzo[1,3]dioxol-5-ylmethylene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl)sulfanyl]acetate ($Ar^1 = 1,3$ -benzodioxol-5-yl, $R^1 = Me$, $R^2 = CH_2CO_2Et$):

Yield = 92%. Yellow powder, mp = $172-174^\circ C$. 1H NMR (300 MHz, $CDCl_3$) δ : 1.26 (t, 3H, J 7.1 Hz, OCH_2CH_3); 3.12 (s, 3H, NMe); 4.02 (s, 2H, SCH_2); 4.23 (q, 2H, J 7.1 Hz, OCH_2CH_3); 5.96 (s, 2H, OCH_2O); 6.80 (d, 1H, J 8.1 Hz); 6.84 (s, 1H, $=CH$); 7.52 (dd, 1H, J 8.1; 1.3 Hz); 7.96 (d, 1H, J 1.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ : 14.1 (qm, J 128 Hz, OCH_2CH_3); 26.6 (q, J

144 Hz, NMe); 32.9 (t, J 144 Hz, SCH₂); 62.3 (tq, J 148; 4.6 Hz, OCH₂); 101.5 (t, J 174 Hz, OCH₂O); 108.4 (d, J 165 Hz); 110.8 (dt, J 168; 6.9 Hz); 124.6 (dt, J 156; 4.1 Hz); 128.4 (dt, J 162; 6.0 Hz); 128.9 (d, J 7.6 Hz); 136.6 (s); 148.0 (m, =C-O); 149.3 (m, =C-O); 162.0 (m, C-2); 168.0 (m, C=O(CO₂Et)); 169.7 (m, C-4). HRMS, m/z : 348.0791 (calc. for C₁₆H₁₆N₂O₅S: 348.0780).

REACTION D:



10

Microwave procedure: A mixture constituted of (5Z)-5-arylidene-2-alkylthio-3,5-dihydroimidazol-4-one **4** (4 mmol, 1 eq.) and of 5-20 mmol of aminoalcohol R³-NH₂ (1.5 to 5 equivalents) is placed in a cylindrical microwave reactor ($\varnothing$ = 4 cm). The reactor is then inserted into the Synthewave 402 microwave oven (trademark Prolabo, Merck-Eurolab group) fitted with a blade stirrer system. The mixture is irradiated for from 15 minutes to 90 minutes at an appropriate temperature and an appropriate power. After a return to ambient temperature, the reaction mixture is then concentrated on a rotary evaporator. Ethanol (1 ml/g of product) is added to the evaporation residue. After trituration of the mixture from ethanol, the insoluble solid is filtered off through sintered glass with a no. 4 porosity and then dried under reduced pressure. The latter is optionally recrystallized from ethanol.

15

20

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Oil bath procedure: A suspension constituted of (5Z)-5-arylidene-2-alkylthio-3,5-dihydroimidazol-4-one **4** (4 mmol, 1 eq.) and of aliphatic amine (40 mmol, 10 eq.) is mixed with

vigorous magnetic stirring and heated at a temperature 10°C below the boiling point of this amine ($T_{\text{exp.}} = Bp_{\text{amine}} - 10^\circ\text{C}$) for 3 to 7 days. After a return to ambient temperature, the volatile products are eliminated under reduced pressure and ether (~10 ml) is added to the reaction medium. Next, the products that are insoluble in ether are collected by filtration through sintered glass with a no. 4 porosity. The residual solvent of the compound **5** is eliminated under a partial vacuum in a desiccator for two hours, and the expected 2-aminoimidazolone **5** is obtained in the form of a yellow powder.

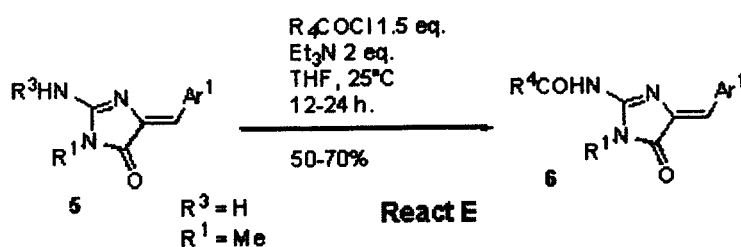
Example of 2-aminoimidazolone **5**:

(5Z)-5-Benzo[1,3]dioxol-5-ylmethylene-3-methyl-2-propylamino-3,5-dihydroimidazol-4-one ($Ar^1 = 1,3\text{-benzodioxol-5-yl}$, $R^1 = \text{Me}$, $R^3 = \text{CH}_2\text{CH}_2\text{CH}_3$):

Yield: 48%. Yellow powder, mp = 190-192°C. ^1H NMR (300 MHz, CDCl_3) δ : 1.02 (t, 3H, J 7.4 Hz); 1.74 (sext, 2H, J 7.3 Hz, NHCH_2CH_2); 3.11 (s, 3H, NMe); 3.54 (t, 2H, J 6.2 Hz, $\text{NHCH}_2\text{C}_2\text{H}_5$); 4.95 (bs, 1H, NH); 5.98 (s, 2H); 6.62 (s, 1H, $=\text{CH}$); 6.81 (d, 1H, J 8.1 Hz); 7.34 (dd, 1H, J 8.1; 1.4 Hz); 7.99 (d, 1H, J 1.2 Hz). ^{13}C NMR (75 MHz, CDCl_3) δ : 11.5 (qt, J 126; 4.0 Hz, $\text{NHC}_2\text{H}_4\text{Me}$); 22.8 (tq, J 135; 3.7 Hz, NHCH_2CH_2); 25.2 (q, J 140 Hz, NMe); 43.7 (tq, J 122; 7.0 Hz, NHCH_2); 101.1 (t, J 173 Hz, C-7'); 108.4 (d, J 164 Hz, C-2'); 110.3 (dt, J 166; 7.1 Hz, C-6); 116.8 (dt, J 157; 3.5 Hz); 126.1 (dt, J 163; 6.2 Hz, C-6'); 130.2 (d, J 7.8 Hz, C-5'); 138.1 (s, C-5); 147.6 (m, C-3'); 147.7 (m, C-4'); 157.2 (m, C-4); 170.4 (sm, C-2). HRMS, m/z : 287.1279 (calc. for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_3$: 287.1270).

