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(54) Title: TREATMENT OF EPILEPSY

(57) Abstract: The present invention relates to the compounds of formula I' for use in the treatment of epilepsy, epileptogenesis, seizure disorders and convulsions.



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Treatment of Epilepsy

INTRODUCTION

Epilepsy refers to a clinical phenomenon rather than a single disease entity and describes a condition in which a person has recurrent seizures due to a chronic, underlying process.

- 5 Four subdivisions of epilepsy are recognized: grand mal epilepsy (with subgroups: generalized, focal, jacksonian), petit mal epilepsy, psychomotor or temporal lobe epilepsy (with subgroups: psychomotor proper or tonic with adverse or torsion movements or masticatory phenomenon, automatic with amnesia, or sensory with hallucinations or dream states) and autonomic or diencephalic epilepsy (with flushing, pallor, tachycardia, 10 hypertension, perspiration or other visceral symptoms).

- While epilepsy is one of the foremost examples of a seizure-related disorder, a wide variety of neurological and psychiatric symptoms and disorders may have, as their etiology, seizures or related seizure-like neurological phenomenon. In simple terms, a seizure or a related seizure-like neurological phenomenon is a single discrete clinical 15 event caused by an excessive electrical discharge from a collection of neurons or a seizure susceptible group of neurons through a process termed "ictogenesis." As such, ictogenic seizures may be merely the symptom of a disease. However, epilepsy and other analogous seizure-related disorders are dynamic and often progressive diseases, with a maturation process characterized by a complex and poorly understood sequence of 20 pathological transformations.

- The development and maturation of such changes is the process of "epileptogenesis," whereby the larger collection of neurons that is the normal brain is altered and subsequently becomes capable of generating abnormal, spontaneous, sudden, recurrent, excessive electrical discharges, i.e., seizures. The maturation of the epileptogenic process 25 results in the development of an "epileptogenic focus," whereby the collections of abnormally discharging neurons or neurons susceptible to seizures form localized groups or "epileptogenic zones" interspersed throughout the cortical tissue. The epileptogenic zones are biochemically inter-connected such that an abnormal ictogenic discharge is able to cascade from zone to zone.

- 30 As epileptogenesis progresses, the involved areas of the nervous system become more excitable and it becomes easier for a seizure to be triggered, resulting in progressively debilitating symptoms of the seizure or seizure-related disorder.

While ictogenesis and epileptogenesis may have a common origin in certain biochemical phenomenon and common neuronal pathways in various diseases, the two processes are not identical. Ictogenesis is the initiation and propagation of a seizure in a discrete time and space, a rapid and definitive electrical/chemical event that occurs over a period of time ranging from seconds to minutes.

Comparatively, epileptogenesis is a gradual biochemical or neuronal restructuring process whereby the normal brain is transformed by ictogenic events into an epileptogenically focused brain, having neuronal circuitry that becomes sensitized and responsive to ictogenic events, making an individual increasingly susceptible to the recurrence of spontaneous, episodic, time- limited seizures, resulting in progressively debilitating symptoms of the seizure or seizure-related disorder and progressive non-responsiveness to treatment. The maturation of an "epileptogenic focus" is a slow biochemical and/or structural process that generally occur over months to years. Epileptogenesis is a Two Phase Process:

"Phase 1 epileptogenesis" is the initiation of the epileptogenic process prior to the first epileptic seizure or symptom of an analogous seizure-related disorder, and is often the result of some kind of injury or trauma to the brain, i.e., stroke, disease (e.g., infection such as meningitis), or trauma, such as an accidental blow to the head or a surgical procedure performed on the brain.

"Phase 2 epileptogenesis" refers to the process during which brain tissue that is already susceptible to epileptic seizures or seizure related phenomena of an analogous seizure-related disorder, becomes still more susceptible to seizures of increasing frequency and/or severity and/or becomes less responsive to treatment. While the processes involved in epileptogenesis have not been clearly identified, it is believed by many scientists that the up regulation of excitatory coupling between neurons, mediated by N-methyl-D-aspartate (NMDA) receptors, is involved. Other scientists implicate down regulation of inhibitory coupling between neurons, mediated by gamma-amino-butyric acid (GABA) receptors. Many other factors may be involved in this process relating to the presence, concentration or activity of NO (nitric oxide) or iron, calcium or zinc ions.

Although epileptic seizures are rarely fatal, large numbers of patients require medication to avoid the disruptive, and potentially dangerous consequences of seizures. In many cases, medication used to manage the epileptic seizures or symptoms of an analogous seizure-related disorder is required for extended periods of time, and in some cases, a patient must continue to take such prescription medication for life. Furthermore, such

drugs are only effective for the management of symptoms and have side effects associated with chronic, prolonged usage.

