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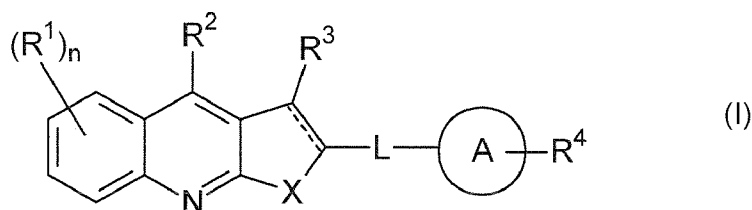
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(54) Title: NOVEL INHIBITORS OF PROTEIN KINASE C EPSILON SIGNALING



(57) Abstract: The present invention relates to novel inhibitors of protein kinase C epsilon (PKCε) signaling, including in particular the compounds of formula (I) as described and defined herein, pharmaceutical compositions comprising these inhibitors, and their use in the treatment or prevention of disorders such as, e.g., a cardiovascular disorder, cardiac hypertrophy, heart failure, anxiety, pain, chronic pain, migraine, an allergy, an inflammatory disorder, an autoimmune disorder, diabetes, diabetic complications, diabetic retinopathy, diabetic nephropathy, diabetic cardiomyopathy, diabetic neuropathy, cancer, metastatic cancer, drug-resistant cancer, stomach cancer, lung cancer, thyroid cancer, colon cancer, breast cancer, a neurological disorder, Alzheimer's disease, Parkinson's disease, bipolar disorder, stroke, alopecia, or alcoholism.



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Novel inhibitors of protein kinase C epsilon signaling

The present invention relates to novel inhibitors of protein kinase C epsilon (PKC ϵ) signaling, including in particular the compounds of formula (I) as described and defined herein, pharmaceutical compositions comprising these inhibitors, and their use in the treatment or prevention of disorders such as, e.g., a cardiovascular disorder, cardiac hypertrophy, heart failure, anxiety, pain, chronic pain, migraine, an allergy, an inflammatory disorder, an autoimmune disorder, diabetes, diabetic complications, diabetic retinopathy, diabetic nephropathy, diabetic cardiomyopathy, diabetic neuropathy, cancer, metastatic cancer, drug-resistant cancer, stomach cancer, lung cancer, thyroid cancer, colon cancer, breast cancer, a neurological disorder, Alzheimer's disease, Parkinson's disease, bipolar disorder, stroke, alopecia, or alcoholism.

Protein kinase C (PKC) is a family of serine/threonine-specific protein kinases. The PKC isozymes can be classified into three groups: i) the conventional isozymes α , β I, β II, and γ ; ii) the novel isozymes δ , ϵ , θ , and η ; and iii) the atypical isozymes λ /I (mouse/human) and ζ . PKC isozymes seem to play important roles in the activation of signal transduction pathways leading to synaptic transmissions, the activation of ion fluxes, secretion, proliferation, cell cycle control, differentiation and tumorigenesis. Because of their role in a complex network of signal transduction pathways, different isoforms have divergent, sometimes opposite roles within a given biological process. However, no simple, unique function can be assigned to a given PKC isozyme. Modulators of PKC isozymes are described, e.g., in: Mochly-Rosen et al., 2012; Sanchez-Bautista et al., 2013; Böhler, 2006; US 2009/0124553; and US 6,376,467.

The PKC ϵ isozyme was reported to participate in neoplastic transformation (Gorin et al., 2009), cardiac hypertrophy (Pass et al., 2001), protection from ischemic insult (Pass et al., 2001; Johnson et al., 1996), nociceptor function (Cesare et al., 1999), macrophage activation (Castrillo et al., 2001), diabetes (Ikeda et al., 2001) and in alcohol consumption (Choi et al., 2002). A PKC ϵ isozyme-specific inhibitor would have pharmaceutical potential,

e.g., for the intervention in stroke, Alzheimer's disease or pain (Akita, 2008; Shirai et al., 2008).

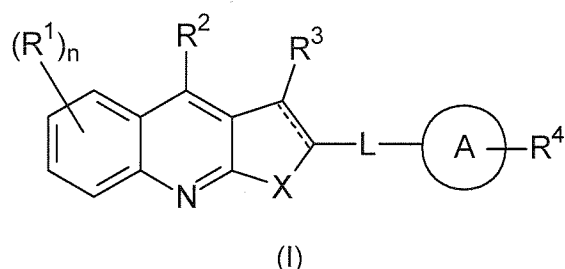
Typically, kinase inhibitors interact with the ATP-binding site, which is well conserved among different kinase families, and is even more so within a family. This poses a serious hurdle for the development of isozyme-specific inhibitors, as there are approximately 518 kinases encoded by the human genome (Manning et al., 2002). Although several selective kinase inhibitors have been reported initially, later it turned out that they also inhibit other targets. For example, the marketed drug imatinib mesylate (Gleevec/Glivec) was developed as an inhibitor of the oncoprotein Bcr-Abl. However, it has turned out to inhibit also other tyrosine kinases such as Kit and platelet-derived growth factor receptor, as well as non-kinase targets. Similarly, relatively unspecific inhibitors initially intended as PKC β -selective inhibitors, such as ruboxistaurine (Fedorov et al., 2007; Nakamura et al., 2010) and enzastaurine (Chen et al., 2008) are in clinical trials for diabetic retinopathy and cancer, respectively. Rottlerin was described as a specific inhibitor of PKC δ . However, also for this compound, additional modes of action have been observed by now (Soltoff, 2007). Due to the high degree of conservation among the ATP-binding sites in PKC isozymes, it is very difficult to develop monospecific inhibitors of a particular PKC isozyme. While monospecificity is not a prerequisite for a successful drug, it would be highly desirable as secondary activities create ambiguity in the interpretation of biochemical, pharmacological, and clinical results.

In the context of the present invention, a different approach was employed to specifically target PKC ϵ signaling. Rather than interacting with the ATP-binding site of PKC ϵ , the signal transduction of PKC ϵ was targeted by preventing the binding of PKC ϵ to its adaptor protein, the PKC ϵ -specific receptor of activated C-kinase 2 (RACK2, β' COP) (Csukai et al., 1997; Schechtman et al., 2001). It has been shown that adaptor proteins bind and translocate activated PKC isozymes to subcellular sites in close proximity to their substrates (Mochly-Rosen et al., 1991). One example of an inhibitor of such protein-protein interactions is aurothiomalate, which interferes with the interaction between PKC ι and its adaptor molecule Par6. The compound blocks oncogenic PKC ι signaling and growth of human lung cancer cells (Erdogan et al., 2006). The adaptor protein RACK2 binds to activated PKC ϵ . The peptide EAVSLKPT, corresponding to amino acids 14 to 21 of PKC ϵ , is known to selectively inhibit the translocation of PKC ϵ by binding to RACK2, but not that of other PKC isozymes (Johnson et al., 1996; Gray et al., 1997). It has also been shown that the PKC ϵ antagonist

EAVSLKPT inhibits protection from hypoxia-induced cell death of cardiac myocytes (Gray et al., 1997).

It is thus an object of the present invention to provide a small molecule peptidomimetic of EAVSLKPT that prevents the PKC ϵ /RACK2 interaction and, hence, selectively inhibits PKC ϵ signaling. Small molecule inhibitors of protein-protein interactions have previously been shown to be useful for pharmacological purposes (Beeley, 2000; Arkin et al., 2004). It is also an object of the invention to provide an isozyme-specific cell-permeable small-molecule inhibitor of PKC ϵ signal transduction, which would be highly useful in therapy, particularly for the treatment or prevention of cancer, stroke, Alzheimer's disease, pain, cardiac hypertrophy, and alcoholism (Shirai et al., 2008), and also as a tool for further research on PKC ϵ . As a solution to the above-mentioned problems, the present invention provides the compounds of formula (I) as described herein below and in the claims. Structurally related compounds have also been disclosed in: Sanam et al., 2010; US 2011/0077250; WO 2013/033037; CN 102757447 A; Pillai et al., 2010; US 2013/0129677; RU 2371444 C1; WO 92/03427; and CAS registry nos. 338433-13-9 and 333330-11-3. The barbituric acid derivative BAS 02104951 has furthermore been disclosed as an inhibitor of PKC ϵ signal transduction in Gruber et al., 2011.

Accordingly, the present invention provides a compound of the following formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof, for use as a medicament:



In formula (I), n is an integer of 0 to 4 (i.e., 0, 1, 2, 3 or 4), and each R^1 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, -OH, -O(C_{1-4} alkyl), -O(C_{1-4} alkyl)-OH, -O(C_{1-4} alkyl)-O(C_{1-4} alkyl), -SH, -S(C_{1-4} alkyl), -S(C_{1-4} alkyl)-SH, or -S(C_{1-4} alkyl)-S(C_{1-4} alkyl), -NH₂, -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), halogen, -CF₃, or -CN. Alternatively, n is 2, 3 or 4, and two groups R^1 attached to adjacent carbon atoms are mutually linked to form a group -O-CH₂-O-, -O-CH₂-CH₂-O- or -O-CH₂-CH₂-CH₂-O-, while the further group(s) R^1 , if present (i.e., if n is 3 or 4), is/are independently selected from C_{1-4} alkyl, C_{2-4} alkenyl,

C₂₋₄ alkynyl, -OH, -O(C₁₋₄ alkyl), -O(C₁₋₄ alkyl)-OH, -O(C₁₋₄ alkyl)-O(C₁₋₄ alkyl), -SH, -S(C₁₋₄ alkyl), -S(C₁₋₄ alkyl)-SH, or -S(C₁₋₄ alkyl)-S(C₁₋₄ alkyl), -NH₂, -NH(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)(C₁₋₄ alkyl), halogen, -CF₃, or -CN. It is to be understood that, if n is 0, the condensed phenyl ring moiety (to which R¹ would be attached) is unsubstituted, i.e. is substituted with hydrogen.

Preferably, n is an integer of 1 to 4 (i.e., 1, 2, 3 or 4), one group R¹ is selected from -O(C₁₋₄ alkyl), -OH, -O(C₁₋₄ alkyl)-OH, or -O(C₁₋₄ alkyl)-O(C₁₋₄ alkyl), and the remaining group(s) R¹, if present (i.e., if n is 2, 3 or 4), is/are independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, -OH, -O(C₁₋₄ alkyl), -O(C₁₋₄ alkyl)-OH, -O(C₁₋₄ alkyl)-O(C₁₋₄ alkyl), -SH, -S(C₁₋₄ alkyl), -S(C₁₋₄ alkyl)-SH, or -S(C₁₋₄ alkyl)-S(C₁₋₄ alkyl), -NH₂, -NH(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)(C₁₋₄ alkyl), halogen, -CF₃, or -CN; or, alternatively, n is 2, 3 or 4, and two groups R¹ attached to adjacent carbon atoms are mutually linked to form a group -O-CH₂-O-, -O-CH₂-CH₂-O- or -O-CH₂-CH₂-CH₂-O-, while the further group(s) R¹, if present (i.e., if n is 3 or 4), is/are independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, -OH, -O(C₁₋₄ alkyl), -O(C₁₋₄ alkyl)-OH, -O(C₁₋₄ alkyl)-O(C₁₋₄ alkyl), -SH, -S(C₁₋₄ alkyl), -S(C₁₋₄ alkyl)-SH, or -S(C₁₋₄ alkyl)-S(C₁₋₄ alkyl), -NH₂, -NH(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)(C₁₋₄ alkyl), halogen, -CF₃, or -CN.

More preferably, n is 1 or 2, one group R¹ is selected from -O(C₁₋₄ alkyl), -OH, -O(C₁₋₄ alkyl)-OH, or -O(C₁₋₄ alkyl)-O(C₁₋₄ alkyl), and the remaining group R¹, if present (i.e., if n is 2), is selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, -OH, -O(C₁₋₄ alkyl), -SH, -S(C₁₋₄ alkyl), -NH₂, -NH(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)(C₁₋₄ alkyl), halogen, -CF₃, or -CN; or, alternatively, n is 2, and the two groups R¹ are attached to adjacent carbon atoms (preferably the same two carbon atoms as in the compounds **1a** and **1b** shown below) and are mutually linked to form a group -O-CH₂-O-, -O-CH₂-CH₂-O- or -O-CH₂-CH₂-CH₂-O-.

Even more preferably, n is 1 and R¹ is selected from -O(C₁₋₄ alkyl), -OH, -O(C₁₋₄ alkyl)-OH, or -O(C₁₋₄ alkyl)-O(C₁₋₄ alkyl), wherein it is particularly preferred that R¹ is selected from -OCH₃ or -OCH₂CH₃; or, alternatively, n is 2 and the two groups R¹ are attached to adjacent carbon atoms (preferably the same two carbon atoms as in the compounds **1a** and **1b** shown below) and are mutually linked to form a group -O-CH₂-O- or -O-CH₂-CH₂-O-.

R² is selected from hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, -OH, -O(C₁₋₄ alkyl), -SH, -S(C₁₋₄ alkyl), -NH₂, -NH(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)(C₁₋₄ alkyl), halogen, -CF₃, or -CN. Preferably, R² is hydrogen.

R³ is selected from -NH₂, -NH(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -OH, -O(C₁₋₄ alkyl), -SH, -S(C₁₋₄ alkyl), or hydrogen. Preferably, R³ is -NH₂, -NH(C₁₋₄ alkyl), -OH, or -SH. More preferably, R³ is -NH₂.

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X is selected from S, O, N(H), or N(C₁₋₄ alkyl). Preferably, X is S or O. More preferably, X is S.

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L is -(CH₂)₁₋₄-, wherein one -CH₂- unit comprised in said -(CH₂)₁₋₄- is replaced by a group selected from -CO-NH-, -CO-N(C₁₋₄ alkyl)-, -NH-CO-, -N(C₁₋₄ alkyl)-CO-, -O-, -CO-, -NH-, -N(C₁₋₄ alkyl)-, -S-, -SO-, or -SO₂-. Preferably, L is -(CH₂)₁₋₃-, wherein one -CH₂- unit comprised in said -(CH₂)₁₋₃- is replaced by a group selected from -CO-NH-, -CO-N(C₁₋₄ alkyl)-, -NH-CO-, or -N(C₁₋₄ alkyl)-CO-. More preferably, L is directionally selected from -CO-NH-, -CO-N(C₁₋₄ alkyl)-, -NH-CO-, or -N(C₁₋₄ alkyl)-CO-. Even more preferably, L is -CO-NH- or -CO-N(C₁₋₄ alkyl)-, wherein the nitrogen atom comprised in said -CO-NH- or said -CO-N(C₁₋₄ alkyl)- is attached to ring A. Most preferably, L is -CO-NH-, wherein the nitrogen atom comprised in said -CO-NH- is attached to ring A.

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A is aryl or heteroaryl, wherein said aryl or said heteroaryl is optionally substituted with one or more groups (such as, e.g., one, two, three or four groups; preferably, one or two groups; more preferably, one group) independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, -OH, -O(C₁₋₄ alkyl), -SH, -S(C₁₋₄ alkyl), -NH₂, -NH(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)(C₁₋₄ alkyl), halogen, -CF₃, or -CN. Said aryl is preferably phenyl or naphthyl, and more preferably said aryl is phenyl. Said heteroaryl is preferably a heteroaryl having 5 or 6 ring atoms, wherein 1, 2 or 3 of said ring atoms are heteroatoms independently selected from oxygen, sulfur or nitrogen, and the remaining ones of said ring atoms are carbon atoms, and further wherein said heteroaryl having 5 or 6 ring atoms is optionally fused to a benzene ring. More preferably, said heteroaryl is selected from thiazolyl (e.g., 1,3-thiazol-2-yl), furanyl, thiophenyl (i.e., thienyl), pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, furazanyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzothiazolyl (e.g., 1,3-benzothiazol-2-yl), benzofuranyl, benzothiophenyl, benzopyrrolyl, benzoimidazolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzofurazanyl, benzopyridinyl, benzopyrimidinyl, benzopyrazinyl, or benzopyridazinyl. Even more preferably, said heteroaryl is thiazolyl (e.g., 1,3-thiazol-2-yl) or benzothiazolyl (e.g., 1,3-benzothiazol-2-yl). Most preferably, said heteroaryl is benzothiazolyl, particularly 1,3-benzothiazol-2-yl. It is furthermore preferred that A is aryl or heteroaryl, including any of the aforementioned preferred aryl or heteroaryl

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groups, wherein said aryl or heteroaryl is unsubstituted (i.e., is not substituted with any groups other than R⁴).

It is preferred that A is phenyl, 1,3-thiazol-2-yl or 1,3-benzothiazol-2-yl, wherein said phenyl, said 1,3-thiazol-2-yl or said 1,3-benzothiazol-2-yl is optionally substituted with one or more (e.g., one, two or three) groups independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, -OH, -O(C₁₋₄ alkyl), -SH, -S(C₁₋₄ alkyl), -NH₂, -NH(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)(C₁₋₄ alkyl), halogen, -CF₃, or -CN, preferably selected independently from C₁₋₄ alkyl, -OH, -O(C₁₋₄ alkyl), -NH₂, -NH(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)(C₁₋₄ alkyl), halogen, -CF₃, or -CN, more preferably selected independently from C₁₋₄ alkyl, -OH, -O(C₁₋₄ alkyl), or halogen (e.g., -F, -Cl, -Br, or -I). It is furthermore preferred that A is phenyl, 1,3-thiazol-2-yl or 1,3-benzothiazol-2-yl, wherein said phenyl, said 1,3-thiazol-2-yl or said 1,3-benzothiazol-2-yl is unsubstituted (i.e., is not substituted with any groups other than R⁴).

More preferably, A is phenyl which is optionally substituted with one or more (e.g., one, two or three) groups independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, -OH, -O(C₁₋₄ alkyl), -SH, -S(C₁₋₄ alkyl), -NH₂, -NH(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)(C₁₋₄ alkyl), halogen, -CF₃, or -CN, particularly from C₁₋₄ alkyl, -OH, -O(C₁₋₄ alkyl), -NH₂, -NH(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)(C₁₋₄ alkyl), halogen, -CF₃, or -CN. Most preferably, A is phenyl, i.e. unsubstituted phenyl (not substituted with any groups other than R⁴).

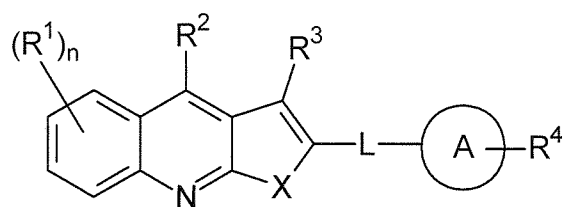
R^4 is selected from -CO-(C₁₋₄ alkyl), -CHO, -O(C₁₋₄ alkyl), -OH, -O-CO-(C₁₋₄ alkyl), -O-CO-O(C₁₋₄ alkyl), -CO-O(C₁₋₄ alkyl), -COOH, -CO-NH₂, -CO-NH-(C₁₋₄ alkyl), -CO-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -O-CO-NH₂, -O-CO-NH-(C₁₋₄ alkyl), -O-CO-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -NH-CO-(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)-CO-(C₁₋₄ alkyl), -NH-CO-O(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)-CO-O(C₁₋₄ alkyl), -NH₂, -NH(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)(C₁₋₄ alkyl), C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, -(C₁₋₄ alkyl)-CO-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-CHO, -(C₁₋₄ alkyl)-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-OH (e.g., -CH(-CH₃)-OH), -(C₁₋₄ alkyl)-O-CO-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-O-CO-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-CO-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-COOH, -(C₁₋₄ alkyl)-CO-NH₂, -(C₁₋₄ alkyl)-CO-NH-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-CO-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-O-CO-NH₂, -(C₁₋₄ alkyl)-O-CO-NH-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-O-CO-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-NH-CO-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-N(C₁₋₄ alkyl)-CO-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-NH-CO-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-N(C₁₋₄ alkyl)-CO-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-NH₂, -(C₁₋₄ alkyl)-NH(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -(C₁₋₄ alkyl)=N-OH (e.g., -C(-CH₃)=N-OH), -(C₁₋₄ alkyl)=N-O(C₁₋₄ alkyl) (e.g., -C(-CH₃)=N-O(C₁₋₄ alkyl)), -(C₁₋₄ alkyl)=N-O-(C₁₋₄ alkyl)-COOH (e.g., -C(-CH₃)=N-O-CH₂-COOH), -(C₁₋₄ alkyl)=N-O-(C₁₋₄ alkyl)-CO-

alkyl)-CO-O(C₁₋₄ alkyl) (e.g., -C(-CH₃)=N-O-(C₁₋₄ alkyl)-CO-O(C₁₋₄ alkyl)), halogen (e.g., -F, -Cl, -Br, or -I), -CF₃, -CN, heterocycloalkyl (e.g., morpholinyl), or hydrogen.

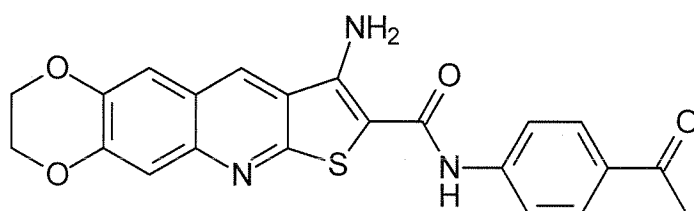
Preferably, R⁴ is selected from -CO-(C₁₋₄ alkyl), -CHO, -O(C₁₋₄ alkyl), -OH, -O-CO-(C₁₋₄ alkyl), -O-CO-O(C₁₋₄ alkyl), -CO-O(C₁₋₄ alkyl), -COOH, -CO-NH₂, -CO-NH-(C₁₋₄ alkyl), -CO-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -O-CO-NH₂, -O-CO-NH-(C₁₋₄ alkyl), -O-CO-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -NH-CO-(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)-CO-(C₁₋₄ alkyl), -NH-CO-O(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)-CO-O(C₁₋₄ alkyl), -NH₂, -NH(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)(C₁₋₄ alkyl), C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, -(C₁₋₄ alkyl)-CO-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-CHO, -(C₁₋₄ alkyl)-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-OH (e.g., -CH(-CH₃)-OH), -(C₁₋₄ alkyl)-O-CO-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-O-CO-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-CO-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-COOH, -(C₁₋₄ alkyl)-CO-NH₂, -(C₁₋₄ alkyl)-CO-NH-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-CO-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-O-CO-NH₂, -(C₁₋₄ alkyl)-O-CO-NH-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-O-CO-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-NH-CO-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-N(C₁₋₄ alkyl)-CO-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-NH-CO-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-N(C₁₋₄ alkyl)-CO-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-NH₂, -(C₁₋₄ alkyl)-NH(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -(C₁₋₄ alkyl)=N-OH (e.g., -C(-CH₃)=N-OH), -(C₁₋₄ alkyl)=N-O(C₁₋₄ alkyl) (e.g., -C(-CH₃)=N-O(C₁₋₄ alkyl)), -(C₁₋₄ alkyl)=N-O-(C₁₋₄ alkyl)-COOH (e.g., -C(-CH₃)=N-O-CH₂-COOH), -(C₁₋₄ alkyl)=N-O-(C₁₋₄ alkyl)-CO-O(C₁₋₄ alkyl) (e.g., -C(-CH₃)=N-O-(C₁₋₄ alkyl)-CO-O(C₁₋₄ alkyl)), halogen (e.g., -F, -Cl, -Br, or -I), -CF₃, -CN, or heterocycloalkyl (e.g., morpholinyl). More preferably, R⁴ is selected from -CO-(C₁₋₄ alkyl), -CHO, -O(C₁₋₄ alkyl), -OH, -CO-O(C₁₋₄ alkyl), -COOH, C₁₋₄ alkyl, -(C₁₋₄ alkyl)-CO-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-CHO, -(C₁₋₄ alkyl)-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-OH, -(C₁₋₄ alkyl)-CO-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-COOH, -C(-CH₃)=N-OH, -C(-CH₃)=N-O(C₁₋₄ alkyl), -C(-CH₃)=N-O-(C₁₋₄ alkyl)-COOH, -C(-CH₃)=N-O-(C₁₋₄ alkyl)-CO-O(C₁₋₄ alkyl), halogen, -CF₃, -CN, or heterocycloalkyl (e.g., morpholinyl). More preferably, R⁴ is selected from -CO-(C₁₋₄ alkyl), -CHO, -O(C₁₋₄ alkyl), or -OH. Even more preferably, R⁴ is -CO-CH₃, -CO-CH₂CH₃, -OCH₃, or -OCH₂CH₃.