30

REACTION E:



General procedure: Triethylamine (2 equiv.) and then acid chloride (1.5 equiv.) are added, at 0°C , to a solution of 0.2 mmol of 2-aminoimidazolone **5** ($\text{R}^3 = \text{H}$, $\text{R}^1 = \text{Me}$) in THF (2 ml). The reaction mixture is stirred at 25°C for 12 h. The solution is then evaporated under reduced pressure and the residue is purified by flash chromatography on silica gel using a mixture of EtOAc/cyclohexane (9/1) as eluant.

10 **Example of compound 6:**

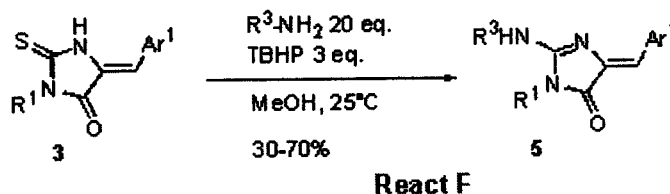
N-[(4*Z*)-4-Benzo[1,3]dioxol-5-ylmethylene-1-methyl-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl]-2,2-dimethylpropanamide ($\text{Ar}^1 = 1,3\text{-benzodioxol-5-yl}$, $\text{R}^1 = \text{Me}$, $\text{R}_4 = \text{C}(\text{CH}_3)_3$).

Yield: 50%. Yellow powder, mp = $145\text{--}147^\circ\text{C}$. ^1H NMR (300 MHz,

15 CDCl_3): $\delta = 1.28$ (s, $\text{C}(\text{CH}_3)_3$, 9H), 3.24 (s, CH_3 , 3H), 6.05 (s, OCH_2O , 2H), 6.76 (s, $=\text{CH}$, 1H), 6.92 (d, $J = 8.0$ Hz, H_{ar} , 1H), 6.93 (s, H_{ar} , 1H), 7.01 (d, $J = 8.0$ Hz, H_{ar} , 1H). ^{13}C NMR (75 MHz, CDCl_3): $\delta = 25.6$ ($\text{C}(\text{CH}_3)_3$), 26.7 ($\text{C}(\text{CH}_3)_3$), 39.7 (NCH_3), 101.6 (OCH_2O), 108.5, 111.2, 128.1, 129.1, 142.5, 146.5, 149.7, 161.8, 171.2, 179.1. HRMS, $m/z = 329.1377$ (calculated for $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_4$ 329.1375).

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REACTION F:



25 **General procedure:** 3 equivalents of *tert*-butyl hydroperoxide TBHP (aqueous solution at 70%) and then 20 equivalents of

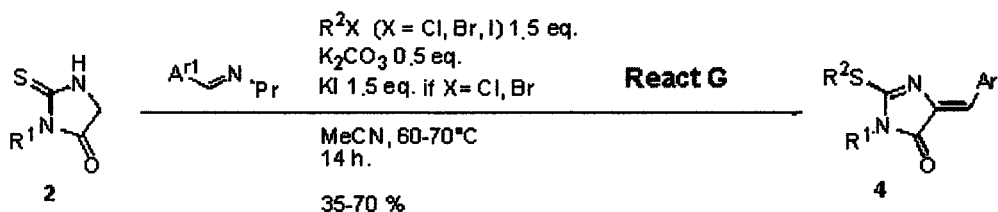
amine are added to a solution of **3** (0.80 mmol) in MeOH (20 ml). The reaction mixture is stirred at 25°C for three days. The solution is then evaporated under reduced pressure and the residue is purified by flash chromatography on silica gel using a mixture of CH₂Cl₂/MeOH (94/6) as eluant.

Example of compound 5:

(5Z)-5-Benzo[1,3]dioxol-5-ylmethylene-2-ethylamino-3,5-dihydro-4H-imidazol-4-one (Ar¹ = 1,3-benzodioxol-5-yl, R³ = Et, R¹ = H).

Yield = 40%. Yellow powder, mp = 222-224°C. ¹H NMR (300 MHz, DMSO-d₆): δ = 1.17 (t, J = 6.9 Hz, CH₃, 3H), 3.34 (m, CH₂, 2H), 6.02 (s, OCH₂O, 2H), 6.23 (s, =CH, 1H), 6.90 (d, J = 8.1 Hz, H_{ar}, 1H), 7.20 (br.s, NH, 1H), 7.38 (d, J = 8.1 Hz, H_{ar}, 1H), 7.93 (s, H_{ar}, 1H), 10.68 (br.s, NH, 1H). ¹³C NMR (75 MHz, DMSO-d₆): δ = 15.5 (CH₃), 36.4 (NHCH₂), 101.4 (OCH₂O), 108.7, 109.8, 125.3, 131.0, 140.6, 146.9, 147.6, 160.2, 174.5. HRMS, m/z = 259.0959 (calculated for C₁₃H₁₃N₃O₃ 259.0957).

