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(54) Title: BENZOFURAN DERIVATIVES FOR USE AS AMPK ACTIVATORS

(57) Abstract: The present invention refers to benzofuran derivatives, capable of efficaciously activating the enzymatic complex AMPK, useful for the prophylaxis and therapeutic treatment of diseases and disorders in particular metabolic disorders such as diabetes and obesity, immune-mediated inflammatory pathologies and tumours.



BENZOFURAN DERIVATIVES FOR USE AS AMPK ACTIVATORS**DESCRIPTION****Field of the Invention**

5 The present invention relates in general to the pharmaceutical field, and more precisely, it relates to benzofuran derivatives of formula (I) herein after illustrated. They are activators of an enzymatic complex, the kinase protein activated by adenosine monophosphate (abbreviated in the following as AMPK, acronym for the English term *5' Adenosine MonoPhosphate-activated protein Kinase*), useful in the prophylaxis and
10 treatment of metabolic disorders, such as diabetes and obesity, and of immune-mediated inflammatory pathologies and tumour.

State of the Art

AMPK is a heterotrimeric kinase of the serine / threonine kinase family, known to be involved in the regulation of metabolic pathways of the energy demand /
15 consumption, and plays a key role in maintaining adequate levels of ATP in the cells in conditions that deplete these levels, such as exercise, hunger, hypoxia and rapid cell growth.

Once activated by phosphorylation of a critical threonine residue (Thr172), the AMPK kinase activates the pathways that generate ATP, such as glucose transport in
20 muscles, fatty acid oxidation, and autophagy, while inhibiting the pathways consuming ATP, such as the synthesis of cholesterol and fatty acids, and the protein synthesis. In addition to regulating metabolic enzymes and other proteins by direct phosphorylation, the AMPK enzyme complex is also known to regulate co-activators and transcription factors such as PGC1 α , FOXO proteins, HDAC, p300 and CREB. It moreover
25 regulates the activity of another key metabolic element, mTOR, with which it allows cells to respond appropriately to metabolic stress and to regulate cell growth and differentiation, as well as autophagy.

Thanks to the central role played by AMP in energy homeostasis in cells and in the whole body, this enzymatic complex represents a very attractive target for the
30 treatment of various metabolic diseases. In particular, the discovery that physical

activity activates AMPK in skeletal muscles leading to increased glucose uptake indicates a therapeutic potential of compounds that are AMPK activators to treat type 2 diabetes. Furthermore, in obese insulin-resistant patients, a reduced AMPK activity in adipose tissue was observed, together with an increased expression of genes
5 associated with inflammation compared to what was observed in control subjects, suggesting also in this case that a reduced activity of AMPK could play a role in the causes of the disease.

Activation of AMPK in hepatic and adipose tissue modulates different biochemical pathways that balance lipogenesis and lipolysis to maintain ATP. The
10 enzyme complex AMPK inhibits the lipid synthesis through the phosphorylation and inhibition of ACC1 and HMG-CoA reductase, together with the transcriptional regulation of lipogenic transcription factors involved in the synthesis of fatty acids and cholesterol, SREBP-1c and SREBP-2, respectively.

Furthermore, this enzyme complex critically contributes to the modulation of
15 immune / inflammatory cell functions (i.e. macrophages, neutrophils, lymphocytes, dendritic cells), such as the production of cytokines, chemotaxis, cytotoxicity, apoptosis and proliferation.

Alterations in the expression of AMPK and / or in its activity have proved to be important in the pathophysiology of immune-mediated inflammatory diseases
20 characterized by abnormal functions of immune cells, such as psoriasis, inflammatory bowel disease, rheumatoid arthritis, atherosclerosis and some neurodegenerative diseases (i.e. of Huntington, Alzheimer's syndrome and Parkinson's disease), thus confirming the relevance of this protein in the modulation of immune / inflammatory responses.

25 In addition to the regulation of the activity of immune cells, the AMPK enzyme complex is also involved in blocking carcinogenesis, by counteracting most of the metabolic changes that occur in rapidly proliferating cells by acting on their metabolic state.

Based on this experimental evidence, AMPK can rightly be considered a relevant
30 molecular target for the treatment of metabolic diseases, including type 2 diabetes and

obesity, as well as of immune-mediated inflammatory diseases and cancer, thus making strongly felt the need to provide powerful and effective AMPK activator compounds.

Up to now, several classes of compounds have been developed that are considered AMPK activators. The main class is that of the so-called "direct activators", which are small molecules able to bind to the enzyme complex and activate it, triggering a change in its conformation that allows further activation by phosphorylation of the Thr172 key residue in one of the subunits of the complex. A first example of compound considered to be a direct AMPK activator is represented by the adenosine analogue 5-aminoimidazole-4-carboxamide riboside, known as AICAR. This molecule, which is an AMP-mimetic and is thus able to regulate AMP-dependent enzymes too, cannot be considered a specific AMPK activator. Furthermore, despite having received the marketing authorization, AICAR is a product characterized by a very short half-life.

Further direct AMPK activators have also been described, the thienopyridone derivative A769662 developed by Abbott Laboratories, and the benzoimidazole derivative 991 developed by Merck Sharp and Dohme. They both bind to the allosteric binding site for drug and metabolite (ADaM) of AMPK, therefore they do not work in the presence of mutations in the enzyme AMPK complex that stabilize the ADaM site. Furthermore, both these compounds are characterized by a modest oral bioavailability.

A further product developed by Metabasis Pharmaceuticals as a direct activator of AMPK is the isoxazolyl-furan-2-phosphonic acid C2 that promotes the activity of AMPK mimicking AMP. Even this product, however, does not meet the requirements for the development of an effective drug: because of its high hydrophilicity, the cell walls are in fact impermeable to C2, which has already been set aside in favour of one of its prodrugs, the corresponding isopropyl phosphoester C13, which exhibits better bioavailability.

Various other compounds have been described in the literature as AMPK activators and many of them are currently in clinical trials; none of them, however, has for the moment still obtained the marketing authorization as a drug.

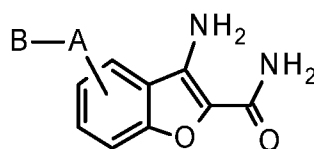
The need to identify novel compounds that are powerful and efficient AMPK

activators without presenting the drawbacks mentioned above for the known compounds, therefore remains very much felt.

Summary of the Invention

Now the Applicant has found that 3-aminobenzofuran-2-carboxamide derivatives
5 suitably substituted in one of the positions 4, 5, 6, or 7 of the benzo-fused ring, are able to significantly stimulate the activity of AMPK enzymatic complex, involved in particular, as explained above, in the regulation of the metabolic pathways for production and consumption of cellular energy.

Subject of the invention are therefore the compounds of general formula (I)



(I)

wherein:

A is absent or selected from O, S, SO, SO₂, NH and N(H)CO;

B is selected from aryl, heteroaryl, and heterocycle; wherein each of them is optionally substituted by one or more substituents, equal or different between each
15 other, selected from the group consisting of halogen, cyano, nitro, trifluoromethyl, methoxy, hydroxy, methylthio, mercapto, amino, carboxy, formyl, carbamoyl, alkylcarbonyl, arylcarbonyl, sulphamoyl, alkylamido, arylamido, alkylureido, arylureido, alkylsulphonamido, arylsulphonamido, aryl, heteroaryl, and heterocycle,

and pharmaceutically acceptable salts thereof,

20 for use as a medicament.

A further subject of the invention are the compounds of general formula (I) defined above for use in the prophylaxis and treatment of diseases and disorders that take advantage from the activation of the enzymatic complex AMPK, for example metabolic disorders, such as diabetes and obesity, immune-mediated inflammatory
25 pathologies and tumour.

A pharmaceutical composition comprising at least a compound of formula (I) in

admixture with one or more pharmaceutically acceptable excipients and/or diluents and/or carriers is still a further subject of the invention.

Further important features of the compounds of formula (I), of the pharmaceutical compositions comprising them and of the related medical use according to the invention are illustrated in the following detailed description.

Brief description of the drawings

The Figures 1 and 2 herein annexed show the most significant results obtained in the experimental studies described below in detail. In particular:

-the Figure 1 illustrates the level of activation of AMPK in the cell line C2C12 following 30 minutes of exposure to the benzofuran compound of formula (I) described in Example 2 below and to berberine, reference product, both tested at a concentration 10 microM.

- the Figure 2 illustrates the level of activation of AMPK in the cell line C2C12 following 30 minutes of exposure to benzofuran compounds 1, 2, 136 e 137, tested at concentration 20 microM, and to acadesine, reference product, tested at concentration 200 microM.