Accepted drugs for the treatment of epilepsy are anticonvulsant agents or, more properly termed, anti-epileptic drugs (AEDs), wherein the term "anti-epileptic" is synonymous with "anti-seizure" or "anti-ictogenic". These drugs therapeutically suppress seizures by blocking the initiation of a single ictogenic event. But those AEDs now clinically available, do not prevent the process of epileptogenesis. In treating seizures or related symptoms of analogous seizure-related disorders, that is for diseases and disorders with seizure-like neurological phenomenon that may apparently be related to seizures disorders, such as mood cycling in Bipolar Disorder, impulsive behavior in patients with Impulse Control Disorders or for seizures resulting from brain injury, some AEDs may also be therapeutically useful. However, those AEDs now approved are unable to prophylactically or therapeutically prevent the initial development or progressive maturation of epileptogenesis to an epileptogenic focus that also characterizes analogous seizure-related disorders.

A wide variety of AEDs are available for the management of epileptic seizures and include older agents such as phenytoin, valproate and carbamazepine, as well as newer agents such as felbamate, gabapentin, topiramate, levetiracetam, lacosamide and tiagabine.

SUMMARY OF THE INVENTION

The present invention relates to a new treatment of an epileptic disorder, in particular of epilepsy, epileptogenesis, seizure disorders and convulsions.

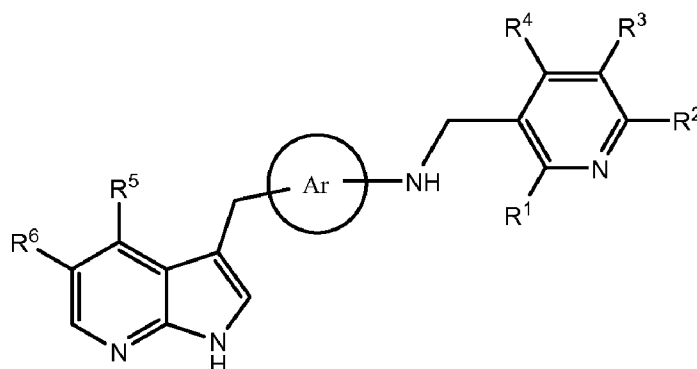
FIGURES

Figure 1 shows the effects of a test compound on the daily frequency of spontaneous recurrent seizures in the pilocarpine model of temporal lobe epilepsy. Baseline seizure frequency was determined during 2-week video-accelerometry monitoring, followed by 2-week treatment phase with 3 and 30 mg/kg (p.o., once daily). * $P < 0.05$ vs. baseline (t -test).

Figure 2 shows the effects of a test compound on cumulative duration of hippocampal paroxysmal discharges (HPD) in the intra-hippocampal kainate model of temporal lobe epilepsy. D5 and D8 – days 5 and 8 after baseline readout, respectively. The test compound (30 mg/kg) was given once daily (p.o.) for 4 days after baseline HPD readout. 120 min. EEG recording was used to calculate the cumulative duration of HPD. * $P < 0.05$ vs. baseline (t -test).

DETAILED DESCRIPTION OF THE INVENTION

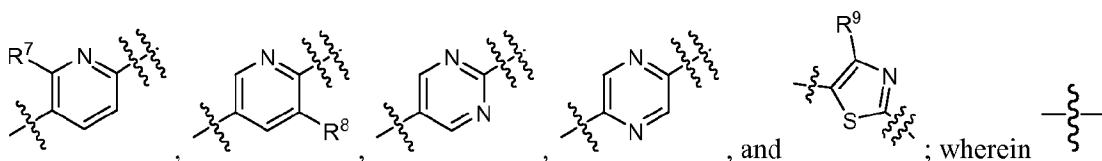
The present invention relates to compounds of Formula I' for the treatment of an epileptic disorder :



Formula I'

Formula I' also comprises the compounds in their salt form, a prodrug, a tautomer or a stereoisomer thereof.

In Formula I', Ar is selected from the group consisting of:



indicates the point of attachment of Ar to -CH₂- of Formula I' and wherein



indicates the point of attachment of Ar to -NH- of Formula I';

R¹, R², R³ and R⁴ are each independently selected from the group consisting of -H, halogen, lower alkyl, halogen substituted lower alkyl, halogen substituted lower alkoxy, alkoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R⁴⁰, -S(O)₂-R⁴¹, -S(O)₂-N(H)-R⁴², -N(H)-R⁴², -N(R⁴²)₂, and -N(H)-S(O)₂-R⁴³, wherein:

R⁴⁰ is lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, or cycloalkyl;

R⁴¹, R⁴² and R⁴³ are lower alkyl;

R⁵ is selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, halogen substituted alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R¹⁰, -C(=O)-N(H)-¹¹,

$-C(=O)-O-R^{11}$, $-S(=O)_2-R^{12}$, $-S(=O)_2-N(H)-R^{12}$, $-N(H)-C(=O)-R^{12}$, and $-N(H)-S(=O)_2-R^{12}$, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl;

R^6 is selected from the group consisting of H, halogen, lower alkyl, halogen substituted alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, $-CN$, $-O-R^{13}$, $-C(=O)-N(H)-R^{14}$, $-C(=O)-O-R^{14}$, $-S(=O)_2-R^{15}$, $-S(=O)_2-N(H)-R^{14}$, $-N(H)-C(=O)-R^{15}$, and $-N(H)-S(=O)_2-R^{15}$, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl;