The bond ----- in formula (I) is a double bond or a single bond. Preferably, ----- is a double bond. Accordingly, it is preferred that the compound of formula (I) has the following structure:

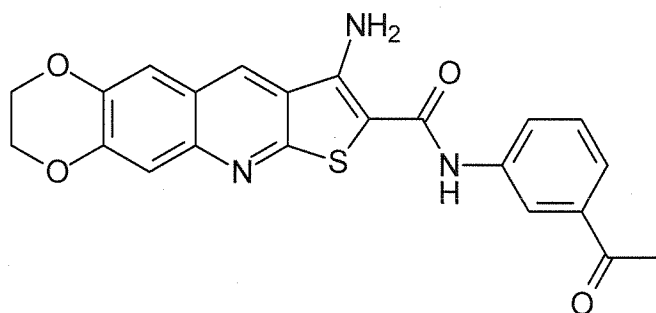
8



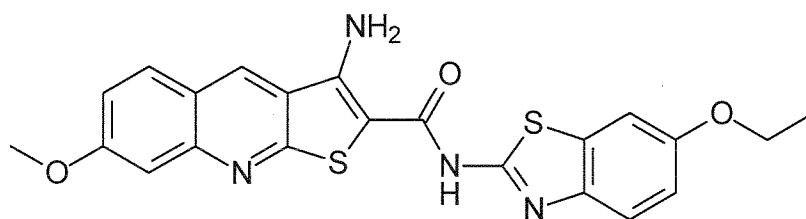
Particularly preferred compounds of formula (I) are the compounds **1a** to **1t** shown below as well as pharmaceutically acceptable salts, solvates and prodrugs of each one of these compounds:

**1a**

(also referred to as "PKCe2138")

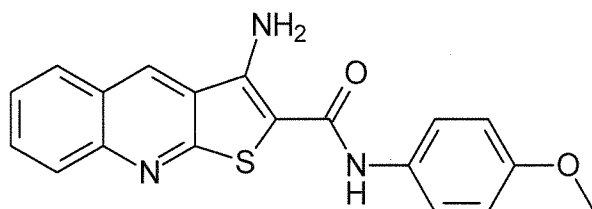
**1b**

(also referred to as "PKCe141")

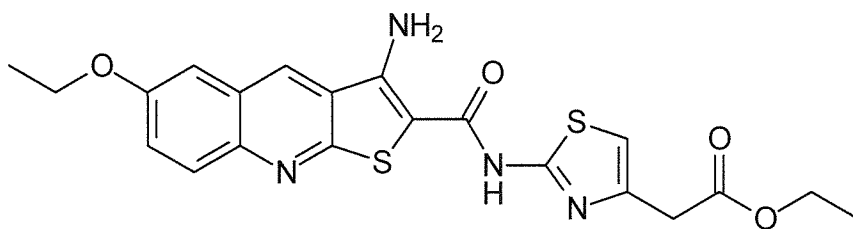
**1c**

(also referred to as "PKCe16")

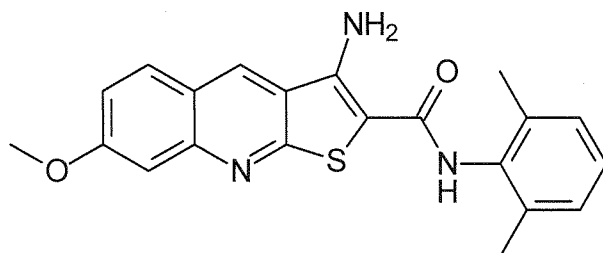
9

**1d**

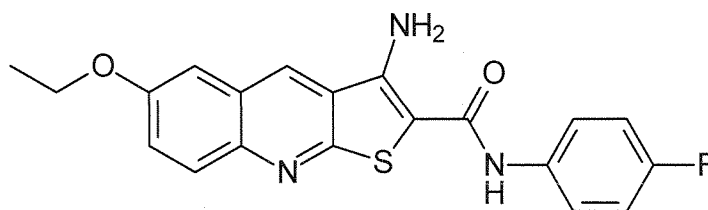
(also referred to as "PKCe119")

**1e**

(also referred to as "PKCe123")

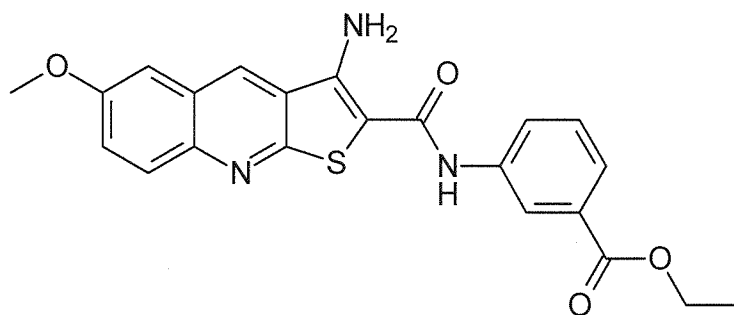
**1f**

(also referred to as "PKCe127")

**1g**

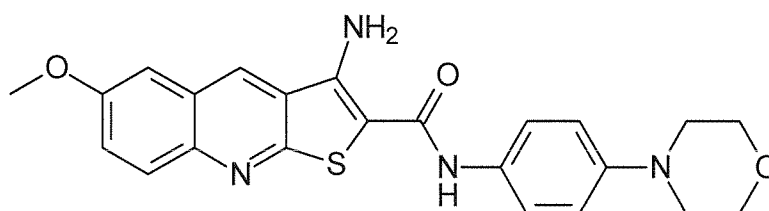
(also referred to as "PKCe129")

10

**1h**

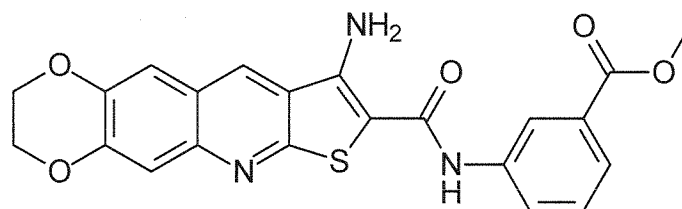
(also referred to as "PKCe133")

5

**1i**

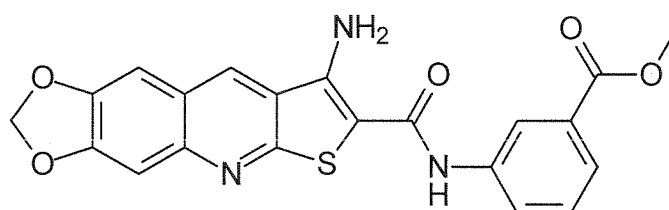
(also referred to as "PKCe140")

10

**1j**

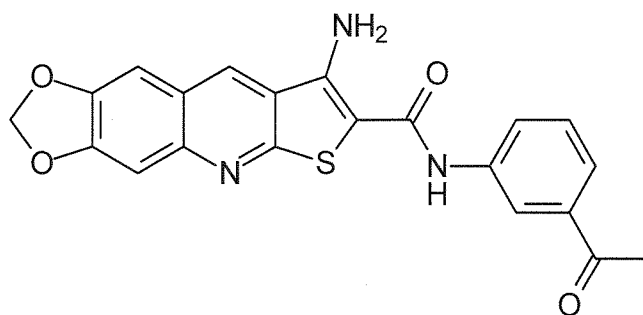
(also referred to as "PKCe2139")

15

**1k**

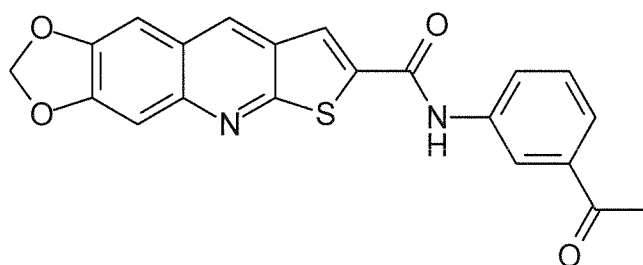
(also referred to as "PKCe2140")

11



1l

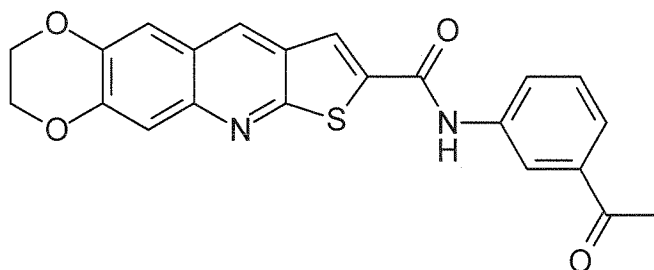
(also referred to as "PKCe2022")



5

1m

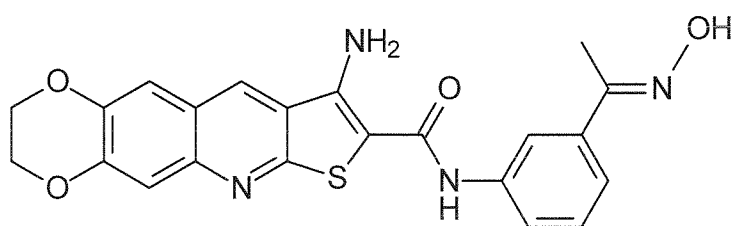
(also referred to as "PKCe2023")



10

1n

(also referred to as "PKCe2024")

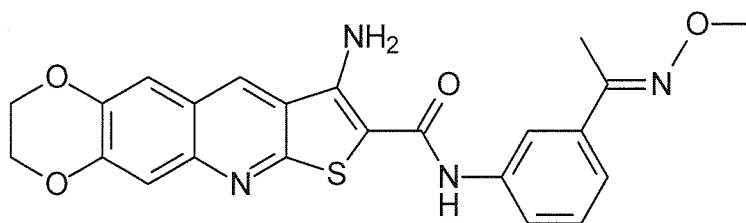


1o

(also referred to as "PKCe2141")

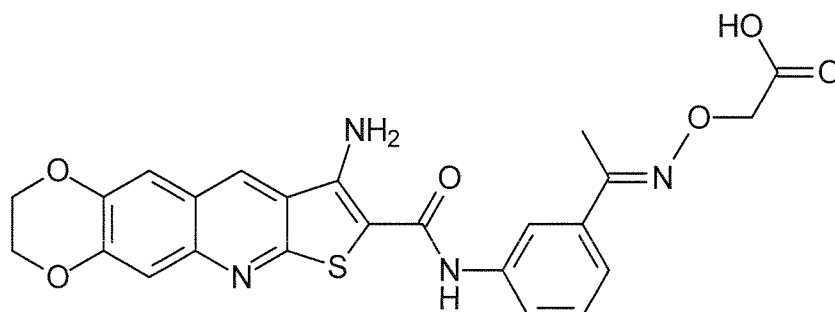
15

12

**1p**

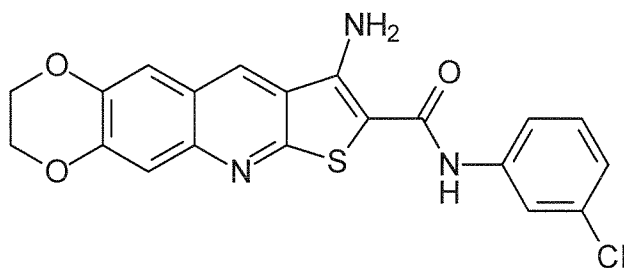
(also referred to as "PKCe2142")

5

**1q**

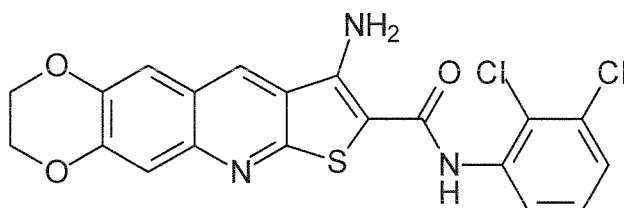
(also referred to as "PKCe2143")

10

**1r**

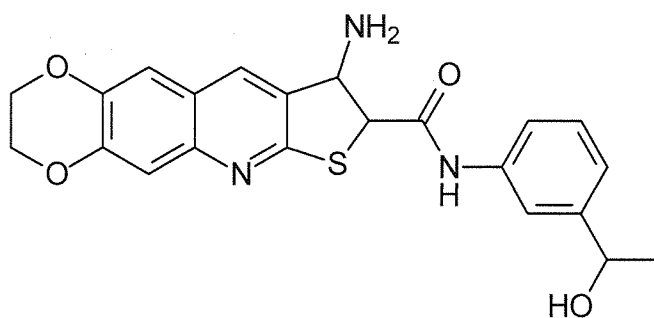
(also referred to as "PKCe2144")

15

**1s**

(also referred to as "PKCe2145")

13

**1t**

(also referred to as "PKCε2092")

5 The present invention also provides a pharmaceutical composition comprising a compound of formula (I) as described and defined herein, or a pharmaceutically acceptable salt, solvate or prodrug thereof, in combination with a pharmaceutically acceptable excipient.

10 The compounds according to the present invention, including in particular the compounds of formula (I), have been found to inhibit the interaction of PKCε with its adaptor protein RACK2, as also shown in Examples 2 and 3. Compound **1b**, for instance, which is an exemplary compound of formula (I) has been demonstrated to inhibit the PKCε/RACK2 interaction *in vitro* with an IC₅₀ of 5.9 μM (see Example 2) and to inhibit the phosphorylation of the PKCε-downstream target Elk-1 in HeLa cells with an IC₅₀ of 11.2 μM (see Example 15 3). A large number of further exemplary compounds of formula (I) has likewise been found to inhibit PKCε signaling (see Example 2). Compound **1a**, for example, has been shown to inhibit the PKCε/RACK2 interaction *in vitro* with an IC₅₀ of 4.1 μM.

20 The compounds of the present invention are particularly advantageous as they allow the isozyme-specific inhibition of PKCε signaling. Accordingly, it has been demonstrated in Example 4 that compound **1b** inhibits the TPA-induced translocation of PKCε – but not that of PKCδ – from the cytosol to the membrane and, furthermore, compound **1b** has been shown to inhibit the PKCε-induced migration of HeLa cells into a gap (see Example 5). The compounds of the present invention thus fulfill all criteria of an inhibitor of PKCε signal 25 transduction, such as inhibition of Elk-1 phosphorylation, inhibition of PKCε translocation to the membrane and inhibition of cell migration. Moreover, the compounds of the invention have been shown not to inhibit cell proliferation (see Example 5), which indicates a lack of toxicity and confirms the suitability of these compounds as medicaments.

The compounds according to the invention, and in particular the compounds of formula (I), can thus be used for the therapeutic intervention in diseases/disorders in which PKC ϵ signaling is implicated (particularly diseases/disorders associated with an increased activity or a hyperactivity of PKC ϵ signaling), such as, e.g., cardiovascular disorders (e.g., cardiac hypertrophy, hypertrophic cardiomyopathy, or heart failure (including, e.g., congestive heart failure)), anxiety, pain (e.g., chronic pain), migraine, allergies, inflammatory disorders, autoimmune disorders, diabetes (including also insulin resistance), diabetic complications (such as, e.g., diabetic retinopathy, diabetic nephropathy, diabetic cardiomyopathy, or diabetic neuropathy), cancer (such as, e.g., stomach cancer, lung cancer, thyroid cancer, colon cancer, breast cancer; including also metastatic cancer, metastasis, drug-resistant cancer, or multidrug-resistant cancer), neurological disorders (e.g., Alzheimer's disease, Parkinson's disease, bipolar disorder, or stroke; including also neurodegenerative disorders), alopecia, or alcoholism (Shirai et al., 2008; Pass et al., 2001; Reichling et al., 2009; Galeotti et al., 2013; Takeishi et al., 2000; Takahashi et al., 2000; Gorin et al., 2009; Akita, 2008; Ferreira et al., 2010; Choi et al., 2002; Johnson et al., 1996; Ikeda et al., 2001; Mochly-Rosen et al., 2012 and references cited therein).

Accordingly, without being bound by theory, the present invention provides a compound of formula (I) as described and defined herein, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising any of the aforementioned entities and a pharmaceutically acceptable excipient, for use in the treatment or prevention of cardiovascular disorders (e.g., cardiac hypertrophy, hypertrophic cardiomyopathy, or heart failure (including, e.g., congestive heart failure)), anxiety, pain (e.g., chronic pain), migraine, allergies, inflammatory disorders, autoimmune disorders, diabetes (including also insulin resistance), diabetic complications (such as, e.g., diabetic retinopathy, diabetic nephropathy, diabetic cardiomyopathy, or diabetic neuropathy), cancer (such as, e.g., stomach cancer, lung cancer, thyroid cancer, colon cancer, breast cancer; including also metastatic cancer, metastasis, drug-resistant cancer, or multidrug-resistant cancer), neurological disorders (e.g., Alzheimer's disease, Parkinson's disease, bipolar disorder, or stroke; including also neurodegenerative disorders), alopecia, or alcoholism.

The invention likewise relates to the use of the compounds provided herein, including the compounds of formula (I) or pharmaceutically acceptable salts, solvates or prodrugs thereof, in the preparation of a medicament for the treatment or prevention of cardiovascular disorders (e.g., cardiac hypertrophy, hypertrophic cardiomyopathy, or heart failure (including, e.g., congestive heart failure)), anxiety, pain (e.g., chronic pain), migraine,

allergies, inflammatory disorders, autoimmune disorders, diabetes (including also insulin resistance), diabetic complications (such as, e.g., diabetic retinopathy, diabetic nephropathy, diabetic cardiomyopathy, or diabetic neuropathy), cancer (such as, e.g., stomach cancer, lung cancer, thyroid cancer, colon cancer, breast cancer; including also metastatic cancer, metastasis, drug-resistant cancer, or multidrug-resistant cancer), neurological disorders (e.g., Alzheimer's disease, Parkinson's disease, bipolar disorder, or stroke; including also neurodegenerative disorders), alopecia, or alcoholism.

The invention also provides a method of treating or preventing a disorder or condition selected from the group consisting of cardiovascular disorders (e.g., cardiac hypertrophy, hypertrophic cardiomyopathy, or heart failure (including, e.g., congestive heart failure)), anxiety, pain (e.g., chronic pain), migraine, allergies, inflammatory disorders, autoimmune disorders, diabetes (including also insulin resistance), diabetic complications (such as, e.g., diabetic retinopathy, diabetic nephropathy, diabetic cardiomyopathy, or diabetic neuropathy), cancer (such as, e.g., stomach cancer, lung cancer, thyroid cancer, colon cancer, breast cancer; including also metastatic cancer, metastasis, drug-resistant cancer, or multidrug-resistant cancer), neurological disorders (e.g., Alzheimer's disease, Parkinson's disease, bipolar disorder, or stroke; including also neurodegenerative disorders), alopecia, and alcoholism, the method comprising the administration of a compound according to the invention, particularly a compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising any of the aforementioned entities and a pharmaceutically acceptable excipient, to a subject (e.g., a human) in need thereof.

Protein-protein interfaces, such as the PKC ϵ /RACK2 interface, are much more difficult to target than classical ligand-binding sites, due to their particular physicochemical properties (extensive, hydrophobic, surface-exposed interfaces). Attempts to tackle protein-protein interactions have been reported in recent years but experience is still quite limited and experimental aspects are challenging as well (Rechfeld et al., 2011). The EAVSLKPT peptide, derived from the binding site of PKC ϵ to RACK2 and used for molecular modeling in the context of the present invention (see Example 1), inhibits this interaction with an IC₅₀ of 1.02 μ M. Therefore, a peptidomimetic of EAVSLKPT such as compound **1b** (PKC ϵ 141) with an IC₅₀ of 5.9 μ M may be close to the optimum already. Also aurothiomalate, which prevents the interaction of PKC α and its adaptor protein Par6, is active in the range of 10 μ M (Erdogan et al., 2006). While a compound with an IC₅₀ in the nanomolar range would be preferable, this is not essential for clinical application. For example, the ribonucleotide

reductase inhibitor hydroxyurea inhibits ribonucleotide reductase with an IC_{50} of 37.2 μ M (Easmon et al., 2001) and is used in the clinic as an anticancer agent. Furthermore, many clinically relevant kinase inhibitors which are active at nanomolar concentrations *in vitro* have cellular IC_{50} values closer to the micromolar range due to the higher physiological concentrations of ATP relative to those typically used for *in vitro* assays.

The invention further relates to novel compounds, namely the compounds **1a**, **1j**, **1k**, **1l**, **1m**, **1n**, **1o**, **1p**, **1q**, **1r**, **1s** and **1t** having the structures shown above, as well as pharmaceutically acceptable salts, solvates and prodrugs of each one of these compounds. These compounds as provided in the context of the present invention are particularly useful as medicaments, e.g., for the treatment or prevention of diseases/disorders in which PKC ϵ signaling is implicated, as described herein above.

Moreover, the present invention also relates to the compounds shown in Table 1 below, including in particular the compounds PKCe22, PKCe39, PKCe40, PKCe48, PKCe49, PKCe52, PKCe67, PKCe73, PKCe76, PKCe86, PKCe87, PKCe89, PKCe95, PKCe96, PKCe97, PKCe106, PKCe107, PKCe109, PKCe114, PKCe125, PKCe143, PKCe145, PKCe2019, PKCe2020, PKCe2021, PKCe2051, PKCe2052, PKCe2053, PKCe2054, PKCe2088, PKCe2089, PKCe2090, and PKCe2091, as well as pharmaceutically acceptable salts, solvates and prodrugs of each one of these compounds. The invention further relates to the use of these compounds as medicaments, including their use in the treatment or prevention of diseases/disorders in which PKC ϵ signaling is implicated, such as the specific diseases/disorders described herein above.

The compounds of the present invention, including the compounds of formula (I), can be prepared by methods known in the field of synthetic chemistry. For example, the compounds of the invention may be prepared in accordance with or in analogy to the synthetic routes described in Example 8. Moreover, certain compounds of formula (I), such as compound **1b** (Asinex ID: ASN 05545158; CAS 602293-00-5) and compound **1c** (Asinex ID: ASN 02538754; CAS 552819-38-2), are also commercially available, e.g., from Asinex Ltd., Moscow, Russia.

As used herein, the term "alkyl" refers to a monovalent saturated aliphatic (i.e. non-aromatic) acyclic hydrocarbon group (i.e., a group consisting of carbon atoms and hydrogen atoms), which may be linear or branched and does not comprise any carbon-to-carbon double bond or any carbon-to-carbon triple bond. The term "C₁₋₄ alkyl" denotes an

alkyl group having 1 to 4 carbon atoms. Preferred exemplary alkyl groups are methyl, ethyl, propyl, or butyl.

As used herein, the term "alkenyl" refers to a monovalent unsaturated aliphatic acyclic hydrocarbon group, which may be linear or branched and comprises at least one carbon-to-carbon double bond while it does not comprise any carbon-to-carbon triple bond. The term "C₂₋₄ alkenyl" denotes an alkenyl group having 2 to 4 carbon atoms. Preferred exemplary alkenyl groups are ethenyl, propenyl, or butenyl.

As used herein, the term "alkynyl" refers to a monovalent unsaturated aliphatic acyclic hydrocarbon group, which may be linear or branched and comprises at least one carbon-to-carbon triple bond and optionally one or more carbon-to-carbon double bonds. The term "C₂₋₄ alkynyl" denotes an alkynyl group having 2 to 4 carbon atoms. Preferred exemplary alkynyl groups are ethynyl, propynyl, or butynyl.

As used herein, the term "aryl" refers to a monovalent aromatic hydrocarbon group, including bridged ring and/or fused ring systems, containing at least one aromatic ring. "Aryl" may, for example, refer to phenyl, naphthyl or anthracenyl.

As used herein, the term "heteroaryl" refers to a monovalent aromatic ring group, which may be a monocyclic ring group or a bridged ring and/or fused ring system (e.g., a bicyclic ring system), said aromatic ring group comprising one or more (such as, e.g., one, two, or three) ring heteroatoms independently selected from O, S, or N, wherein the aromatic ring group may, e.g., have 5 to 14 (particularly 5 or 6) ring atoms. Non-limiting examples of "heteroaryl" groups include thiazolyl (e.g., 1,3-thiazol-2-yl), furanyl, thiophenyl (i.e., thienyl), pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, furazanyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzothiazolyl (e.g., 1,3-benzothiazol-2-yl), benzofuranyl, benzothiophenyl, benzopyrrolyl, benzoimidazolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzofurazanyl, benzopyridinyl, benzopyrimidinyl, benzopyrazinyl, or benzopyridazinyl.

As used herein, the term "heterocycloalkyl" refers to a 3 to 10 atom ring or ring system containing one or more (e.g., one, two or three) ring heteroatoms independently selected from O, S, or N. "Heterocycloalkyl" may, for example, refer to tetrahydrofuranyl, piperidinyl, piperazinyl, aziridinyl, azetidiny, pyrrolidinyl, imidazolidinyl, morpholinyl (e.g., morpholin-4-yl), pyrazolidinyl, tetrahydrothienyl, octahydroquinolinyl, octahydroisoquinolinyl, oxazolidinyl, or isoxazolidinyl.

As used herein, the term "halogen" refers to fluoro (-F), chloro (-Cl), bromo (-Br) or iodo (-I).

The scope of the invention embraces all pharmaceutically acceptable salt forms of the compounds provided herein, including in particular the compounds of formula (I), which may be formed, e.g., by protonation of an atom carrying an electron lone pair which is susceptible to protonation, such as an amino group, with an inorganic or organic acid, or as a salt of a carboxylic acid group with a physiologically acceptable cation as they are well-known in the art. Exemplary base addition salts comprise, for example, alkali metal salts such as sodium or potassium salts; alkaline earth metal salts such as calcium or magnesium salts; ammonium salts; aliphatic amine salts such as trimethylamine, triethylamine, dicyclohexylamine, ethanolamine, diethanolamine, triethanolamine, procaine salts, meglumine salts, or ethylenediamine salts; aralkyl amine salts such as N,N-dibenzylethylenediamine salts, benethamine salts; heterocyclic aromatic amine salts such as pyridine salts, picoline salts, quinoline salts or isoquinoline salts; quaternary ammonium salts such as tetramethylammonium salts, tetraethylammonium salts, benzyltrimethylammonium salts, benzyltriethylammonium salts, benzyltributylammonium salts, methyltriocetyl ammonium salts or tetrabutylammonium salts; and basic amino acid salts such as arginine salts or lysine salts. Exemplary acid addition salts comprise, for example, mineral acid salts such as hydrochloride, hydrobromide, hydroiodide, sulfate salts, nitrate salts, phosphate salts (such as, e.g., phosphate, hydrogenphosphate, or dihydrogenphosphate salts), carbonate salts, hydrogencarbonate salts or perchlorate salts; organic acid salts such as acetate, propionate, butyrate, pentanoate, hexanoate, heptanoate, octanoate, cyclopentanepropionate, undecanoate, lactate, maleate, oxalate, fumarate, tartrate, malate, citrate, nicotinate, benzoate, salicylate or ascorbate salts; sulfonate salts such as methanesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, benzenesulfonate, p-toluenesulfonate (tosylate), 2-naphthalenesulfonate, 3-phenylsulfonate, or camphorsulfonate salts; and acidic amino acid salts such as aspartate or glutamate salts.

Moreover, the scope of the invention embraces the compounds provided herein, including in particular the compounds of formula (I), in any solvated form, including, e.g., solvates with water, for example hydrates, or with organic solvents such as, e.g., methanol, ethanol or acetonitrile, i.e., as a methanolate, ethanolate or acetonitrilate, respectively, or in the form of any polymorph.

Furthermore, the formulae in the present specification are intended to cover all possible stereoisomers, including enantiomers and diastereomers, of the indicated compounds. Thus, all stereoisomers of the compounds of the present invention, including the compounds of formula (I), are contemplated as part of the present invention, either in admixture or in pure or substantially pure form. The scope of the compounds according to the invention embraces all of the possible stereoisomers and their mixtures. It particularly embraces the racemic forms and the isolated optical isomers. The racemic forms can be resolved by physical methods, such as, e.g., fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates using conventional methods, such as, e.g., salt formation with an optically active acid followed by crystallization. The present invention also embraces all possible tautomers of the compounds provided herein, including the compounds of formula (I).

Pharmaceutically acceptable prodrugs of the compounds according to the present invention are derivatives which have chemically or metabolically cleavable groups and become, by solvolysis or under physiological conditions, the compounds of the invention which are pharmaceutically active *in vivo*. Prodrugs of compounds according to the the present invention may be formed in a conventional manner with a functional group of the compounds such as, e.g., with an amino, hydroxy or carboxy group. The prodrug derivative form often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, Bundgaard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to the person skilled in the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. When a compound of the present invention has a carboxyl group, an ester derivative prepared by reacting the carboxyl group with a suitable alcohol or an amide derivative prepared by reacting the carboxyl group with a suitable amine is exemplified as a prodrug. An especially preferred ester derivative as a prodrug is methylester, ethylester, n-propylester, isopropylester, n-butylester, isobutylester, tert-butylester, morpholinoethylester, N,N-diethylglycolamidoester or α -acetoxyethylester. When a compound of the present invention has a hydroxy group, an acyloxy derivative prepared by reacting the hydroxyl group with a suitable acylhalide or a suitable acid anhydride is exemplified as a prodrug. An especially preferred acyloxy derivative as a prodrug is $-\text{OC}(=\text{O})-\text{CH}_3$, $-\text{OC}(=\text{O})-\text{C}_2\text{H}_5$, $-\text{OC}(=\text{O})-(\text{tert-Bu})$, $-\text{OC}(=\text{O})-\text{C}_{15}\text{H}_{31}$, $-\text{OC}(=\text{O})-(\text{m-COONa-Ph})$, $-\text{OC}(=\text{O})-\text{CH}_2\text{CH}_2\text{COONa}$, $-\text{O}(\text{C}=\text{O})-\text{CH}(\text{NH}_2)\text{CH}_3$ or $-\text{OC}(=\text{O})-\text{CH}_2-\text{N}(\text{CH}_3)_2$. When a compound of the present

invention has an amino group, an amide derivative prepared by reacting the amino group with a suitable acid halide or a suitable mixed anhydride is exemplified as a prodrug. An especially preferred amide derivative as a prodrug is $\text{-NHC(=O)-(CH}_2\text{)}_2\text{OCH}_3$ or $\text{-NHC(=O)-CH(NH}_2\text{)CH}_3$.

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The compounds described herein may be administered as compounds *per se* or may be formulated as medicaments. The medicaments/pharmaceutical compositions may comprise one or more pharmaceutically acceptable excipients, such as carriers, diluents, fillers, disintegrants, lubricating agents, binders, colorants, pigments, stabilizers, preservatives, antioxidants, or solubility enhancers.