Detailed Description of the Invention

In the present invention, the term "halogen" refers to fluorine, chloro, bromo or iodo.

The term "alkyl" refers to a monovalent hydrocarbon radical bearing a linear or branched residue. The "alkyl" group in the present invention, when consisting of 2 or more carbon atoms, may comprise double or triple carbon-carbon bonds or, when consisting of 3 or more carbon atoms, may form cyclic residues.

The term "aryl" refers to a cyclic or bicyclic aromatic group, consisting of a minimum of 6 to a maximum of 10 carbon atoms, for example phenyl or naphthyl, except differently defined.

The terms "heteroaryl" and "heterocycle" refer respectively to heteroaromatic compounds and to non-aromatic heterocyclic compounds, formed by a minimum of 5 to a maximum of 12 members and containing from 1 to 3 heteroatoms, selected from the group consisting of N, O, S, SO and SO₂.

In the present invention, the term “pharmaceutically acceptable salt” refers to derivatives of the 3-aminobenzofuran-2-carboxamide compounds of general formula (I) wherein the compound has been suitably modified by conversion of any basic or acid group, if present, into the corresponding addition salt with any acid or base
5 conventionally considered as acceptable for pharmaceutical uses.

Suitable examples of these salts may include in particular addition salts of basic residues in the compound (I) such as the amino groups with organic or mineral acids. Possibly, the compounds of general formula (I) described in the present invention can be salified with amino acids too.

10 Preferably, the 3-aminobenzofuran-2-carboxamide derivatives of general formula (I) according to the present invention are substituted at position 5 or at position 6 of the benzo-fused ring.

According to an embodiment of this invention, the 3-aminobenzofuran-2-carboxamide derivatives of general formula (I) are substituted in the position 7 of the
15 benzo-fused ring, for example with a group AB wherein A is absent and B is phenyl, possibly substituted.

According to a preferred embodiment of the present invention the 3-aminobenzofuran-2-carboxamide derivatives have general formula (I) wherein A is absent and B is phenyl optionally substituted with one or more substituents selected
20 from hydroxyl and methoxy.

According to a further preferred embodiment of the present invention the 3-aminobenzofuran-2-carboxamide derivatives have general formula (I) wherein A is absent and B is phenyl optionally substituted with one or more atoms of fluoro.

Non-limitative examples of 3-aminobenzofuran-2-carboxamide derivatives of
25 general formula (I) of the present invention are selected from the following:

- 1: 3-amino-5-phenylbenzofuran-2-carboxamide;
- 2: 3-amino-5-(2-methoxyphenyl)benzofuran-2-carboxamide;
- 3: 3-amino-5-(3-methoxyphenyl)benzofuran-2-carboxamide;
- 4: 3-amino-5-(4-methoxyphenyl)benzofuran-2-carboxamide;
- 30 5: 3-amino-5-(3,4-dimethoxyphenyl)benzofuran-2-carboxamide;
- 6: 3-amino-5-(3,5-dimethoxyphenyl)benzofuran-2-carboxamide;

- 7: 3-amino-5-(2,6-dimethoxyphenyl)benzofuran-2-carboxamide;
8: 3-amino-5-(2-hydroxyphenyl)benzofuran-2-carboxamide;
9: 3-amino-5-(3-hydroxyphenyl)benzofuran-2-carboxamide;
10: 3-amino-5-(4-hydroxyphenyl)benzofuran-2-carboxamide;
5 11: 3-amino-5-(3,4-dihydroxyphenyl)benzofuran-2-carboxamide;
12: 3-amino-5-(3,5-dihydroxyphenyl)benzofuran-2-carboxamide;
13: 3-amino-5-(2,6-dihydroxyphenyl)benzofuran-2-carboxamide;
14: 3-amino-5-(2-aminophenyl)benzofuran-2-carboxamide;
15: 3-amino-5-(3-aminophenyl)benzofuran-2-carboxamide;
10 16: 3-amino-5-(4-aminophenyl)benzofuran-2-carboxamide;
17: 3-amino-5-(2-nitrophenyl)benzofuran-2-carboxamide;
18: 3-amino-5-(3-nitrophenyl)benzofuran-2-carboxamide;
19: 3-amino-5-(4-nitrophenyl)benzofuran-2-carboxamide;
20: 3-amino-5-(2-fluorophenyl)benzofuran-2-carboxamide;
15 21: 3-amino-5-(3-fluorophenyl)benzofuran-2-carboxamide;
22: 3-amino-5-(4-fluorophenyl)benzofuran-2-carboxamide;
23: 3-amino-5-(2-chlorophenyl)benzofuran-2-carboxamide;
24: 3-amino-5-(3-chlorophenyl)benzofuran-2-carboxamide;
25: 3-amino-5-(4-chlorophenyl)benzofuran-2-carboxamide;
20 26: 3-amino-5-(2-bromophenyl)benzofuran-2-carboxamide;
27: 3-amino-5-(3-bromophenyl)benzofuran-2-carboxamide;
28: 3-amino-5-(4-bromophenyl)benzofuran-2-carboxamide;
29: 3-amino-5-(2-trifluoromethylphenyl)benzofuran-2-carboxamide;
30: 3-amino-5-(3-trifluoromethylphenyl)benzofuran-2-carboxamide;
25 31: 3-amino-5-(4-trifluoromethylphenyl)benzofuran-2-carboxamide;
32: 3-amino-5-(2-cyanophenyl)benzofuran-2-carboxamide;
33: 3-amino-5-(3-cyanophenyl)benzofuran-2-carboxamide;
34: 3-amino-5-(4-cyanophenyl)benzofuran-2-carboxamide;
35: 5-([1,1'-biphenyl]-4-yl)-3-aminobenzofuran-2-carboxamide;
30 36: 3-amino-5-(2'-methoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;

- 37: 3-amino-5-(3'-methoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
38: 3-amino-5-(4'-methoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
39: 3-amino-5-(3',4'-dimethoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
40: 3-amino-5-(3',5'-dimethoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
5 41: 3-amino-5-(2',6'-dimethoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
42: 3-amino-5-(2'-hydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
43: 3-amino-5-(3'-hydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
44: 3-amino-5-(4'-hydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
45: 3-amino-5-(3',4'-dihydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
10 46: 3-amino-5-(3',5'-dihydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
47: 3-amino-5-(2',6'-dihydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
48: 3-amino-5-(2'-amino-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
49: 3-amino-5-(3'-amino-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
50: 3-amino-5-(4'-amino-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
15 51: 3-amino-5-(2'-nitro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
52: 3-amino-5-(3'-nitro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
53: 3-amino-5-(4'-nitro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
54: 3-amino-5-(2'-trifluoromethyl-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
55: 3-amino-5-(3'-trifluoromethyl-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
20 56: 3-amino-5-(4'-trifluoromethyl-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
57: 3-amino-5-(2'-cyano-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
58: 3-amino-5-(3'-cyano-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
59: 3-amino-5-(4'-cyano-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
60: 3-amino-5-(2'-fluoro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
25 61: 3-amino-5-(3'-fluoro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
62: 3-amino-5-(4'-fluoro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
63: 3-amino-5-(2'-chloro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
64: 3-amino-5-(3'-chloro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
65: 3-amino-5-(4'-chloro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
30 66: 3-amino-5-(2'-bromo-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;