REACTION G:



General procedure: A suspension constituted of 5 mmol of aldimine Ar¹CH=N-Pr, 5 mmol of thiohydantoin **2** (R¹ = Me, Bu, Ph), 7.5 mmol of haloalkane R²X, 0.345 g (2.5 mmol) of potassium carbonate and, optionally, 1.25 g (7.5 mmol) of KI (if use is made of a halogenated derivative R²X with X = Br or Cl) in 10 ml of acetonitrile is heated for 14 hours at a temperature close to the boiling point of the haloalkane R²X (T_{exp.} = Bp_{R²X} - 10°C). The reaction solvent is then eliminated

on a rotary evaporator under reduced pressure. The solid obtained after evaporation is triturated with dichloromethane (10 ml/g of product) and then the insoluble inorganic salts are eliminated by filtration through paper. After evaporation of the filtrate, the crude reaction medium is treated (1 g/10 ml) with a mixture of pentane/ethanol (1/1). The expected product **4** precipitates, and is then collected through sintered glass with a no. 4 porosity and dried in a desiccator under a partial vacuum.

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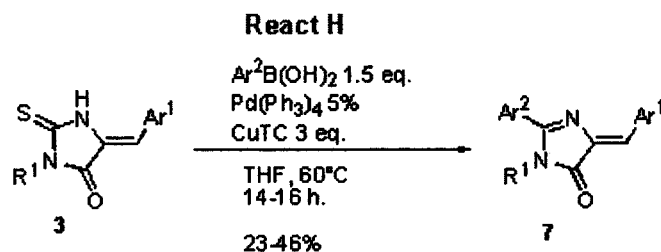
Example of compound **4**:

(5Z)-5-(1,3-benzodioxol-5-ylmethylene)-3-methyl-2-(ethylthio)-3,5-dihydro-4H-imidazol-4-one ($\text{Ar}^1 = 1,3\text{-benzodioxol-5-yl}$, $\text{R}^1 = \text{Me}$, $\text{R}^3 = \text{Et}$):

Yield = 92%. Orange-yellow powder, mp = 152-154°C. ^1H NMR (300 MHz, CDCl_3) δ : 1.55 (t, 3H, $\text{J} = 7.4\text{Hz}$, SCH_2CH_3); 3.17 (s, 3H, NCH_3); 3.40 (q, 2H, $\text{J} = 7.4\text{Hz}$, SCH_2CH_3); 6.00 (s, 2H, OCH_2O); 6.82 (d, 1H, $\text{J} = 8.1\text{ Hz}$, H-5); 6.83 (s, 1H, =CH); 7.37 (dd, 1H, $\text{J} = 8.1; 1.0\text{ Hz}$, H-6); 8.05 (s, 1H, H-2). ^{13}C NMR (75 MHz, CDCl_3) δ : 14.7 (SCH_2CH_3); 25.6 (SCH_2CH_3); 26.9 (NCH_3); 101.8 (OCH_2O); 108.8 (C-5); 111.2 (C-2); 124.0 (=CH); 128.4 (C-6); 129.5 (C-1); 137.5 ($\text{NC}=\text{C}$); 148.3 (C-4); 149.5 (C-3); 164.1 (C-S); 170.3 (C=O). HRMS, $m/z = 290.0730$ found (calculated for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$: 290.0725, M^{+}).

25

REACTION H:



General procedure: A solution constituted of (5Z)-5-arylidene thiohydantoin **3** (1 equivalent), of boronic acid $\text{Ar}^2\text{B}(\text{OH})_2$ (1.5

equivalents), of $\text{Pd}(\text{PPh}_3)_4$ (5 mol%) and of CuTC (3 equivalents) in anhydrous THF (0.06 M) is introduced into a Schlenk tube. The reaction mixture is brought to the reflux of THF overnight with vigorous magnetic stirring. After a return to ambient
 5 temperature, the reaction medium is extracted with dichloromethane (twice). The organic phase is washed with a solution of sodium hydrogen sulfate (1M), and then with a saturated solution of sodium chloride and, finally, with a solution of sodium hydrogen carbonate (1M). The organic phase
 10 is dried over MgSO_4 and filtered through paper, and the filtrate is concentrated on a rotary evaporator under vacuum. The evaporation residue is solubilized under hot conditions in diethyl ether. After cooling, the crystals are collected by filtration through sintered glass with a no. 4 porosity, under
 15 a partial vacuum, and then purified by silica gel chromatography with a cyclohexane/ethyl acetate mixture (70/30) as eluant. The chromatography fraction is then concentrated on a rotary evaporator and dried under a partial vacuum, resulting in the expected product **7**.

20

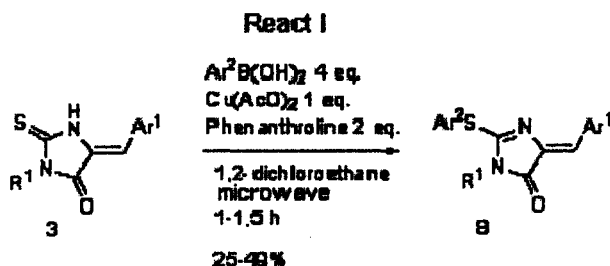
Example of compound **7**:

(5Z)-5-(1,3-Benzodioxol-5-ylmethylene)-3-methyl-2-phenyl-3,5-dihydro-4H-imidazol-4-one ($\text{Ar}^1 = 1,3\text{-benzodioxol-5-yl}$, $\text{R}^1 = \text{Me}$, $\text{Ar}^2 = \text{C}_6\text{H}_5$):

25 Yield = 46%. Yellow powder, mp = 209-211°C. ^1H NMR (300 MHz, CDCl_3): δ = 3.35 (s, 3H, NCH_3); 6.01 (s, 2H, OCH_2O); 6.84 (d, 1H, $J = 8.1$ Hz, H-5'); 7.16 (s, 1H, $\text{C}=\text{CH}$); 7.47 (dd, 1H, $J = 8.1$ Hz, $J = 1.2$ Hz, H-6'); 7.53 (m, 3H, H-3'', H-4''); 7.84 (dd, 2H, $J = 7.4$ Hz, $J = 2.2$ Hz, H-2''); 8.14 (d, 1H, $J =$
 30 1.2 Hz, H-2'). ^{13}C NMR (75 MHz, CDCl_3) δ = 29.1 (NMe); 101.5 (OCH_2O); 108.5 (C-5'); 111.5 (C-2'); 128.7 (C-2''); 128.8 (C-3''); 128.8 (C=CH); 129.0 (C-6'); 129.4 (C-1''); 131.4 (C-4''); 137.5 (C=CH); 137.5 (C-1'); 148.1 (C-3'); 149.7 (C-4');

161.4 (C=N); 171.6 (C=O). HRMS, m/z : 306.0995 (calculated for $C_{18}H_{14}N_2O_3$: 306.10044).