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In particular, the pharmaceutical compositions may comprise one or more solubility enhancers, such as, e.g., poly(ethylene glycol), including poly(ethylene glycol) having a molecular weight in the range of about 200 to about 5,000 Da, ethylene glycol, propylene glycol, non-ionic surfactants, tyloxapol, polysorbate 80, macrogol-15-hydroxystearate, phospholipids, lecithin, dimyristoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, distearoyl phosphatidylcholine, cyclodextrins, hydroxyethyl- β -cyclodextrin, hydroxypropyl- β -cyclodextrin, hydroxyethyl- γ -cyclodextrin, hydroxypropyl- γ -cyclodextrin, dihydroxypropyl- β -cyclodextrin, glucosyl- α -cyclodextrin, glucosyl- β -cyclodextrin, diglucosyl- β -cyclodextrin, maltosyl- α -cyclodextrin, maltosyl- β -cyclodextrin, maltosyl- γ -cyclodextrin, maltotriosyl- β -cyclodextrin, maltotriosyl- γ -cyclodextrin, dimaltosyl- β -cyclodextrin, methyl- β -cyclodextrin, carboxyalkyl thioethers, hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, vinyl acetate copolymers, vinyl pyrrolidone, sodium lauryl sulfate, dioctyl sodium sulfosuccinate, or any combination thereof.

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The pharmaceutical compositions can be formulated by techniques known to the person skilled in the art, such as the techniques published in Remington's Pharmaceutical Sciences, 20th Edition. The pharmaceutical compositions can be formulated as dosage forms for oral, parenteral, such as intramuscular, intravenous, subcutaneous, intradermal, intraarterial, intracardial, rectal, nasal, topical, aerosol or vaginal administration. Dosage forms for oral administration include coated and uncoated tablets, soft gelatin capsules, hard gelatin capsules, lozenges, troches, solutions, emulsions, suspensions, syrups, elixirs, powders and granules for reconstitution, dispersible powders and granules, medicated gums, chewing tablets and effervescent tablets. Dosage forms for parenteral administration include solutions, emulsions, suspensions, dispersions and powders and granules for reconstitution. Emulsions are a preferred dosage form for parenteral administration. Dosage

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forms for rectal and vaginal administration include suppositories and ovula. Dosage forms for nasal administration can be administered via inhalation and insufflation, for example by a metered inhaler. Dosage forms for topical administration include creams, gels, ointments, salves, patches and transdermal delivery systems.

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The compounds according to the invention, in particular the compounds of formula (I), or the above described pharmaceutical compositions comprising one or more compounds of formula (I) may be administered to a subject by any convenient route of administration, whether systemically/peripherally or at the site of desired action, including but not limited to one or more of: oral (e.g., as a tablet, capsule, or as an ingestible solution), topical (e.g., transdermal, intranasal, ocular, buccal, and sublingual), parenteral (e.g., using injection techniques or infusion techniques, and including, for example, by injection, e.g., subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, or intrasternal by, e.g., implant of a depot, for example, subcutaneously or intramuscularly), pulmonary (e.g., by inhalation or insufflation therapy using, e.g., an aerosol, e.g., through mouth or nose), gastrointestinal, intrauterine, intraocular, subcutaneous, ophthalmic (including intravitreal or intracameral), rectal, and vaginal.

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If said compounds or pharmaceutical compositions are administered parenterally, then examples of such administration include one or more of: intravenously, intraarterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracardially, intracranially, intramuscularly or subcutaneously administering the compounds or pharmaceutical compositions, and/or by using infusion techniques. For parenteral administration, the compounds are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

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Said compounds or pharmaceutical compositions can also be administered orally in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavoring or coloring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications.

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The tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycolate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included. Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the agent may be combined with various sweetening or flavoring agents, coloring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

Alternatively, said compounds or pharmaceutical compositions can be administered in the form of a suppository or pessary, or it may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder. The compounds of the present invention may also be dermally or transdermally administered, for example, by the use of a skin patch.

Said compounds or pharmaceutical compositions may also be administered by sustained release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained-release matrices include, e.g., polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., *Biopolymers* 22:547-556 (1983)), poly(2-hydroxyethyl methacrylate) (R. Langer et al., *J. Biomed. Mater. Res.* 15:167-277 (1981), and R. Langer, *Chem. Tech.* 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al., *Id.*) or poly-D-(-)-3-hydroxybutyric acid (EP133988). Sustained-release pharmaceutical compositions also include liposomally entrapped compounds. Liposomes containing a compound of the present invention can be prepared by methods known in the art, such as, e.g., the methods described in any one of: DE3218121; Epstein et al., *Proc. Natl. Acad. Sci. (USA)* 82:3688-3692 (1985); Hwang et al., *Proc. Natl. Acad. Sci. (USA)* 77:4030-4034 (1980); EP0052322; EP0036676; EP088046; EP0143949; EP0142641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP0102324.

Said compounds or pharmaceutical compositions may also be administered by the pulmonary route, rectal routes, or the ocular route. For ophthalmic use, they can be formulated as micronized suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

It is also envisaged to prepare dry powder formulations of the compounds of the present invention, including the compounds of formula (I), for pulmonary administration, particularly inhalation. Such dry powders may be prepared by spray drying under conditions which result in a substantially amorphous glassy or a substantially crystalline bioactive powder. Accordingly, dry powders of the compounds of the present invention can be made according to the emulsification/spray drying process disclosed in WO 99/16419 or WO 01/85136. Spray drying of solution formulations of the compounds of the present invention is carried out, for example, as described generally in the "Spray Drying Handbook", 5th ed., K. Masters, John Wiley & Sons, Inc. , NY, NY (1991), and in WO 97/41833 or WO 03/053411.

For topical application to the skin, said compounds or pharmaceutical compositions can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, 2-octyldodecanol, benzyl alcohol and water.

Typically, a physician will determine the actual dosage which will be most suitable for an individual subject. The specific dose level and frequency of dosage for any particular individual subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the individual subject undergoing therapy.

A proposed, yet non-limiting dose of the compounds according to the invention, particularly the compounds of formula (I), for oral administration to a human (of approximately 70 kg

body weight) may be 0.05 to 2500 mg, preferably 0.1 mg to 1000 mg, of the active ingredient per unit dose. The unit dose may be administered, for example, 1 to 3 times per day. The unit dose may also be administered 1 to 7 times per week, e.g., with not more than one administration per day. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient/subject as well as the severity of the condition to be treated. The precise dose and also the route of administration will ultimately be at the discretion of the attendant physician or veterinarian.

The subject or patient, such as the subject in need of treatment or prevention, may be an animal (e.g., a non-human animal), a vertebrate animal, a mammal, a rodent (e.g., a guinea pig, a hamster, a rat, a mouse), a murine (e.g., a mouse), a canine (e.g., a dog), a feline (e.g., a cat), a porcine (e.g., a pig), an equine (e.g., a horse), a primate, a simian (e.g., a monkey or ape), a monkey (e.g., a marmoset, a baboon), an ape (e.g., a gorilla, chimpanzee, orang-utan, gibbon), or a human. The meaning of the terms "eukaryote", "animal", "mammal", etc. is well known in the art and can, for example, be deduced from Wehner und Gehring (1995; Thieme Verlag). In the context of this invention, it is particularly envisaged that animals are to be treated which are economically, agronomically or scientifically important. Scientifically important organisms include, but are not limited to, mice, rats, and rabbits. Lower organisms such as, e.g., fruit flies like *Drosophila melagonaster* and nematodes like *Caenorhabditis elegans* may also be used in scientific approaches. Non-limiting examples of agronomically important animals are sheep, cattle and pigs, while, for example, cats and dogs may be considered as economically important animals. Preferably, the subject/patient is a mammal; more preferably, the subject/patient is a human or a non-human mammal (such as, e.g., a guinea pig, a hamster, a rat, a mouse, a rabbit, a dog, a cat, a horse, a monkey, an ape, a marmoset, a baboon, a gorilla, a chimpanzee, an orang-utan, a gibbon, a sheep, cattle, or a pig); even more preferably, the subject/patient is a human.

The term "treatment of a disorder or disease" as used herein is well known in the art. "Treatment of a disorder or disease" implies that a disorder or disease is suspected or has been diagnosed in a patient/subject. A patient/subject suspected of suffering from a disorder or disease typically shows specific clinical and/or pathological symptoms which a skilled person can easily attribute to a specific pathological condition (i.e., diagnose a disorder or disease).

“Treatment of a disorder or disease” may, for example, lead to a halt in the progression of the disorder or disease (e.g., no deterioration of symptoms) or a delay in the progression of the disorder or disease (in case the halt in progression is of a transient nature only).

“Treatment of a disorder or disease” may also lead to a partial response (e.g., amelioration of symptoms) or complete response (e.g., disappearance of symptoms) of the subject/patient suffering from the disorder or disease. “Amelioration” of a disorder or disease may, for example, lead to a halt in the progression of the disorder or disease or a delay in the progression of the disorder or disease. Such a partial or complete response may be followed by a relapse. It is to be understood that a subject/patient may experience a broad range of responses to a treatment (e.g., the exemplary responses as described herein above).

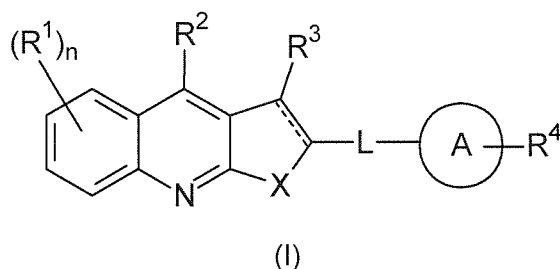
Treatment of a disorder or disease may, inter alia, comprise curative treatment (preferably leading to a complete response and eventually to healing of the disorder or disease) and palliative treatment (including symptomatic relief).

Also the term “prevention of a disorder or disease” as used herein is well known in the art. For example, a patient/subject suspected of being prone to suffer from a disorder or disease as defined herein may, in particular, benefit from a prevention of the disorder or disease. The subject/patient may have a susceptibility or predisposition for a disorder or disease, including but not limited to hereditary predisposition. Such a predisposition can be determined by standard assays, using, for example, genetic markers or phenotypic indicators. It is to be understood that a disorder or disease to be prevented in accordance with the present invention has not been diagnosed or cannot be diagnosed in the patient/subject (for example, the patient/subject does not show any clinical or pathological symptoms). Thus, the term “prevention” comprises the use of compounds of the present invention before any clinical and/or pathological symptoms are diagnosed or determined or can be diagnosed or determined by the attending physician.

In this specification, a number of documents including patent applications, scientific literature and manufacturers’ manuals are cited. The disclosure of these documents, while not considered relevant for the patentability of this invention, is herewith incorporated by reference in its entirety. More specifically, all referenced documents are incorporated by reference to the same extent as if each individual document was specifically and individually indicated to be incorporated by reference.

The present invention particularly relates to the following items:

1. A compound of the following formula (I)



wherein:

10 n is an integer of 0 to 4, and each R^1 is independently selected from C_{2-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, -OH, -O(C_{1-4} alkyl), -O(C_{1-4} alkyl)-OH, -O(C_{1-4} alkyl)-O(C_{1-4} alkyl), -SH, -S(C_{1-4} alkyl), -S(C_{1-4} alkyl)-SH, or -S(C_{1-4} alkyl)-S(C_{1-4} alkyl), -NH₂, -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), halogen, -CF₃, or -CN;

15 or, alternatively, n is 2, 3 or 4, and two groups R^1 attached to adjacent carbon atoms are mutually linked to form a group -O-CH₂-O-, -O-CH₂-CH₂-O- or -O-CH₂-CH₂-CH₂-O-, while the further group(s) R^1 , if present, is/are independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, -OH, -O(C_{1-4} alkyl), -O(C_{1-4} alkyl)-OH, -O(C_{1-4} alkyl)-O(C_{1-4} alkyl), -SH, -S(C_{1-4} alkyl),
 20 -S(C_{1-4} alkyl)-SH, or -S(C_{1-4} alkyl)-S(C_{1-4} alkyl), -NH₂, -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), halogen, -CF₃, or -CN;

25 R^2 is selected from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, -OH, -O(C_{1-4} alkyl), -SH, -S(C_{1-4} alkyl), -NH₂, -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), halogen, -CF₃, or -CN;

R^3 is selected from -NH₂, -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), -OH, -O(C_{1-4} alkyl), -SH, -S(C_{1-4} alkyl), or hydrogen;

30 X is selected from S, O, N(H), or N(C_{1-4} alkyl);

L is $-(CH_2)_{1-4}-$, wherein one $-CH_2-$ unit comprised in said $-(CH_2)_{1-4}-$ is replaced by a group selected from $-CO-NH-$, $-CO-N(C_{1-4} \text{ alkyl})-$, $-NH-CO-$, $-N(C_{1-4} \text{ alkyl})-CO-$, $-O-$, $-CO-$, $-NH-$, $-N(C_{1-4} \text{ alkyl})-$, $-S-$, $-SO-$, or $-SO_2-$;

A is aryl or heteroaryl, wherein said aryl or said heteroaryl is optionally substituted with one or more groups independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, $-OH$, $-O(C_{1-4} \text{ alkyl})$, $-SH$, $-S(C_{1-4} \text{ alkyl})$, $-NH_2$, $-NH(C_{1-4} \text{ alkyl})$, $-N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$, halogen, $-CF_3$, or $-CN$;

R^4 is selected from $-CO-(C_{1-4} \text{ alkyl})$, $-CHO$, $-O(C_{1-4} \text{ alkyl})$, $-OH$, $-O-CO-(C_{1-4} \text{ alkyl})$, $-O-CO-O(C_{1-4} \text{ alkyl})$, $-CO-O(C_{1-4} \text{ alkyl})$, $-COOH$, $-CO-NH_2$, $-CO-NH-(C_{1-4} \text{ alkyl})$, $-CO-N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$, $-O-CO-NH_2$, $-O-CO-NH-(C_{1-4} \text{ alkyl})$, $-O-CO-N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$, $-NH-CO-(C_{1-4} \text{ alkyl})$, $-N(C_{1-4} \text{ alkyl})-CO-(C_{1-4} \text{ alkyl})$, $-NH-CO-O(C_{1-4} \text{ alkyl})$, $-N(C_{1-4} \text{ alkyl})-CO-O(C_{1-4} \text{ alkyl})$, $-NH_2$, $-NH(C_{1-4} \text{ alkyl})$, $-N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, $-(C_{1-4} \text{ alkyl})-CO-(C_{1-4} \text{ alkyl})$, $-(C_{1-4} \text{ alkyl})-CHO$, $-(C_{1-4} \text{ alkyl})-O(C_{1-4} \text{ alkyl})$, $-(C_{1-4} \text{ alkyl})-OH$, $-(C_{1-4} \text{ alkyl})-O-CO-(C_{1-4} \text{ alkyl})$, $-(C_{1-4} \text{ alkyl})-O-CO-O(C_{1-4} \text{ alkyl})$, $-(C_{1-4} \text{ alkyl})-CO-O(C_{1-4} \text{ alkyl})$, $-(C_{1-4} \text{ alkyl})-COOH$, $-(C_{1-4} \text{ alkyl})-CO-NH_2$, $-(C_{1-4} \text{ alkyl})-CO-NH-(C_{1-4} \text{ alkyl})$, $-(C_{1-4} \text{ alkyl})-CO-N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$, $-(C_{1-4} \text{ alkyl})-O-CO-NH_2$, $-(C_{1-4} \text{ alkyl})-O-CO-NH-(C_{1-4} \text{ alkyl})$, $-(C_{1-4} \text{ alkyl})-O-CO-N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$, $-(C_{1-4} \text{ alkyl})-NH-CO-(C_{1-4} \text{ alkyl})$, $-(C_{1-4} \text{ alkyl})-N(C_{1-4} \text{ alkyl})-CO-(C_{1-4} \text{ alkyl})$, $-(C_{1-4} \text{ alkyl})-NH-CO-O(C_{1-4} \text{ alkyl})$, $-(C_{1-4} \text{ alkyl})-N(C_{1-4} \text{ alkyl})-CO-O(C_{1-4} \text{ alkyl})$, $-(C_{1-4} \text{ alkyl})-NH_2$, $-(C_{1-4} \text{ alkyl})-NH(C_{1-4} \text{ alkyl})$, $-(C_{1-4} \text{ alkyl})-N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$, $-(C_{1-4} \text{ alkyl})=N-OH$, $-(C_{1-4} \text{ alkyl})=N-O(C_{1-4} \text{ alkyl})$, $-(C_{1-4} \text{ alkyl})=N-O-(C_{1-4} \text{ alkyl})-COOH$, $-(C_{1-4} \text{ alkyl})=N-O-(C_{1-4} \text{ alkyl})-CO-O(C_{1-4} \text{ alkyl})$, halogen, $-CF_3$, $-CN$, heterocycloalkyl, or hydrogen; and

----- is a double bond or a single bond;

or a pharmaceutically acceptable salt, solvate or prodrug thereof

for use in the treatment or prevention of a cardiovascular disorder, cardiac hypertrophy, heart failure, anxiety, pain, chronic pain, migraine, an allergy, an inflammatory disorder, an autoimmune disorder, diabetes, diabetic complications, diabetic retinopathy, diabetic nephropathy, diabetic cardiomyopathy, diabetic

neuropathy, cancer, metastatic cancer, drug-resistant cancer, stomach cancer, lung cancer, thyroid cancer, colon cancer, breast cancer, bipolar disorder, stroke, alopecia, or alcoholism.

- 5 2. The compound for use according to item 1, wherein n is an integer of 1 to 4, one group R^1 is selected from $-O(C_{1-4} \text{ alkyl})$, $-OH$, $-O(C_{1-4} \text{ alkyl})-OH$, or $-O(C_{1-4} \text{ alkyl})-O(C_{1-4} \text{ alkyl})$, and the remaining group(s) R^1 , if present, is/are independently selected from $C_{2-4} \text{ alkyl}$, $C_{2-4} \text{ alkenyl}$, $C_{2-4} \text{ alkynyl}$, $-OH$, $-O(C_{1-4} \text{ alkyl})$, $-O(C_{1-4} \text{ alkyl})-OH$, $-O(C_{1-4} \text{ alkyl})-O(C_{1-4} \text{ alkyl})$, $-SH$, $-S(C_{1-4} \text{ alkyl})$, $-S(C_{1-4} \text{ alkyl})-SH$, $-S(C_{1-4} \text{ alkyl})-S(C_{1-4} \text{ alkyl})$, $-NH_2$, $-NH(C_{1-4} \text{ alkyl})$, $-N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$, halogen, $-CF_3$, or $-CN$.
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- 15 3. The compound for use according to item 1, wherein n is 2, 3 or 4, and two groups R^1 attached to adjacent carbon atoms are mutually linked to form a group $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$ or $-O-CH_2-CH_2-CH_2-O-$, while the further group(s) R^1 , if present, is/are independently selected from $C_{1-4} \text{ alkyl}$, $C_{2-4} \text{ alkenyl}$, $C_{2-4} \text{ alkynyl}$, $-OH$, $-O(C_{1-4} \text{ alkyl})$, $-O(C_{1-4} \text{ alkyl})-OH$, $-O(C_{1-4} \text{ alkyl})-O(C_{1-4} \text{ alkyl})$, $-SH$, $-S(C_{1-4} \text{ alkyl})$, $-S(C_{1-4} \text{ alkyl})-SH$, $-S(C_{1-4} \text{ alkyl})-S(C_{1-4} \text{ alkyl})$, $-NH_2$, $-NH(C_{1-4} \text{ alkyl})$, $-N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$, halogen, $-CF_3$, or $-CN$.
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- 25 4. The compound for use according to any of items 1 to 3, wherein R^3 is $-NH_2$.
- 30 5. The compound for use according to any of items 1 to 4, wherein X is S.
- 35 6. The compound for use according to any of items 1 to 5, wherein L is $-CO-NH-$ or $-CO-N(C_{1-4} \text{ alkyl})-$, wherein the nitrogen atom comprised in said $-CO-NH-$ or said $-CO-N(C_{1-4} \text{ alkyl})-$ is attached to ring A.
7. The compound for use according to any of items 1 to 6, wherein A is phenyl, 1,3-thiazol-2-yl or 1,3-benzothiazol-2-yl, wherein said phenyl, said 1,3-thiazol-2-yl or said 1,3-benzothiazol-2-yl is optionally substituted with one or more groups independently selected from $C_{1-4} \text{ alkyl}$, $C_{2-4} \text{ alkenyl}$, $C_{2-4} \text{ alkynyl}$, $-OH$, $-O(C_{1-4} \text{ alkyl})$, $-SH$, $-S(C_{1-4} \text{ alkyl})$, $-NH_2$, $-NH(C_{1-4} \text{ alkyl})$, $-N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$, halogen, $-CF_3$, or $-CN$.

8. The compound for use according to any of items 1 to 7, wherein R⁴ is selected from -CO-(C₁₋₄ alkyl), -CHO, -O(C₁₋₄ alkyl), -OH, -CO-O(C₁₋₄ alkyl), -COOH, C₁₋₄ alkyl, -(C₁₋₄ alkyl)-CO-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-CHO, -(C₁₋₄ alkyl)-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-OH, -(C₁₋₄ alkyl)-CO-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-COOH, -C(-CH₃)=N-OH, -C(-CH₃)=N-O(C₁₋₄ alkyl), -C(-CH₃)=N-O-(C₁₋₄ alkyl)-COOH, -C(-CH₃)=N-O-(C₁₋₄ alkyl)-CO-O(C₁₋₄ alkyl), halogen, -CF₃, -CN, or heterocycloalkyl.
9. The compound for use according to any of items 1 to 8, wherein X is S, and further wherein L is -CO-NH- wherein the nitrogen atom comprised in said -CO-NH- is attached to ring A.
10. The compound for use according to item 1, wherein said compound is a compound of one of the formulae **1a** to **1t**, or a pharmaceutically acceptable salt, solvate or prodrug thereof:
11. A pharmaceutical composition comprising a compound as defined in any of items 1 to 10 or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient, for use in the treatment or prevention of a cardiovascular disorder, cardiac hypertrophy, heart failure, anxiety, pain, chronic pain, migraine, an allergy, an inflammatory disorder, an autoimmune disorder, diabetes, diabetic complications, diabetic retinopathy, diabetic nephropathy, diabetic cardiomyopathy, diabetic neuropathy, cancer, metastatic cancer, drug-resistant cancer, stomach cancer, lung cancer, thyroid cancer, colon cancer, breast cancer, bipolar disorder, stroke, alopecia, or alcoholism.
12. A method of treating or preventing a disorder or condition selected from the group consisting of a cardiovascular disorder, cardiac hypertrophy, heart failure, anxiety, pain, chronic pain, migraine, an allergy, an inflammatory disorder, an autoimmune disorder, diabetes, diabetic complications, diabetic retinopathy, diabetic nephropathy, diabetic cardiomyopathy, diabetic neuropathy, cancer, metastatic cancer, drug-resistant cancer, stomach cancer, lung cancer, thyroid cancer, colon cancer, breast cancer, bipolar disorder, stroke, alopecia, and alcoholism, the method comprising the administration of a compound as defined in any of items 1 to 10 or a pharmaceutically acceptable salt, solvate or prodrug thereof, or the pharmaceutical composition of item 11, to a subject in need thereof.

13. The compound for use according to any of items 1 to 10, or the pharmaceutical composition for use according to item 11, or the method of item 12, wherein said compound or said pharmaceutical composition is to be administered by any one of: an oral route; topical route, including by transdermal, intranasal, ocular, buccal, or sublingual route; parenteral route using injection techniques or infusion techniques, including by subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, intrasternal, intraventricular, intraurethral, or intracranial route; pulmonary route, including by inhalation or insufflation therapy; gastrointestinal route; intrauterine route; intraocular route; subcutaneous route; ophthalmic route, including by intravitreal, or intracameral route; rectal route; or vaginal route.
14. The method of item 12 or 13, wherein said subject is a human.
15. A compound having one of the formulae **1a** or **1j** to **1t** or a pharmaceutically acceptable salt, solvate or prodrug thereof.
16. A compound having one of the formulae **1a**, **1d**, **1g**, **1h** or **1j** to **1t** or a pharmaceutically acceptable salt, solvate or prodrug thereof for use as a medicament.
17. A pharmaceutical composition comprising a compound as defined in item 16 or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

The invention is also described by the following illustrative figures. The appended figures show:

- Figure 1:** Structure-based modeling of the mimic of the PKC ϵ protein fragment EAVSLKPT (see Example 1). **(A)** X-ray structure of PKC ϵ (PDB 1gmi). The protein backbone is illustrated as cartoon, while the EAVSLKPT is highlighted as sticks in a light grey box. **(B)** Extracted protein fragment EAVSLKPT in its conformation observed in the X-ray structure. Hydrogen bond donor and acceptor features (dark grey spheres) as well as the hydrophobic interaction area (light grey sphere) are indicated for the pharmacophore model that retrieved compound **1c** (PKC ϵ 16) as a hit.

Figure 2: Effects of compounds **1a** (PKCe2138) and **1b** (PKCe141) *in vitro* and *in vivo* (see Examples 2 and 3). (A) Compound **1b** (referred to as “compound 141”) prevents the *in vitro* interaction of PKC ϵ with RACK2 in a dose-dependent manner. (B) Compound **1b** (PKCe141) inhibits the phosphorylation of Elk-1 in PathDetect HeLa HLR cells. Luciferase activity following activation of Elk-1 is shown. Data shown are the means (+/-SD) of 3 independent experiments. (C) Compound **1b** (PKCe141) does not prevent the *in vitro* interaction between PKC β II and RACK1. (D) Compound **1a** (PKCe2138) inhibits the phosphorylation of Elk-1. (E) Compound **1a** (PKCe2138) prevents RACK2-binding to PKC ϵ *in vitro* in a dose-dependent manner. (F) Inhibition of RACK2-binding to PKC ϵ *in vitro* by EAVSLKPT which was tagged with seven arginines. A scrambled octapeptide tagged with seven arginines was used as control.

Figure 3: PKC ϵ induces phosphorylation of Elk-1. (A) In HeLa cells, a doxycycline-inducible constitutively active PKC ϵ (Xuan et al., 2005) leads to phosphorylation of Elk-1. The cells were left untreated or induced with doxycycline (2 μ g/ml) for 24 hours. Additional stimulation with TPA (50 nM) was performed for 10 minutes. Phosphorylation of Elk-1 was detected with a phospho-specific antibody against the Ser383 residue of Elk-1. GAPDH was used as loading control. (B) Densitometric analysis of Western blots. Elk-1 phosphorylation was normalized to the GAPDH loading control and data are expressed relative to untreated cells (control). Bar graphs represent quantitation of three independent experiments (+/- S.E.). Dox = doxycycline. Fold of control is calculated from - Dox -TPA.

Figure 4: Effect of compound **1b** (PKCe141) on PKC ϵ and PKC δ translocation (see Example 4). IGFI- β R and GAPDH were used as loading controls for the membrane and the cytosolic fraction, respectively. The means of three independent experiments were scanned and shown in a graph (+/-SD).

Figure 5: Effect of compound **1b** (PKCe141) on PKC isozymes. 50 μ M compound **1b** were used in a PKC assay as described in Examples 4 and 6.

Figure 6: Cell proliferation following treatment with compound **1b** (PKCe141). Cell proliferation was determined as described in Example 5. The means (+/-SD) of three independent experiments, in which three samples were taken within each experiment, are shown.

Figure 7: Effect of compound **1b** (PKCe141) on PKC ϵ translocation by immunofluorescence. PC-3 cells were employed for these experiments. TPA induces translocation of PKC ϵ to the plasma membrane. Compound **1b** inhibits this TPA-induced translocation of PKC ϵ . Experiments 1, 2 and 3 are three independent experiments.

Figure 8: PKC ϵ -induced migration of HeLa cells into a gap. The expression of constitutively active PKC ϵ was induced by doxycycline for 24 hours after a scratch was made into monolayer cells with a pipette tip.