- 67: 3-amino-5-(3'-bromo-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
68: 3-amino-5-(4'-bromo-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
69: 3-amino-6-(2-methoxyphenyl)benzofuran-2-carboxamide;
70: 3-amino-6-(3-methoxyphenyl)benzofuran-2-carboxamide;
5 71: 3-amino-6-(4-methoxyphenyl)benzofuran-2-carboxamide;
72: 3-amino-6-(3,4-dimethoxyphenyl)benzofuran-2-carboxamide;
73: 3-amino-6-(3,5-dimethoxyphenyl)benzofuran-2-carboxamide;
74: 3-amino-6-(2,6-dimethoxyphenyl)benzofuran-2-carboxamide;
75: 3-amino-6-(2-hydroxyphenyl)benzofuran-2-carboxamide;
10 76: 3-amino-6-(3-hydroxyphenyl)benzofuran-2-carboxamide;
77: 3-amino-6-(4-hydroxyphenyl)benzofuran-2-carboxamide;
78: 3-amino-6-(3,4-dihydroxyphenyl)benzofuran-2-carboxamide;
79: 3-amino-6-(3,5-dihydroxyphenyl)benzofuran-2-carboxamide;
80: 3-amino-6-(2,6-dihydroxyphenyl)benzofuran-2-carboxamide;
15 81: 3-amino-6-(2-aminophenyl)benzofuran-2-carboxamide;
82: 3-amino-6-(3-aminophenyl)benzofuran-2-carboxamide;
83: 3-amino-6-(4-aminophenyl)benzofuran-2-carboxamide;
84: 3-amino-6-(2-nitrophenyl)benzofuran-2-carboxamide;
85: 3-amino-6-(3-nitrophenyl)benzofuran-2-carboxamide;
20 86: 3-amino-6-(4-nitrophenyl)benzofuran-2-carboxamide;
87: 3-amino-6-(2-fluorophenyl)benzofuran-2-carboxamide;
88: 3-amino-6-(3-fluorophenyl)benzofuran-2-carboxamide;
89: 3-amino-5-(4-fluorophenyl)benzofuran-2-carboxamide;
90: 3-amino-6-(2-chlorophenyl)benzofuran-2-carboxamide;
25 91: 3-amino-6-(3-chlorophenyl)benzofuran-2-carboxamide;
92: 3-amino-6-(4-chlorophenyl)benzofuran-2-carboxamide;
93: 3-amino-6-(2-bromophenyl)benzofuran-2-carboxamide;
94: 3-amino-6-(3-bromophenyl)benzofuran-2-carboxamide;
95: 3-amino-6-(4-bromophenyl)benzofuran-2-carboxamide;
30 96: 3-amino-6-(2-trifluoromethylphenyl)benzofuran-2-carboxamide;

- 5 **97:** 3-amino-6-(3-trifluoromethylphenyl)benzofuran-2-carboxamide;
98: 3-amino-6-(4-trifluoromethylphenyl)benzofuran-2-carboxamide;
99: 3-amino-6-(2-cyanophenyl)benzofuran-2-carboxamide;
100: 3-amino-6-(3-cyanophenyl)benzofuran-2-carboxamide;
101: 3-amino-6-(4-cyanophenyl)benzofuran-2-carboxamide;
102: 5-([1,1'-biphenyl]-4-yl)-3-aminobenzofuran-2-carboxamide;
103: 3-amino-6-(2'-methoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
104: 3-amino-6-(3'-methoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
105: 3-amino-6-(4'-methoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
10 **106:** 3-amino-6-(3',4'-dimethoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
107: 3-amino-6-(3',5'-dimethoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
108: 3-amino-6-(2',6'-dimethoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
109: 3-amino-6-(2'-hydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
110: 3-amino-6-(3'-hydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
15 **111:** 3-amino-6-(4'-hydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
112: 3-amino-6-(3',4'-dihydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
113: 3-amino-6-(3',5'-dihydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
114: 3-amino-5-(2',6'-dihydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
115: 3-amino-6-(2'-amino-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
20 **116:** 3-amino-6-(3'-amino-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
117: 3-amino-6-(4'-amino-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
118: 3-amino-6-(2'-nitro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
119: 3-amino-6-(3'-nitro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
120: 3-amino-6-(4'-nitro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
25 **121:** 3-amino-6-(2'-trifluoromethyl-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
122: 3-amino-6-(3'-trifluoromethyl-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
123: 3-amino-6-(4'-trifluoromethyl-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
30

- 124: 3-amino-6-(2'-cyano-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
125: 3-amino-6-(3'-cyano-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
126: 3-amino-6-(4'-cyano-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
127: 3-amino-6-(2'-fluoro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
5 128: 3-amino-6-(3'-fluoro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
129: 3-amino-6-(4'-fluoro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
130: 3-amino-6-(2'-chloro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
131: 3-amino-6-(3'-chloro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
132: 3-amino-6-(4'-chloro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
10 133: 3-amino-6-(2'-bromo-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
134: 3-amino-6-(3'-bromo-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
135: 3-amino-6-(4'-bromo-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
136: 3-amino-7-(4'-fluorophenyl)benzofuran-2-carboxamide; and
137: 3-amino-7-(1',2',3'-trimethoxyphenyl)benzofuran-2-carboxamide.

15 The present description provides also a process for the preparation of 3-aminobenzofuran-2-carboxamide derivatives of general formula (I) wherein A is selected from O, S, SO, SO₂, NH and N(H)CO and B is defined as above, and pharmaceutically acceptable salts thereof, as defined above, comprising the steps of:

20 i) alkylation of 2-hydroxy-benzonitrile suitably substituted with a nitro group on the benzene ring at position 4, 5, 6 or 7 depending on the desired compound of formula (I), to obtain the corresponding nitro derivative of 2-(2-cyano-phenoxy)acetamide;

ii) cyclization of the acetamide derivative coming from step i) to obtain the nitro derivative of 3-amino-benzofuran-2-carboxamide;

25 iii) protection of the amino group at position 3 of the benzofuran derivative coming from step ii) with a suitable protective group;

iv) reduction of the nitro group of the protected benzofuran derivative coming from step iii) and transformation into an amino group;

30 v) suitable functionalization of the amino group on the benzo-fused ring obtained from reduction in step iv) and subsequent deprotection of the amino group at position 3 to obtain the compounds of general formula (I).

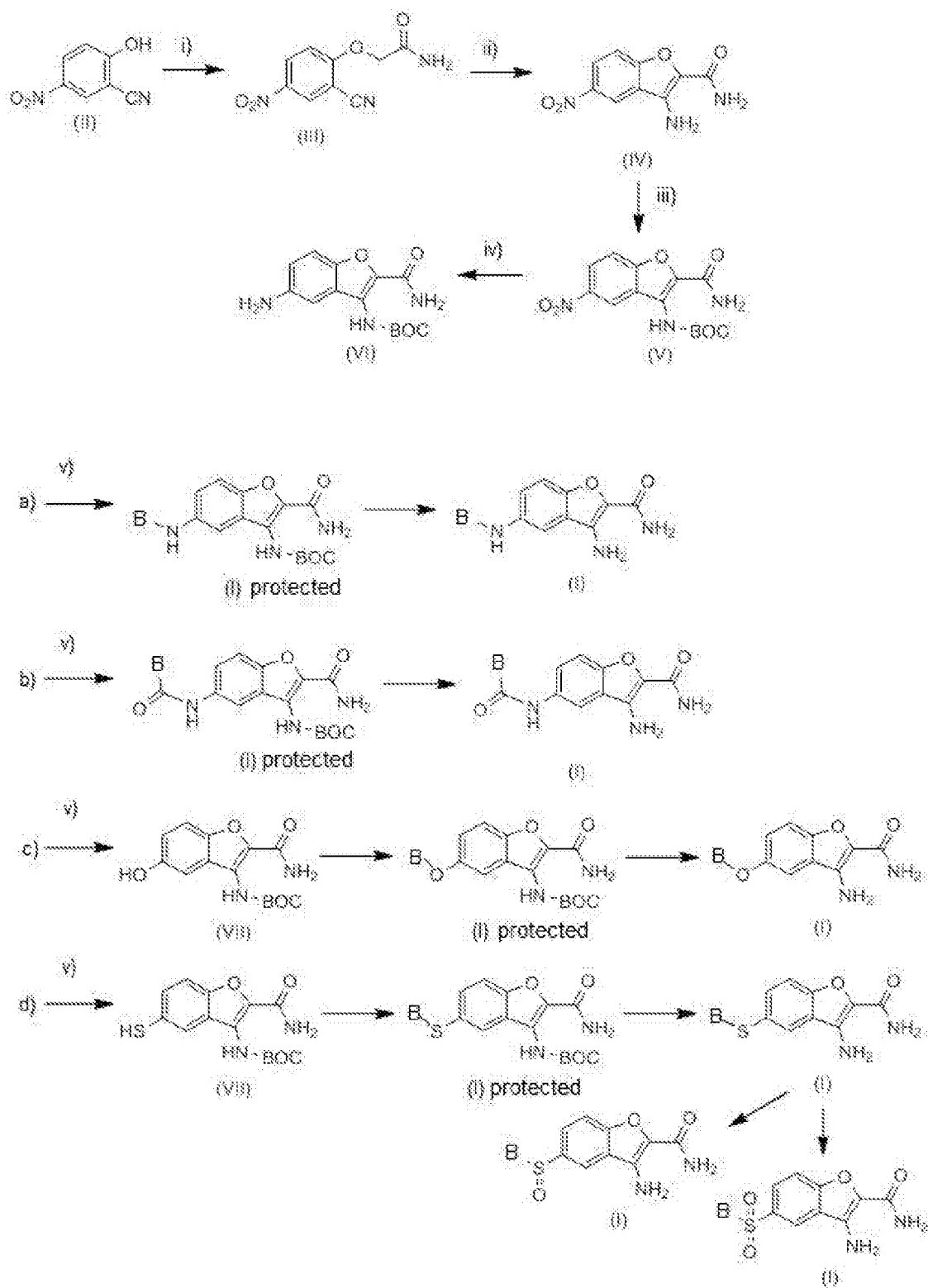
Depending on the desired compound of general formula (I) wherein A is selected from O, S, SO, SO₂, NH and N(H)CO and B is defined as above, a different functionalization will be carried out with different reagents in the step v) of the above said process, according to procedures and with reagents that can be easily identified by any experts with ordinary skills in the art. For example, if a compound of general formula (I) is desired wherein A is NH, the amino group on the benzo-fused ring in step v) is transformed by reaction with alkyl halides; if it is indeed desired a compound of general formula (I) wherein A is N(H)CO, the same amino group is transformed by reaction with alkyl halides. If a compound of general formula (I) wherein A is O is indeed desired, the amine group on the benzo-fused ring is transformed in step v) into a hydroxyl group then made to react with alkyl halides. Finally, if a compound of general formula (I) wherein A is S or SO or SO₂ is desired, the amine group on the benzo-fused ring is transformed in step v) of the above said process into a sulfhydryl group that is then made to react with alkyl halides to obtain the compounds of formula (I) wherein A is S, or further oxidized to obtain the compounds of formula (I) wherein A is SO or SO₂.