R^7 is H, halogen or lower alkyl;

R^8 is H, halogen or lower alkoxy;

R^9 is H or halogen;

R^{10} and R^{13} are independently -H, lower alkyl, lower alkyl substituted with $-O-CH_3$, lower alkyl substituted with di-alkylamine, or lower alkyl substituted with heterocycloalkyl;

R^{11} and R^{14} are independently hydrogen or lower alkyl; and

R^{12} and R^{15} are each independently lower alkyl,

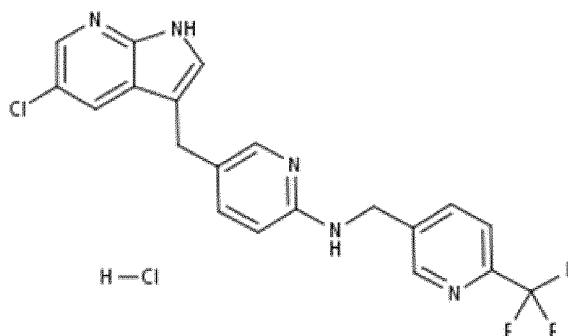
In a specific embodiment, Ar is a pyridyl moiety.

In a specific embodiment, R^6 is selected from a halogen, lower alkyl, halogen substituted alkyl.

In a specific embodiment, R^5 is selected from a halogen, lower alkyl, halogen substituted alkyl.

In a specific embodiment, one of R^1 , R^2 , R^3 and R^4 is selected from a halogen, lower alkyl, halogen substituted lower alkyl, whereas the others are hydrogen.

In a specific embodiment, the compound for the treatment according to this invention has the following structure in its salt form or in its free base form :



Further compounds according to Formula I' that are useful for the treatment of an epileptic disorder are the following :

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,6-dimethoxy-pyridin-3-ylmethyl) amine

[6-Fluoro-5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl) amine

- 5 N-(3-{2-Fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino] -pyridin-3-yl-methyl}-1H-pyrrolo[2,3-b]pyridin-5-yl) acetamide

N-(3-{6-[(6-Chloro-pyridin-3-ylmethyl)-amino]-2-fluoro-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-methanesulfonamide

- 10 [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl) amine

[6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl) amine

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl) amine

- 15 [6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl) amine

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-methoxy-pyridin-3-ylmethyl) amine

- 20 [6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-yl-methyl) amine

[6-Fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl) amine

(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine

- 25 (5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl) amine

(6-Methoxy-pyridin-3-yl-methyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl] amine

(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl] amine

- 5 [6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl) amine

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl) amine

- 10 [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl) amine

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methyl-pyridin-4-ylmethyl) amine

[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl) amine

- 15 (5-Fluoro-2-methoxy-pyridin-4-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl] amine

(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl] amine

- 20 [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(2-methyl-pyridin-4-ylmethyl) amine

(6-Chloro-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl] amine

(6-Chloro-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl] amine

- 25 (2,6-Dimethoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl] amine

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-fluoro-pyridin-3-ylmethyl) amine

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-fluoro-pyridin-4-ylmethyl) amine

(2-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl] -amine

- 5 3-{[5-(5-Chloro-1 H-pyrrolo [2,3 -b]pyridin-3-ylmethyl)-pyrimidin-2-ylamino]-methyl}-5-fluoro-1-methyl-1H-pyridin-2-one

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl) amine

- 10 [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-pyridin-3-ylmethyl) amine

3-{2-Fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile

5-[(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]pyridin-2-amine

- 15 3-[[2-fluoro-6-[(5-fluoro-6-methoxy-3-pyridyl)methylamino]-3-pyridyl]methyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile

6-chloro-N-[(5-fluoro-2-methoxy-3-pyridyl)methyl]-5-[(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]pyridin-2-amine

- 20 6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]-5-[[5-(trifluoromethyl)-1H-pyrrolo-[2,3- b]pyridin-3-yl]methyl]pyridin-2-amine

(6-Methoxy-pyridin-3-yl-methyl)-[3-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl] amine

[3-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl) amine

- 25 (6-Chloro-pyridin-3-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl] amine

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-fluoro-pyridin-3-yl-methyl) amine

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3,4-difluorobenzyl) amine

[5-(5-Chloro-1H-pyrrolo [2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-methyl-benzyl) amine

- 5 [5-(5-Methyl-1 H-pyrrolo [2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethylpyridin-3-ylmethyl) amine

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl) amine

- 10 (4-Chloro-benzyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl] amine

(4-Chloro-benzyl)-[6-fluoro-5-(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine

(6-Methyl-pyridin-2-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl] -amine

- 15 [5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-morpholin-4-ylpyridin-2-ylmethyl) amine

[5-(5-Methyl-1H-pyrrolo [2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-pyrrolidin-1-ylpyridin-2-ylmethyl) amine

- 20 [6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-methylpyridin-2 -ylmethyl)-amine