Figure 9: Inhibition of angiogenesis *in vitro* (see Example 7). (A) Spheroid sprouting assay. Bortez = bortezomib; DMF = dimethyl fumarate; 141 = compound **1b** (PKCe141); 2138 = compound **1a** (PKCe2138). (B) Chicken egg assay. 141 = compound **1b** (PKCe141).

Figure 10: ^1H -NMR spectrum (A) and mass spectrum (B) of compound **1a** (PKCe2138).

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

EXAMPLES

Compound **1c** (PKCe16; 3-amino-N-(6-ethoxy-2-benzothiazolyl)-7-methoxy-thieno[2,3-b]quinoline-2-carboxamide; Asinex ID: ASN 02538754; CAS 552819-38-2) and compound **1b** (PKCe141, N-(3-acetylphenyl)-9-amino-2,3-dihydro-1,4-dioxino[2,3-g]thieno[2,3-b]quinoline-8-carboxamide; Asinex ID: ASN 05545158, CAS 602293-00-5) were purchased from Asinex Ltd, Moscow, Russia. 25 mM stock solutions were prepared in DMSO. Identity and purity (>95%) of compound **1b** were determined using thin-layer chromatography and LC-MS (liquid chromatography-mass spectrometry). IC₅₀ values were determined with CalcuSyn (Biosoft, Cambridge, UK).

Example 1: Molecular Modeling

A pharmacophore model was derived from the PKC ϵ protein fragment EAVSLKPT using its conformation observed in the crystal structure of PDB entry 1gmi (Figs. 1A and 1B). Catalyst (version 4.11, Accelrys Inc., San Diego, CA, USA) was employed for pharmacophore modeling and subsequent screening of commercial molecular libraries. The

pharmacophore model consists of three hydrogen bond donor/acceptor features and one hydrophobic feature. The latter attempts to resemble the hydrophobic area presented to RACK2 by Val16, while the hydrogen bond donor/acceptor features characterize the side chain properties of Ser17, Lys19, and Glu14. The rationale behind selecting those four features was their solvent exposure and, hence, their likelihood to be involved in the interaction with RACK2. In order to account (as far as possible) for protein flexibility, without becoming overly unspecific, the tolerance spheres of the pharmacophore feature and projection points were set to 1.5 and 2.0 Angstroms, respectively.

Screening of the Asinex Gold and Platinum libraries (Asinex Ltd, Moscow, Russia) resulted in a total of 468 identified candidate molecules (hit structures). The hit list was further refined according to the geometric fit value of the candidate molecules to the pharmacophore model (using the Catalyst-internal scoring function) and by visual inspection. Sixteen of the most promising candidate molecules were purchased from Asinex and one of them, i.e. compound **1c** (PKCe16; 3-amino-N-(6-ethoxy-2-benzothiazolyl)-7-methoxy-thieno[2,3-b]quinoline-2-carboxamide; Asinex ID: ASN 02538754; CAS 552819-38-2), was found to significantly disrupt the PKC ϵ /RACK2 interaction (see also Example 2 below).

Compound **1c** (PKCe16) was subsequently used as a template for the search of structurally related compounds available from commercial molecular libraries. During this iterative optimization process (PKCe22 to PKCe145), compound **1b** (PKCe141; (N-(3-acetylphenyl)-9-amino-2,3-dihydro-1,4-dioxino[2,3-g]thieno[2,3-b]quinoline-8-carboxamide; Asinex ID: ASN 05545158; CAS 602293-00-5) was identified as the strongest disruptor/inhibitor of the PKC ϵ /RACK2 interaction. This screening process was followed by custom synthesis and testing of a series of further compounds related to compound **1b** (PKCe2019 to PKCe2145).

Example 2: Inhibition of PKC ϵ /RACK2 interaction *in vitro*

PKC ϵ /RACK2 *in vitro* binding assay: Recombinant RACK2 tagged with maltose-binding protein (RACK2-MBP) was purified on columns with amylose resin (New England Biolabs) as described by the manufacturer. The recombinant protein was analyzed by Coomassie Blue staining and Western blotting after SDS-PAGE. Aliquots were stored in liquid nitrogen. The interaction between PKC ϵ and RACK2 was measured using an ELISA-based assay. 96-well EIA/RIA high binding plates (Costar) were coated with 100 ng recombinant PKC ϵ

(ProQinase) in buffer A (20 mM Tris-HCl/100 mM NaCl, pH 7.5) at 4°C on a shaker with gentle agitation overnight. The plate was washed twice with 225 µl/well buffer A. After blocking of unspecific binding sites with 225 µl sterile-filtered 3 % bovine serum albumin (BSA; Sigma) in buffer A at room temperature for 3 h, the plate was washed twice with 225 µl of this buffer. PKCε was left untreated or activated by addition of 60 µg/ml phosphatidylserine (Sigma) and 100 nM TPA (Sigma) in a volume of 50 µl buffer A for 10 min at 30°C. Recombinant purified RACK2-MBP was either left untreated or incubated with EAVSLKPT-R7 or compound **1b** (PKCe141) at room temperature for 30 min in a final volume of 50 µl buffer A. 500 ng RACK2-MBP was added to untreated or activated PKCε for 1 hour at room temperature for binding. The plate was washed twice with 225 µl buffer A. 100 µl RACK2-specific rabbit anti-RACK2 polyclonal antibody (Prof. F. Wieland, University of Heidelberg, Germany) diluted 1:20,000 in 3 % BSA/buffer A was added for 1 h at room temperature. The plate was subsequently washed 3 times with 225 µl buffer A and a goat anti-rabbit HRP-conjugated IgG (Santa Cruz Biotechnology) diluted 1:20,000 in 100 µl 3 % BSA/buffer A was added for 1 h at room temperature. After 3 washes with 225 µl buffer A, 100 µl of ABTS substrate (0.5 mg/ml) diluted in ABTS buffer (Roche) was added and the plate was incubated in the dark for 30-180 min. Color development was measured on a plate reader at a wavelength of 420 nm. Compound **1a** (PKCe2138) was tested in a similar manner.

PKCβII/RACK1 *in vitro* binding assay: This assay was similar to the PKCε/RACK2 binding assay described above. 6-his-tagged RACK1 was cloned into a pET-30a(+) vector (Novagen) and purified with Ni-NTA Agarose (Qiagen). Final elution was performed with 500 nM imidazole in elution buffer (20 mM Tris-HCl/300 mM NaCl, 20% glycerol, pH 7.5). The integrity of purified recombinant protein was analyzed by Coomassie Blue staining and Western blotting. 200 ng RACK1 was coated onto 96-well EIA/RIA high binding plates (Costar) at 4°C on a shaker with gentle agitation overnight. Compound **1b** (PKCe141) was added at room temperature for 30 min. 500 ng of recombinant GST-tagged PKCβII (ProQinase) was activated with CaCl₂, phosphatidylserine and TPA for 10 min. The RACK1-coated plates with and without compound **1b** were incubated for 1 h with activated PKCβII. The interaction was determined with a primary rabbit anti-GST antibody (Santa Cruz) and corresponding HRP-conjugated goat anti-rabbit HRP conjugated secondary antibody (Santa Cruz) as described above for the PKCε/RACK2 interaction.

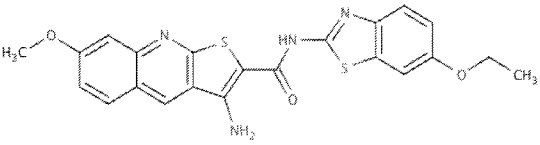
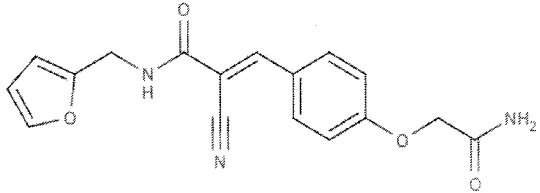
Results: Compound **1b** (PKCe141) led to a dose-dependent inhibition of the PKCε/RACK2 interaction and exhibited an IC₅₀ of 5.9 µM, as also shown in Fig. 2A. Corresponding results

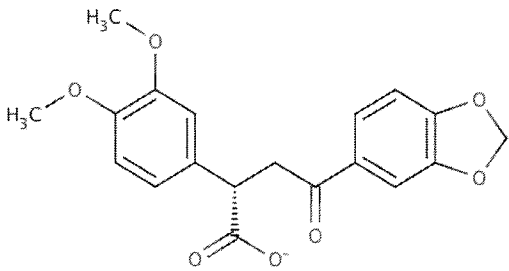
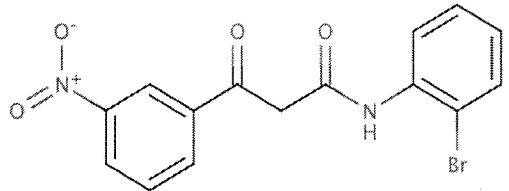
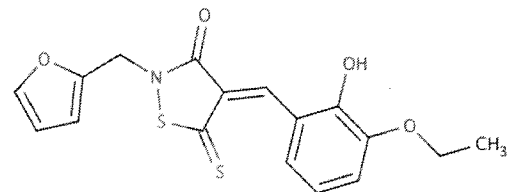
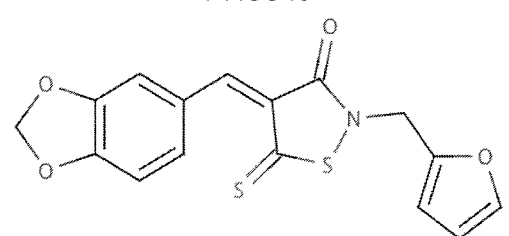
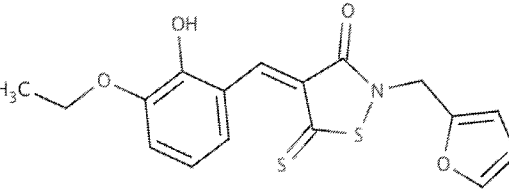
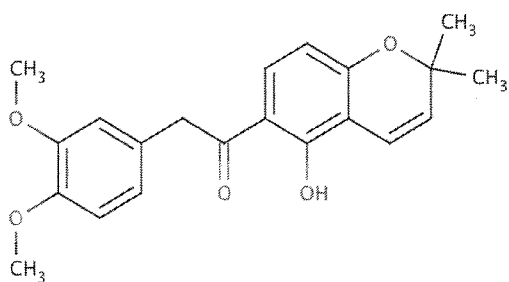
were obtained with compound **1a** (PKCe2138) which was likewise found to inhibit the PKC ϵ /RACK2 interaction in a dose-dependent manner (see Fig. 2E), with an IC₅₀ of 4.1 μ M. The peptide EAVSLKPT-RRRRRRR was used as a control. Seven arginines were added to EAVSLKPT to increase internalization of the peptide into intact cells in *in vivo* experiments.

IC₅₀ for the inhibition of the PKC ϵ /RACK2 interaction by EAVSLKPT-RRRRRRR in this assay was 1.02 μ M (Fig. 2F). It has been shown previously that PKC β II interacts with the adaptor protein RACK1 (Ron et al., 1999). Therefore, it was investigated whether compound **1b** can also prevent the PKC β II/RACK1 interaction. As shown in Fig. 2C, compound **1b** does not prevent the PKC β II/RACK1 interaction, indicating specificity of this compound for the PKC ϵ /RACK2 interaction.

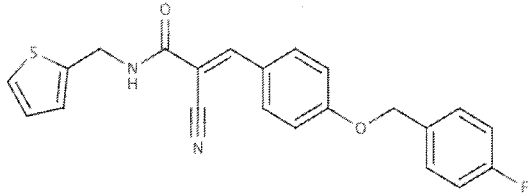
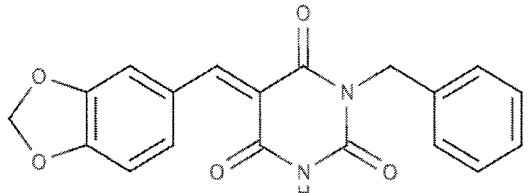
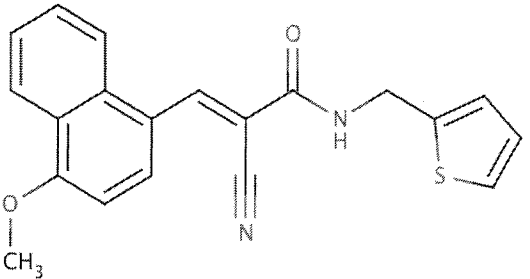
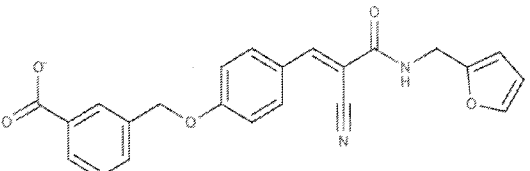
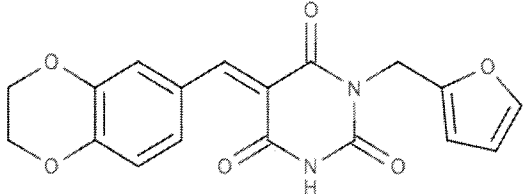
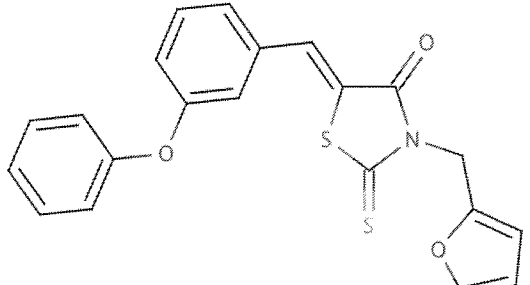
These results indicate that compounds of formula (I), such as, e.g., compounds **1a** and **1b**, selectively inhibit PKC ϵ signaling by preventing the interaction between PKC ϵ and its adaptor protein RACK2. The compounds of the invention are therefore suitable as therapeutic agents for the treatment or prevention of diseases/disorders related to PKC ϵ signaling, as also described herein above.

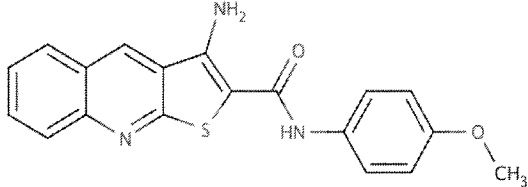
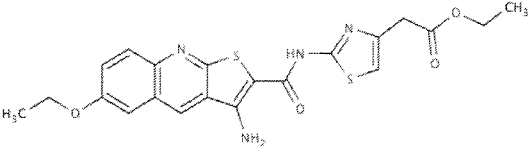
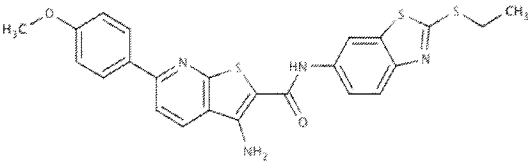
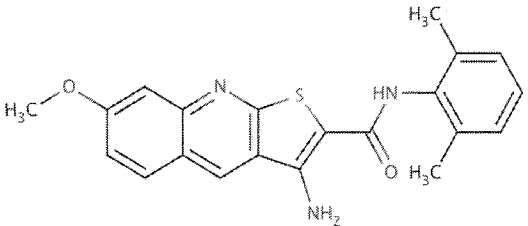
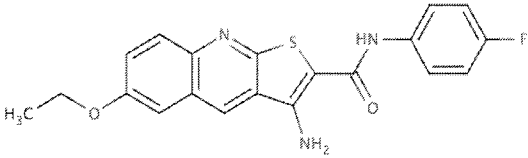
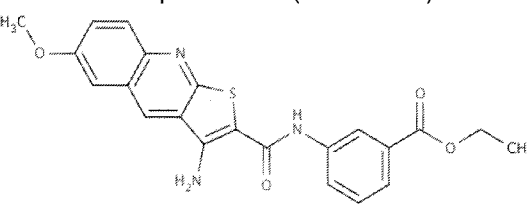
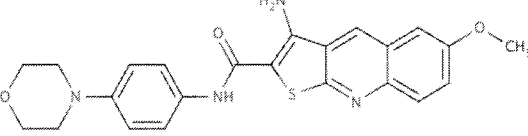
Further compounds according to the invention, including further compounds of formula (I), have been tested in the above-described PKC ϵ /RACK2 *in vitro* binding assay and have likewise been found to inhibit PKC ϵ signaling, as shown in the following Table 1:

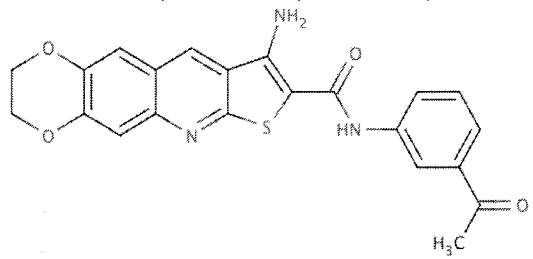
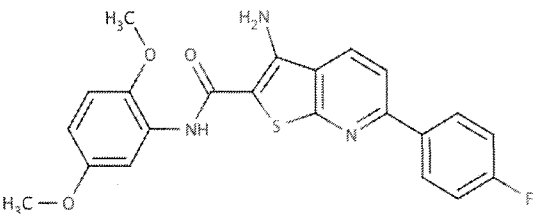
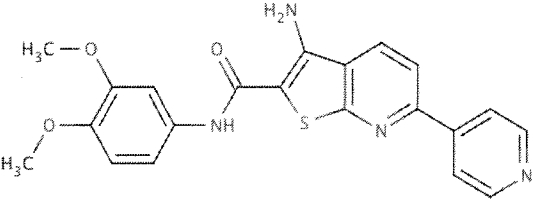
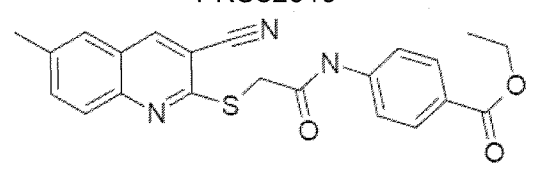
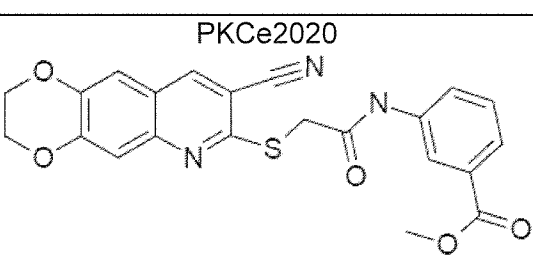
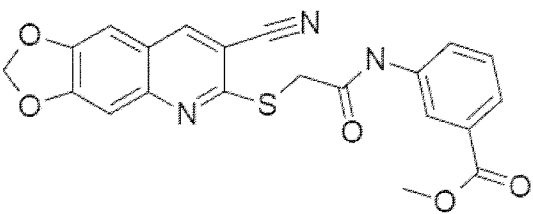
Compound	Inhibition (% of untreated control) Mean	SD	SEM	n
Compound 1c (PKCe16) 	37.7	24.9	14.4	12
PKCe22 	93.3	15.7	3.9	12

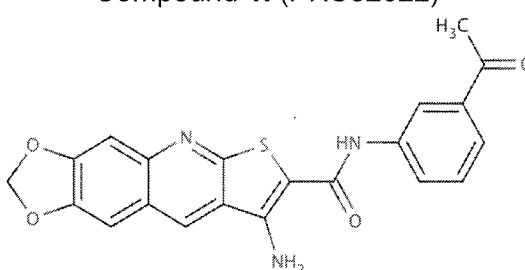
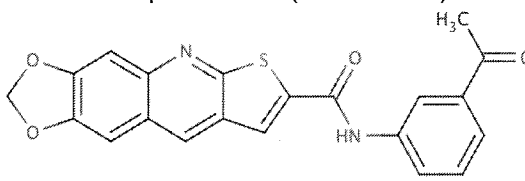
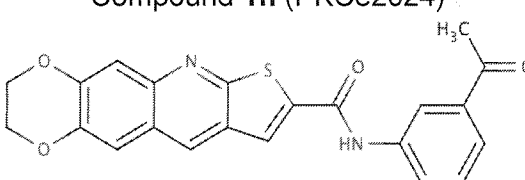
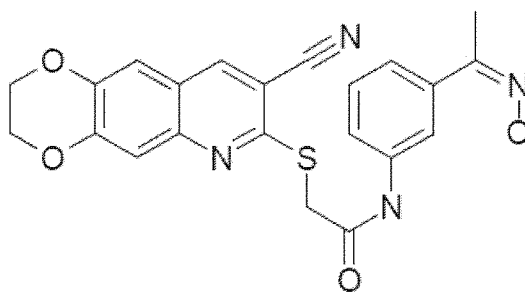
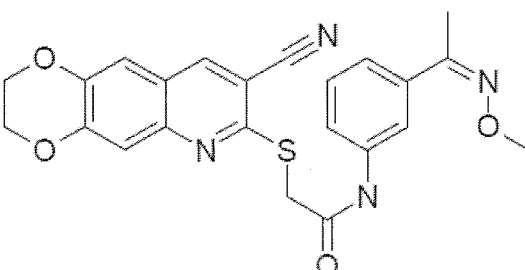
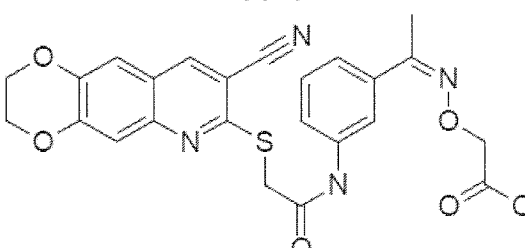
PKCe39 	57.8	29.9	8.6	12
PKCe40 	71.1	27.6	8.0	12
PKCe48 	85.3	40.1	11.6	12
PKCe49 	77.5	20.6	5.9	12
PKCe52 	63.2	17.2	4.4	15
PKCe67 	76.9	16.4	4.7	12

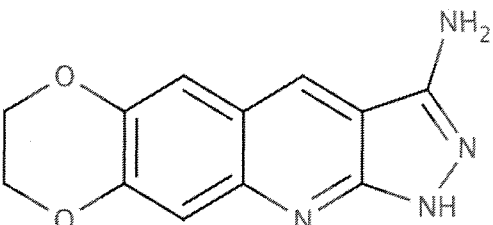
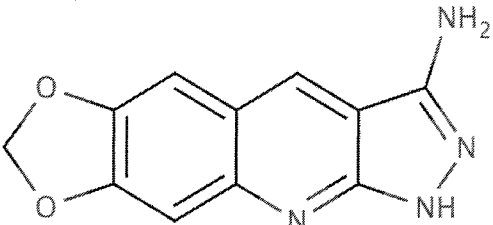
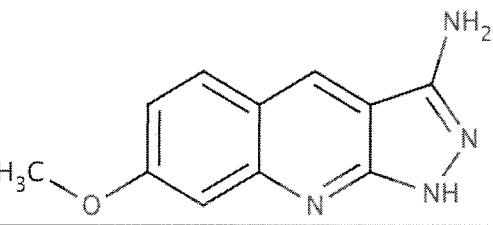
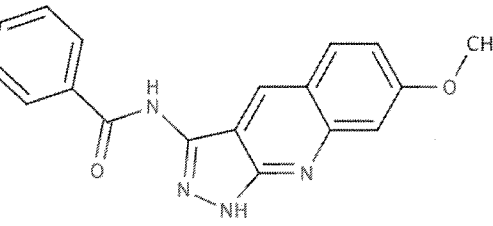
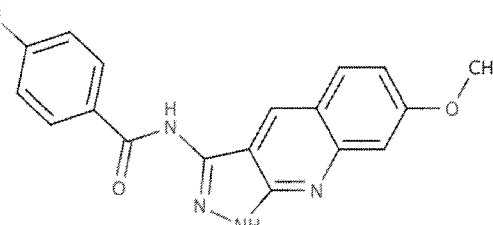
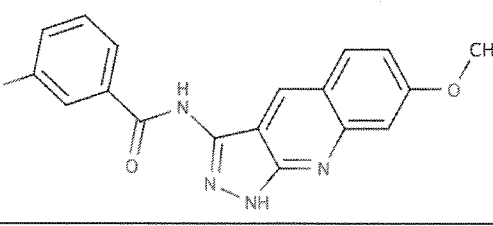
PKCe73	77.3	21.6	6.2	12
PKCe76	53.5	16.2	6.6	6
PKCe86	67.2	13.6	3.9	12
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PKCe89	72.3	11.0	3.2	12
PKCe95	54.8	14.1	4.1	12

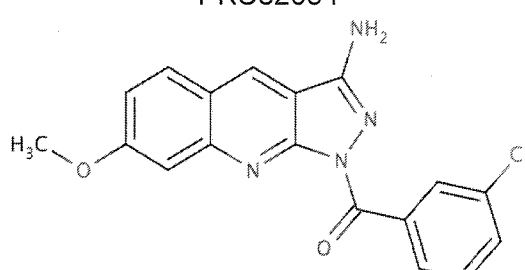
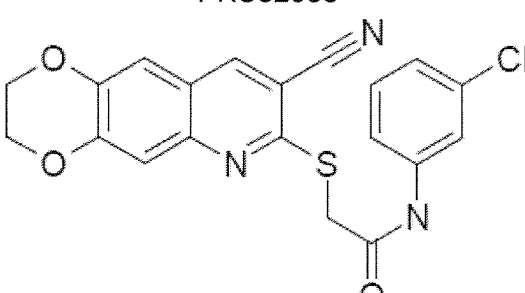
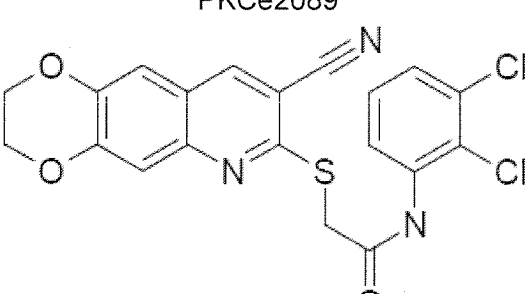
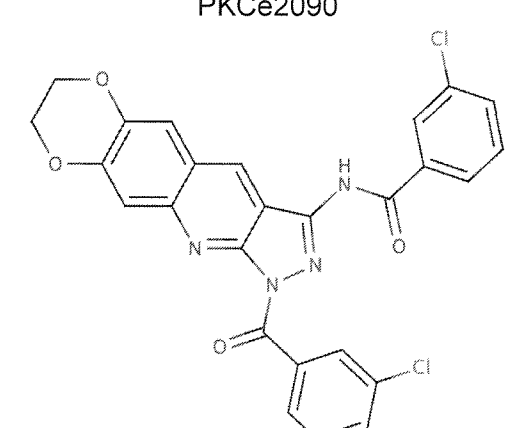
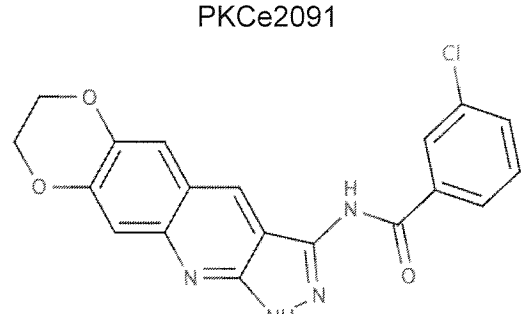
PKCe96 	57.7	10.6	3.1	12
PKCe97 	47.9	13.1	3.8	12
PKCe106 	60.4	14.1	4.1	12
PKCe107 	56.9	9.6	2.8	12
PKCe109 	58.2	12.0	3.5	12
PKCe114 	63.4	8.6	2.5	12

