Alzheimer´s desease is an age-related disorder characterized in part by the appearance of intracellular lesions composed of filamentous aggregates of the microtubule-assiciated protein tau. Abnormal tau phosphorylation accompanies tau aggregation and is considered to be an upstream pathological event in this desease. Enzymes implicated in tau hyperphosphorylation in Alzheimer´s desease include members of the casein kinase 1 family. (Kannanayakal, TJ et al. Nuerosci Lett. 2008; 432(2): 141-5.)

The circadian clock links our daily cycles of sleep and activity to the external environment. Deregulation of the clock is implicated in a number of human disorders, including depression, seasonal affective disorder and metabolic disorders. Casein kinase 1 epsilon (CK1ε) and casein kinase 1 delta (CK1δ) are Ser-Thr protein kinases, which are closely related to each other and serve as key clock regulators. This was demonstrated by mutations in CK1δ and CK1ε that dramatically alter the circadian period. Therefore, inhibitors of CK1 have utility in treating circadian disorders. (Walten, K. M. et al. JPET 330:430–439, 2009.)

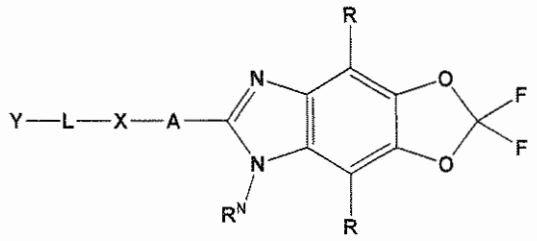
Several publications describe casein kinase inhibitors: Wager Travis et. al. Abstracts of Papers, 238th ACS National Meeting, Washington, DC, United States, August 16-20, 2009; Oumata Nassima et al. Journal of Medicinal Chemistry Volume 51 Issue 17 Pages 5229-5242 Journal 2008; Mashhoon N. et al. J Biol Chem 200; 275(26): 20052-60; Pfeifer C. et al. J Med Chem. 2009 Dec 10; 52(23):7618-30.

In addition several patent applications regarding CK1 δ and/or ε inhibitors were published: US 2010/0179154 A1; US 2004/0110808 A1; US 2008/0027124 A1; US 2009/0099237 A1.

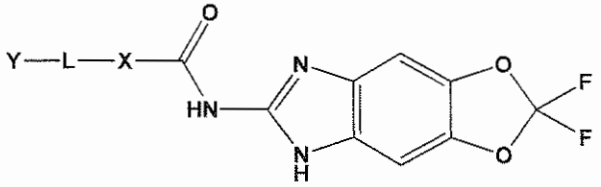
Several patents and patent applications described certain specific acyl-amino- benzimidazoles with pharmacological activity: EP 1 388 341 A1 and US 2004/0110808 A1; US 7,132,438 B2; WO 2007/064932 A2; DE 27 54 930 A1; US 2003/0144286.

BRIEF SUMMARY OF THE INVENTION

In one ~~aspect~~embodiment, the present ~~invention~~ disclosure provides compounds of Formula (I), and in further embodiments compounds of Formula (Ia), and their respective physiologically functional derivatives or salts, where the groups A, X, L, and Y are detailed further herein below.

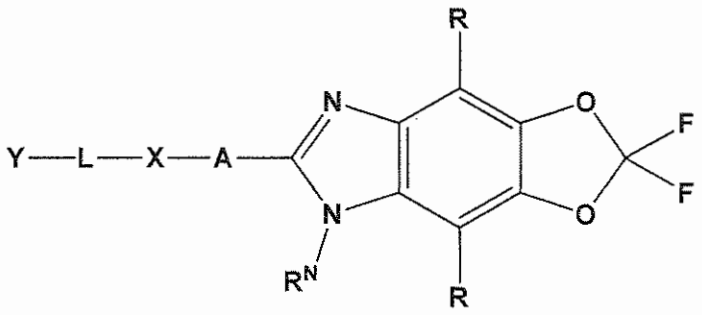


(I)