[3-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3 -ylmethyl) amine

[3-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl) amine

- 25 (2-Cyclopentyloxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo [2,3-b]pyridin-3-ylmethyl)- pyrimidin-2-yl] amine

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-3- ylmethyl) amine

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-2-ylmethyl) amine

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3-fluoro-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl) amine

- 5 Ethanesulfonic acid (2- {[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-phenyl) amide

Ethanesulfonic acid (3-fluoro-5-[[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl]-phenyl) amide

- 10 (6-Trifluoromethyl-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine

(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl] amine

[5-(5-Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl) amine

- 15 (6-Chloro-pyridin-3-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridinyl] amine

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-fluoro-pyridin-3-ylmethyl) amine

- 20 [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-fluoro-5-trifluoromethyl-benzyl) amine

[5-(5-Methyl-1H-pyrrolo [2,3-b]pyridin-3-yl-methyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl) amine

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl) amine

- 25 [6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl) amine

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl) amine

(4-Chloro-benzyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl] amine

(2-Chloro-benzyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl] amine

5 (4-Chloro-benzyl)-[6-fluoro-5-(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]amine

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-methoxy-pyridin-3-ylmethyl) amine

10 (5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl] amine

(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl] amine

(5-Chloro-pyridin-2-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl] amine

15 (5-Chloro-pyridin-2-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl] amine

(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl] amine

20 (4-Chloro-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl] amine

(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl] amine

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl) amine

25 All atoms designated within a Formula described herein, either within a structure provided, or within the definitions of variables related to the structure, is intended to include any isotope thereof, unless clearly indicated to the contrary. It is understood that for any given atom, the isotopes may be present essentially in ratios according to their natural occurrence, or one or more particular atoms may
30 be enhanced with respect to one or more isotopes using synthetic methods known

to one skilled in the art.

"Halogen" or "Halo" refers to all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), or iodo (I).

5 "Lower alkyl" alone or in combination means an alkane-derived radical containing from 1 to 6 carbon atoms (unless specifically defined) that includes a straight chain alkyl or branched alkyl. In many embodiments, a lower alkyl is a straight or branched alkyl group containing from 1-6, 1-4, or 1-2, carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and the like. A lower alkyl may be independently substituted as described herein, unless indicated otherwise, with
10 one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, wherein the substituents are as indicated.

Furthermore, possible substitutions are attached at any available atom to produce a stable compound. For example "halo substituted lower alkyl" denotes a lower alkyl group substituted with one or more halogen atoms, where preferably the
15 lower alkyl is substituted with 1, 2, 3, 4 or 5 halogen atoms, also 1, 2, or 3 halogen atoms. Furthermore, possible substitutions are attached at any available atom to produce a stable compound. For example "fluoro substituted lower alkyl" denotes a lower alkyl group substituted with one or more fluoro atoms, such as perfluoroalkyl, where preferably the lower alkyl is substituted with 1, 2, 3, 4 or 5
20 fluoro atoms, also 1, 2, or 3 fluoro atoms. Exemplary fluoro substituted lower alkyl includes, but is not limited to, CF_3 , CF_2CF_3 , CH_2CF_3 , and the like. It is understood that substitutions are chemically feasible and attached at any available atom to provide a stable compound.

25 "Lower alkoxy" refers to those lower alkyl groups as defined herein attached to the remainder of the molecule via an oxygen atom. Representative alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, n-pentoxy, n-heptoxy, and the like, as well as isomers thereof.

"Lower alkenyl" alone or in combination means a straight or branched hydrocarbon containing 2-6 carbon atoms (unless specifically defined) and at least one,
30 preferably 1-3, more preferably 1-2, most preferably one, carbon to carbon double bond. Carbon to carbon double bonds may be either contained within a straight chain or branched portion. The straight chain or branched lower alkenyl group is chemically feasible and attached at any available point to provide a stable compound. Examples of lower alkenyl groups include ethenyl, propenyl,

isopropenyl, butenyl, and the like.

"Lower alkynyl" alone or in combination means a straight or branched hydrocarbon containing 2-6 carbon atoms (unless specifically defined) containing at least one, preferably one, carbon to carbon triple bond. The straight chain or branched lower alkynyl group is chemically feasible and attached at any available point to provide a stable compound. Examples of alkynyl groups include ethynyl, propynyl, butynyl, and the like.

"Cycloalkyl" refers to saturated or unsaturated, non-aromatic monocyclic, bicyclic or tricyclic carbon ring systems of 3-10, also 3-8, more preferably 3-6, ring members per ring, such as cyclopropyl, cyclopentyl, cyclohexyl, adamantyl, and the like.

"Heterocycloalkyl" refers to a saturated or unsaturated non-aromatic cycloalkyl group having from 5 to 10 atoms in which from 1 to 3 carbon atoms in the ring are replaced by heteroatoms of O, S or N, and are optionally fused with benzo or heteroaryl of 5-6 ring members. Heterocycloalkyl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. Heterocycloalkyl is also intended to include compounds in which a ring carbon may be oxo substituted, i.e. the ring carbon is a carbonyl group, such as lactones and lactams. The point of attachment of the heterocycloalkyl ring is at a carbon or nitrogen atom such that a stable ring is retained. Examples of heterocycloalkyl groups include, but are not limited to, morpholino, tetrahydrofuranyl, dihydropyridinyl, piperidinyl, pyrrolidinyl, pyrrolidonyl, piperazinyl,

The compounds claimed herein may be obtained according to the methods described in WO 2008/064265 and WO 2011/057022.