REACTION I:



General procedure: 0.4 mmol of (5Z)-5-arylidene thiohydantoin **3**, 1.6 mmol (4 equivalents) of boronic acid, 0.4 mmol (1 equivalent) of $Cu(OAc)_2$, 0.8 mmol (2 equivalents) of phenanthroline and 4 ml of dichloroethane are placed in a cylindrical microwave reactor ($\varnothing = 2.8$ cm). This reactor is then inserted into the microwave oven fitted with a blade stirrer system. The mixture is irradiated for 60 to 90 minutes at 80°C (2-minute hold) with a maximum power of 300 Watts (Prolabo microwave). After cooling to ambient temperature, the reaction mixture is then concentrated on a rotary evaporator under a partial vacuum. The expected product **8** is purified on alumina gel, elution being carried out with a pentane/ethyl acetate mixture (85/15), followed by washing with pentane.

Example of compound **8**:

(5Z)-5-(1,3-Benzodioxol-5-ylmethylene)-3-methyl-2-(phenylthio)-3,5-dihydro-4H-imidazol-4-one ($Ar^1 = 1,3\text{-benzodioxol-5-yl}$, $R^1 = Me$, $Ar^2 = C_6H_5$):

Yield: 49%. Yellow powder, mp = 171-173°C. 1H NMR (300 MHz, Acetone- d_6): δ = 3.22 (s, 3H, NCH_3); 6.03 (s, 2H, OCH_2O); 6.77 (s, 1H, C=CH); 6.82 (d, 1H, $J = 8.1$ Hz, H-5'); 7.36 (dd, 1H, $J = 8.1$ Hz, $J = 1.2$ Hz, H-6'); 7.56 (d, 1H, $J = 1.7$ Hz, H-2'); 7.58 (d, 2H, $J = 1.7$ Hz, H-2''); 7.78 (m, 2H, H-3''); 7.83 (d, 1H, $J = 1.3$ Hz, H-4''). ^{13}C NMR (75 MHz, DMSO- d_6) δ = 26.6

(NMe); 101.5 (OCH₂O); 108.3 (C-5'); 109.9 (C-2'); 123.4 (C=CH); 125.1 (C-1''); 128.3 (C-6'); 128.4 (C-1'); 129.4 (C-2''); 130.0 (C-4''); 134.8 (C-3''); 136.5 (C=CH); 147.5 (C-4'); 148.9 (C-3'); 162.8 (C=N); 168.5 (C=O). HRMS, *m/z*: 338.0738
 5 (calculated for C₁₈H₁₄N₂O₃S: 338.07251).

Assaying of the kinase activity of DYRK1A

Biochemical reagents

10 Sodium ortho-vanadate, EGTA, Mops, β-glycerophosphate, phenylphosphate, dithiothreitol (DTT), glutathione-agarose, glutathione, nitrophenylphosphate and myelin basic protein were obtained from Sigma Chemicals. [γ-³³P]-ATP comes from Amersham.

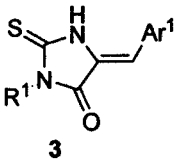
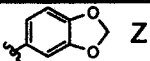
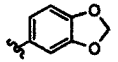
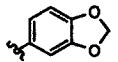
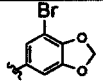
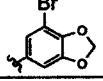
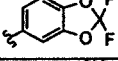
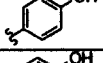
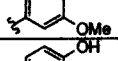
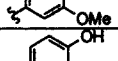
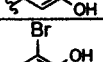
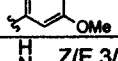
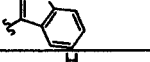
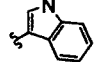
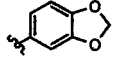
15 Preparation of the DYRK1A kinase and enzyme assay for the activity thereof

Rat recombinant DYRK1A was expressed in *E. coli* as a GST fusion protein. It was purified by affinity chromatography on beads of immobilized glutathione (elution with free
 20 glutathione). The kinase activity was assayed in buffer C (60 mM β-glycerophosphate, 15 mM p-nitrophenylphosphate, 25 mM Mops (pH 7.2), 5 mM EGTA, 15 mM MgCl₂, 1 mM DTT, 1 mM sodium vanadate, 1 mM phenylphosphate), with 1 mg of myelin basic protein /ml, in the presence of 15 μM [γ-³³P]-ATP
 25 (3.000 Ci/mmol; 10 mCi/ml) in a final volume of 30 μL. After incubation at 30°C for 30 min, 25-μL aliquots of supernatant were spotted onto Whatman P81 phosphocellulose filters and the filters were washed five times in a solution of phosphoric acid (10 ml/L water). The radioactivity incorporated into the
 30 substrate, retained on the moist filters, was then counted in the presence of ACS scintillation fluid (Amersham). The control values were subtracted and the activities were expressed as % of the maximum value, i.e. the value obtained

in the absence of inhibitors. The IC_{50} values were calculated from dose-response curves and are given in μM .