(Ia)

In one aspect, the present disclosure provides compound of the general formula (I) or a physiologically functional derivative, solvate or salt thereof,



(I) , wherein

R is independently selected from the group comprising H, halogen, C_{1-6}-alkyl, C_{1-6}-haloalkyl, C_{1-6}-haloalkoxy, OH, C_{1-6}-alkoxy, -S-R''', -SO-R''', nitro, $-N(R''')_2$, -NH(R'''), -NHCO(R'''), $-CONH_2$, -CONH(R'''), -CO(R'''), -COH, -COO(R'''), -COOH, $-SO_2NH_2$, $-SO_2NH(R''')$, $-SO_2(R''')$, and $-NH-SO_2(R''')$,

wherein in the cases where said group R is C_{1-6}-alkyl, C_{1-6}-haloalkyl, C_{1-6}-haloalkoxy, or C_{1-6}-alkoxy,said group R may be substituted with one or more substituents R'' independently selected from the group comprising H, halogen, OH, nitro, $-NH_2$, $-N(C_{1-6}\text{-alkyl})_2$, $-NH(C_{1-6}\text{-alkyl})$, $-NHCO(C_{1-6}\text{-alkyl})$, $-CONH_2$, $-CONH(C_{1-6}\text{-alkyl})$, $-CO(C_{1-6}\text{-alkyl})$, -COH, $-COO(C_{1-6}\text{-alkyl})$, -COOH, and -CN,

and wherein R''' is independently selected from the group comprising H, C_{1-6}-alkyl, C_{1-6}-haloalkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl;

R^N is independently selected from the group comprising H, alkyl, haloalkyl, OH, aryl, heteroaryl, cycloalkyl, heterocyclyl, -SO-R''', $-NH_2$, $-N(R''')_2$, -NH(R'''), -NHCO(R'''), $-CONH_2$, -CONH(R'''), -CO(R'''), -COH, -COO(R'''), -COOH, $-SO_2NH_2$, $-SO_2NH(R''')$, $-SO_2(R''')$, and $-NH-SO_2(R''')$, wherein R''' is as defined above,

wherein in the cases where said group R^N is alkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl, said group R^N may be substituted with one or more substituents R''' as defined above;

A is independently selected from $*-N(R^a)CO-$, $*-CON(R^a)-$, $*-SO_2N(R^a)-$, and $*-N(R^a)-SO_2-$,

wherein R^a is selected from H and C_{1-4}-alkyl,

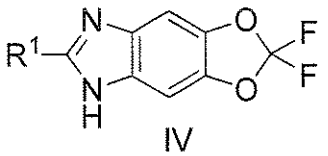
and wherein * specifies the point of attachment to X;

X is independently selected from the group comprising aryl, cycloalkyl, aralkyl, heterocyclyl and heteroaryl, wherein said group X may be substituted with one or more R^X independently selected from the group comprising halogen, C_{1-6}-alkyl, C_{1-6}-haloalkyl, C_{1-6}-haloalkoxy, OH, C_{1-6}-alkoxy, aryl, heteroaryl, cycloalkyl, heterocyclyl, $-S-C_{1-6}$-alkyl, $-S-C_{1-6}$-haloalkyl, nitro, $-NH_2$, $-N(C_{1-6}\text{-alkyl})_2$, $-NH(C_{1-6}\text{-alkyl})$, $-NHCO(C_{1-6}\text{-alkyl})$, $-CONH_2$, $-CONH(C_{1-6}\text{-alkyl})$, $-CO(C_{1-6}\text{-alkyl})$, -COH, $-COO(C_{1-6}\text{-alkyl})$, -COOH, $-SO_2NH_2$, $-SO_2NH(C_{1-6}\text{-alkyl})$, $-SO_2(C_{1-6}\text{-alkyl})$, $-NH-SO_2(C_{1-6}\text{-alkyl})$, C_{3-6}-cycloalkyl, and -CN;