EXAMPLES

Example 1 : Pilocarpine mouse of model of temporal lobe epilepsy

The pilocarpine model of temporal lobe epilepsy and epileptogenesis was performed as previously described (Mazzuferi et al., 2012). Male NMRI mice (Charles River, France) weighing 28-32 g were used for all experiments. Procedures involving animals and their care were conducted in accordance with current European Community regulations. N-Methylscopolamine was dissolved in saline and injected ip 30 min (1 mg/kg) before administration of pilocarpine 300 mg/kg, ip. Within minutes after injection of pilocarpine

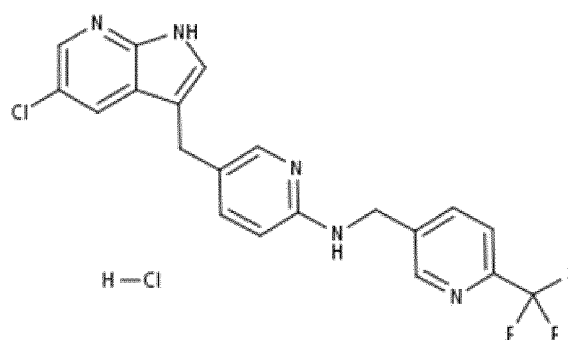
the mice start to develop convulsive seizures and $\pm$ 30-40% of the animals will develop a long-lasting continuous seizure (i.e. status epilepticus; SE). SE was stopped after 3-h duration by bolus (ip) injection of diazepam (10 mg/kg). The mice surviving SE develop spontaneous recurrent seizures (SRSs) starting from 24-72 h after SE. These initial SRSs are typically stage 3/4 on Racine's seizure severity scale and fairly frequent (4-5 seizures per 24 h), then after 1-2 weeks the seizures become more severe (stage 4/5 mainly), but less frequent (1-2 seizures per week).

Example 2 : Intra-hippocampal kainate model of temporal lobe epilepsy

Unilateral injection of a small dose of kainate (KA) in the dorsal hippocampus of mice results in neuronal losses in CA1, CA3 areas and hilus, mossy fiber sprouting and dispersion of the dentate gyrus, which are all features of human temporal lobe epilepsy. Three weeks after KA injection, spontaneous and recurrent hippocampal paroxysmal discharges (HPD), lasting about 15-20 s, are observed in the EEG concomitantly with behavioral arrest and/or automatisms. These focal seizures typically remain stable during the rest of the life of the animals and occur regularly at a frequency of about 40/h (Bouilleret et al., 1999 and Riban et al., 2002).

In this study C57/BL6 mice, from Janvier (France) were used. After surgery, animals were housed in individual cages with access to food and water ad libitum under a 12/12h light and dark cycle (light on at 8:00 a.m). Procedures involving animals and their care were conducted in accordance with current European Community regulations. Stereotaxic injection and implantation of electrodes were performed under general anaesthesia using isoflurane (3% in oxygen). A stainless steel cannula (outer diameter, 0.28 mm) connected to a 0.5 μ l micro-syringe via PE20 tubing containing distilled water, is filled with a 20 mM kainic acid solution (KA; Sigma, Lyon, France) in 0.9% sterile NaCl and positioned in the right dorsal hippocampus (AP = - 2, ML = -1.5, DV = - 2 mm with bregma as reference (Paxinos and Franklin, 2001). Mice receive 50 nl of the KA solution (1 nmol) over 1 min using a micro-pump. After injection, the cannula is left in place for an additional 1-min period to avoid reflux along the cannula track. After KA injection, mice were implanted with a bipolar electrode in the ipsilateral dorsal hippocampus and a reference electrode over the cerebellum.

The test compound according to Formula I' was



which was synthesized by UCB Biopharma Sprl, dissolved in in methylcellulose 1%, Tween 80 0.1%, silicone Antifoam 1510 0.1% in water to concentrations of 0.326 and 3.26 mg/ml

5 Testing:

Pilocarpine model

A stable seizure number and typical clustering of SRSs are observed from 6-8 weeks onwards in the pilocarpine model (Mazzuferi et al., 2012). Therefore 6 weeks after SE, the mice were screened during 2 weeks monitoring by video-accelerometry to confirm
10 presence of SRSs and their frequency. Only the mice that reliably displayed SRSs were then selected for the next part of the experiment. At this time they were divided into three groups (N=20) and monitored for 2 weeks by continuous video-accelerometry to establish their SRS baseline frequency. After this period each group of animals received either
15 vehicle (p.o.) or the above test compound (PLX-3397) (p.o) at either 10 or 30 mg/kg (single daily administration for 2 weeks). Pilot pharmacokinetics data indicated that p.o. administration of the test compound (10 mg/kg) in NMRI mice produced brain exposures of ~1.1 μ M in mice and brain/plasma ratios were equal to ~0.25 at 2h and ~0.5 at 6h following the drug administration.