In the following Scheme 1 an illustrative scheme is shown that is non-limitative of the above said process of the invention, useful in particular to obtain the compounds of general formula (I) wherein A, at position 5 on the benzo-fused ring, is selected from O, S, SO, SO₂, NH and N(H)CO and B is defined as above. The starting reagent in the first step i), the 2-hydroxy-5-nitrobenzonitrile of formula (II), is turned into the 2-(2-cyano-4-nitrophenoxy)acetamide of formula (III), which is the subjected to cyclization in the subsequent step ii), to obtain the benzofuran derivative of formula (IV). The protection step iii) follows, wherein the benzofuran derivative (IV) is turned into the derivative with the amino group (V) protected with a suitable protective group, for example with a protective group tert-butyloxycarbonyl (BOC); and the step iv) of reduction of the amine group on the benzo-fused ring to obtain the 5-amino substituted derivative of formula (VI). The so obtained derivative of formula (VI) can be at this point transformed in the desired compounds of general formula (I) according to the different alternative procedures illustrated in the Scheme 1 below as a), b), c) and d) wherein

the amine group on the benzo-fused ring can be functionalised or converted into hydroxyl or sulfhydryl (intermediate (VII)), as explained above, depending on the type of spacer A and of substituent B that is wanted in compounds (I), before deprotection of the amine group at position 5 of the benzofuran nucleus.

5

Scheme 1



wherein B is defined as above.

The compounds of general formula (I) wherein A is absent and B is aryl at position 5 of the benzo-fused ring can be prepared in general with a process of preparation comprising the steps of:

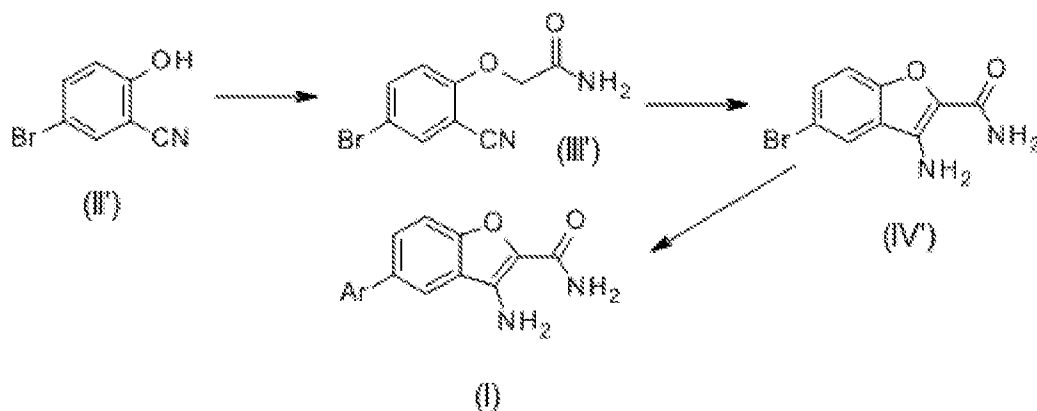
5 -alkylation of a 2-hydroxybenzonitrile derivative suitably substituted on the benzene ring depending on the substituent B in the desired compound (I), to provide the corresponding 2-(2-cyanophenoxy)acetamide;

 -cyclization of the so obtained acetamide derivative to yield the benzofuran derivative;

10 -substitution wherein the benzofuran derivative is converted into the AMPK activator of the invention of formula (I) wherein A is absent and B is one of the substituents defined above.

 In a particular embodiment of the present invention, the compounds of general formula (I) wherein A is absent and B is aryl at position 5 of the benzo-fused ring can for example be prepared according to the procedure described in the following Scheme 2.

Scheme 2



More specifically, with reference to the Scheme 2 above, the synthesis of the desired products includes the following subsequent steps:

20 -a first step of alkylation, wherein the 5-bromo-2-hydroxybenzonitrile of formula (II') is transformed into the 2-(4-bromo-2-cyanophenoxy)acetamide of formula (III');

–a second step of cyclization, wherein the acetamide derivative (III') is converted into the benzofuran derivative (IV');

–a third step of substitution, wherein the benzofuran derivative (IV') is converted into the AMPK activator of the invention of formula (I) wherein A is absent and B is aryl.

5 In the first step, the 5-bromo-2-hydroxybenzonitrile (II'), commercial product, reacts with an amount of bromoacetamide in the presence of a suitably selected base, for example caesium carbonate in solvent DMF, to form 2-(4-bromo-2-cyanophenoxy)acetamide (III'). To this in the second step a KOH solution in ethanol is then added and left to react under reflux to obtain the cyclized product, in particular the
10 3-amino-5-bromobenzofuran-2-carboxamide of formula (IV').

Finally, in the third step, the benzofuran derivative of formula (IV') is turned into the AMPK activator of formula (I) wherein A is absent and B is aryl by substitution of the bromo atom with an aryl group. This substitution can be for example carried out with the aryl group used in the form of boronic acid, in the presence of a catalyst, such
15 as triphenylphosphine palladium acetate, and of a base, such as sodium carbonate, in a suitable solvent, such as toluene.

The compounds of general formula (I) according to the invention wherein A is absent and B is different from aryl can be prepared with procedures analogues to that described above in the Scheme 2, or by transformation of the so obtained compound
20 (I) wherein B is aryl, according to procedures and with reagents and conditions that can be easily identified by any expert with ordinary skills in the art.

The compounds of general formula (I) defined above according to the invention are useful in the prophylaxis and/or in the treatment of diseases or disorders that take advantages from the activation of the AMPK enzymatic complex, in particular metabolic
25 diseases, immuno-mediated inflammatory diseases and tumour. They can be used, alone or in combinations of two or more compounds, in pharmaceutical compositions with pharmaceutically acceptable vehicles, excipients and/or diluents, and possible further active principles with known activity, such as antidiabetic agents, anti-inflammatory agents and antitumor agents, chemotherapeutics or non-
30 chemotherapeutics, with the aim of increasing their therapeutic efficacy. The present

compounds can be present in the compositions as such or in the form of pharmaceutically acceptable salts.

The present pharmaceutical compositions can be formulated in various pharmaceutical forms, through different administration routes, for example as oral, 5 topical or injectable compositions, according to the conventional methods, in form of tablets, granules, powders, capsules, syrup, aqueous solution, aqueous suspension, oil solution, oil suspension, emulsion or microemulsion, to be used for the oral, intramuscular, intravenous, subcutaneous or topical administration.

