Kinase target	Disease
CLK2	Autism, Phelan-McDermid syndrome (PMDS)
CLK2	Knee osteoarthritis
CLK2	Breast cancer, Triple negative breast cancer, Glioblastoma
CLK2	Alzheimer's disease (alternative splicing of Tau exon 10)
CLK3	Hepatocellular carcinoma, Prostate cancer
CLKs	Body temperature
CLKs	Prostate cancer, Gastrointestinal cancer
PfCLKs	Malaria
DYRKs/CLKs	Glioblastoma and numerous other cancers

DYRKs and CLK inhibitors

Several DYRK1A inhibitors have been reported in recent years. Most DYRK1A inhibitors also inhibit DYRK1B, 2, 3, 4, as well as the closely related CLK1, 2, 3, 4, with several possible inhibition profiles.

Some imidazolone derivatives, named **Leucettines** in the text below, were disclosed in WO2009/050352 as kinase inhibitors and more particularly as inhibitors of the DYRK1A kinase.

There is still a need to identify new compounds for treating and/or preventing the diseases as recited above, and particularly through the inhibition, and in particular selective inhibition, of DYRK1A, other DYRKs and the related CLKs kinases.

SUMMARY ~~OF THE INVENTION~~

It has now been found that the compounds as defined in formula (I) herein after are useful in the treatment and/or prevention of a disease selected from cognitive deficits associated with Down syndrome; Alzheimer's disease and related diseases; dementia; tauopathies; Parkinson's disease; other neurodegenerative diseases; CDKL5 Deficiency Disorder; Phelan-McDermid syndrome; autism; type 1 and type 2 diabetes; abnormal folate and methionine metabolism; osteoarthritis; several cancers and leukemias,; neuroinflammation, anemia, infections caused by unicellular parasites, viral infections and for regulating body temperature.

The present ~~invention~~disclosure therefore relates to a compound of formula (I), as defined below.

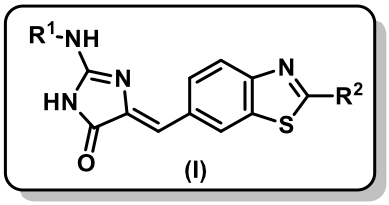
The present ~~invention~~disclosure further relates to a compound of formula (I) as defined below for use as a medicament.

The present ~~invention~~ disclosure further relates to a compound of formula (I) as defined below for use in the treatment and/or prevention of a disease selected from cognitive deficits associated with Down syndrome; Alzheimer's disease and related diseases; dementia; tauopathies; Parkinson's disease; other neurodegenerative diseases; CDKL5 Deficiency Disorder; Phelan-McDermid syndrome; autism; type 1 and type 2 diabetes; abnormal folate and methionine metabolism; osteoarthritis; several cancers and leukemias, neuroinflammation, anemia, infections caused by unicellular parasites, viral infections and for regulating body temperature.

The present ~~invention~~ disclosure further relates to a pharmaceutical composition comprising it and to a process for manufacturing it.

The present ~~invention~~ disclosure at last relates to synthetic intermediates of formula (II) as defined below.

In an aspect, there is provided a compound of formula (I)



(I)

wherein R^1 represents:

(i). a (C_1-C_6)alkyl group substituted by one or two groups selected from a -$COOR^a$ group, a hydroxy group, a halogen atom, a (C_1-C_4)alkoxy group and a benzyloxy group, said benzyloxy being optionally substituted on its phenyl group by one to three halogen atoms,

(ii). a spiro(C_5-C_{11})bicyclic ring,

(iii). a fused phenyl group, selected from phenyl groups fused with a (C_5-C_6)cycloalkyl or (C_5-C_6)heterocycloalkyl, which (C_5-C_6)cycloalkyl and (C_5-C_6)heterocycloalkyl ring optionally comprise an insaturation and is optionally substituted by a (C_1-C_4) alkyl group, a hydroxy group, a halogen atom, a (C_1-C_3)alkoxy group or a -COR^a group,