20 *Kainate model*

One baseline EEG recording (2 hours duration) was performed 4 weeks after kainate (KA) injection and before the beginning of chronic treatment (D0). Only mice with confirmed and stable spontaneous and recurrent hippocampal paroxysmal discharges (HPD) were selected for the study (i.e. with a mean number of ~40 hippocampal discharges/hour).
25 Then these mice (n=8) were given the test compound at 30 mg/kg p.o. (one injection per

day between 8 and 9 AM) for four consecutive days. An EEG recording (2 hours) was performed on the fifth day (i.e the day after the last drug treatment). A washout period of 2 days was then allowed and an additional EEG recording (2 hours) was performed on D8.

Results:

- 5 As shown in Figure 1, the test compound produced dose-dependent reduction in the daily frequency of SRSs, when compared to baseline values in the pilocarpine model of temporal lobe epilepsy. This effects reached statistical significance ($P<0.05$, t -test) at the dose of 30 mg/kg.

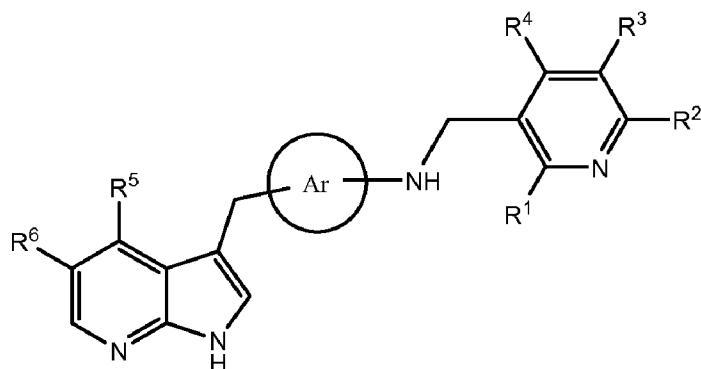
- 10 Treatment with the test compound at 30 mg/kg produced a significant decrease in cumulative duration of HPD in the kainate model when compared to the baseline period at D5 ($P<0.05$; t -test). This effect was no longer seen on D8 and the cumulative duration of HPD returned to the baseline value (Figure 2).

REFERENCES

- 15 • Bouilleret V, Ridoux V, Depaulis A, Marescaux C, Nehlig A, Le Salle G.G. Recurrent seizures and hippocampal sclerosis following intrahippocampal kainate injection in adult mice: electroencephalography, histopathology and synaptic reorganization similar to mesial temporal lobe epilepsy. *Neuroscience* 1999; 89: 717-29.
- 20 • Mazzuferi M, Kumar G, Rospo C, Kaminski RM. Rapid epileptogenesis in the mouse pilocarpine model: video-EEG, pharmacokinetic and histopathological characterization. *Exp Neurol*. 2012; 238: 156-167.
- 25 • Riban, V., Bouilleret, V., Pham-Le, B., & Fritschy, J. (2002) Evolution of hippocampal epileptic activity during the development of hippocampal sclerosis in a mouse model of temporal lobe epilepsy. *Neuroscience* 2002; 112: 101-111.

CLAIMS

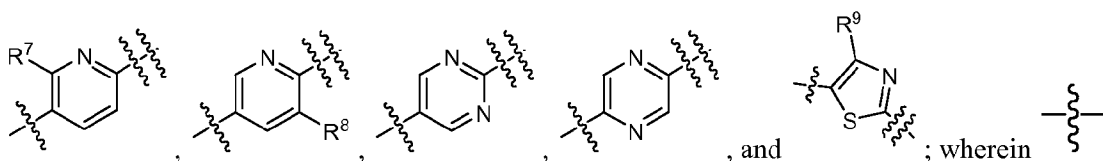
1. A compound of Formula I' for use in the treatment of an epileptic disorder :



Formula I'

or a salt, a prodrug, a tautomer or a stereoisomer thereof, wherein

Ar is selected from the group consisting of:



indicates the point of attachment of Ar to -CH₂- of Formula I' and wherein



indicates the point of attachment of Ar to -NH- of Formula I';

R¹, R², R³ and R⁴ are each independently selected from the group consisting of -H, halogen, lower alkyl, halogen substituted lower alkyl, halogen substituted lower alkoxy, alkoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R⁴⁰, -S(O)₂-R⁴¹, -S(O)₂-N(H)-R⁴², -N(H)-R⁴², -N(R⁴²)₂, and -N(H)-S(O)₂-R⁴³, wherein:

R⁴⁰ is lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, or cycloalkyl;

R⁴¹, R⁴² and R⁴³ are lower alkyl;

R⁵ is selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, halogen substituted alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R¹⁰, -C(O)-N(H)-R¹¹, -C(O)-O-R¹¹, -S(O)₂-R¹², -S(O)₂-N(H)-R¹², -N(H)-C(O)-R¹², and -