EXAMPLES

10 In the following examples, the described synthetic procedures refer to the following experimental conditions, where not indicated otherwise:

- the temperatures are expressed in Celsius degrees (°C);
- the organic solutions were dried on anhydrous magnesium sulphate; the solvent evaporation was achieved by using a rotary evaporator and operating at 15 reduced pressure;
- the thin layer chromatography (TLC) was carried out on Merck 60 F-254 plates; the column chromatography was carried out using silica gel as the stationary phase and the Biotage chromatographic system;
- the time indicated in each procedure, necessary to obtain the desired product, 20 was determined by TLC on the reaction mixture;
- the final product of each reaction was characterised by chemical-physical and spectroscopic data;
- the yield reported for each product is indicative and it does not correspond necessarily to that that may be obtained by a reaction carried out under optimal 25 conditions;
- the melting points were determined with a Reichert-Köfler equipment and are without correction;
- the proton nuclear magnetic resonance spectra (¹H-NMR) were registered with a Bruker Ultrashield equipment operating at 400 MHz, using dimethylsulphoxide

(DMSO-d₆) as solvent. The following abbreviations have been used: s for singlet; d for doublet, t for triplet, q for quartet, m for multiplet.

Example 1. Preparation of 2-(4-bromo-2-cyanophenoxy)acetamide

1.00 mmol of 5-bromo-2-hydroxybenzonitrile, commercial product, was solubilized in 1.0 mL of DMF and added with 1.20 mmol of commercial 2-bromoacetamide and 1.20 mmol of caesium carbonate, then heated up to 80°C for 1 hour. After cooling, the reaction mixture was added with water/ice and the solid that separates was collected by filtration, dried under vacuum and purified by crystallization from water. 224.5 mg of the desired product of the title were so obtained (yield 88%).

The product was characterized by chemical-physical and spectroscopic data.

M.p. (°C): 246-247. ¹H-NMR (δ, DMSO, d₆): 4.686 (s, 2H, CH), 7.032 (d, 1H, Ar, J=9.13), 7.440 (s, 1H, NH, exc.), 7.539 (s, 1H, NH, exc.), 7.815 (dd, 1H, Ar, J=2.529, J=9.08), 8.010 (d, 1H, Ar, J=2.48).

Example 2. Preparation of 3-amino-5-bromobenzofuran-2-carboxamide

1.00 mmol of 2-(4-bromo-2-cyanophenoxy)acetamide was added with 5.0 mL of potassium hydroxide in ethanolic solution (0.70 M) and the so obtained mixture was heated under reflux for 1.5 hour. After cooling, the solvent was evaporated under reduced pressure and the obtained residue was added with water. The solid that separates was collected by filtration, dried under vacuum and purified by crystallization from acetone. 232.1 mg of the desired product of the title were so obtained (yield 91%). This product was characterized by chemical-physical and spectroscopic data.

M.p. (°C): 220-222. ¹H-NMR (δ, DMSO, d₆): 6.030 (s, 2H, NH, exc.), 7.327 (as, 2H, NH, exc.), 7.425 (d, 1H, Ar, J=8.81), 7.564 (dd, 1H, Ar, J=1.33, J=8.81), 8.074 (d, 1H, Ar, J=2.24).

Example 3. Preparation of 3-amino-5-phenylbenzofuran-2-carboxamide (compound 1)

1.00 mmol of 3-amino-5-bromobenzofuran-2-carboxamide was solubilized in toluene and added with 0.05 mmol of palladium acetate and 0.10 mmol of triphenylphosphine, then left under stirring at room temperature. After 30 minutes, 1.20 mmol of phenylboronic acid and 0.20 mL of potassium carbonate in aqueous solution

(2.0 M) were added and the resulting mixture was heated under reflux for 8 hours. After cooling, the solvent was evaporated under reduced pressure and the obtained residue was added with water. The solid that separates was collected by filtration, dried under vacuum and purified by crystallization from ethyl acetate. 116.0 mg of the desired product of the title were so obtained, (yield 46%). This product was characterized by chemical-physical and spectroscopic data.

M.p. (°C): 163-165. ¹H-NMR (δ, DMSO, d₆): 6.067 (s, 2H, NH, exc.), 7.294 (as, 2H, NH, exc.), 7.376 (t, 1H, Ar, J=7.36), 7.519-7.481 (m, 3H, Ar), 7.694 (d, 2H, Ar, J=8.44), 7.734 (dd, 1H, Ar, J=1.96, J=8.69), 8.203 (d, 1H, Ar, J=1.52).

The experimental procedures described in the Examples 1, 2, and 3 have been then repeated and the benzofuran derivatives 2-13 of the present invention listed above have been prepared.

Example 4. Preparation of 3-amino-5-(4-fluorophenyl)benzofuran-2-carboxamide (compound 22)

1.00 mmol of 3-amino-5-bromobenzofuran-2-carboxamide was solubilized in toluene and added with 0.05 mmol of palladium acetate and 0.10 mmol of triphenylphosphine, then left under stirring at room temperature. After 30 minutes, 1.20 mmol of 4-fluorophenylboronic acid and 0.20 mL of potassium carbonate in aqueous solution (2.0 M) were added and the resulting mixture was heated under reflux for 8 hours. After cooling, the solvent was evaporated under reduced pressure and the thus obtained residue was added with water. The solid that separates was collected by filtration, dried under vacuum and purified by crystallization from ethyl acetate. 148.5 mg of the desired product of the title were so obtained, (yield 55%). This product was characterized by chemical-physical and spectroscopic data.

¹H-NMR (δ, DMSO, d₆): 6.049 (s, 2H, NH, exc.), 7.273 (as, 2H, NH, exc.), 7.334 (t, 2H, Ar, J=6.81), 7.492 (d, 1H, Ar, J=8.61), 7.736-7.696 (m, 3H, Ar), 8.176 (d, 1H, Ar, J=1.68).

Example 5. Preparation of 3-amino-7-(4-fluorophenyl)benzofuran-2-carboxamide (compound 136)

1.00 mmol of 3-amino-7-bromobenzofuran-2-carboxamide was solubilized in toluene and added with 0.05 mmol of palladium acetate and 0.10 mmol of triphenylphosphine, then left under stirring at room temperature. After 30 minutes, 1.20 mmol of 4-fluorophenylboronic acid and 0.20 mL of potassium carbonate in aqueous solution (2.0 M) were added and the resulting mixture was heated under reflux for 8 hours. After cooling, the solvent was evaporated under reduced pressure and the obtained residue was added with water. The solid that separates was collected by filtration, dried under vacuum and purified by crystallization from ethyl acetate. 113.4 mg of the desired product of the title were so obtained, (yield 42%). This product was characterized by chemical-physical and spectroscopic data.

¹H-NMR (δ, DMSO, d₆): 6.064 (s, 2H, NH, exc.), 7.237 (as, 2H, NH, exc.), 7.360-7.295 (m, 3H, Ar), 7.684 (dd, 1H, Ar, J=1.08, J=7.52), 7.847 (dd, 1H, Ar, J=1.08, J=7.80), 8.03-8.037 (m, 2H, Ar).

Example 6. Preparation of 3-amino-7-(3,4,5-trimethoxyphenyl)benzofuran-2-carboxamide (compound 137)

1.00 mmol of 3-amino-7-bromobenzofuran-2-carboxamide was solubilized in toluene and added with 0.05 mmol of palladium acetate and 0.10 mmol of triphenylphosphine, then left under stirring at room temperature. After 30 minutes, 1.20 mmol of 3,4,5-trimethoxyphenylboronic acid and 0.20 mL of potassium carbonate in aqueous solution (2.0 M) were then added and the resulting mixture was heated under reflux for 8 hours. After cooling, the solvent was evaporated under reduced pressure and the obtained residue was added with water. The solid that separates was collected by filtration, dried under vacuum and purified by crystallization from ethyl acetate. 154.0 mg of the desired product of the title were so obtained, (yield 45%). This product was characterized by chemical-physical and spectroscopic data.

¹H-NMR (δ, DMSO, d₆): 3.731(s, 3H, OMe), 3.888 (s, 6H, OMe), 6.065 (s, 2H, NH, exc.), 7.294 (as, 2H, NH, exc.), 7.135-7.120 (m, 4H, Ar), 7.329 (t, 1H, Ar, J=7.69), 7.655 (d, 1H, Ar, J=7.58), 7.831 (d, 1H, Ar, J=7.80).

Example 7. *In vitro* assays

The functional efficacy of the present benzofuran derivatives of general formula (I) was verified by *in vitro* assays, carried out on cell lines of C2C12 murine myoblasts. The cells were treated with the benzofuran derivatives under examination, used at concentration of 10 microM. After 30 minutes, the level of phosphorylation of the AMPK protein at the Thr172 residue was determined, using the Western Blot technique. The results obtained, in terms of ratio between the phosphorylated protein and the native protein, were compared with the analogous data acquired in the presence of berberine, AMPK activator of natural origin used as reference product. Figure 1 illustrates the level of activation of AMPK in the C2C12 cell line after 30 minutes of exposure to the benzofuran compound 1 obtained as described above in Example 3 and to berberine, reference product, both tested at concentration of 10 microM. In analogous way the functional efficacy of the benzofuran derivatives 2-13 of the present invention, prepared as described above, was studied and verified.