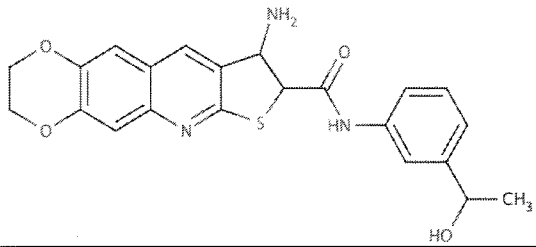
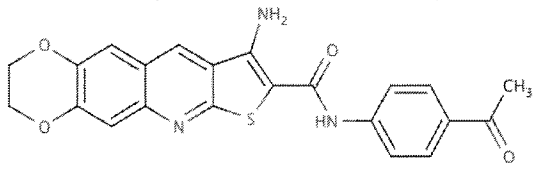
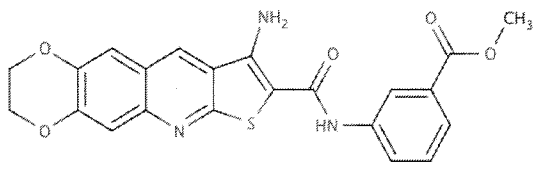
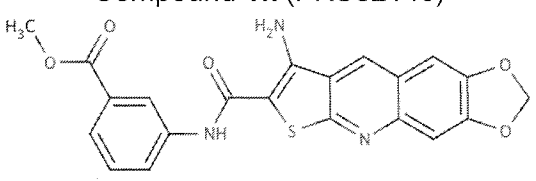
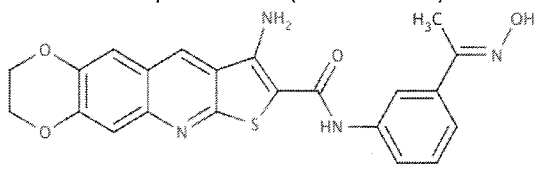
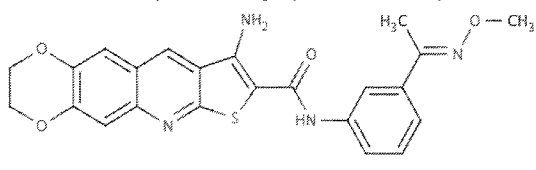
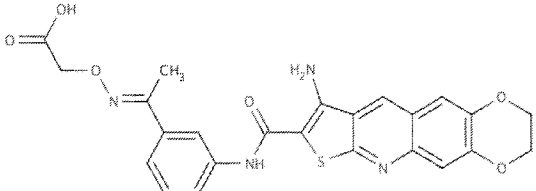
Compound 1d (PKCe119) 	42.7	8.9	2.2	16
Compound 1e (PKCe123) 	32.4	8.7	2.2	16
PKCe125 	48.7	11.5	2.9	16
Compound 1f (PKCe127) 	60.8	13.2	3.3	16
Compound 1g (PKCe129) 	60.5	13.0	3.3	16
Compound 1h (PKCe133) 	29.6	9.9	2.5	16
Compound 1i (PKCe140) 	32.9	7.3	2.1	12

Compound 1b (PKCe141) 	13.3 (at a concentration of 25 μ M)	6.1	0.7	80
	23.6 (at a concentration of 10 μ M)	10.2	1.5	48
PKCe143 	34.4	5.4	1.5	12
PKCe145 	47.3	6.2	1.8	12
PKCe2019 	82.1	14.2	4.1	12
PKCe2020 	90.4	23.2	6.7	12
PKCe2021 	69.9	12.5	3.6	12

Compound 1l (PKCe2022) 	58.9	17.6	5.1	12
Compound 1m (PKCe2023) 	51.2	12.9	3.7	12
Compound 1n (PKCe2024) 	64.9	12.3	3.6	12
PKCe2045 	116.7	13.1	4.6	8
PKCe2046 	127.2	19.6	6.9	8
PKCe2047 	114.8	12.7	4.5	8

PKCe2048 	141.2	18.1	6.4	8
PKCe2049 	141.7	17.1	6.1	8
PKCe2050 	130.4	18.3	6.5	8
PKCe2051 	103.3	19.4	6.9	8
PKCe2052 	95.6	11.0	3.9	8
PKCe2053 	32.6	10.8	3.8	8

PKCe2054 	50.4	12.9	4.6	8
PKCe2088 	66.4	24.0	8.5	8
PKCe2089 	79.5	30.1	10.6	8
PKCe2090 	73.2	28.3	10.0	8
PKCe2091 	63.6	15.4	5.4	8

Compound 1t (PKCe2092) 	101.6	49.0	17.3	8
Compound 1a (PKCe2138) 	22.8	5.8	1.7	12
Compound 1j (PKCe2139) 	90.9	29.0	14.5	4
Compound 1k (PKCe2140) 	30.8	9.9	2.9	12
Compound 1o (PKCe2141) 	46.2	7.5	3.7	4
Compound 1p (PKCe2142) 	48.3	6.2	3.1	4
Compound 1q (PKCe2143) 	59.3	5.4	2.7	4

Compound 1r (PKCe2144)	58.0	7.3	3.7	4
Compound 1s (PKCe2145)	57.6	19.6	9.8	4

Table 1: Inhibition of PKC ϵ signaling. The inhibition of the PKC ϵ /RACK2 interaction is expressed as a percentage of untreated control. Accordingly, a value of, e.g., 37.7% denotes an inhibition of the PKC ϵ /RACK2 interaction to 37.7% of the untreated control (which is set to 100%). Compounds having a percentage inhibition of 100% or greater were not found to inhibit PKC ϵ signaling in this assay. The compounds PKCe16 to PKCe145 were employed at a concentration of 25 μ M, while the compounds PKCe2019 to PKCe2145 were tested at a concentration of 10 μ M; compound **1b** (PKCe141) was tested at both 25 μ M and 10 μ M. SD = standard deviation; SEM = standard error of the mean; n = number of samples tested.

Example 3: Inhibition of PKC ϵ -induced Elk-1 phosphorylation *in vivo*

PKC ϵ is situated in the signal transduction cascade upstream of Raf-1 (Xuan et al., 2005). In a HeLa cell line containing a doxycycline-inducible constitutively active PKC ϵ (Garczarczyk et al., 2009), active PKC ϵ leads to phosphorylation of the transcription factor Elk-1 (see Fig. 3). In order to obtain information whether compound **1b** (PKCe141) is able to prevent the PKC ϵ /RACK2 interaction in intact cells, compound **1b** was tested for inhibition of Elk-1 phosphorylation in a PathDetect HeLa Luciferase (HLR) *trans*-reporting HeLa cell line, as described in the following. In these cells, activation of PKC by 12-O-tetradecanoyl phorbol-13-acetate (TPA) leads to the expression of luciferase. Compound **1a** (PKCe2138) was tested in a similar manner.

Cells and cell proliferation: HeLa cells containing a tetracycline/doxycycline-inducible constitutively active PKC ϵ were described previously (Garczarczyk et al., 2009). A PathDetect HeLa HLR cell line was obtained from Agilent. PC-3 prostate adenocarcinoma cells were obtained from Dr. Helmut Klocker, Department of Urology, Innsbruck Medical University. For cell proliferation HeLa HLR and PC-3 cells were seeded at ~10,000 cells per well in 96-well plates. After 4 h various concentrations of compound **1b** (PKCe141) were added and left for 72 h. Cell proliferation was determined by the SRB-assay (Skehan et al., 1990).

Elk-1 phosphorylation: Elk-1 phosphorylation was determined with the PathDetect System (Agilent). PathDetect HeLa HLR-ELK-1 cells contain a luciferase reporter cassette and express a unique, stably integrated, *trans*-acting fusion protein. The fusion protein consists of the activation domain of the Elk-1 transcriptional activator (Rao et al., 1989; Price et al., 1995; Marais et al., 1993), that is fused to the yeast GAL4 DBD (residues 1–147). The transcriptional activator domain of Elk-1 is activated. 200,000 PathDetect HeLa HLR-Elk-1 cells per well were seeded in a 6-well plate and grown for 24 hours. Cells were washed with phosphate buffered saline and starved for 16 hours in starvation medium (DMEM-containing 0.5% fetal bovine serum and 1% glutamine). Compounds were added in DMEM for 30 min. Following treatment with 50 nM TPA for 5 min the cells were washed twice with phosphate buffered saline and incubated for 4 h in starvation medium and compound **1b** (PKCe141). 200 μ l lysis buffer as described by the manufacturer was added. The plates were shaken intensively at 4°C for 20 min. Lysates were collected and centrifuged at 11,000 x g at 4°C for 2 min and used immediately for luciferase activity measurement. Protein concentration was determined according to Bradford (Bradford, 1976) and 20 μ g of each sample was transferred to a white, opaque 96-well plate. 150 μ l luciferase assay buffer as described by the manufacturer was injected and light emission from the reaction was measured for 3 seconds after a delay time of 2 sec. Relative light units were measured with a 1450 Microbeta Wallac Jet Luminometer (Perkin-Elmer).

Results: Compound **1b** (PKCe141) inhibited the phosphorylation of Elk-1 in a dose dependent manner with an IC₅₀ of 11.2 μ M in intact cells, as also shown in Fig. 2B. Compound **1a** (PKCe2138) was likewise found to inhibit the phosphorylation of Elk-1 (see Fig. 2D). These results confirm that compounds of formula (I), such as compounds **1a** and **1b**, inhibit PKC ϵ signaling *in vivo* and can thus be used as therapeutic agents in the intervention of diseases/disorders in which PKC ϵ signaling is implicated, as described herein above.

Example 4: Effect on PKC ϵ translocation

- 5 Upon activation, PKC ϵ associates with RACK2 and is translocated from the cytosolic to the membrane fraction (Brodie et al., 1999; Fenton et al., 2009). It was investigated whether compound **1b** (PKC ϵ 141) also inhibits the translocation of PKC ϵ to the membrane.

Cell fractionation and Western blotting: For PKC ϵ translocation PC-3 cells were starved
10 for 16 h, treated with compound **1b** (PKC ϵ 141) for 30 min, stimulated with 50 nM TPA for 5 min, lysed and fractionated with a CNMCS/CNM compartmental protein extraction kit (BioChain Institute). Western Blotting was performed by a standard procedure as described by Garczarczyk et al., 2009 and Garczarczyk et al., 2010. Cytosolic and membrane fractions were loaded onto SDS gels and transferred to an Immobilon membrane (Millipore).
15 The membranes were incubated with rabbit polyclonal IgG antibodies for detection of PKC ϵ (Santa Cruz Biotechnology, dilution 1:2,000), of PKC ϵ phosphoSer⁷²⁹ (Millipore, dilution 1:1,000) and of PKC δ (Santa Cruz; dilution 1:1,000). For the loading control and as marker for the membrane fraction, an IGFI- β R rabbit polyclonal IgG antibody (Santa Cruz Biotechnology; dilution 1:1,000) and as secondary antibodies peroxidase-conjugated
20 AffiniPure Goat Anti-Rabbit IgG (Jackson Immuno Research Laboratories, dilution 1:20,000) were used. GAPDH (Chemicon; 1:10,000) was used as loading control for the cytosolic fraction. A peroxidase-conjugated secondary antibody (AffiniPure Goat Anti-Mouse IgG; Jackson Immuno Research Laboratories, dilution 1:20,000) was employed for detection.

- 25 ***In vitro* PKC assay:** 150 ng of recombinant purified PKC isozyme (see Fig. 5) were combined with 10 μ l 10 x kinase assay buffer (200 mM Tris-HCl, pH 7.5, 200 mM MgCl₂), phosphatidylserine (final 10 μ M), TPA (final 1 μ M) and substrate peptide RFARKGSLRQKNV (Alexis) (final 50 μ M) in a volume of 100 μ l. 90 μ l/well were pipetted in a 96-well plate and incubated for 1 min at 30°C. 10 μ l ATP mix containing 0.4 μ l of 10 mM
30 ATP 1 μ Ci γ -³³P-ATP (PerkinElmer). After another incubation step for 10 min at 30°C the plate was transferred on ice to stop the kinase reaction. 50 μ l of the kinase assay-mix are added onto phosphocellulose sheets (Whatman) in a 6-well plate. The sheets were washed 3 times with 1.5% H₃PO₄ and twice with distilled water. The phosphocellulose sheets are transferred to scintillation vials, 4 ml of scintillation fluid (Ultima Gold, Perkin-Elmer) were
35 added and counted in a β -counter. The effect of compound **1b** (PKC ϵ 141) on the different PKC isozymes is shown in Fig. 5.

Results: In PC-3 prostate adenocarcinoma cells, treatment with TPA led to an increase of PKC ϵ in the membrane fraction. Accordingly, the amount of PKC ϵ in the cytosol decreased (Fig. 4). Furthermore, activated PKC ϵ is phosphorylated at Ser729. TPA increased the phosphorylated form of PKC ϵ . Compound **1b** (PKCe141) does not inhibit PKC ϵ *in vitro*, as also shown in Fig. 5. Treatment of cells with compound **1b** similarly did not reduce Ser729-phosphorylated PKC ϵ at the membrane (Fig. 4). This result illustrates that PKC ϵ is phosphorylated following treatment with TPA, and compound **1b** does not prevent this phosphorylation. However, compound **1b** partially inhibits the cellular translocation of activated and phosphorylated PKC ϵ to the membrane fraction. PKC δ shows a high degree of homology with PKC ϵ . Therefore, the influence of compound **1b** on PKC δ was investigated. As shown in Fig. 4, compound **1b** does not decrease PKC δ in the membrane. A similar result was obtained with immunocytochemistry (Fig. 7). Short-term treatment with TPA led to an increase of PKC ϵ in the plasma membrane. Compound **1b** prevented the TPA-induced PKC ϵ translocation to the plasma membrane, as shown in Fig. 7.

Compound **1b** has thus been demonstrated to inhibit the TPA-induced translocation of PKC ϵ , but not that of PKC δ , from the cytosol to the membrane. These results indicate that compounds of formula (I), such as compound **1b**, allow for an isozyme-specific inhibition of PKC ϵ signaling, which makes them particularly advantageous as therapeutic agents in the treatment of prevention of diseases/disorders associated with PKC ϵ signaling.

Example 5: Effects on cell proliferation and cell migration

As shown above, compound **1b** (PKCe141) exhibits the features of an inhibitor of PKC ϵ signaling *in vitro* and also in intact cells. A major question is whether such an inhibitor affects cell proliferation or, in other words, whether it is toxic. Therefore, compound **1b** was tested for inhibition of cell proliferation in HeLa-HLR and PC-3 cells. These cells were employed for Elk-1 phosphorylation and for the PKC ϵ translocation experiments described above.

Immunofluorescence: PC-3 cells were grown on glass coverslips coated with poly-L-lysine (Sigma). After treatment with compound **1b** (PKCe141) for 30 min and with 100 nM TPA for 5 min, the cells were rinsed twice with phosphate buffered saline (PBS) and fixed with filter sterilized 4% (w/v) paraformaldehyde/4% sucrose (w/v) (both from Sigma) in PBS at room

temperature for 10 min. Subsequently the cells were washed three times with PBS and permeabilized with 0.2% Triton X-100/0.2% IgG-free BSA in PBS at room temperature for 10 min. After blocking with 5% normal goat serum diluted in PBS as described above for 30 min, cells were incubated with the primary antibodies for PKC ϵ (Santa Cruz; diluted 1:500) in 0.2% Triton X-100/0.2% IgG-free BSA in PBS at 4°C overnight. Subsequently, the cells were washed three times with the same buffer and incubated with the labeled secondary antibody (Alexa Fluor, Invitrogen, 1:4,000) at room temperature for 1 h. After three more washes with 0.2% Triton X-100/0.2% IgG-free BSA in PBS, cells were mounted with Mowiol (Sigma) and images were taken with an Olympus BX 50 optical microscope (Olympus).

Cell migration: For cell migration and motility, a scratch migration assay described by Cha et al., 1996 was employed. In a tissue culture dish, with logarithmically growing HeLa cells containing a doxycycline-inducible constitutively active PKC ϵ , a migration gap of approximately 1 mm was created by introducing a 'scratch' to the adherent layer of cultured cells using a sterile Gilson 200 μ l pipette tip. The scratch was administered by hand with sufficient pressure to remove adherent cells from the polystyrene substrate, but without causing a physical damage to the polystyrene surface. The dish was washed with PBS to remove the cells and further incubated with 2 μ g/ml doxycyclin and 25 μ M compound **1b** (PKC ϵ 141) for 24 hours. Controls were left either untreated or were incubated with 2 μ g/ml doxycyclin and DMSO. Migration into the scratch was observed with an Olympus microscope.

Results: As shown in Fig. 6, in both of the cell lines even 50 μ M of compound **1b** (PKC ϵ 141) did not show any inhibition of cell proliferation. It has been shown previously that PKC ϵ does not increase cell proliferation. However, it increases cell migration (Akita, 2008; Garczarczyk et al., 2009) and it is associated with metastatic spread and invasiveness of human cancer cells (Stensman et al., 2008). Therefore, it was investigated whether PKC ϵ inhibits migration. As shown in Fig. 8, untreated HeLa cells containing a constitutively active doxycycline-inducible PKC ϵ showed only low migration into a scratch made with a pipette tip on a tissue culture dish. If the scratch was made into the monolayer cells and the expression of constitutively active PKC ϵ was induced by doxycycline after 24 hours a significant part of the scratch was covered with cells. PKC ϵ increased migration of cells into a gap and compound **1b** (PKC ϵ 141) indeed inhibited this PKC ϵ -induced migration (Fig. 8), which indicates its potential as an inhibitor of metastasis. Moreover, these data also indicate that compound **1b** does not exhibit toxicity, which is a particularly favorable characteristic for therapeutic application as an inhibitor of PKC ϵ signaling and, accordingly,

as a medicament to treat diseases such as myocardial hypertrophy (Takeishi et al., 2000; Ferreira et al., 2010), diabetes (Ikeda et al., 2001), stroke, Alzheimer's disease or pain (Akita, 2008; Shirai et al., 2008).

5

Example 6: Inhibition of kinases

In earlier studies it was found that the barbituric acid derivative PKCe97 (BAS 02104951) prevented the PKC ϵ /RACK2 interaction (IC_{50} = 28.5 μ M). In addition, this compound also
10 inhibited PKC η and PKC ϵ directly (Gruber et al., 2011). Compound **1b** (PKCe141) was therefore tested for its inhibition of PKC isozymes.

In vitro PKC assay: 150 ng of recombinant purified PKC isozyme (see Fig. 5) were combined with 10 μ l 10 x kinase assay buffer (200 mM Tris-HCl, pH 7.5, 200 mM MgCl₂),
15 phosphatidylserine (final 10 μ M), TPA (final 1 μ M) and substrate peptide RFARKGSLRQKNV (Alexis) (final 50 μ M) in a volume of 100 μ l. 90 μ l/well were pipetted in a 96-well plate and incubated for 1 min at 30°C. 10 μ l ATP mix containing 0.4 μ l of 10 mM ATP 1 μ Ci γ -³³P-ATP (PerkinElmer). After another incubation step for 10 min at 30°C the
20 plate was transferred on ice to stop the kinase reaction. 50 μ l of the kinase assay-mix are added onto phosphocellulose sheets (Whatman) in a 6-well plate. The sheets were washed 3 times with 1.5% H₃PO₄ and twice with distilled water. The phosphocellulose sheets are transferred to scintillation vials, 4 ml of scintillation fluid (Ultima Gold, Perkin-Elmer) were added and counted in a β -counter.

25 The effect of compound **1b** (PKCe141) on the different PKC isozymes is shown in Fig. 5. As shown therein, 50 μ M of compound **1b** (PKCe141) inhibited several PKC isozymes to approximately 65% of controls. If compared to the inhibition of the PKC ϵ /RACK2 interaction (IC_{50} = 5.90 μ M), however, this is not a major effect.

30 Furthermore, a screen of 109 kinases showed that many kinases are not or only slightly affected by compound **1b** (PKCe141). ERK1, NUA1, PIM3, BTK and RSK2 are the kinases inhibited most by compound **1b**, as also shown below in Table 2.

25 μ M PKCe141		
	% of control	SD
Control	100	0
ERK1	55	5
RSK2	27	1
NUAK1	49	6
PIM3	46	4
BTK	42	1

Table 2: Profile of kinase inhibition by 25 μ M compound 1b (PKCe141). 109 different protein kinases were tested for their inhibition by compound 1b (PKCe141). The five kinases inhibited most are shown in the table. All other kinases were affected less. Screening was performed by the National Centre for Protein Kinase Profiling, Division of Signal Transduction Therapy, University of Dundee. The data is portrayed as mean % activity and standard deviation (SD) of assay duplicates.

Compound 1b (PKCe141), however, affected these kinases less than the PKC ϵ /RACK2 interaction. As shown in Fig. 2A, 25 μ M compound 1b (PKCe141) inhibited the PKC ϵ /RACK2 interaction to approximately 10% of untreated controls, whereas 25 μ M of compound 1b inhibited the most affected kinase RSK2 to 27%, as shown in Table 2 above. All other kinases were less affected. This level of selectivity is quite acceptable.

Example 7: Inhibition of angiogenesis

Compounds according to the invention were tested for their effect on angiogenesis *in vitro* in a spheroid sprouting assay and in a chicken egg assay.

Spheroid sprouting assay (Korff et al., 1999): Human umbilical vein endothelial (HUVEC) spheroids were generated overnight in hanging-drop culture consisting of 400 cells in EBM-2 medium, 2% FCS and 20% methylcellulose (Sigma Biochemicals). Spheroids were embedded in collagen type I from rat tail (Becton Dickinson) and stimulated with 50 ng/ml VEGF (Sigma Biochemicals) in the presence or absence of 5 ml solution containing the

corresponding test compound (see Fig. 9A). Sprouts were analyzed by inverted transmission-microscopy (Zeiss Axiovert 200 M) and documented by digital imaging (Axiovision Software, Zeiss). The cumulative sprout length (CSL) was analyzed after printing of high quality pictures and counting by two independent blinded observers.

5

Chicken egg assay: Eggs from hen are incubated at 37°C for 3 days, opened and incubated for further 7 days. On day ten the growth factor VEGF and compound **1b** (PKCe141) are added at the concentrations indicated in Fig. 9B. After further incubation for 5 days angiogenesis is observed by microscope.

10

Results: As shown in Fig. 9A, compound **1a** (PKCe2138) was found to considerably reduce VEGF-induced sprouting from the HUVEC spheroids at a concentration of only 250 nM. Compound **1b** (PKCe141) was further tested in a chicken egg angiogenesis assay. In this assay, blood vessels were observed after the addition of VEGF to the eggs but not after the combined addition of VEGF and compound **1b** (see arrows in Fig. 9B). This data indicates that compounds according to the invention, including compounds **1a** and **1b**, inhibit angiogenesis and can thus be particularly useful, e.g., in the treatment or prevention of cancer.

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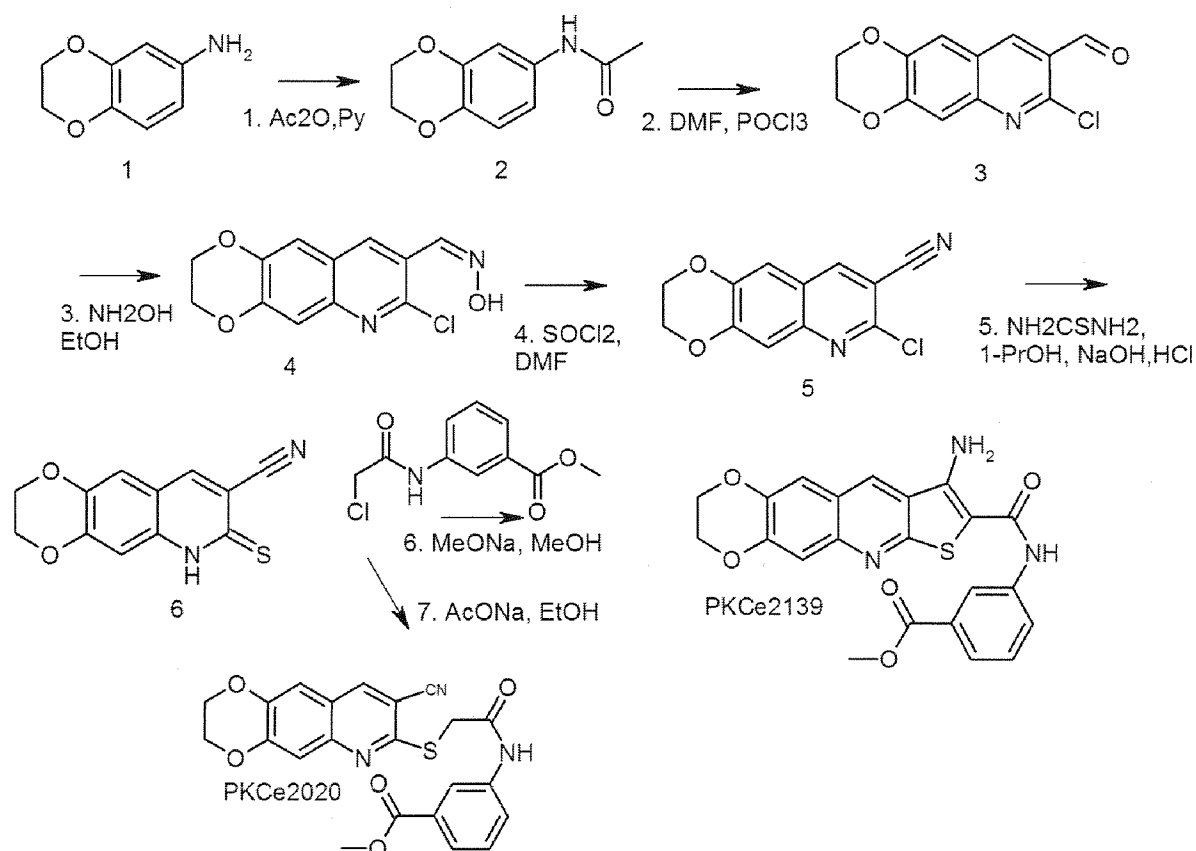
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Example 8: Preparation of compounds according to the invention

Compounds **1a**, **1j**, **1k**, **1o**, **1p**, **1q**, **1r**, and **1s** (PKCe2138 to PKCe2145) were prepared as illustrated in Scheme 1 with reference to compound **1j** (PKCe2139) and as further described in the following.

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Scheme 1: Synthesis of compounds **1j** (PKCe2139) and PKCe2020. Ac₂O = acetic anhydride; Py = pyridine; DMF = dimethylformamide; POCl₃ = phosphoryl chloride; NH₂OH = hydroxylamine; EtOH = ethanol; SOCl₂ = thionyl chloride; NH₂CSNH₂ = thiourea; 1-ProOH = propanol-1; MeONa = sodium methylate; MeOH = methanol; AcONa = sodium acetate.

Acetanilide (2): A solution of amine **1** (1 eq) in pyridine was cooled to 5°C and acetic anhydride (1.25 eq) was added dropwise with stirring. The mixture was stirred for 45 min at 60°C and poured into ice-water and stirred for 30 min at 0-10°C. The precipitate was filtered off, washed with water (100 ml) and dried.

Chloroquinolinecarbaldehyde (3) in phosphoryl chloride: Dimethylformamide (9.13 g, 9.6 ml, 0.125 mol) was cooled to 0°C in a flask equipped with a drying tube and phosphoryl chloride (53.7 g, 32.2 ml, 0.35 mol) was added dropwise with stirring. To this solution was added the acetanilide **2** (0.05 mol) and after 5 min the solution was heated to 75°C for 12-16 h. The reaction mixture was poured into ice-water (300 ml) and stirred for 30 min at 0-10°C. The chloroquinolinecarbaldehyde **3** was filtered off, washed with water (100 ml) and dried. The chloroquinolinecarbaldehyde **3** was crystallized with ethylacetate.

Hydroxyimine (4): Hydroxylamine hydrochloride (1.25 eq) was added to the suspension of chloroquinolinecarbaldehyde **3** in ethanol and this mixture was refluxed for 6 h. The hydroxyimine **4** was filtered off, washed with ethanol and dried.