L is independently a bond or a linker group selected from the group comprising *-NHCO-, *-CONH-, *-NH-, $*-N(C_{1-4}\text{-alkyl})-$, $*-C=N(C_{1-4}\text{-alkyl})-$, $*-NH-C_{1-4}$-alkyl-, $*-C_{1-4}$-alkyl-NH-, *-NHCONH-, *-CO-, $*-SO_2-$, C_{1-4}-alkyl, $*-C_{1-2}\text{-alkyl-O-}C_{1-2}$-alkyl-, *-NHCO-CH=CH-, *-CH=CH-CONH-, * $-SO_2NH-$, * $-NHSO_2-$, and pyridinyl, wherein * specifies the point of attachment to X; and

Y is independently selected from the group comprising H, alkyl, aryl, aralkyl, cycloalkyl, heterocyclyl and heteroaryl, wherein said group Y may optionally be substituted with one or more R^Y independently selected from the group comprising halogen, C_{1-6}-alkyl, C_{1-6}-haloalkyl, C_{1-6}-haloalkoxy, OH, C_{1-6}-alkoxy, aryl, heteroaryl, cycloalkyl, heterocyclyl, -S-C_{1-6}-alkyl, -S-C_{1-6}-haloalkyl, nitro, $-NH_2$, $-N(C_{1-6}\text{-alkyl})_2$, $-NH(C_{1-6}\text{-alkyl})$, $-NHCO(C_{1-6}\text{-alkyl})$, $-CONH_2$, $-CONH(C_{1-6}\text{-alkyl})$, $-CO(C_{1-6}\text{-alkyl})$, -COH, $-COO(C_{1-6}\text{-alkyl})$, -COOH, $-SO_2NH_2$, $-SO_2NH(C_{1-6}\text{-alkyl})$, $-SO_2(C_{1-6}\text{-alkyl})$, $-NH\text{-}SO_2(C_{1-6}\text{-alkyl})$, C_{1-6}-alkyl-heterocyclyl, cycloalkyl and -CN.

In another ~~aspect~~embodiment, the present ~~invention~~ disclosure provides methods for preparation of compounds of Formulae (I) or (Ia), physiologically functional derivatives or salts thereof, as detailed further herein below. In another aspect, the present disclosure provides a process for the preparation of a compound as disclosed herein, wherein A is an -CONH- or -NHCO-, the process comprising the step of coupling a compound of below Formula IV with a compound of below formula II;



IV



II

wherein Y, L and X are as defined above, and

wherein either R^1 is NH_2 and R^2 is COOH or COOCl, or wherein R^2 is NH_2 and R^1 is COOH or COOCl.

In another ~~aspect~~embodiment, the present ~~invention~~ disclosure provides methods for the treatment or prevention of certain medical conditions, the method comprising the administration of compounds of Formulae (I) or (Ia), physiologically functional derivatives or salts thereof, to a subject in need thereof, as detailed further herein below.

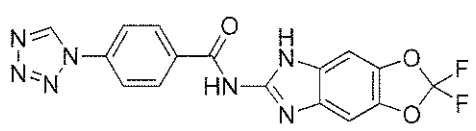
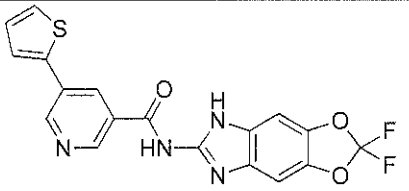
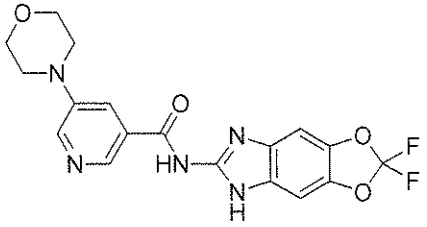
In another ~~aspect~~embodiment, the present ~~invention~~ disclosure provides the use of compounds of Formulae (I) or (Ia), physiologically functional derivatives or salts thereof, in the manufacture of a medicament for the treatment or prevention of certain medical conditions, as detailed further herein below. In another aspect, the present disclosure provides the use of a compound as