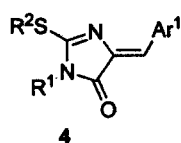
The results are given in table 2 hereinafter:

Table 2

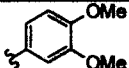
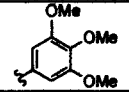
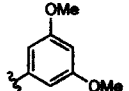
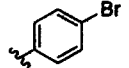
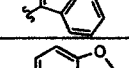
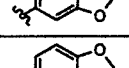
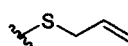
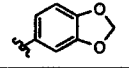
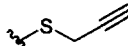
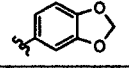
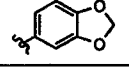
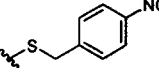
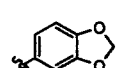
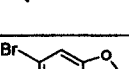
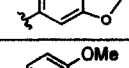
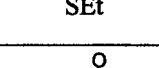
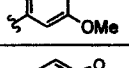
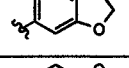
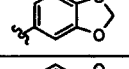
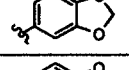
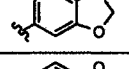
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References:

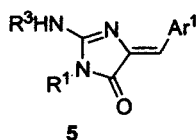
- 5 1: Microwave mediated solventless synthesis of new derivatives of marine alkaloid *Leucettamine B*.
Jean René Chérourvriér, François Carreaux, Jean Pierre Bazureau
Tetrahedron Letters **2002**, *43*, 3581-3584.
- 2: The isolation and synthesis of polyandrocarpamines A and B. Two new 2-aminoimidazolone compounds from the Fijian ascidian, *Polyandrocarpa* sp.
10 Rohan A. Davis, William Aalbersberg, Semisi Meo, Rosan Moreira da Rocha, Chris M. Ireland
Tetrahedron **2002**, *58*, 3263-3269.



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SB11	0.9	Me			G
SB24	0.47	Me			C
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ST101	2.3	Me	Sn-Bu		C
ST102	1.5	Me			C
SA197	2.5	Me			C
JR404	5.8	Me			C
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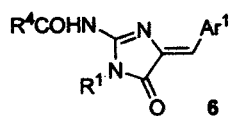
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ST135	0.46	H	Si-Pr		C

ST209	0.17	H			C
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ST262	0.65	H			C
ST281	0.5	H			C
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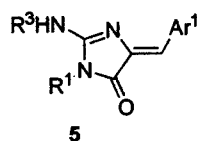


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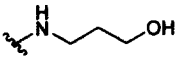
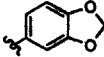
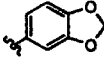
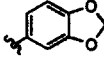
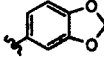
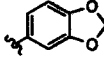
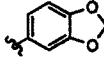
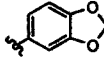
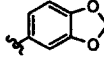
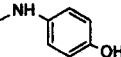
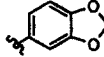
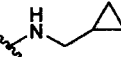
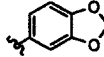
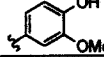
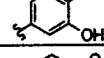
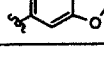
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MADE12	4.6	Me			D Microwave

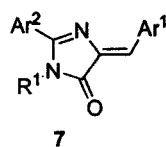


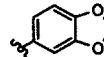
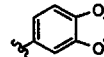
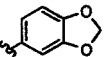
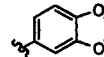
IA32	15	Me			E
IA31	3.4	Me			E
IA33	>10	Me			E
IA25	>10	Me			E
IA35	>10	Me			E

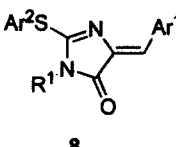
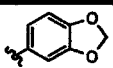
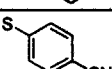
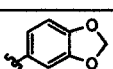


ST092	>10	Me	NH <i>n</i> -Pr		D Oil bath
FCFD14	>10	Me	NH <i>n</i> -Pr		D Oil bath
FC104b	>10	Me	NH <i>i</i> -Pr		D Oil bath
FCFD11	>10	Me	NH <i>n</i> -Pr		D Oil bath
FCFD08	>10	Me	NH <i>n</i> -Pr		D Oil bath
FC095	>10	Me	NH <i>i</i> -Pr		D Oil bath
FC092	>10	Me	NH <i>n</i> -Pr		D Oil bath
FC109	>10	Me	NH <i>i</i> -Pr		D Oil bath

SA164	>10	<i>n</i> -Bu			D Microwave
JR442	>10	<i>n</i> -Bu	NH <i>n</i> -Pr		D Oil bath
FCJR464	>10	<i>n</i> -Bu	NH <i>n</i> -Bu		D Oil bath
JR445	>10	Ph	NH <i>n</i> -Pr		D Oil bath
FC085	1.7	H	NHMe		F
FC090	1.1	H	NHEt		F
FC092	0.89	H	NH <i>n</i> -Pr		F
MADE44	0.071	H			D Microwave
MADE48	0.084	H			D Microwave
FC112	0.5	H			F
ST325	0.17	H	NH ₂		F
ST326	>10	H	NH ₂		F
ST033	0.3	Me			F



NL39	3.2	Me	Ph		H
NL96	0.43	Me	C ₆ H ₅ -pOH		H
NL39A	0.22	Me			H

 8					
ST379	1.9	Me			I
ST385	>10	Me			I

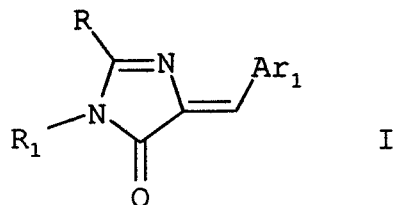
References:

- 5 1: Microwave mediated solventless synthesis of new derivatives of marine alkaloid *Leucettamine B*.
Jean René Chérouvrier, François Carreaux, Jean Pierre Bazureau
Tetrahedron Letters **2002**, *43*, 3581-3584.
- 10 2: Parallel solution phase synthesis of 2-alkylthio-3,5-dihydro-4*H*-imidazol-4-one by one-pot three component domino reaction.
Stéven Renault, Sarah Bertrand, François Carreaux*, Jean Pierre Bazureau*.
Journal of Combinatorial Chemistry **2007**, *9*, accepted for publication (awaiting authorization for ACS in ASAP).
- 15 3: Synthesis of the marine alkaloid Leucettamine B
Nathalie Roué, Ian Bergman
Tetrahedron **1999**, *55*, 14729-14738.
- 20 4: The isolation and synthesis of polyandrocarpamines A and B. Two new 2-aminoimidazolone compounds from the Fijian ascidian, *Polyandrocarpa sp.*
Rohan A. Davis, William Aalbersberg, Semisi Meo, Rosan Moreira da Rocha, Chris M. Ireland
Tetrahedron **2002**, *58*, 3263-3269.