Figure 2 illustrates the level of AMPK activation in the C2C12 cell line after 30 minutes of exposure to the benzofuran derivatives 1, 22, 136 and 137 obtained as described above in the Examples 3-6 and by comparison to acadesine (ACA), only AMPK agonist product put on the market until today. The samples of the compounds of the invention have been all tested at concentration of 20 microM, whereas the reference product acadesine was tested at concentration of 200 microM. The tested benzofuran derivatives 1, 22, 136, 137 significantly activate the target protein with respect to the vehicle group and they do not show a significantly different efficacy with respect to the reference product ACA, which was however used at a concentration 10 times higher than the derivatives tested.

The values indicated in the figures are expressed as mean $\pm$ DS (n=2,3), * p <0.05, ** p <0.01 e *** p <0.001, with respect to the vehicle group.

Example 8. *In vivo* assays

The anti-inflammatory efficacy of the benzofuran compound 1 obtained as described above in Example 3 was evaluated in an animal model of experimental colitis, induced in rats through intrarectal administration of 2,4-dinitrobenzensulphonic acid (DNBS, 15 mg in 0.25 ml/rat of a 50% aqueous solution of ethanol). For these

experiments, it was adopted the animal model of colitis already described by Antonioli L. et al. in *Journal of Pharmacology and Experimental Therapeutics*, August 2007, 322(2) 435-442. The animals were fed with food and water *ad libitum* and were not subjected to experimental procedures for at least 1 week after their delivery to the laboratory. The animals' care and all experiments done involving animals were carried out in accordance with the provisions of the European Union Council Directive 2010/63/EU, recognized and adopted by the Italian national guidelines, approved by the ethical committee of Animal Welfare Office of the Italian Labour Ministry and in conformity with the legal mandates and Italian guidelines for the care and maintenance of laboratory animals.

The tested compound 1 was administered intraperitoneally for 7 days, with a dosing regimen ranging between 1 and 30 mg/Kg/die, starting 1 day before the colitis induction. In parallel, two groups of control rats, the positive and the negative one, were respectively treated with DNBS only and with the vehicle only (50% aqueous solution of ethanol).

6 days after colitis induction, the analysis of the control rats that had received just DNBS has revealed a decreased body weight ($-40.6 \pm 4.1\%$ vs. vehicle, $p < 0.05$), together with an increased spleen weight ($+ 38.6 \pm 5.5\%$ vs. vehicle; $p < 0.05$). In the colon evident macroscopic damages have appeared and the tissue pro-inflammatory cytokine levels [tumour necrosis factor, TNF] as well as the oxidative stress markers levels (malondialdehyde, MDA) were increased. At the same time, the colon length was markedly reduced. On the contrary, the animals treated with the benzofuran compound 1 have shown a more restrained body weight loss and a lower increase of the spleen weight. Furthermore, in their colon, the macroscopic damage was more restrained, as well as the decrease in colon length. Moreover, it was also observed a reduction in TNF and MDA tissue levels.

The macroscopic damage was scored on a 0- to 6-point scale, defined as reported in Table 1 below.

Table 1

Score	Appearance
0	Normal

1	Localized hyperemia, no ulcers
2	Ulceration without hyperemia or bowel wall thickening
3	Ulceration with hyperemia at one site
4	Two or more sites of ulceration and hyperemia
5	Major sites of damage extending > 1 cm along the length of colon
6	Area of damage extending > 2 cm along the length of colon

The following Table 2 reports the results obtained for such tissue levels of TNF and MDA at the different dosages of the administered compound 1 of the invention, and for the macroscopic damage done with the scoring system explained above, evaluated by two different operators blind to the treatment. In the Table 2 below are furthermore reported, by way of a comparison, the results obtained repeating the experiments with the same dosages of acadesine (indicated in the table as ACA), also known as AICAR (5-aminoimidazol-4-carboxamide-1- β -D-ribofuranoside) and present in the only product on the market up to today as AMPK agonist.

Table 2

	Macroscopic damage	TNF (pg/mg tissue)	MDA (μmol/mg tissue)
only vehicle	1.3 $\pm$ 0.4	3 $\pm$ 1.6	26.3 $\pm$ 3.2
only DNBS	8.1 $\pm$ 1.2*	9.1 $\pm$ 1*	83.5 $\pm$ 5.5 *
DNBS+compound 1 1 mg/kg/die	6.9 $\pm$ 1.3*	8.3 $\pm$ 2.1*	94.8 $\pm$ 8.2*
DNBS+compound 1 3 mg/kg/die	3.5 $\pm$ 0.8*,a	4.8 $\pm$ 0.8*,a	40.6 $\pm$ 6.6*,a
DNBS+compound 1 10 mg/kg/die	3.1 $\pm$ 0.9*,a	3.1 $\pm$ 0.5 ^a	45.7 $\pm$ 4.1*,a
DNBS+compound 1 30 mg/kg/die	2.8 $\pm$ 1*,a	4.6 $\pm$ 1.4*,a	48.5 $\pm$ 3.8*,a
DNBS+ACA 1 mg/kg/die	7.6 $\pm$ 1.1*	10.7 $\pm$ 2.5*	93.7 $\pm$ 4.4*

<i>DNBS+ACA</i> <i>3 mg/kg/die</i>	6.9±0.5*	9.4±0.7*	82.7±5.1*
<i>DNBS+ACA</i> <i>10 mg/kg/die</i>	2.8±0.6*, ^a	5±0.5*, ^a	68.6±4.3*, ^a
<i>DNBS+ACA</i> <i>30 mg/kg/die</i>	3.5±0.9*, ^a	4.2±1.8*, ^a	51.5±2.8*, ^a

^a*p*<0.05 vs positive control (vehicle)

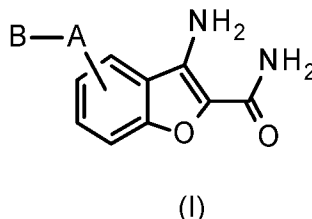
**p*<0.05 vs negative control (DNBS)

* * * * *

The present invention was described above with reference to preferred
 5 embodiments thereof. It is to be understood that other embodiments may exist which
 belong to the same inventive core, as defined by the scope of the protection of the
 claims set forth below.

CLAIMS

1. Compounds of general formula (I)



wherein

5 A is absent or is selected from O, S, SO, SO₂, NH and N(H)CO;

B is selected from aryl, heteroaryl, and heterocycle; wherein each of them is optionally substituted by one or more substituents, equal or different between each other, selected from the group consisting of halogen, cyano, nitro, trifluoromethyl, methoxy, hydroxy, methylthio, mercapto, amino, carboxy, formyl, carbamoyl, alkylcarbonyl, arylcarbonyl, sulphamoyl, alkylamido, arylamido, 10 alkylureido, arylureido, alkylsulphonamido, arylsulphonamido, aryl, heteroaryl, and heterocycle, and pharmaceutically acceptable salts thereof, for use as a medicament.

15 2. The compounds for use according to claim 1, wherein -A-B is at position 5 or at position 6 of the benzo-fused ring.

3. The compounds for use according to claim 1 or 2, having general formula (I) wherein A is absent and B is phenyl optionally substituted by one or more substituents selected from between hydroxy and methoxy.