(iv). a phenyl group, substituted by one or two groups selected from a (C_1-C_8)alkyl, a (C_1-C_3)fluoroalkyl, a fluoro(C_1-C_4)alkoxy group, a halogen atom, and a (C_4-C_7)heterocycloalkyl group, said

(C_4-C_7)heterocycloalkyl group being itself optionally substituted by a (C_1-C_4) alkyl group, or

(v). a R'-L- group, wherein L is either a single bond or a (C_1-C_3)alkanediyl group, optionnally susbstituted by a group selected from a hydroxy group and a (C_1-C_3)alkoxy group, and

R' represents:

(v.1) a (C_3-C_8)cycloalkyl group, optionally substituted by one, two or three groups selected from a (C_1-C_4)alkyl group, a hydroxy group, a halogen atom and a (C_1-C_3) alkoxy group,

(v.2) a bridged (C_6-C_{10})cycloalkyl group, optionally substituted by one to three groups selected from a (C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halogen atom, a hydroxy group, a -O-C(O)-R^d group, a -O-C(O)-NHR^d group, a -NH-C(O)-R^d group, a -SO_2-R^d group, a -N(R^e)$_2$ group and a -COOR^a group,

(v.3) a (C_3-C_8)heterocycloalkyl group, optionally substituted by one to three groups selected from a -COOR^a group, a hydroxy group, a halogen atom, a (C_1-C_4)alkyl group and an oxo group,

(v.4) a (C_3-C_8)heteroaryl group, optionally substituted by one to three groups selected from a halogen atom, a (C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group and a *N*-methylpiperazinyl group, or

(v.5) a bridged (C_6-C_{10})heterocycloalkyl group, or

(vi). a R'-L- group wherein L is a (C_1-C_3)alkanediyl group, optionally substituted by a group selected from a -N$R^b$$R^c$ group, a (C_1-C_4)alkoxy group, a hydroxy group, a -COOR^a group and a halogen atom, and

R' is a phenyl group, optionally substituted by one to three groups selected from the group consisting of (C_1-C_6)alkyl group, a fluoro(C_1-C_4)alkyl group and a fluoro(C_1-C_4)alkoxy group, a halogen atom and a hydroxy group,

R^a represents a (C_1-C_4)alkyl group or a hydrogen atom,

R^b and R^c independently represent a (C_1-C_6)alkyl group or a hydrogen atom,

R^d represents a $(C_1$-$C_4)$alkyl group or a cyclopropyl group,

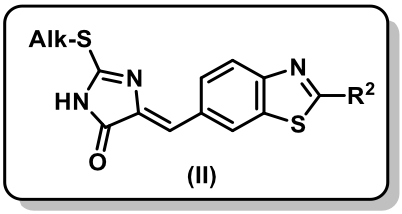
R^e represents a $(C_1$-$C_3)$alkyl group, and

R^2 represents a hydrogen atom or a $(C_1$-$C_3)$alkyl group,

or any of its pharmaceutically acceptable salt.

In another aspect, there is provided a pharmaceutical composition comprising at least one compound as defined above or or any of its pharmaceutically acceptable salt or as defined above.

In another aspect, there is provided a synthesis process for manufacturing a compound of formula (I) as defined above or or any of its pharmaceutically acceptable salt or as defined above or any of its pharmaceutically acceptable salts, comprising at least a step of coupling a compound of formula (II) below



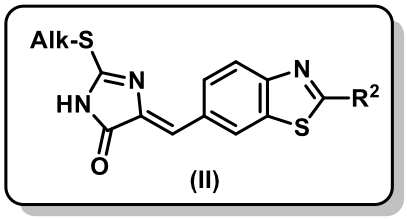
(II)

wherein Alk is a $(C_1$-$C_5)$alkyl,

with an amine of formula R^1NH_2

wherein R^1 and R^2 are as defined above.