5 **Chloro-3-cyano-quinoline (5):** The mixture of the hydroxyimine **4** (1 eq) in DMF was cooled to 0°C in a flask equipped with a drying tube and thionyl chloride (1.5 eq) was added dropwise with stirring and cooling for 10-15 min. Then this mixture was stirred overnight at room temperature. The reaction mixture was poured into ice-water and stirred for 30 min at 0-10°C. The nitrile **5** was filtered off, washed with water and dried. Raw material was
10 purified by flash-chromatography on silica gel with chloroform and hexane (4:1).

2-Thio-3-cyano-quinoline (6): A mixture of 2-chloro-3-cyano-quinoline **5** (1 eq) and thiourea (3 eq) in propanol-1 was heated under reflux for 6 h, then this mixture was cooled and sodium hydroxide (10% 10 eq) was added. The reaction mixture was cooled, acidified
15 with concentrated HCl and the solid product was filtered off and dried.

3-Amino-thieno[2,3-b]quinoline-2-carboxylamide (PKCe2139): A mixture of the 2-thio-3-cyano-quinoline **6** (1 eq), the respective halo compound (1.25 eq) and sodium methylate (3 eq) in absolute methanol was refluxed for 1 h. The formed solid was collected by filtration,
20 washed several times with methanol and finally with water and recrystallized from suitable solvent (DMF-methanol). The compounds **1a**, **1j**, **1k**, **1o**, **1p**, **1q**, **1r**, and **1s** according to the invention (i.e., PKCe2138 to PKCe2145) were prepared in this manner.

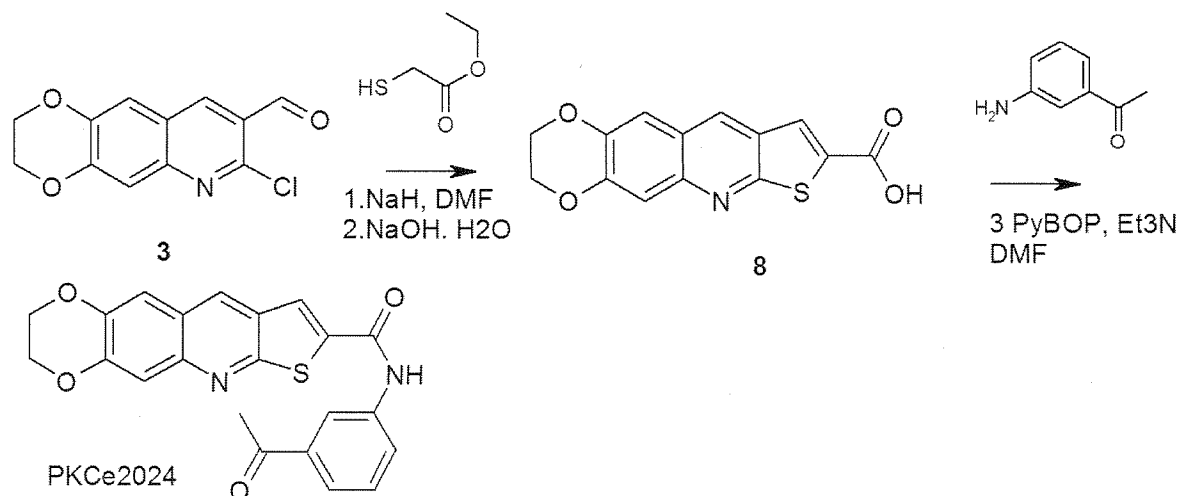
The identity of compound **1a** (PKCe2138) was confirmed by ¹H-NMR and mass
25 spectrometry, as also shown in Figs. 10A and 10B.

Compound **1a** (PKCe2138): ¹H-NMR, DMSO-D₆, δ: 2.53 (3H, s, CH₃), 4.41 (1H, dd, J 3, 3, -CH₂-CH₂-), 7.44 (2H, s, H-5, H-8), 7.62 (2H, s, NH₂), 7.91 (4H, dd, J 3, 3, arom), 8.89 (1H, s, H-4), 9.68 (1H, s, HN-C=O). MW Calc. for C₂₂H₁₇N₃O₄S 419.0938. Found in ESI-ms
30 420.1047 (M+H) 100%

2-[(3-Cyanoquinolin-2-yl)thio]-N-phenylacetamide (PKCe2020): A mixture of the 2-thio-3-cyano-quinoline **6** (1 eq), the respective halo compound (1.25 eq) and fused sodium acetate (3 eq) in absolute ethanol was refluxed for 3 h. The formed solid was collected by
35 filtration, washed several times with methanol and finally with water and recrystallized from

suitable solvent (DMF-methanol). Compounds such as PKCe2019, PKCe2020, PKCe2021, PKCe2088 and PKCe2089 were prepared in this manner.

Compounds **1m** and **1n** (i.e., PKCe2023 and PKCe2024) were prepared as described in the following Scheme 2 with reference to compound **1n** (PKCe2024).



Scheme 2: Synthesis of compound **1n** (PKCe2024). NaH = sodium hydride; DMF = dimethyl-formamide; PyBOP = benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate; Et₃N = triethylamine.

Thieno[2,3-b]quinoline-2-carboxylate (8): A mixture of the quinoline **3** (1 eq; see Scheme 1) with 2-mercaptoacetic acid ethyl ester (1.5 eq) in dry DMF was cooled and NaH (60% in oil, 5 eq) was added. This mixture was stirred for 30 min at 10°C and then 2 h at 60°C. After that 25% solution of NaOH (10 eq) was added dropwise and the mixture was heated under reflux for 2 h. The reaction mixture was cooled and extracted 3 times by benzene. Water layer was acidified with concentrated HCl and the solid product was filtered off and dried.

Thieno[2,3-b]quinoline-2-carboxylanilide (PKCe2024): A mixture of the thieno[2,3-b]quinoline-2-carboxylate **8** (1 eq) and PyBOP (1.3 eq) in DMF was stirred for 15 min, then appropriate aniline (1.25 eq), catalytic amount of 4-dimethylaminopyridine (DMAP) and Et₃N (2 eq) was added. The reaction mixture was stirred overnight at 50°C then it was poured into ice-water and precipitate was filtered off. Raw material was heated under reflux with methanol-DMF (3:2) and filtered off and dried. The anilide PKCe2024 was purified by flash-

chromatography with CHCl₃-methanol (9:1). The compounds **1m** and **1n** according to the invention (i.e., PKCe2023 and PKCe2024) were prepared in this manner.

The compounds PKCe2048 to PKCe2054 were prepared as described in Lapa et al., 2012.

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PKCe2053: 3-Chloro-N-(7-methoxy-1H-pyrazolo[3,4-b]quinolin-3-yl)benzamide. Yield 74%.
1H-NMR, DMSO-D₆, δ: 3.94 (3H, s, CH₃), 7.11 (1H, dd, J 2.2, 9.2, H-6), 7.29 (1H, d, J 2.2, H-8), 7.61 (1H, t, J 8.0, H-5'), 7.71 (1H, d, J 8.0, H-6'), 8.02 (1H, d, J 9.2, H-5), 8.07 (1H, d, J 8.0, H-4'), 8.17 (1H, s, H-2'), 8.90 (1H, s, H-4), 11.27 (1H, s, NH), 13.02 (1H, s, HN-C=O).
10 MW Calc. for C₁₈H₁₃ClN₄O₂ 352.0727. Found in ESI-ms 353.0708 (M+H) 100%, 355.0773 (M+H) 30%.

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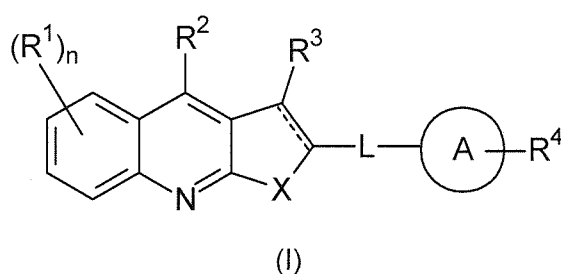
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Claims

1. A compound of the following formula (I)



wherein:

n is an integer of 0 to 4, and each R^1 is independently selected from C_{2-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, -OH, -O(C_{1-4} alkyl), -O(C_{1-4} alkyl)-OH, -O(C_{1-4} alkyl)-O(C_{1-4} alkyl), -SH, -S(C_{1-4} alkyl), -S(C_{1-4} alkyl)-SH, or -S(C_{1-4} alkyl)-S(C_{1-4} alkyl), -NH₂, -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), halogen, -CF₃, or -CN; or, alternatively, n is 2, 3 or 4, and two groups R^1 attached to adjacent carbon atoms are mutually linked to form a group -O-CH₂-O-, -O-CH₂-CH₂-O- or -O-CH₂-CH₂-CH₂-O-, while the further group(s) R^1 , if present, is/are independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, -OH, -O(C_{1-4} alkyl), -O(C_{1-4} alkyl)-OH, -O(C_{1-4} alkyl)-O(C_{1-4} alkyl), -SH, -S(C_{1-4} alkyl), -S(C_{1-4} alkyl)-SH, or -S(C_{1-4} alkyl)-S(C_{1-4} alkyl), -NH₂, -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), halogen, -CF₃, or -CN;

R^2 is selected from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, -OH, -O(C_{1-4} alkyl), -SH, -S(C_{1-4} alkyl), -NH₂, -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), halogen, -CF₃, or -CN;

R^3 is selected from -NH₂, -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), -OH, -O(C_{1-4} alkyl), -SH, -S(C_{1-4} alkyl), or hydrogen;

X is selected from S, O, N(H), or N(C₁₋₄ alkyl);

L is -(CH₂)₁₋₄-, wherein one -CH₂- unit comprised in said -(CH₂)₁₋₄- is replaced by a group selected from -CO-NH-, -CO-N(C₁₋₄ alkyl)-, -NH-CO-, -N(C₁₋₄ alkyl)-CO-, -O-, -CO-, -NH-, -N(C₁₋₄ alkyl)-, -S-, -SO-, or -SO₂-;

A is aryl or heteroaryl, wherein said aryl or said heteroaryl is optionally substituted with one or more groups independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, -OH, -O(C₁₋₄ alkyl), -SH, -S(C₁₋₄ alkyl), -NH₂, -NH(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)(C₁₋₄ alkyl), halogen, -CF₃, or -CN;

R⁴ is selected from -CO-(C₁₋₄ alkyl), -CHO, -O(C₁₋₄ alkyl), -OH, -O-CO-(C₁₋₄ alkyl), -O-CO-O(C₁₋₄ alkyl), -CO-O(C₁₋₄ alkyl), -COOH, -CO-NH₂, -CO-NH-(C₁₋₄ alkyl), -CO-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -O-CO-NH₂, -O-CO-NH-(C₁₋₄ alkyl), -O-CO-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -NH-CO-(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)-CO-(C₁₋₄ alkyl), -NH-CO-O(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)-CO-O(C₁₋₄ alkyl), -NH₂, -NH(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)(C₁₋₄ alkyl), C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, -(C₁₋₄ alkyl)-CO-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-CHO, -(C₁₋₄ alkyl)-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-OH, -(C₁₋₄ alkyl)-O-CO-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-O-CO-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-CO-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-COOH, -(C₁₋₄ alkyl)-CO-NH₂, -(C₁₋₄ alkyl)-CO-NH-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-CO-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-O-CO-NH₂, -(C₁₋₄ alkyl)-O-CO-NH-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-O-CO-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-NH-CO-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-N(C₁₋₄ alkyl)-CO-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-NH-CO-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-N(C₁₋₄ alkyl)-CO-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-NH₂, -(C₁₋₄ alkyl)-NH(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -(C₁₋₄ alkyl)=N-OH, -(C₁₋₄ alkyl)=N-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)=N-O-(C₁₋₄ alkyl)-COOH, -(C₁₋₄ alkyl)=N-O-(C₁₋₄ alkyl)-CO-O(C₁₋₄ alkyl), halogen, -CF₃, -CN, heterocycloalkyl, or hydrogen; and

==== is a double bond or a single bond;

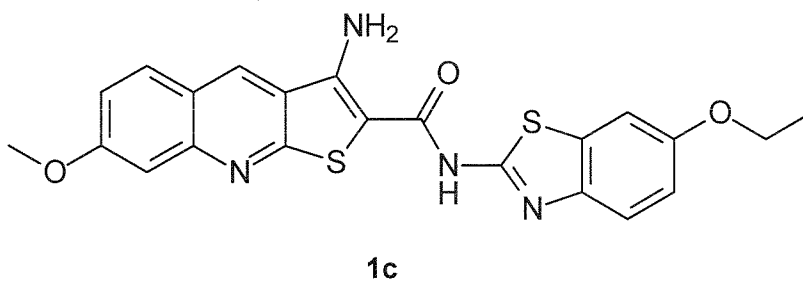
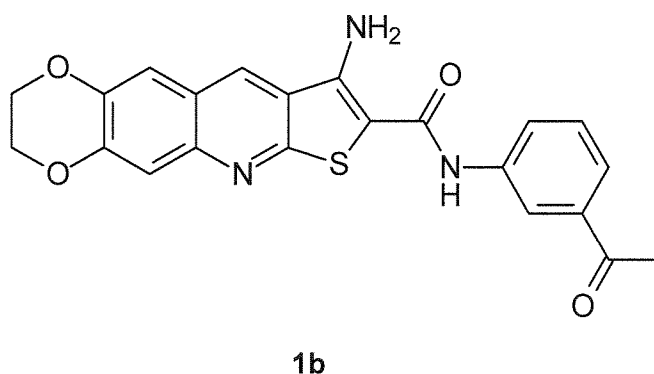
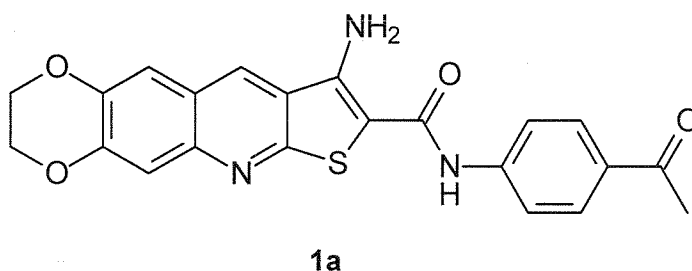
or a pharmaceutically acceptable salt, solvate or prodrug thereof

for use in the treatment or prevention of a cardiovascular disorder, cardiac hypertrophy, heart failure, anxiety, pain, chronic pain, migraine, an allergy, an inflammatory disorder, an autoimmune disorder, diabetes, diabetic complications,

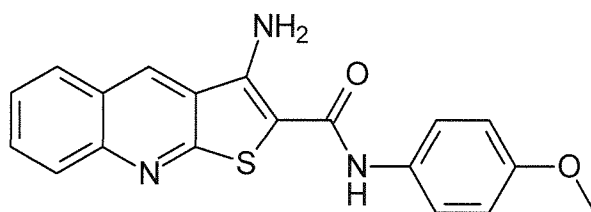
diabetic retinopathy, diabetic nephropathy, diabetic cardiomyopathy, diabetic neuropathy, cancer, metastatic cancer, drug-resistant cancer, stomach cancer, lung cancer, thyroid cancer, colon cancer, breast cancer, bipolar disorder, stroke, alopecia, or alcoholism.

2. The compound for use according to claim 1, wherein n is an integer of 1 to 4, one group R¹ is selected from -O(C₁₋₄ alkyl), -OH, -O(C₁₋₄ alkyl)-OH, or -O(C₁₋₄ alkyl)-O(C₁₋₄ alkyl), and the remaining group(s) R¹, if present, is/are independently selected from C₂₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, -OH, -O(C₁₋₄ alkyl), -O(C₁₋₄ alkyl)-OH, -O(C₁₋₄ alkyl)-O(C₁₋₄ alkyl), -SH, -S(C₁₋₄ alkyl), -S(C₁₋₄ alkyl)-SH, -S(C₁₋₄ alkyl)-S(C₁₋₄ alkyl), -NH₂, -NH(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)(C₁₋₄ alkyl), halogen, -CF₃, or -CN.
3. The compound for use according to claim 1, wherein n is 2, 3 or 4, and two groups R¹ attached to adjacent carbon atoms are mutually linked to form a group -O-CH₂-O-, -O-CH₂-CH₂-O- or -O-CH₂-CH₂-CH₂-O-, while the further group(s) R¹, if present, is/are independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, -OH, -O(C₁₋₄ alkyl), -O(C₁₋₄ alkyl)-OH, -O(C₁₋₄ alkyl)-O(C₁₋₄ alkyl), -SH, -S(C₁₋₄ alkyl), -S(C₁₋₄ alkyl)-SH, -S(C₁₋₄ alkyl)-S(C₁₋₄ alkyl), -NH₂, -NH(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)(C₁₋₄ alkyl), halogen, -CF₃, or -CN.
4. The compound for use according to any of claims 1 to 3, wherein R³ is -NH₂.
5. The compound for use according to any of claims 1 to 4, wherein X is S.
6. The compound for use according to any of claims 1 to 5, wherein L is -CO-NH- or -CO-N(C₁₋₄ alkyl)-, wherein the nitrogen atom comprised in said -CO-NH- or said -CO-N(C₁₋₄ alkyl)- is attached to ring A.
7. The compound for use according to any of claims 1 to 6, wherein A is phenyl, 1,3-thiazol-2-yl or 1,3-benzothiazol-2-yl, wherein said phenyl, said 1,3-thiazol-2-yl or said 1,3-benzothiazol-2-yl is optionally substituted with one or more groups independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, -OH, -O(C₁₋₄ alkyl), -SH, -S(C₁₋₄ alkyl), -NH₂, -NH(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)(C₁₋₄ alkyl), halogen, -CF₃, or -CN.

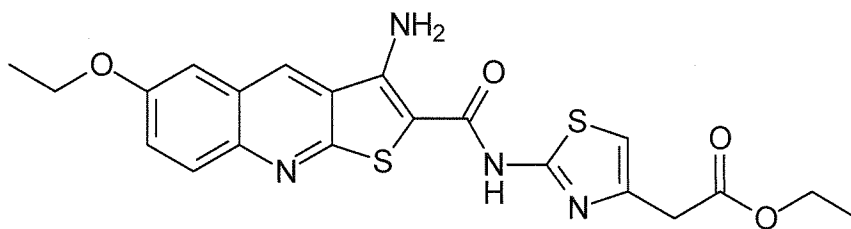
8. The compound for use according to any of claims 1 to 7, wherein R^4 is selected from -CO-(C₁₋₄ alkyl), -CHO, -O(C₁₋₄ alkyl), -OH, -CO-O(C₁₋₄ alkyl), -COOH, C₁₋₄ alkyl, -(C₁₋₄ alkyl)-CO-(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-CHO, -(C₁₋₄ alkyl)-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-OH, -(C₁₋₄ alkyl)-CO-O(C₁₋₄ alkyl), -(C₁₋₄ alkyl)-COOH, -C(-CH₃)=N-OH, -C(-CH₃)=N-O(C₁₋₄ alkyl), -C(-CH₃)=N-O-(C₁₋₄ alkyl)-COOH, -C(-CH₃)=N-O-(C₁₋₄ alkyl)-CO-O(C₁₋₄ alkyl), halogen, -CF₃, -CN, or heterocycloalkyl.
9. The compound for use according to any of claims 1 to 8, wherein X is S, and further wherein L is -CO-NH- wherein the nitrogen atom comprised in said -CO-NH- is attached to ring A.
10. The compound for use according to claim 1, wherein said compound is a compound of one of the following formulae **1a** to **1t**, or a pharmaceutically acceptable salt, solvate or prodrug thereof:



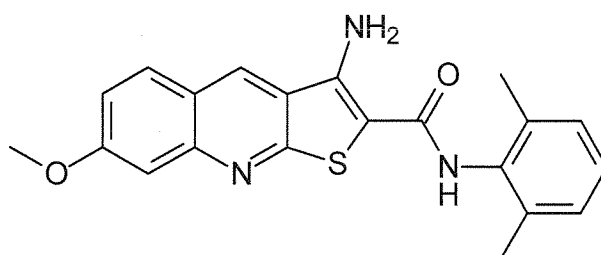
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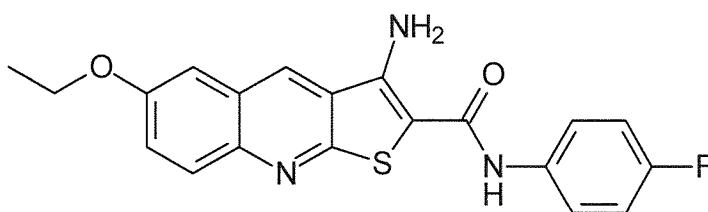
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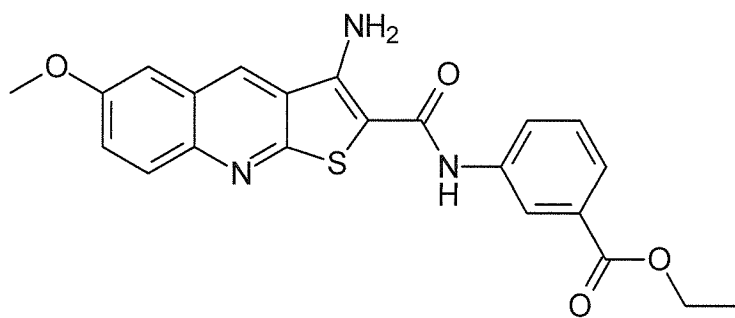


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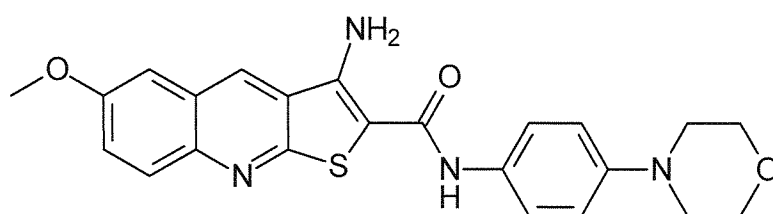


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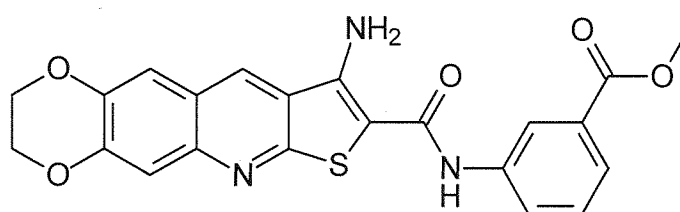
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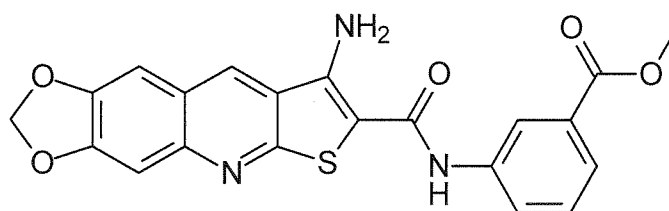
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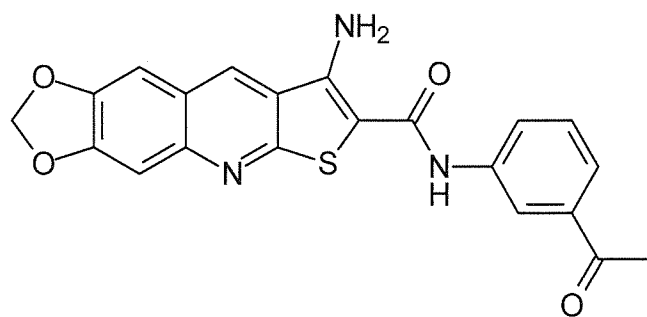


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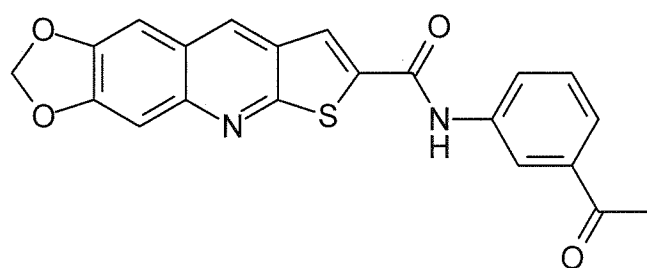


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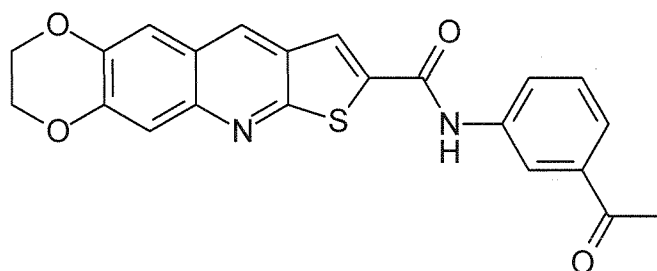
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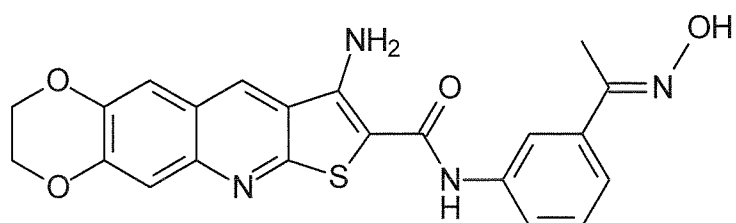
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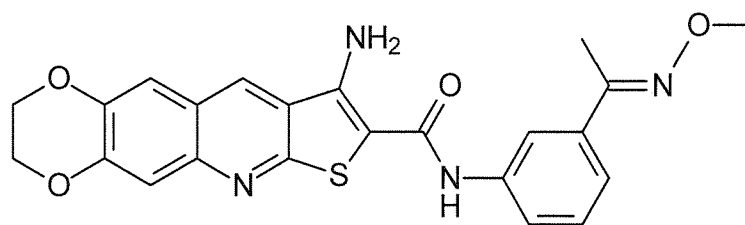


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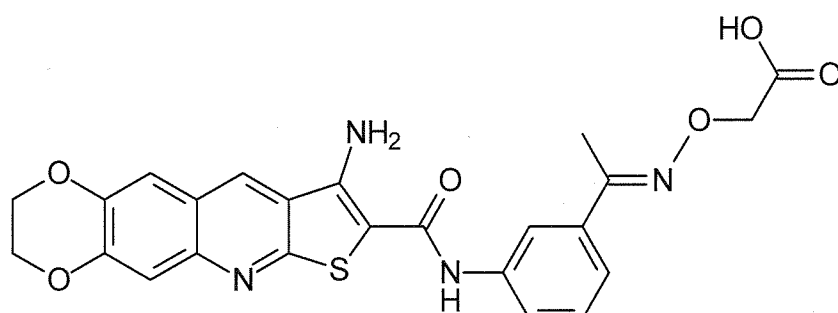


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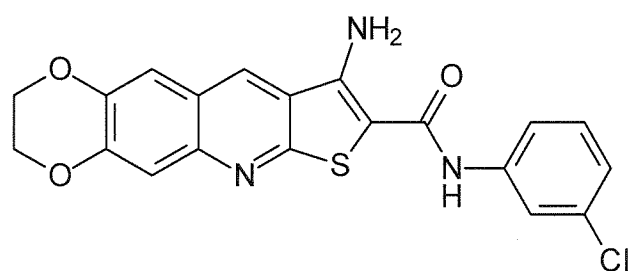
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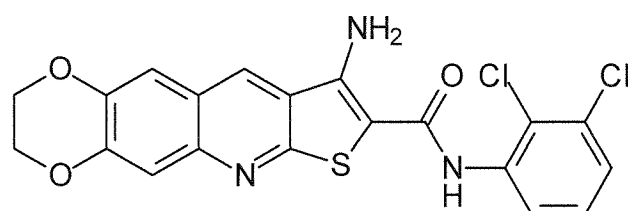
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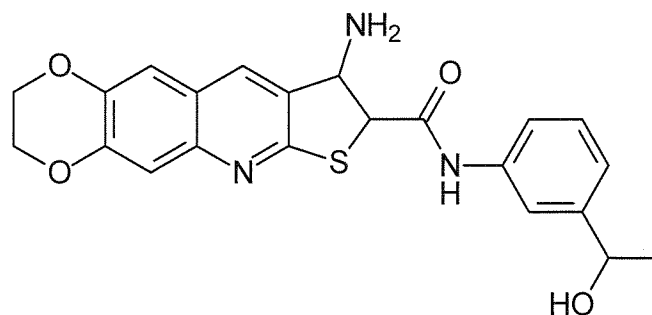