20 4. The compounds according to claim 1, selected from the group consisting of:

- 1: 3-amino-5-phenylbenzofuran-2-carboxamide;
- 2: 3-amino-5-(2-methoxyphenyl)benzofuran-2-carboxamide;
- 3: 3-amino-5-(3-methoxyphenyl)benzofuran-2-carboxamide;
- 4: 3-amino-5-(4-methoxyphenyl)benzofuran-2-carboxamide;
- 25 5: 3-amino-5-(3,4-dimethoxyphenyl)benzofuran-2-carboxamide;
- 6: 3-amino-5-(3,5-dimethoxyphenyl)benzofuran-2-carboxamide;

- 7: 3-amino-5-(2,6-dimethoxyphenyl)benzofuran-2-carboxamide;
8: 3-amino-5-(2-hydroxyphenyl)benzofuran-2-carboxamide;
9: 3-amino-5-(3-hydroxyphenyl)benzofuran-2-carboxamide;
10: 3-amino-5-(4-hydroxyphenyl)benzofuran-2-carboxamide;
5 11: 3-amino-5-(3,4-dihydroxyphenyl)benzofuran-2-carboxamide;
12: 3-amino-5-(3,5-dihydroxyphenyl)benzofuran-2-carboxamide;
13: 3-amino-5-(2,6-dihydroxyphenyl)benzofuran-2-carboxamide;
14: 3-amino-5-(2-aminophenyl)benzofuran-2-carboxamide;
15: 3-amino-5-(3-aminophenyl)benzofuran-2-carboxamide;
10 16: 3-amino-5-(4-aminophenyl)benzofuran-2-carboxamide;
17: 3-amino-5-(2-nitrophenyl)benzofuran-2-carboxamide;
18: 3-amino-5-(3-nitrophenyl)benzofuran-2-carboxamide;
19: 3-amino-5-(4-nitrophenyl)benzofuran-2-carboxamide;
20: 3-amino-5-(2-fluorophenyl)benzofuran-2-carboxamide;
15 21: 3-amino-5-(3-fluorophenyl)benzofuran-2-carboxamide;
22: 3-amino-5-(4-fluorophenyl)benzofuran-2-carboxamide;
23: 3-amino-5-(2-chlorophenyl)benzofuran-2-carboxamide;
24: 3-amino-5-(3-chlorophenyl)benzofuran-2-carboxamide;
25: 3-amino-5-(4-chlorophenyl)benzofuran-2-carboxamide;
20 26: 3-amino-5-(2-bromophenyl)benzofuran-2-carboxamide;
27: 3-amino-5-(3-bromophenyl)benzofuran-2-carboxamide;
28: 3-amino-5-(4-bromophenyl)benzofuran-2-carboxamide;
29: 3-amino-5-(2-trifluoromethylphenyl)benzofuran-2-carboxamide;
30: 3-amino-5-(3-trifluoromethylphenyl)benzofuran-2-carboxamide;
25 31: 3-amino-5-(4-trifluoromethylphenyl)benzofuran-2-carboxamide;
32: 3-amino-5-(2-cyanophenyl)benzofuran-2-carboxamide;
33: 3-amino-5-(3-cyanophenyl)benzofuran-2-carboxamide;
34: 3-amino-5-(4-cyanophenyl)benzofuran-2-carboxamide;
35: 5-([1,1'-biphenyl]-4-yl)-3-aminobenzofuran-2-carboxamide;
30 36: 3-amino-5-(2'-methoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;

- 37: 3-amino-5-(3'-methoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
38: 3-amino-5-(4'-methoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
39: 3-amino-5-(3',4'-dimethoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
40: 3-amino-5-(3',5'-dimethoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
5 41: 3-amino-5-(2',6'-dimethoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
42: 3-amino-5-(2'-hydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
43: 3-amino-5-(3'-hydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
44: 3-amino-5-(4'-hydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
45: 3-amino-5-(3',4'-dihydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
10 46: 3-amino-5-(3',5'-dihydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
47: 3-amino-5-(2',6'-dihydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
48: 3-amino-5-(2'-amino-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
49: 3-amino-5-(3'-amino-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
50: 3-amino-5-(4'-amino-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
15 51: 3-amino-5-(2'-nitro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
52: 3-amino-5-(3'-nitro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
53: 3-amino-5-(4'-nitro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
54: 3-amino-5-(2'-trifluoromethyl-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
55: 3-amino-5-(3'-trifluoromethyl-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
20 56: 3-amino-5-(4'-trifluoromethyl-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
57: 3-amino-5-(2'-cyano-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
58: 3-amino-5-(3'-cyano-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
59: 3-amino-5-(4'-cyano-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
60: 3-amino-5-(2'-fluoro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
25 61: 3-amino-5-(3'-fluoro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
62: 3-amino-5-(4'-fluoro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
63: 3-amino-5-(2'-chloro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
64: 3-amino-5-(3'-chloro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
65: 3-amino-5-(4'-chloro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
30 66: 3-amino-5-(2'-bromo-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;

- 67: 3-amino-5-(3'-bromo-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
68: 3-amino-5-(4'-bromo-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
69: 3-amino-6-(2-methoxyphenyl)benzofuran-2-carboxamide;
70: 3-amino-6-(3-methoxyphenyl)benzofuran-2-carboxamide;
5 71: 3-amino-6-(4-methoxyphenyl)benzofuran-2-carboxamide;
72: 3-amino-6-(3,4-dimethoxyphenyl)benzofuran-2-carboxamide;
73: 3-amino-6-(3,5-dimethoxyphenyl)benzofuran-2-carboxamide;
74: 3-amino-6-(2,6-dimethoxyphenyl)benzofuran-2-carboxamide;
75: 3-amino-6-(2-hydroxyphenyl)benzofuran-2-carboxamide;
10 76: 3-amino-6-(3-hydroxyphenyl)benzofuran-2-carboxamide;
77: 3-amino-6-(4-hydroxyphenyl)benzofuran-2-carboxamide;
78: 3-amino-6-(3,4-dihydroxyphenyl)benzofuran-2-carboxamide;
79: 3-amino-6-(3,5-dihydroxyphenyl)benzofuran-2-carboxamide;
80: 3-amino-6-(2,6-dihydroxyphenyl)benzofuran-2-carboxamide;
15 81: 3-amino-6-(2-aminophenyl)benzofuran-2-carboxamide;
82: 3-amino-6-(3-aminophenyl)benzofuran-2-carboxamide;
83: 3-amino-6-(4-aminophenyl)benzofuran-2-carboxamide;
84: 3-amino-6-(2-nitrophenyl)benzofuran-2-carboxamide;
85: 3-amino-6-(3-nitrophenyl)benzofuran-2-carboxamide;
20 86: 3-amino-6-(4-nitrophenyl)benzofuran-2-carboxamide;
87: 3-amino-6-(2-fluorophenyl)benzofuran-2-carboxamide;
88: 3-amino-6-(3-fluorophenyl)benzofuran-2-carboxamide;
89: 3-amino-5-(4-fluorophenyl)benzofuran-2-carboxamide;
90: 3-amino-6-(2-chlorophenyl)benzofuran-2-carboxamide;
25 91: 3-amino-6-(3-chlorophenyl)benzofuran-2-carboxamide;
92: 3-amino-6-(4-chlorophenyl)benzofuran-2-carboxamide;
93: 3-amino-6-(2-bromophenyl)benzofuran-2-carboxamide;
94: 3-amino-6-(3-bromophenyl)benzofuran-2-carboxamide;
95: 3-amino-6-(4-bromophenyl)benzofuran-2-carboxamide;
30 96: 3-amino-6-(2-trifluoromethylphenyl)benzofuran-2-carboxamide;

- 5 **97:** 3-amino-6-(3-trifluoromethylphenyl)benzofuran-2-carboxamide;
98: 3-amino-6-(4-trifluoromethylphenyl)benzofuran-2-carboxamide;
99: 3-amino-6-(2-cyanophenyl)benzofuran-2-carboxamide;
100: 3-amino-6-(3-cyanophenyl)benzofuran-2-carboxamide;
101: 3-amino-6-(4-cyanophenyl)benzofuran-2-carboxamide;
102: 5-([1,1'-biphenyl]-4-yl)-3-aminobenzofuran-2-carboxamide;
103: 3-amino-6-(2'-methoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
104: 3-amino-6-(3'-methoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
105: 3-amino-6-(4'-methoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
10 **106:** 3-amino-6-(3',4'-dimethoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
107: 3-amino-6-(3',5'-dimethoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
108: 3-amino-6-(2',6'-dimethoxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
109: 3-amino-6-(2'-hydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
110: 3-amino-6-(3'-hydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
15 **111:** 3-amino-6-(4'-hydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
112: 3-amino-6-(3',4'-dihydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
113: 3-amino-6-(3',5'-dihydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
114: 3-amino-5-(2',6'-dihydroxy-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
115: 3-amino-6-(2'-amino-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
20 **116:** 3-amino-6-(3'-amino-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
117: 3-amino-6-(4'-amino-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
118: 3-amino-6-(2'-nitro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
119: 3-amino-6-(3'-nitro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
120: 3-amino-6-(4'-nitro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;
25 **121:** 3-amino-6-(2'-trifluoromethyl-[1,1'-biphenyl]-4-yl)benzofuran-2-
carboxamide;
122: 3-amino-6-(3'-trifluoromethyl-[1,1'-biphenyl]-4-yl)benzofuran-2-
carboxamide;
123: 3-amino-6-(4'-trifluoromethyl-[1,1'-biphenyl]-4-yl)benzofuran-2-
30 carboxamide;

124: 3-amino-6-(2'-cyano-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;