disclosed herein, or a physiologically functional derivative, solvate or salt thereof in the manufacture of a medicament for the treatment or prevention of a medical condition selected from the group comprising autoimmune inflammatory disorders, CNS disorders, sleeping disorders, and proliferative diseases including cancer.

In another aspect, the present disclosure provides a compound as disclosed herein or a physiologically functional derivative, solvate or salt thereof for use as a medicament. In another ~~aspect~~embodiment, the present ~~invention~~ disclosure provides compounds of Formulae (I) or (Ia), physiologically functional derivatives or salts thereof, for use in the treatment or prevention of certain medical conditions, as detailed further herein below.

In another aspect, the present ~~invention~~ disclosure provides pharmaceutical compositions comprising compounds of Formulae (I) or (Ia), physiologically functional derivatives or salts thereof and one or more pharmaceutically acceptable excipients.

BRIEF DESCRIPTION OF THE FIGURES

22B	 *N*-(2,2-difluoro-5*H*-[1,3]dioxolo[4',5':4,5]benzo[1,2-*d*]imidazol-6-yl)-4-(1*H*-tetrazol-1-yl)benzamide	23 B	 *N*-(2,2-difluoro-5*H*-[1,3]dioxolo[4',5':4,5]benzo[1,2-*d*]imidazol-6-yl)-5-(thiophen-2-yl)nicotinamide
25B	 *N*-(2,2-difluoro-5*H*-[1,3]dioxolo[4',5':4,5]benzo[1,2-*d*]imidazol-6-yl)-5-morpholinonicotinamide		

or a physiologically functional derivative, solvate or salt thereof.

8. The compound according to any of claims 1 to 7 or a physiologically functional derivative, solvate or salt thereof for use as a medicament.

9. The compound according to any of claims 1 to 7 or a physiologically functional derivative, solvate or salt thereof for use in the treatment or prevention of a medical condition selected from the group comprising autoimmune inflammatory disorders, CNS disorders, sleeping disorders, and proliferative diseases including cancer.

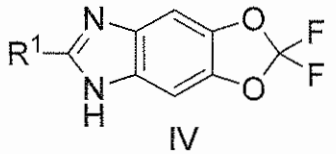
10. A pharmaceutical composition comprising a compound according to any of claims 1 to 7 or a physiologically functional derivative, solvate or salt thereof and one or more pharmaceutically acceptable excipients.

~~11. A method of treatment or prevention of a medical condition selected from the group comprising autoimmune inflammatory disorders, CNS disorders, sleeping disorders, and proliferative diseases including cancer, which comprises the administration of an effective amount of a compound according to any of claims 1 to 7, or a physiologically~~

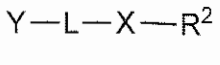
~~functional derivative, solvate or salt thereof to a subject in need thereof.~~

~~12.~~11. Use of a compound according to any of claims 1 to 7, or a physiologically functional derivative, solvate or salt thereof in the manufacture of a medicament for the treatment or prevention of a medical condition selected from the group comprising autoimmune inflammatory disorders, CNS disorders, sleeping disorders, and proliferative diseases including cancer.

~~13.~~12. Process for the preparation of a compound according to any of claims 1 to 7, wherein A is an -CONH- or -NHCO-, the process comprising the step of coupling a compound of below Formula IV with a compound of below formula II;



IV



II ,

wherein Y, L and X are as defined above, and

wherein either R^1 is NH_2 and R^2 is COOH or COOCl, or wherein R^2 is NH_2 and R^1 is COOH or COOCl.