1r



1s

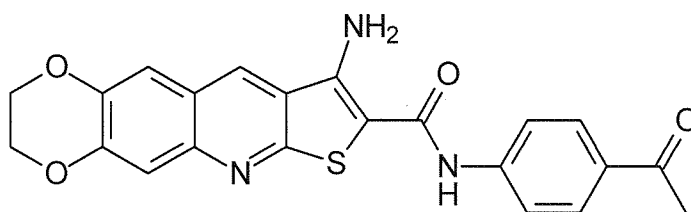
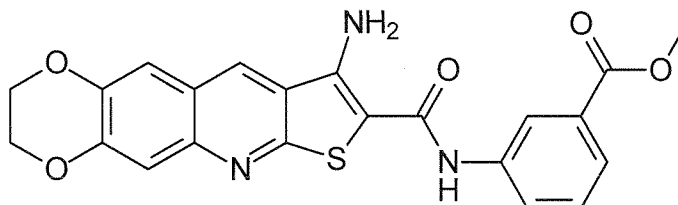
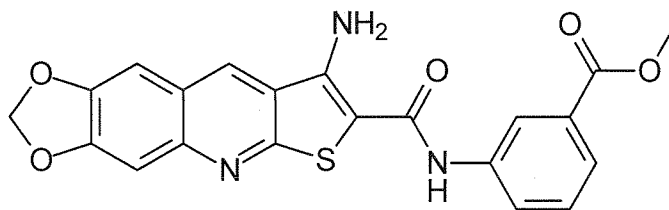
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**1t**

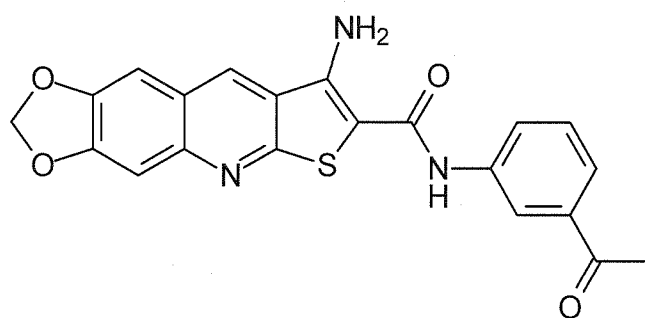
11. A pharmaceutical composition comprising a compound as defined in any of claims 1 to 10 or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient, for use in the treatment or prevention of a cardiovascular disorder, cardiac hypertrophy, heart failure, anxiety, pain, chronic pain, migraine, an allergy, an inflammatory disorder, an autoimmune disorder, diabetes, diabetic complications, diabetic retinopathy, diabetic nephropathy, diabetic cardiomyopathy, diabetic neuropathy, cancer, metastatic cancer, drug-resistant cancer, stomach cancer, lung cancer, thyroid cancer, colon cancer, breast cancer, bipolar disorder, stroke, alopecia, or alcoholism.
12. A method of treating or preventing a disorder or condition selected from the group consisting of a cardiovascular disorder, cardiac hypertrophy, heart failure, anxiety, pain, chronic pain, migraine, an allergy, an inflammatory disorder, an autoimmune disorder, diabetes, diabetic complications, diabetic retinopathy, diabetic nephropathy, diabetic cardiomyopathy, diabetic neuropathy, cancer, metastatic cancer, drug-resistant cancer, stomach cancer, lung cancer, thyroid cancer, colon cancer, breast cancer, bipolar disorder, stroke, alopecia, and alcoholism, the method comprising the administration of a compound as defined in any of claims 1 to 10 or a pharmaceutically acceptable salt, solvate or prodrug thereof, or the pharmaceutical composition of claim 11, to a subject in need thereof.
13. The compound for use according to any of claims 1 to 10, or the pharmaceutical composition for use according to claim 11, or the method of claim 12, wherein said compound or said pharmaceutical composition is to be administered by any one of: an oral route; topical route, including by transdermal, intranasal, ocular, buccal, or sublingual route; parenteral route using injection techniques or infusion techniques, including by subcutaneous, intradermal, intramuscular, intravenous, intraarterial,

intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, intrasternal, intraventricular, intraurethral, or intracranial route; pulmonary route, including by inhalation or insufflation therapy; gastrointestinal route; intrauterine route; intraocular route; subcutaneous route; ophthalmic route, including by intravitreal, or intracameral route; rectal route; or vaginal route.

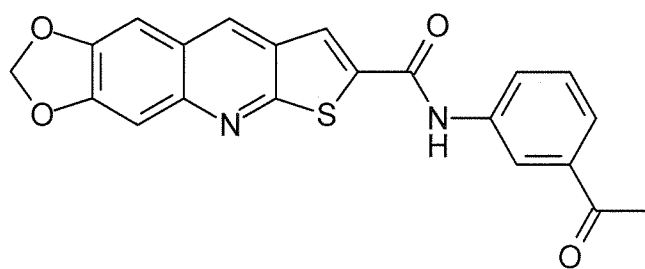
14. The method of claim 12 or 13, wherein said subject is a human.
15. A compound having one of the following formulae **1a** or **1j** to **1t**:

**1a****1j****1k**

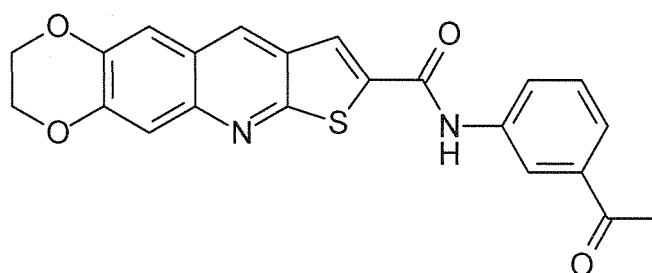
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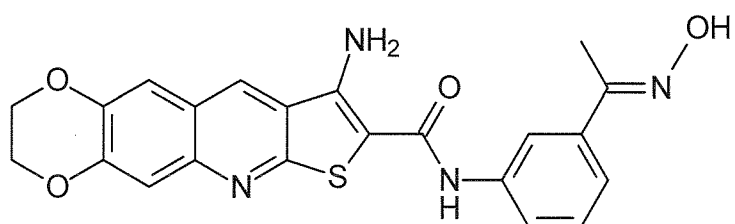
1l



1m

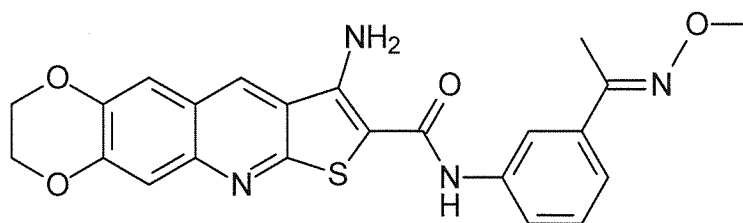


1n

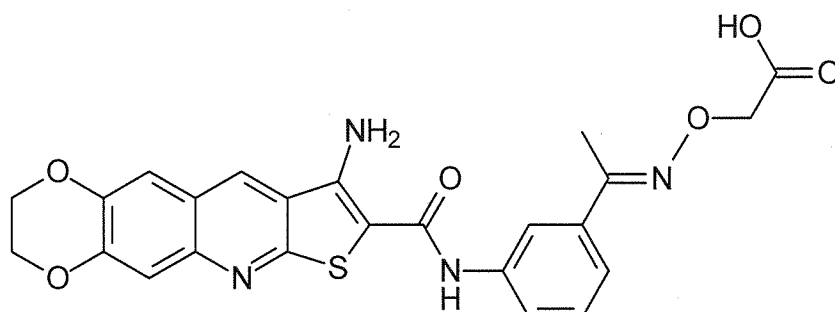


1o

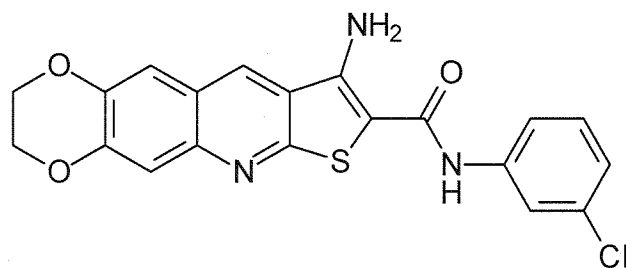
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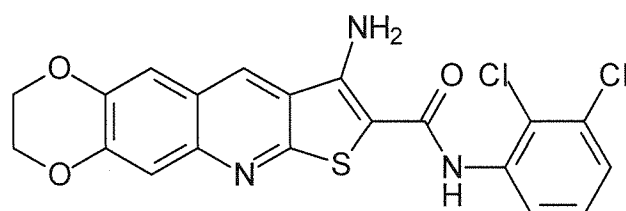
1p



1q

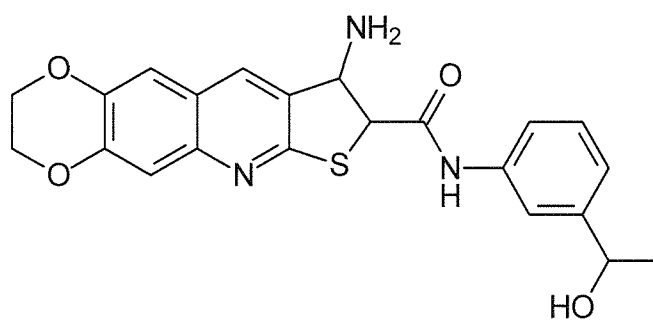


1r



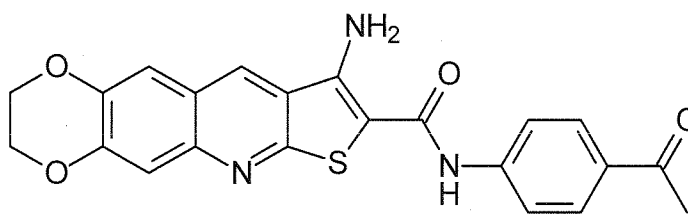
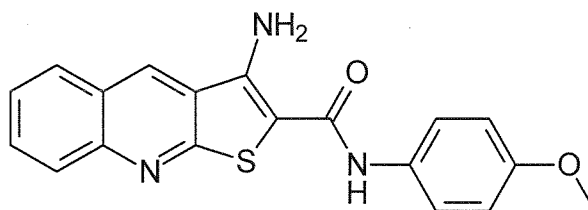
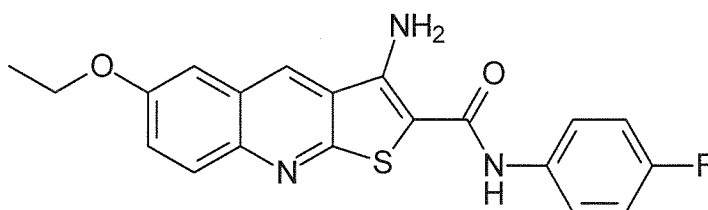
1s

70

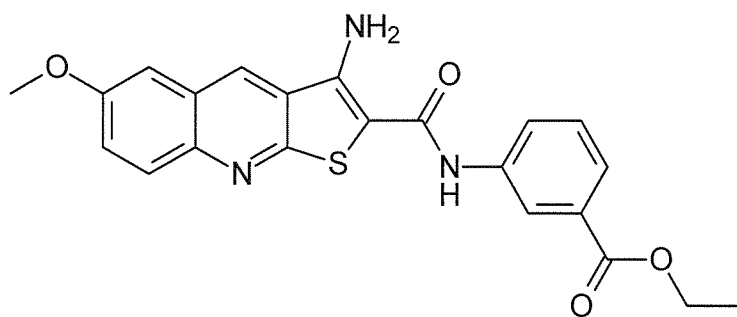
**1t**

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

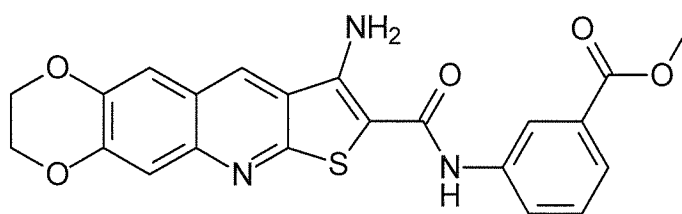
16. A compound having one of the following formulae **1a**, **1d**, **1g**, **1h** or **1j** to **1t**:

**1a****1d****1g**

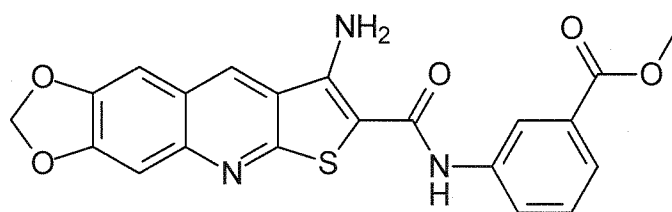
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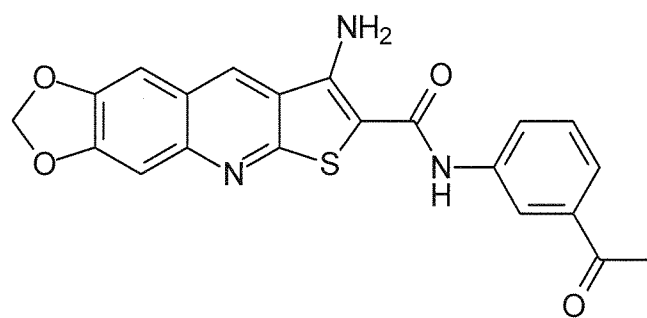
1h



1j

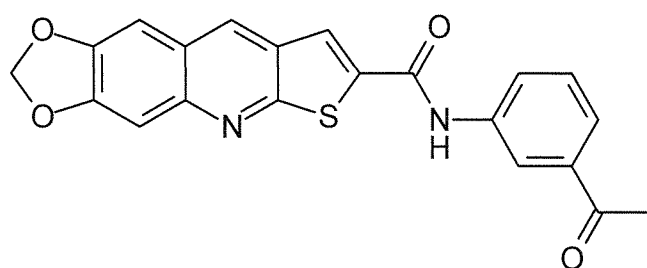


1k

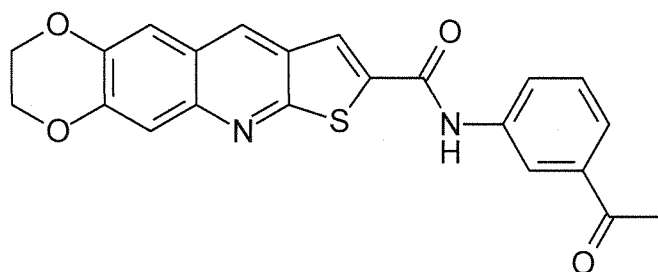


1l

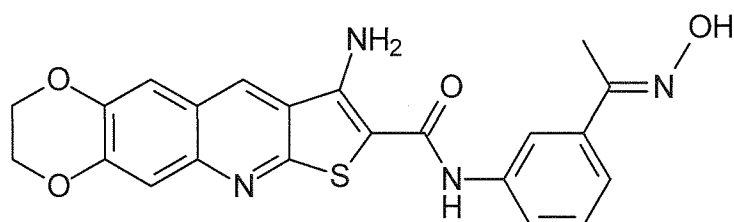
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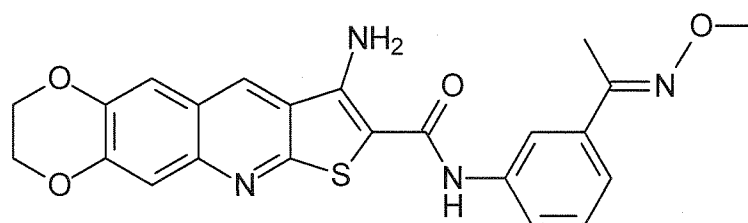
1m



1n

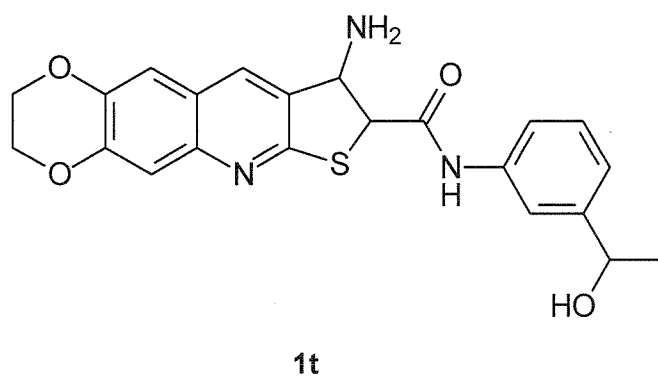
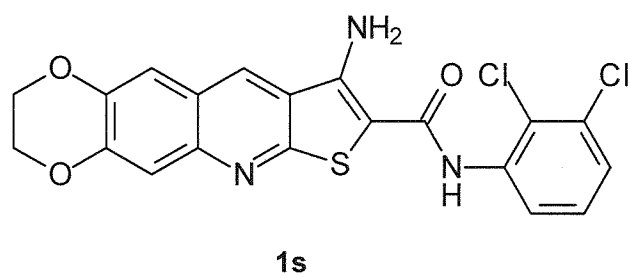
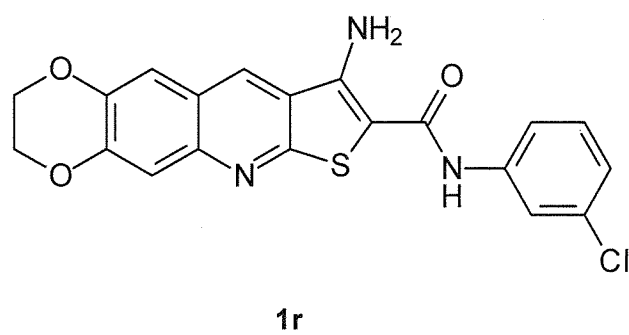
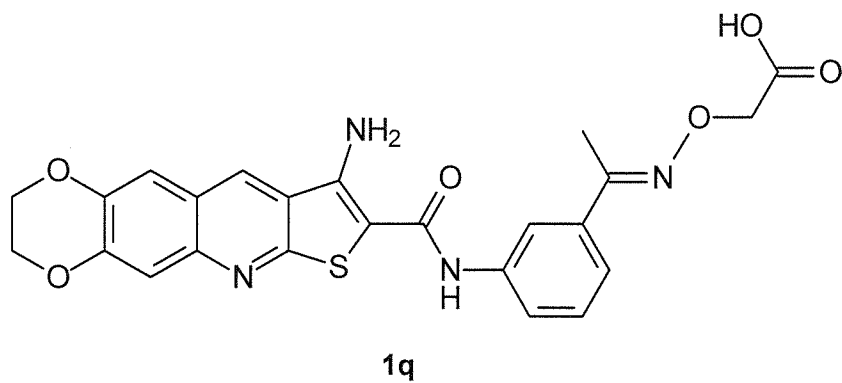


1o



1p

73



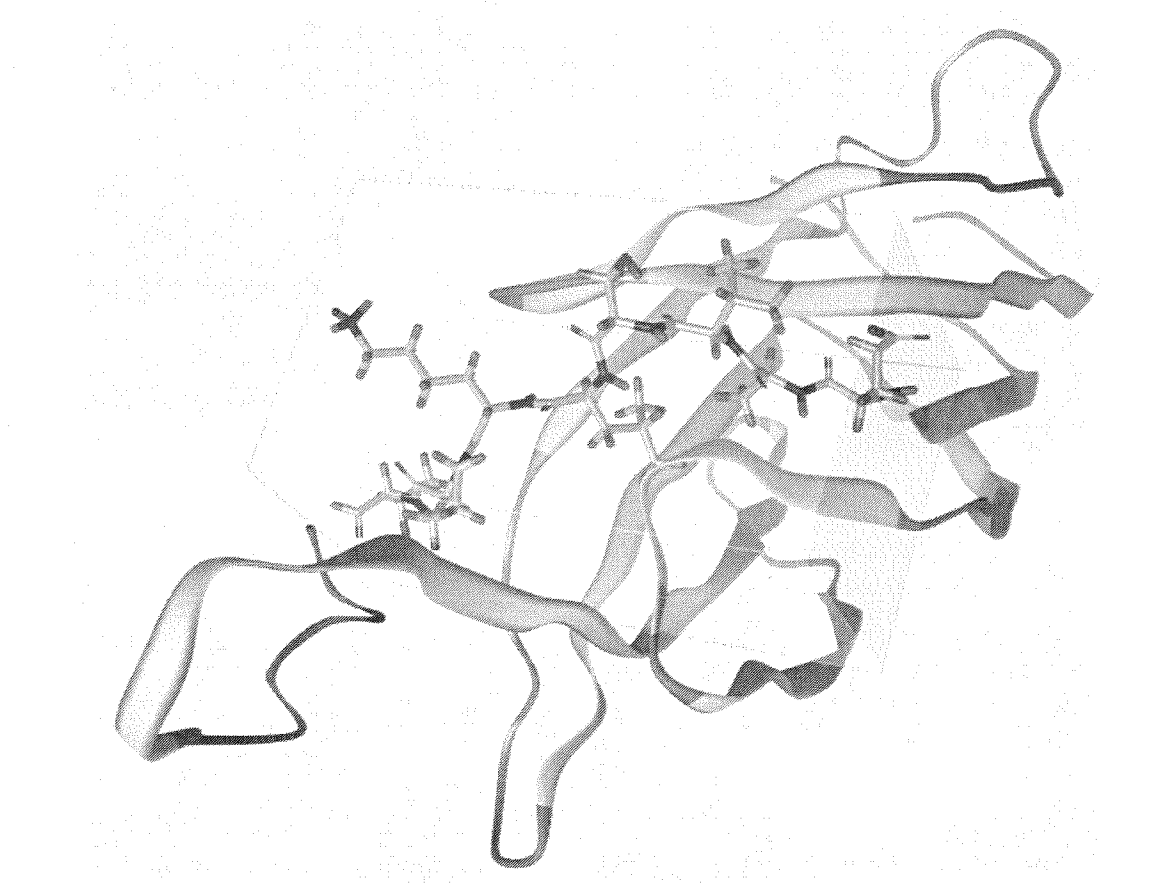
or a pharmaceutically acceptable salt, solvate or prodrug thereof

for use as a medicament.

17. A pharmaceutical composition comprising a compound as defined in claim 16 or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

Fig. 1

A)



B)