N(H)-S(O)₂-R¹², wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl;

R⁶ is selected from the group consisting of H, halogen, lower alkyl, halogen substituted alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R¹³, -C(O)-N(H)-R¹⁴, -C(O)-O-R¹⁴, -S(O)₂-R¹⁵, -S(O)₂-N(H)-R¹⁴, -N(H)-C(O)-R¹⁵, and -N(H)-S(O)₂-R¹⁵, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl;

R⁷ is H, halogen or lower alkyl;

R⁸ is H, halogen or lower alkoxy;

R⁹ is H or halogen;

R¹⁰ and R¹³ are independently -H, lower alkyl, lower alkyl substituted with -O-CH₃, lower alkyl substituted with di-alkylamine, or lower alkyl substituted with heterocycloalkyl;

R¹¹ and R¹⁴ are independently hydrogen or lower alkyl; and

R¹² and R¹⁵ are each independently lower alkyl.

2. Compound according to claim 1, wherein Ar is a pyridyl moiety.
3. Compound according to claim 1 or 2, wherein R⁶ is a halogen, lower alkyl, halogen substituted alkyl.
4. Compound according to any of claim 1-3, wherein R⁵ is a halogen, lower alkyl, halogen substituted alkyl.
5. Compound according to any of claim 1-4, wherein one of R¹, R², R³ and R⁴ is a halogen, lower alkyl, halogen substituted lower alkyl, whereas the others are hydrogen.
6. Compound according to any of claim 1-5, wherein a lower alkyl is a methyl, ethyl, propyl, isopropyl, butyl, t-butyl group.
7. Compound according to any of claim 1-5, wherein a lower alkyl is a methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, n-pentoxy, n-heptoxy group.
8. Compound according to any of claim 1-7, having the following structure :

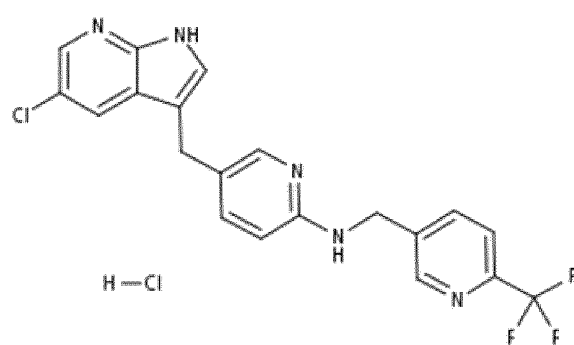
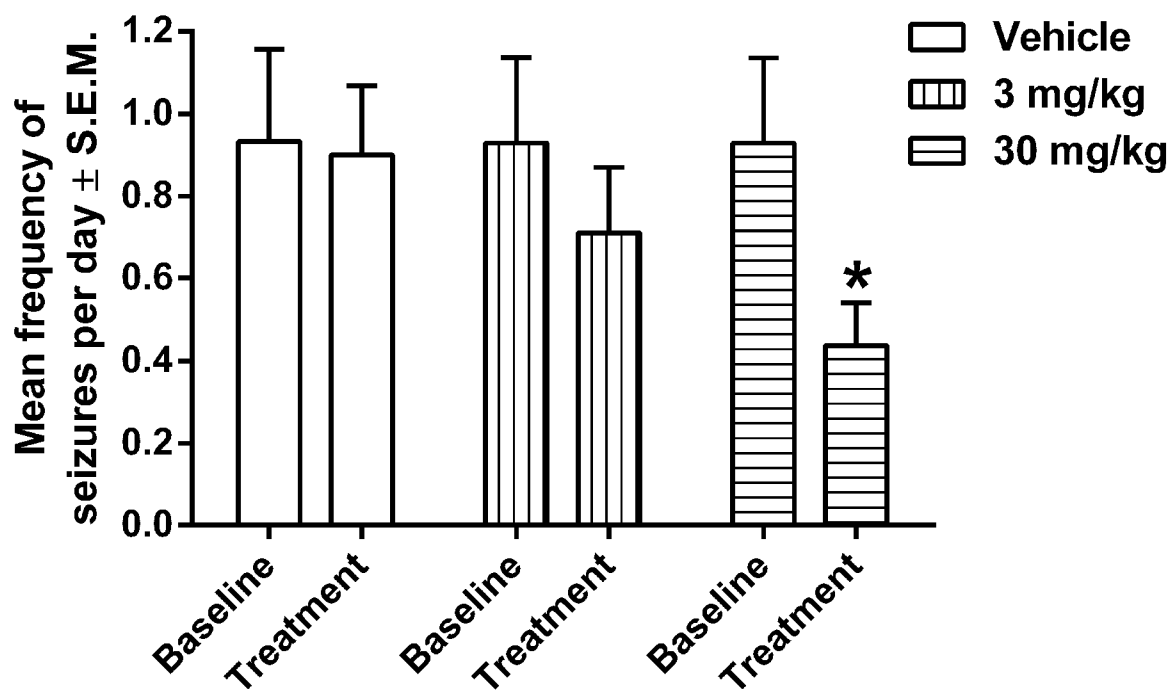
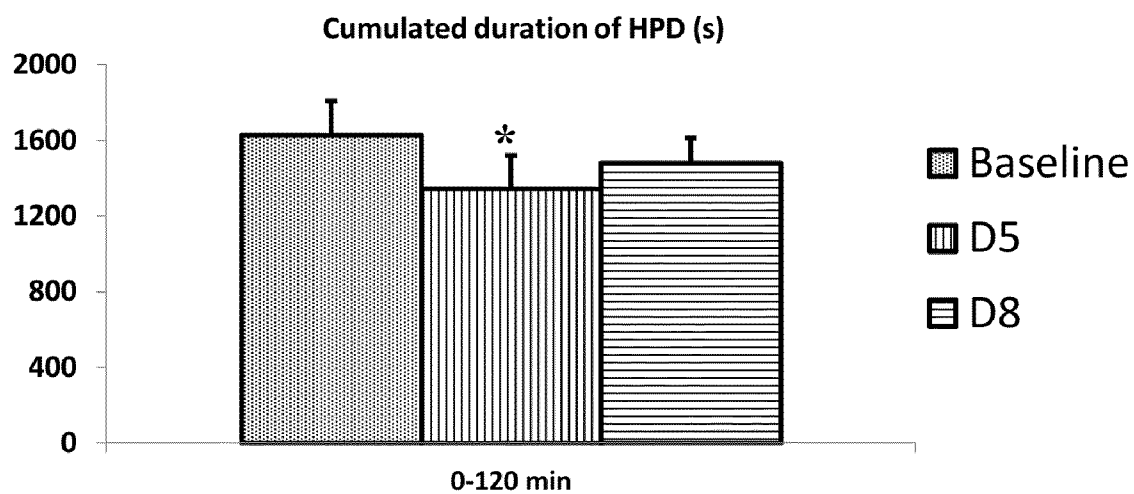