CLAIMS

1. An imidazolone derivative for use as a medicament,
characterized in that said derivative corresponds to formula

5 (I)



in which:

- 10 • R₁ represents H, a linear or branched, optionally substituted, C₁ to C₅ alkyl radical; an aryl group, or a 5- or 6-membered heterocyclic group, the aryl group and the heterocyclic group optionally comprising one or more substituents, which may be identical or different, occupying any positions;
- 15 • Ar₁ represents an aryl group with optionally one or more substituents, it being possible for two adjacent substituents to form a 5- or 6-membered ring, this ring being, where appropriate, substituted; or an aromatic heterocycle with

20 optionally one or more substituents and/or condensed with a 5- or 6-membered aromatic ring, the heteroatom being chosen from N, S and O;
- 25 • R represents R₂-S-, R₃-HN-, R₄COHN or Ar₂, with
- R₂ = a linear, branched or cyclic C₁-C₅ alkyl radical; a vinyl or vinyl(C₁-C₅)alkyl radical, a nitrile or nitrile(C₁-C₅)alkyl radical, or an aryl or benzyl radical, said radicals being optionally substituted on one or more carbon atoms with one or more groups, which may be identical or

different, occupying any positions, it being possible for two adjacent substituents to form a 5- or 6-membered ring, this ring being, where appropriate, substituted,

- R_3 = the meanings given above and may also represent H;

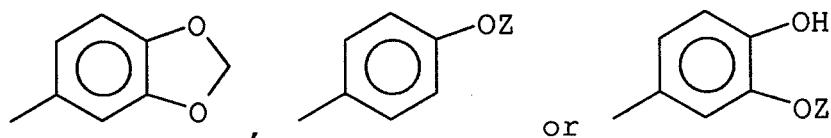
- Ar_2 representing a substituted or unsubstituted aryl radical, it being possible for two adjacent substituents to form a 5 or 6-membered ring, this ring being optionally substituted.

2. The derivative as claimed in claim 1, characterized in that the aryl group represents a phenyl or naphthyl radical and the heterocycle is a 5- or 6-membered ring with N, O and/or S as heteroatom(s), the substituents of R_1 , Ar_1 , Ar_2 and R are chosen from: OH, OZ, COH, COZ, COOH, COOZ, NH_2 , $NHalk.$, $N(alk.)_2$, $NHCOOH$, $NHCOOZ$, Z representing a linear or branched C_1 - C_5 alkyl, aryl, benzyl, substituted benzyl or aryl, or benzodioxolyl radical, one or more halogens and/or a CCl_3 group, and alk. representing a C_1 - C_3 alkyl radical.

3. The derivative as claimed in claim 1 or 2, characterized in that it has an IC_{50} of less than 5 μM with respect to DYRK1A.

4. The derivative as claimed in claim 3, characterized in that it has an IC_{50} of less than 5 μM and corresponds to formula I above in which:

- R_1 represents a C_1 - C_3 alkyl radical or a hydrogen atom, and/or an aryl radical
- Ar_1 is chosen from



- R represents

- an R_3 -S- group, R_3 then being chosen from radicals of

$T_1-(CH_2)_n$ type, with $n = 0, 1, 2$ or 3 and T_1 representing one of the following radicals: methyl, vinyl, alkyl, alkynyl, nitrile, cycloalkyl, which may be C_3 or C_4 , $Z-O$, $Z-CO$, with $Z = C_1-C_3$ alkyl, or hal, hal representing F, Cl, Br or I or a CCl_3 group,

or

- an R_4-NH- group, R_4 then being chosen from radicals of $T_2-(CH_2)_n$ type, with $n = 0, 1$ or 2 , and T_2 representing one of the following radicals: methyl, vinyl, ZO , $ZO-CONH-$, $-CH-(OZ)_2$, ZCO , with $Z = H$ or linear or branched C_1-C_4 alkyl, NH_2 , C_3 cycloalkyl, aryl or substituted aryl, or $R_2 = H$,

or

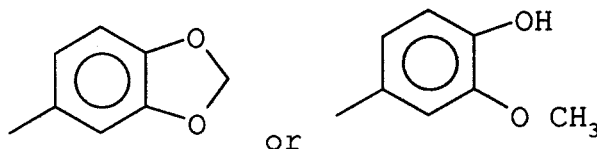
- an $R_2-CONH-$ group, R_2 then being a branched C_3-C_5 alkyl radical,

or

- $Y = Ar_2$, Ar_2 being chosen from a phenyl, substituted phenyl or benzodioxolyl radical.

5. The derivative as claimed in claim 3, characterized in that it has an IC_{50} of less than $1 \mu M$ and corresponds to formula (I) in which:

- R_1 represents H or CH_3
- Ar_1 represents the radical



- R_2 represents

- an R_2-S- group, R_2 then being chosen from radicals of $T_1-(CH_2)_n$ type, with $T_1 =$ a methyl, alkynyl, nitrile, hal, CH_3O , cyclopropyl or cyclobutyl radical, $n = 0, 1, 2$ or 3 , "hal" representing a halogen atom or a CCl_3 group,

or

- an $R_3\text{-HN-}$ group, R_3 then being chosen from radicals of $T_2\text{-(CH}_2)_n$ type, with $T_2 = \text{C}_3$ alkyl, OH, cyclopropyl, phenyl, phenyl substituted with OH, OCH₃, COOH and OH, CH₂OH, C(CH₃, OH), CH₂-CH₂OH, CH₂-COOH or benzodioxolyl, or $R_2 = \text{H}$, $n = 0, 1$ or 2 ,

or

- an Ar_2 group chosen from a para-hydroxyphenyl or benzodioxolyl group.