125: 3-amino-6-(3'-cyano-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;

126: 3-amino-6-(4'-cyano-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;

127: 3-amino-6-(2'-fluoro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;

5 **128:** 3-amino-6-(3'-fluoro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;

129: 3-amino-6-(4'-fluoro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;

130: 3-amino-6-(2'-chloro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;

131: 3-amino-6-(3'-chloro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;

132: 3-amino-6-(4'-chloro-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;

10 **133:** 3-amino-6-(2'-bromo-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;

134: 3-amino-6-(3'-bromo-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;

135: 3-amino-6-(4'-bromo-[1,1'-biphenyl]-4-yl)benzofuran-2-carboxamide;

136: 3-amino-7-(4'-fluorophenyl)benzofuran-2-carboxamide; and

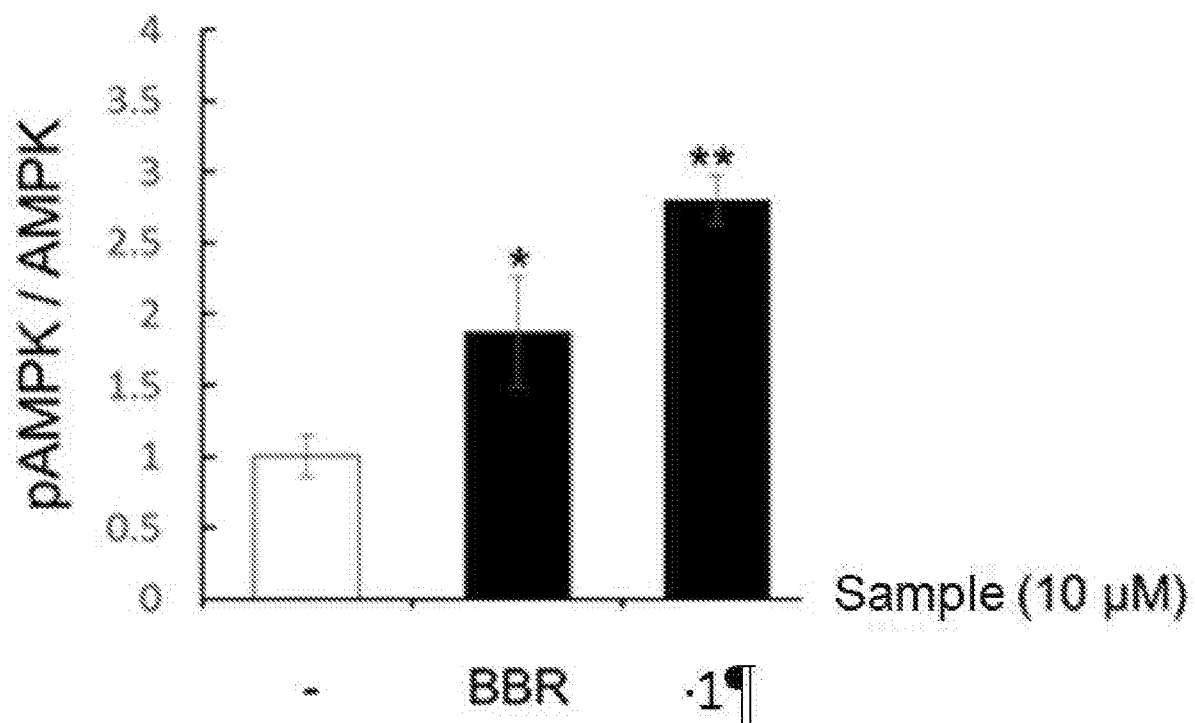
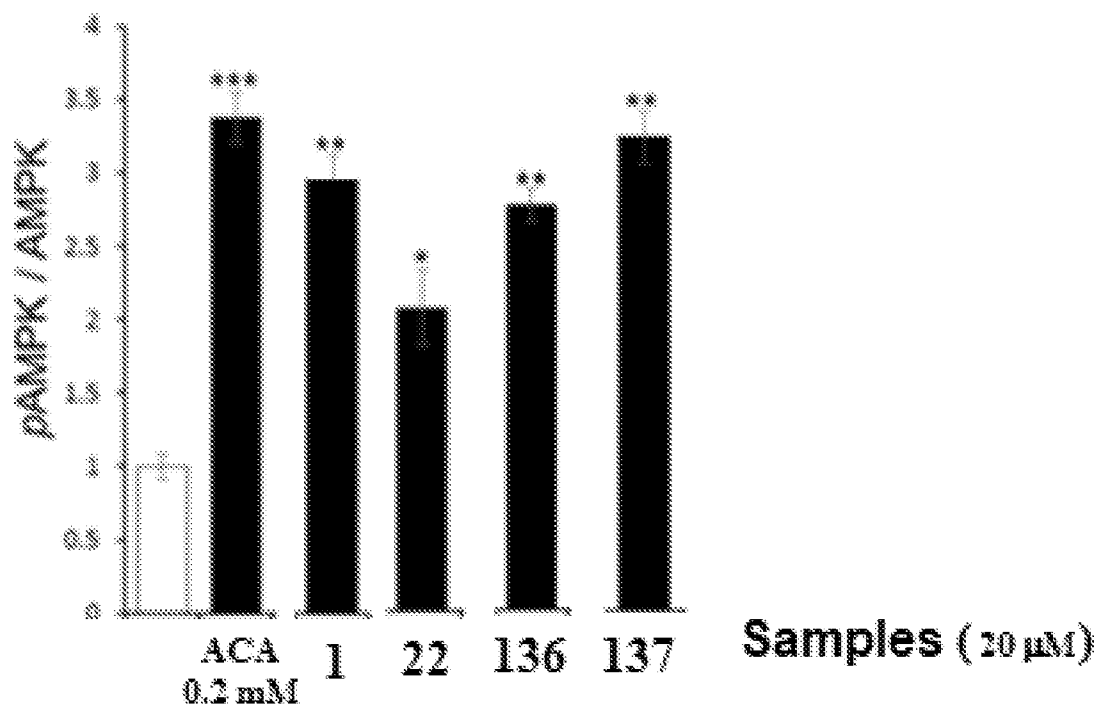
137: 3-amino-7-(1',2',3'-trimethoxyphenyl)benzofuran-2-carboxamide.

15 5. A pharmaceutical composition comprising as active principle at least a compound of general formula (I) as defined in the claims from 1 to 4, in mixture with one or more pharmaceutically acceptable excipients and/or diluents and/or carriers.

20 6. The pharmaceutical composition according to claim 5, further comprising one or more other active principles.

7. The compounds of general formula (I) as defined in the claims from 1 to 4, for use in the prophylaxis and/or therapeutic treatment of diseases or disorders that benefit from the activation of the enzymatic complex AMPK.

25 8. The compounds for use according to claim 7, wherein said diseases or disorders are selected from the group consisting of metabolic disorders, such as diabetes and obesity, immuno-mediated inflammatory pathologies and tumour.

**Fig. 1****Fig. 2**

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2018/052517

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D307/85 A61K31/343 A61P3/00 A61P29/00 A61P35/00
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)

C07D A61P

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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AMY LEW TSUHAKO ET AL: "The design, synthesis, and biological evaluation of PIM kinase inhibitors", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 22, no. 11, 2012, pages 3732-3738, XP028423353, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2012.04.025 [retrieved on 2012-04-11] compounds 4g, 10	4
A	----- WO 2006/020767 A2 (AMPHORA DISCOVERY CORP [US]; DICKSON JOHN K JR [US]; HODGE CARL NICHOL) 23 February 2006 (2006-02-23) paragraphs [0082], [0086] - [0088] examples 2,19-23 claims 1,31,33 -----	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

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

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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

18 June 2018

Date of mailing of the international search report

26/06/2018

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Fanni, Stefano

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2018/052517

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006020767	A2	23-02-2006	
		AR 050917 A1	06-12-2006
		AU 2005272815 A1	23-02-2006
		BR PI0515012 A	01-07-2008
		CA 2575466 A1	23-02-2006
		EP 1781287 A2	09-05-2007
		EP 2168578 A2	31-03-2010
		EP 2620150 A2	31-07-2013
		ES 2401138 T3	17-04-2013
		JP 2008509923 A	03-04-2008
		KR 20070049655 A	11-05-2007
		SG 155222 A1	30-09-2009
		TW 200621253 A	01-07-2006
		US 2006052416 A1	09-03-2006
		US 2009048313 A1	19-02-2009
		WO 2006020767 A2	23-02-2006
		ZA 200701189 B	25-09-2008