Figure 1



5

Figure 2.



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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/061110

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/427 A61K31/437 A61K31/444 A61K31/497 A61K31/506
A61P25/08

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010/055127 A1 (NEUROSEARCH AS [DK]; LARSEN JANUS S [DK]; AHRING PHILIP K [DK]; NIELSE) 20 May 2010 (2010-05-20) claims 1, 5, 10 -----	1-8
A	WO 2013/142427 A1 (PLEXXIKON INC [US]) 26 September 2013 (2013-09-26) page 77 Claims -----	1-8
A	WO 2011/057022 A1 (PLEXXIKON INC [US]; ZHANG JIAZHONG [US]; IBRAHIM PRABHA N [US]; BREMER) 12 May 2011 (2011-05-12) cited in the application Claims -----	1-8
	-/-	



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

4 August 2016

Date of mailing of the international search report

18/08/2016

Name and mailing address of the ISA/

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Authorized officer

Collura, Alessandra

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/061110

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CATHERINE C SMITH ET AL: "764: PLX3397 Is An Investigational Selective FLT3 Inhibitor That Retains Activity Against the Clinically-Relevant FLT3-ITD/F691L "Gatekeeper" Mutation in Vitro", BLOOD, vol. 118, no. 21, 18 November 2011 (2011-11-18), - 13 December 2011 (2011-12-13), page 347, XP055193708, US ISSN: 0006-4971 the whole document -----	1-8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2016/061110

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010055127	A1	20-05-2010	NONE
WO 2013142427	A1	26-09-2013	AU 2013235298 A1 30-10-2014 CA 2867918 A1 26-09-2013 CN 104703623 A 10-06-2015 EA 201491721 A1 27-02-2015 EP 2827904 A1 28-01-2015 HK 1204995 A1 11-12-2015 JP 2015510944 A 13-04-2015 KR 20140144229 A 18-12-2014 SG 11201405764Y A 30-10-2014 US 2014037617 A1 06-02-2014 WO 2013142427 A1 26-09-2013
WO 2011057022	A1	12-05-2011	AR 078920 A1 14-12-2011 AU 2010315126 A1 31-05-2012 BR 112012012156 A2 08-09-2015 CA 2780190 A1 12-05-2011 CN 102695417 A 26-09-2012 CO 6541546 A2 16-10-2012 CR 20120221 A 30-07-2012 EA 201290210 A1 30-10-2012 EC SP12011868 A 28-09-2012 EP 2496086 A1 12-09-2012 JP 2013510166 A 21-03-2013 JP 2016106090 A 16-06-2016 KR 20120102669 A 18-09-2012 MA 33975 B1 01-02-2013 NZ 599866 A 26-09-2014 NZ 629615 A 29-01-2016 PE 13272012 A1 18-10-2012 SG 10201407129S A 30-12-2014 TW 201121969 A 01-07-2011 UA 105813 C2 25-06-2014 US 2011112127 A1 12-05-2011 US 2014045840 A1 13-02-2014 UY 33016 A 31-05-2011 WO 2011057022 A1 12-05-2011