6. The derivative as claimed in claim 3, characterized in that it is chosen from the derivatives of formula (I) in which

$R = R_2S$

$R_2 = \text{CH}_2\text{C}\equiv\text{CH}$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_2 = \text{CH}_2\text{C}\equiv\text{N}$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_2 = \text{CH}_2\text{CH}_2\text{Cl}$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_2 = \text{CH}_3$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_2 = \text{CH}_2\text{CH}_3$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_2 = \text{CH}_2\text{CH}_2\text{CH}_3$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_2 = \text{CH}(\text{CH}_3)_2$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_2 = \text{CH}_2\text{C}\equiv\text{N}$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_2 = \text{CH}_2(\text{CH}_2)_2\text{CH}_3$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_2 = \text{CH}_2\text{CH}_2\text{OCH}_3$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_2 = \text{CH}_2\text{T}_1$ with $\text{T}_1 = \text{cyclopropyl}$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_2 = \text{CH}_2\text{T}_1$ with $\text{T}_1 = \text{cyclobutyl}$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R = R_3\text{NH}$

$R_3 = \text{CH}_2\text{CH}_3$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = \text{CH}_2\text{CH}_2\text{OH}$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = \text{CH}_2\text{T}_1$ with $\text{T}_1 = \text{cyclopropyl}$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

5 $R_3 = \text{CH}_2\text{CH}_3$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = o\text{-HO-C}_6\text{H}_4$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = \text{C}_6\text{H}_5$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = p\text{-HO-C}_6\text{H}_4$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = p\text{-HO-m-HO}_2\text{C-C}_6\text{H}_3$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

10 $R_3 = p\text{-m-OCH}_2\text{O-C}_6\text{H}_3$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = p\text{-CH}_3\text{-C}_6\text{H}_4$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = \text{HOCH}_2\text{CHOHCH}_2$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = p\text{-m-OCH}_2\text{CH}_2\text{O-C}_6\text{H}_3$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = p\text{-CH}_3\text{O-C}_6\text{H}_4$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

15 $R_3 = m\text{-HOCH}_2\text{-C}_6\text{H}_4$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = m\text{-HOCH(CH}_3\text{)-C}_6\text{H}_4$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = p\text{-HOCH}_2\text{CH}_2\text{-C}_6\text{H}_4$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = p\text{-HO}_2\text{CCH}_2\text{O-C}_6\text{H}_4$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = \text{CH}_2\text{CH}_2\text{CH}_3$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

20 $R_3 = \text{CH}_2\text{T}_1$ with $\text{T}_1 = \text{cyclopropyl}$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = \text{C}_6\text{H}_5$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = p\text{-HO-C}_6\text{H}_4$; $R_1 = \text{H}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$R_3 = \text{H}$; $R_1 = \text{H}$; $\text{Ar}_1 = p\text{-HO-m-MeO-C}_6\text{H}_3$

25

$R = \text{Ar}_2$

$\text{Ar}_2 = p\text{-HO-C}_6\text{H}_4$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$

$\text{Ar}_2 = p\text{-m-OCH}_2\text{O-C}_6\text{H}_3$; $R_1 = \text{Me}$; $\text{Ar}_1 = 1,3\text{-benzodioxol-5-yl}$.

30

7. A novel imidazolone derivative, characterized in that it corresponds to formula I of claim 1, with the exclusion of the derivatives in which:

R = R₂S and

- Ar₁ = 1,3-benzodioxol-5-yl; R₁ = CH₃ and R₂ = CH₃, CH₃CH₂, CH₂ = CH-CH₂, CH ≡ C-CH₂, CH₃-CH₂-OCO-CH₂, C₆H₄-CH₂
- Ar₁ = p, m-OCH₃; R₁ = CH₃ and R₂ = CH₃CH₂
- 5 • Ar₁ = m, m'-OCH₃ C₆H₄; R₁ = CH₃ and R₂ = CH₃CH₂
- Ar₁ = 1,3-benzodioxol-5-yl; R₁ = n-butyl; R₂ = CH₃, CH₃-CH₂, CH₂=CH-CH₂, CH≡CH₂, C₆H₄-CH₂, p NO₂-C₆H₄-CH₂, CH₃CH₂OCO-CH₂
- Ar₁ = 1,3-bromobenzodioxol-5-yl; R₁ = n butyl; R₂ = CH₃-CH₂
- 10 • Ar₁ = m, p OCH₃-C₆H₄; R₁ = n butyl; R₂ = CH₃CH₂
- Ar₁ = 1,3-benzodioxol-5-yl; R₁ = CH₃; R₂ = C₆H₅ or p-OHC₆H₄

R = R₃HN and

- 15 • Ar₁ = 1,3-benzodioxol-5-yl; R₁ = CH₃; R₂ = H, CH₃-(CH₂)₂, CH₃-(CH₂)₃, p COOH-C₆H₄CH₂
- Ar₁ = 1,3-benzodioxol-5-yl; R₁ = CH₃-(CH₂)₃; R₂ = CH₃-(CH₂)₂ or CH₃-(CH₂)₃
- Ar₁ = 1,3-benzodioxol-5-yl; R₁ = C₆H₅, R₂ = CH₃-(CH₂)₂
- 20 • Ar₁ = p OH, m-OCH₃-C₆H₄ or m, p OH-C₆H₄; R₁ = H; R₂ = H.