In another aspect, there is provided a synthetic intermediate of formula (II) below



(II)

wherein Alk is a $(C_1$-$C_5)$alkyl, in particular Alk is selected from the group consisting of an ethyl and a methyl and R^2 is as defined above.

In another aspect, there is provided a compound of formula (I) as defined above or any of its pharmaceutically acceptable salts, or at least any of compounds (1) to (216) as defined above or any of its pharmaceutically acceptable salts, for use as a medicament.

In another aspect, there is provided the use of the compound of formula (I) as defined above or any of its pharmaceutically acceptable salts, or at least any of compounds (1) to (216) as defined above or any of its pharmaceutically acceptable salts in the

manufacture of a medicament for the treatment and/or in the prevention of a disease selected from cognitive deficits associated with Down syndrome (Trisomy 21); Alzheimer's disease and related diseases; dementia; tauopathies; and other neurodegenerative diseases (Parkinson's disease; Pick disease, including Niemann-Pick Type C Disease); CDKL5 Deficiency Disorder; McDermid syndrome; autism; type 1 and type 2 diabetes; abnormal folate and methionine metabolism; osteoarthritis, in particular knee osteoarthritis; Duchenne muscular dystrophy; several cancers, such as brain cancer, including glioblastoma, leukemia, including megakaryoblastic leukemia and acute lymphoblastic leukemia, head and neck squamous cell carcinoma, pancreatic cancer, including pancreatic ductal adenocarcinoma, prostate cancer, gastrointerstinal cancer, breast cancer, such as Triple-negative breast cancer (TNBC), tissue cancer, including liposarcoma, Hedgehog/GLI-dependent cancer, liver cancer, including Hepatocellular carcinoma and viral infections, such as caused by Human immunodeficiency virus type 1 (HIV-1), Human cytomegalovirus (HCMV), Influenza A, Herpes virus, rhesus macaque cytomegalovirus, varicella-zoster virus, herpes simplex virus (HSV), Hepatitis C virus, Chikungunya virus, Dengue virus, Influenza virus and Severe acute respiratory syndrome (SARS) coronavirus, Cytomegalovirus and Human papillomavirus; neuroinflammation; anemia; infections caused by unicellular parasites, such as malaria, Leishmaniasis, Chagas and sleeping sickness (*Trypanosoma* sp.), and cattle diseases due to unicellular pathogens,and for regulating body temperature.

In another aspect, there is provide the use of the compound of formula (I) as defined above or any of its pharmaceutically acceptable salts, or at least any of compounds (1) to (216) as defined above or any of its pharmaceutically acceptable salts in the manufacture of a medicament for the treatment and/or prevention of a disease selected from Down syndrome, Alzheimer's disease, dementia, tauopathies, Parkinson's disease, Niemann-Pick Type C Disease, CDKL5 Deficiency Disorder and Phelan-McDermid syndrome and their associated cognitive and motor conditions and type 1 and type 2 diabetes.

DEFINITIONS

As used herein, the term "patient" refers to either an animal, such as a valuable animal for breeding, company or preservation purposes, or preferably a human or a human

child, which is afflicted with, or has the potential to be afflicted with one or more diseases and conditions described herein.

In particular, as used in the present application, the term “patient” refers to a mammal such as a rodent, cat, dog, primate or human, preferably said subject is a human and also extends to birds.

The identification of those patients who are in need of treatment of herein-described diseases and conditions is well within the ability and knowledge of one skilled in the art. A veterinarian or a physician skilled in the art can readily identify, by the use of clinical tests, physical examination, medical/family history or biological and diagnostic tests, those patients who are in need of such treatment.

In the context of the invention, the term “treating” or “treatment”, as used herein, means preventing, reversing, alleviating, inhibiting the progress of, or preventing the disease and its cognitive, motor or metabolic changes resulting from high DYRK1A kinase and/or CLK1 expression and activity, and optionally associated with the abnormalities in other DYRKs (DYRK1B, 2, 3, 4) and the closely related further cdc2-like kinases (CLKs)