8. A pharmaceutical composition, characterized in that it contains a therapeutically effective amount of at least one derivative as claimed in any one of claims 1 to 7.

25 9. The pharmaceutical composition as claimed in claim 8, for the treatment of neurodegenerative diseases, in particular Alzheimer's disease and other tau pathologies.

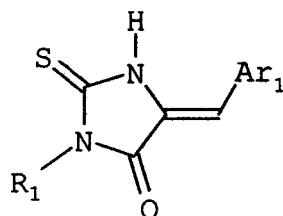
10. The pharmaceutical composition as claimed in claim 8, for the treatment of Pick's disease.

30 11. The pharmaceutical composition as claimed in claim 8, for the treatment of trisomy 21.

12. The use of the imidazolone derivatives as claimed in any one of claims 1 to 7, as DYRK1A inhibitors.

13. A method for synthesizing the imidazolone

derivatives of formula I as claimed in any one of claims 1 to 7, characterized in that it comprises the use of an arylidene thiohydantoin derivative corresponding to formula 3



(3)

in which:

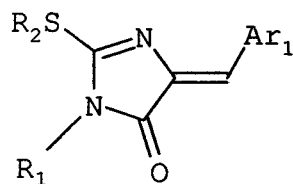
R₁, R₂ and Ar₁ are as defined in said claims.

14. The method as claimed in claim 13, characterized in that, in order to prepare the imidazolone derivatives in which R = R₂S, said method comprises reacting a thiohydantoin derivative 3 with a halogenated derivative 3' of formula



with X = Cl, Br or I

under conditions which make it possible to obtain an imidazolone derivative 4, of formula



(4)

in which:

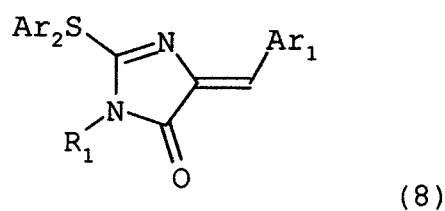
R₁, R₂ and Ar₁ are as defined above.

15. The method as claimed in claim 12, characterized in that, in order to prepare the imidazolone derivatives of

formula (I) in which $R = R_2S$ with R_2 representing an aryl group, said method comprises reacting the thiohydantoin derivative 3 with an arylboronic acid 7' of formula



under conditions which give the derivatives of formula 8

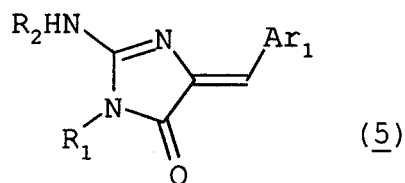


16. The method as claimed in claim 13, characterized in that, in order to prepare the imidazolone derivatives in which $R = R_3HN$, said method comprises:

- either reacting an imidazolone derivative 4 with an amine 4' of formula

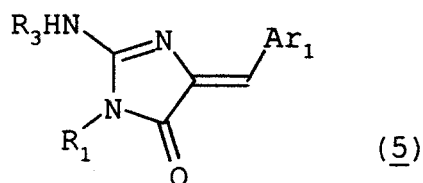


under conditions which make it possible to obtain the imidazolone derivative 5 of formula



- or reacting a hydantoin derivative 3 with an amine 4'.

17. The method as claimed in claim 13, characterized in that, in order to prepare the imidazolone derivatives of formula (I) in which $R = R_4COHN$, said method comprises reacting an imidazolone derivative 5 of formula

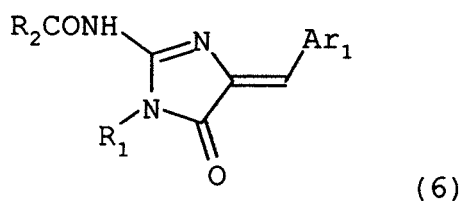


5

with an acid chloride 5' of formula



10 under conditions which make it possible to obtain an imidazolone derivative 6 of formula



15

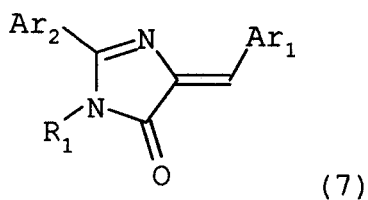
18. The method as claimed in claim 13, characterized in that, in order to prepare the imidazolone derivatives in which $R = \text{Ar}^2$, said method comprises reacting a thiohydantoin derivative of formula 3 with an arylboronic acid 7'

20



under conditions which make it possible to obtain an imidazolone derivative 7

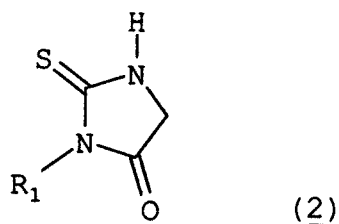
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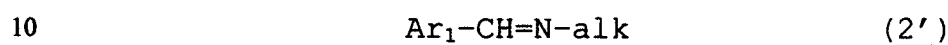
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19. The method as claimed in claim 13, characterized in that the thiohydantoin derivative 3 is obtained by reacting

the derivative of formula 2



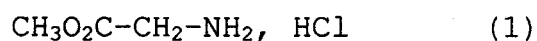
with an aldimine derivative of formula 2'



the substituents being as defined above and "alk" representing a C₃-C₅ alkyl radical.

15 20. The method as claimed in claim 19, characterized in that the aldimine derivative 2' is obtained by reacting an aldehyde 2'' $\text{Ar}_1\text{-CH=O}$ and propylamine 2''' $\text{CH}_3\text{-(CH}_2\text{)}_2\text{-NH}_2$.

20 21. The method as claimed in claim 19, characterized in that the thiohydantoin derivative 2 is obtained by reacting methyl glycinate hydrochloride 1



25 with an isothiocyanate 1' of formula