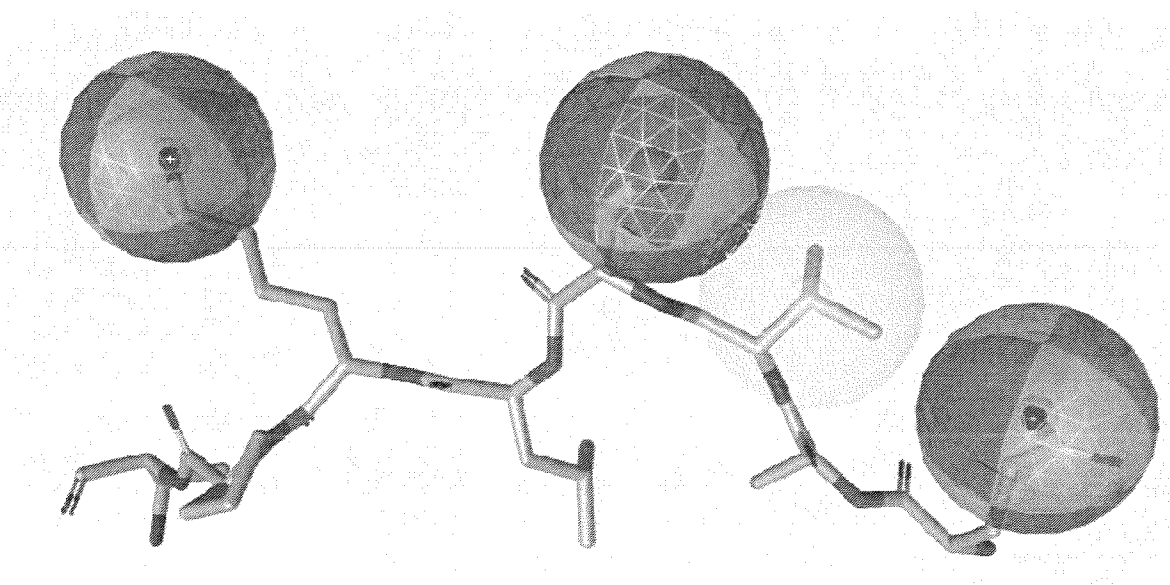


Fig. 2

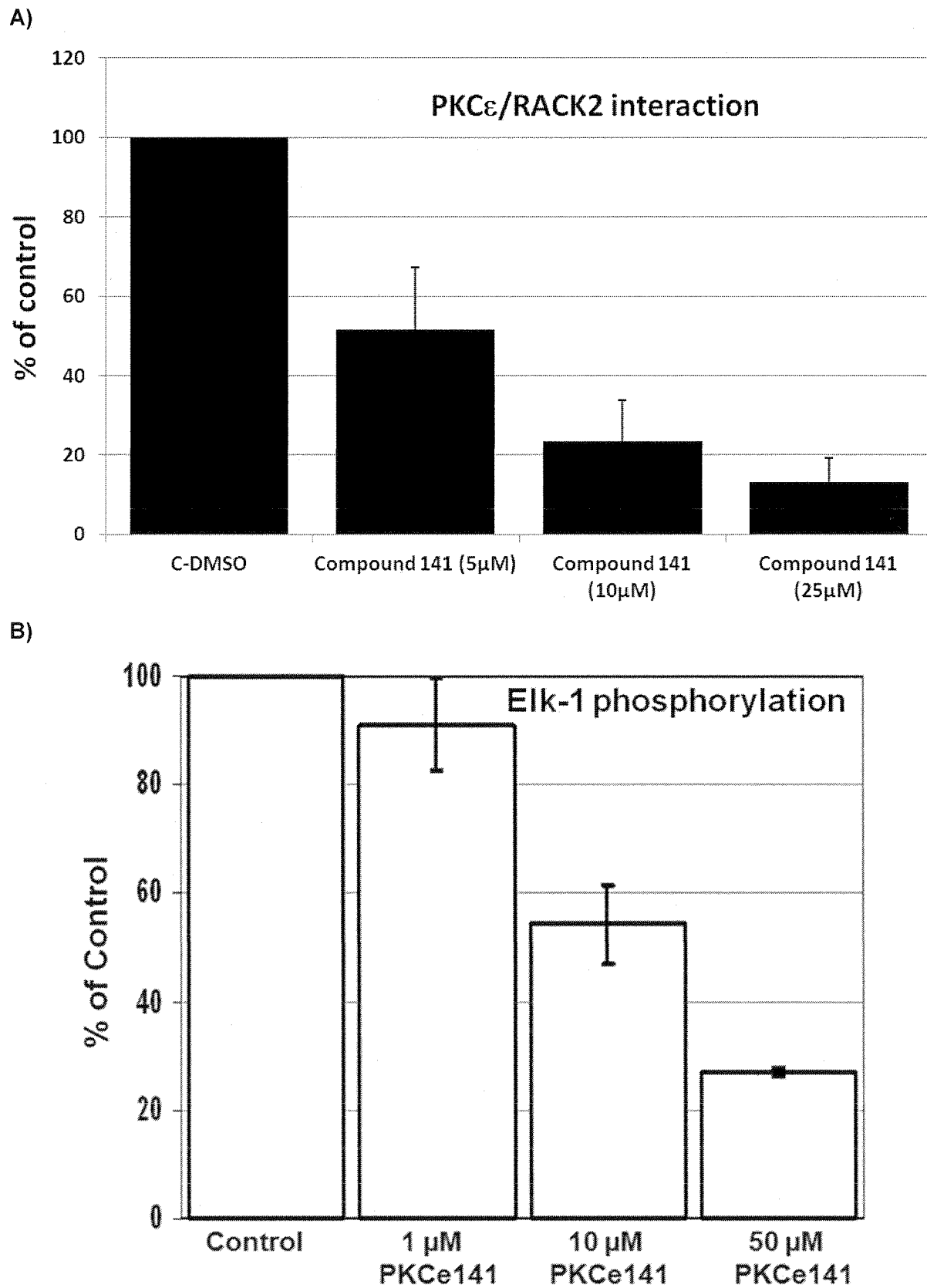
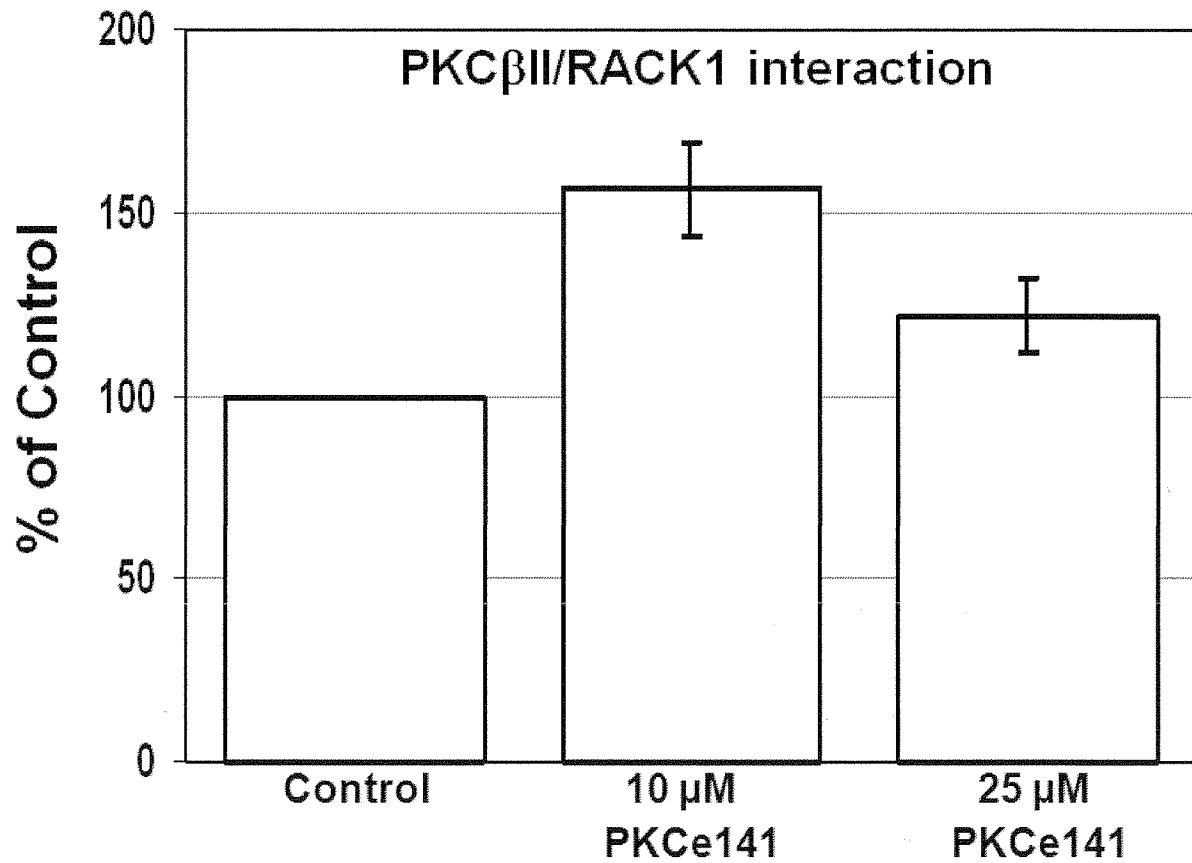


Fig. 2 (cont.)

c)



D)

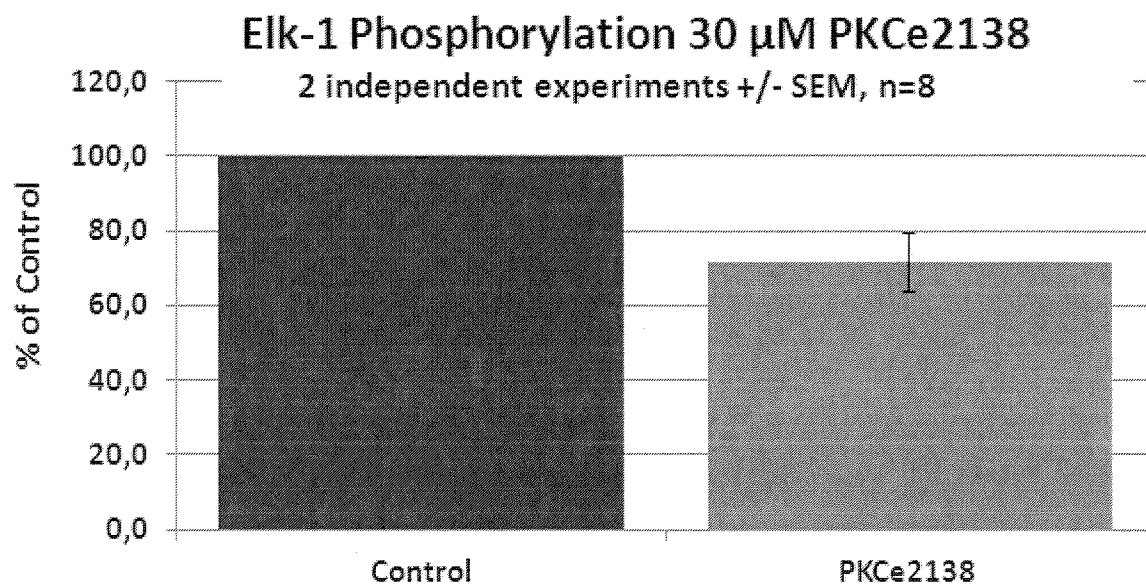
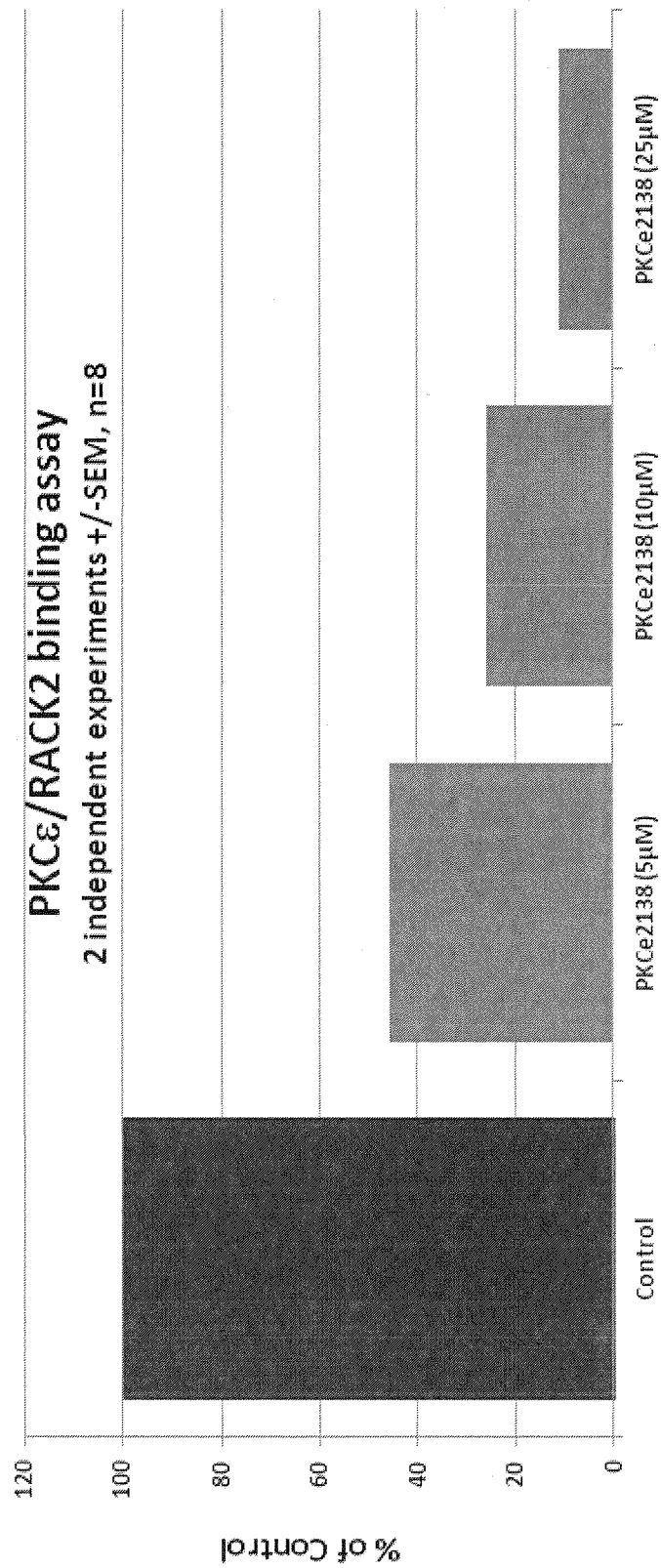


Fig. 2 (cont.)

E)



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Fig. 2 (cont.)

F)

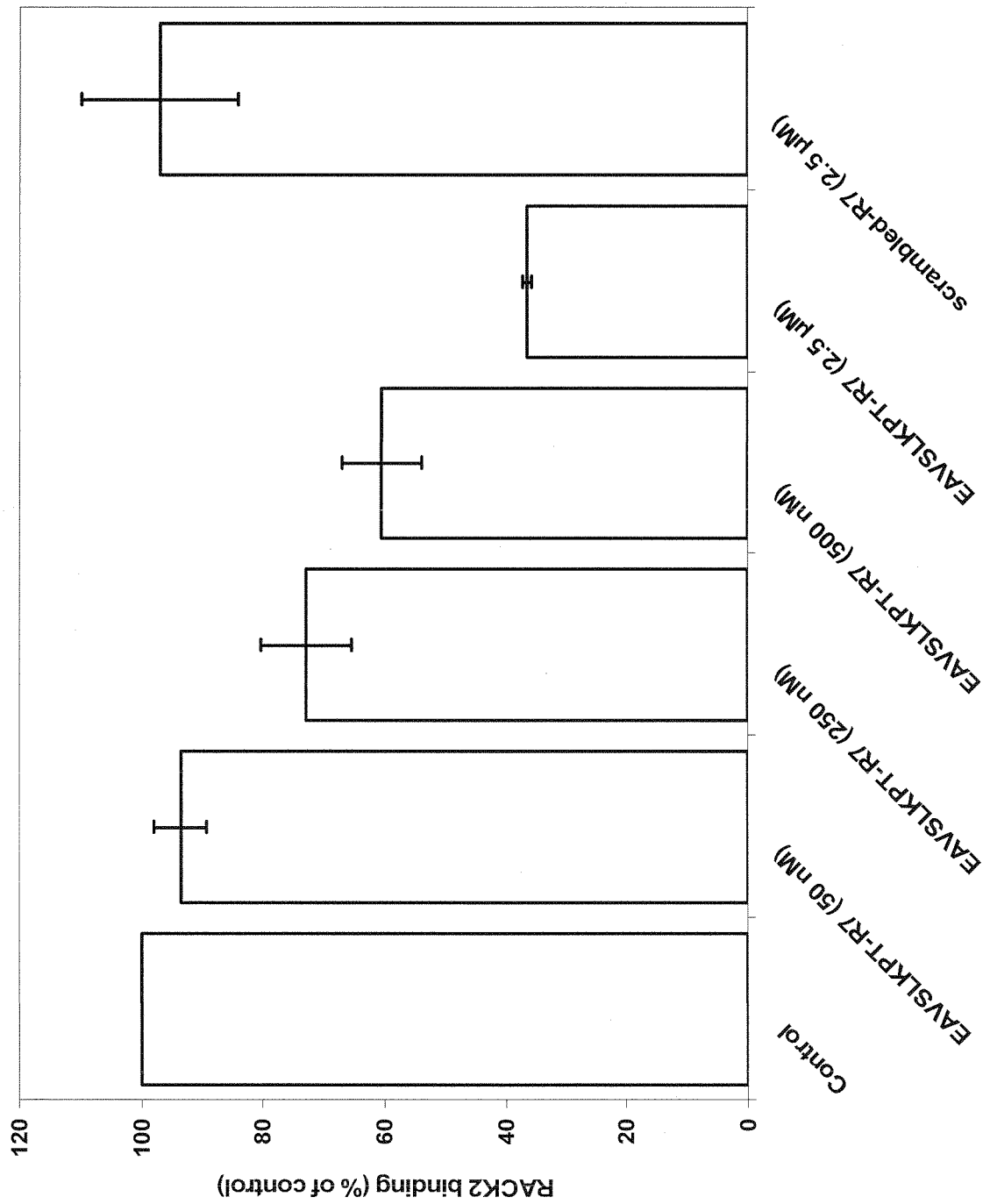


Fig. 3

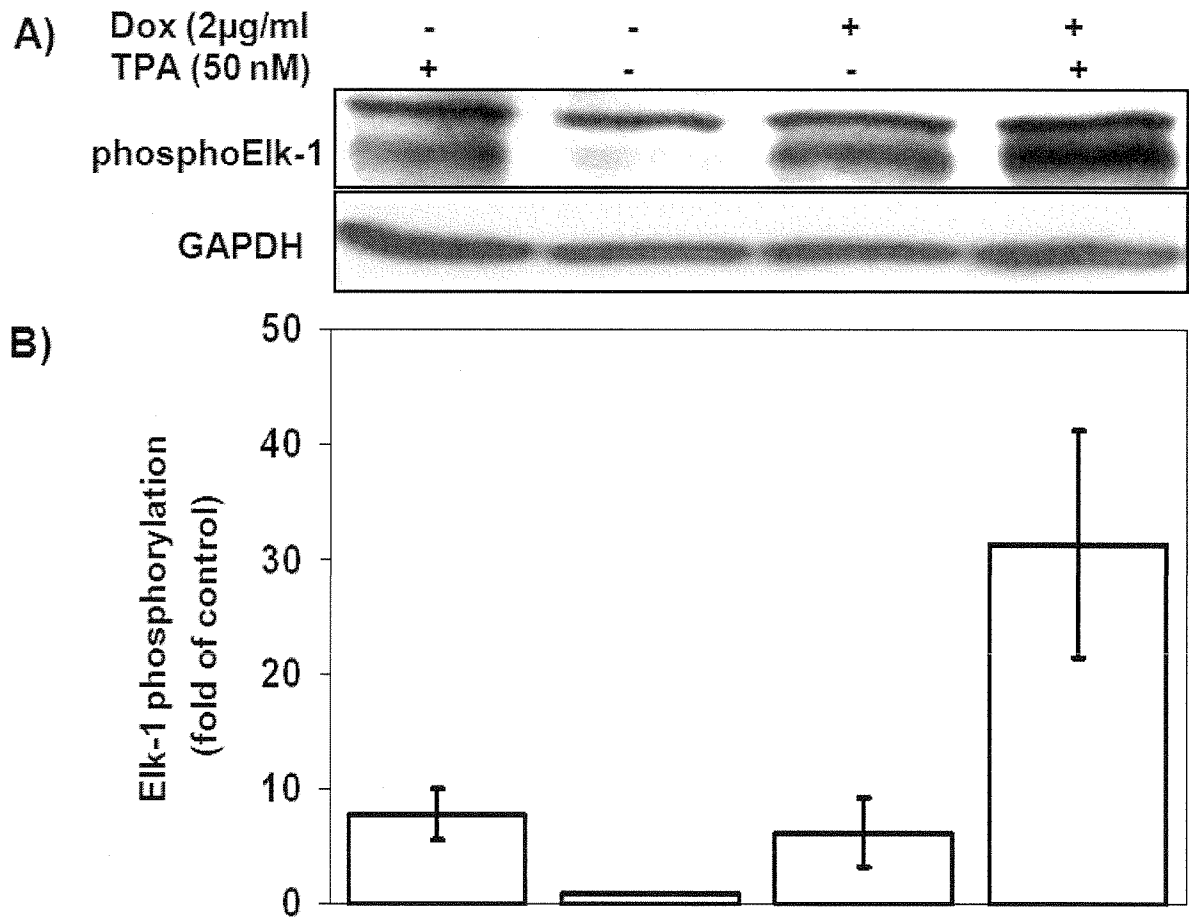


Fig. 4

A)

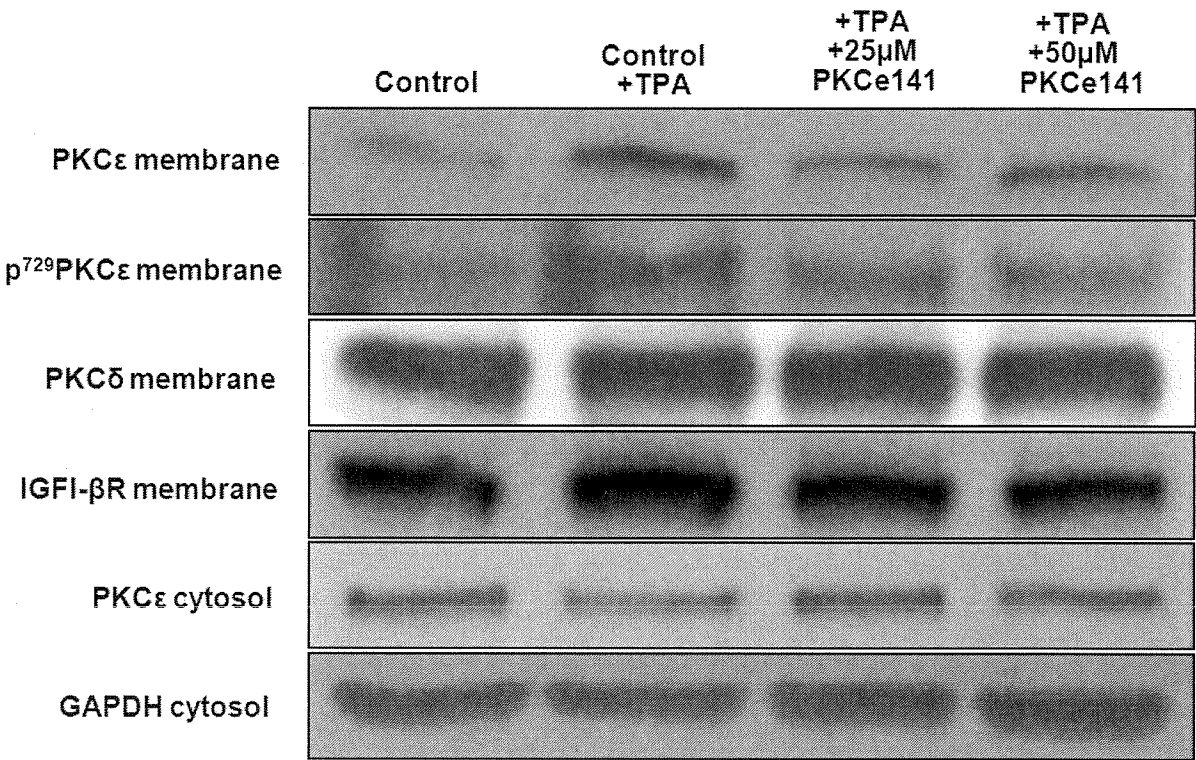
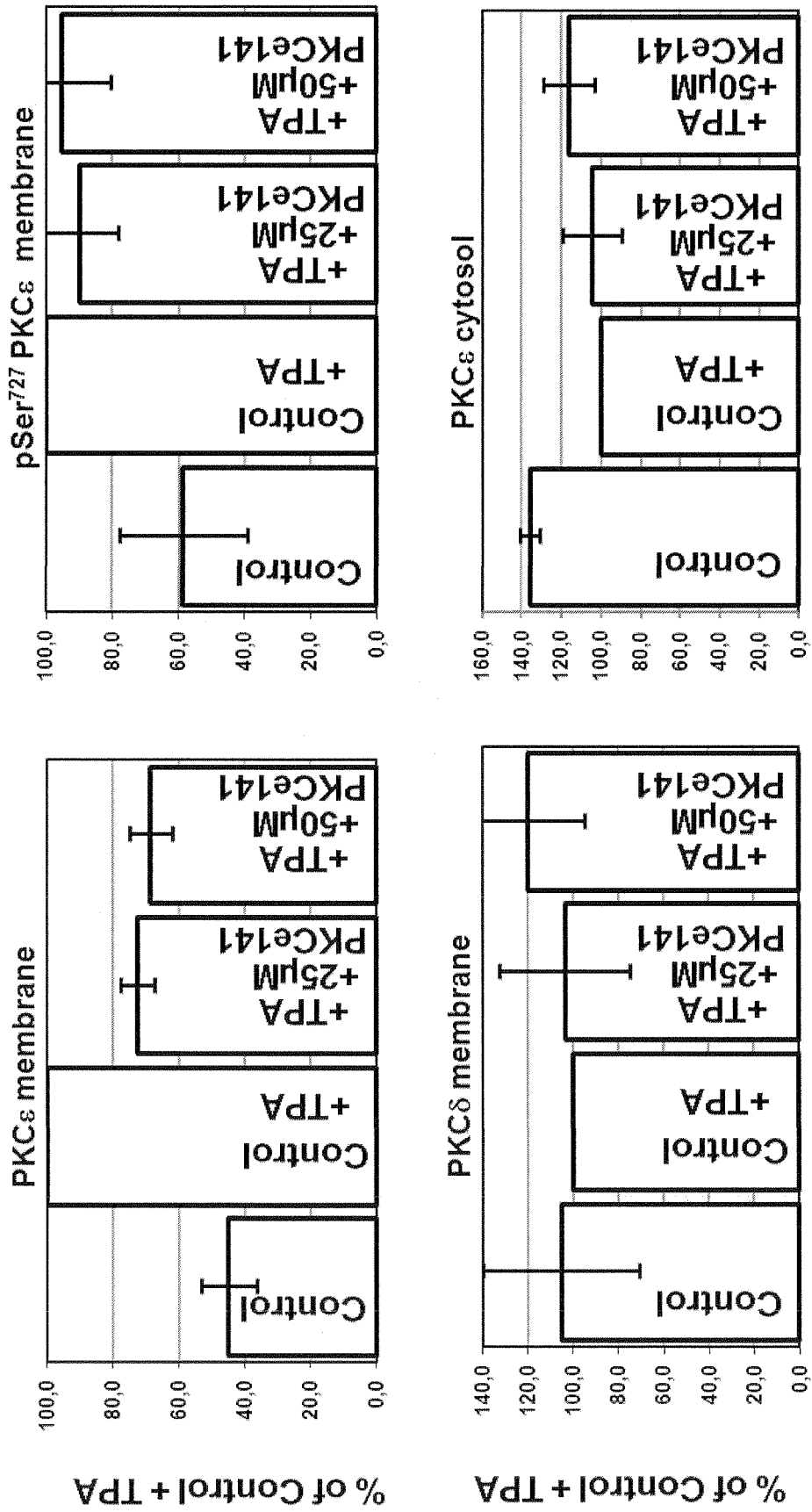
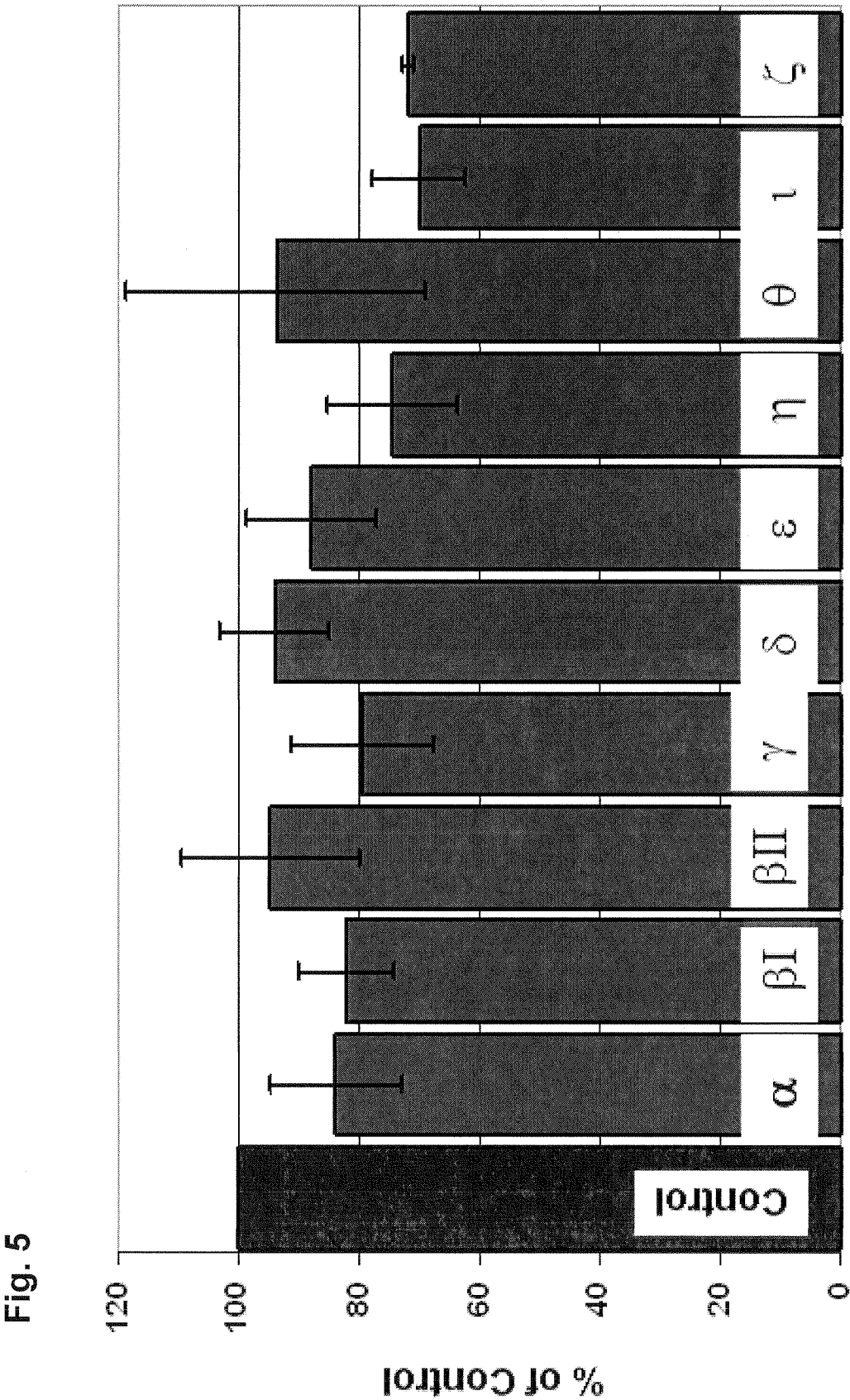
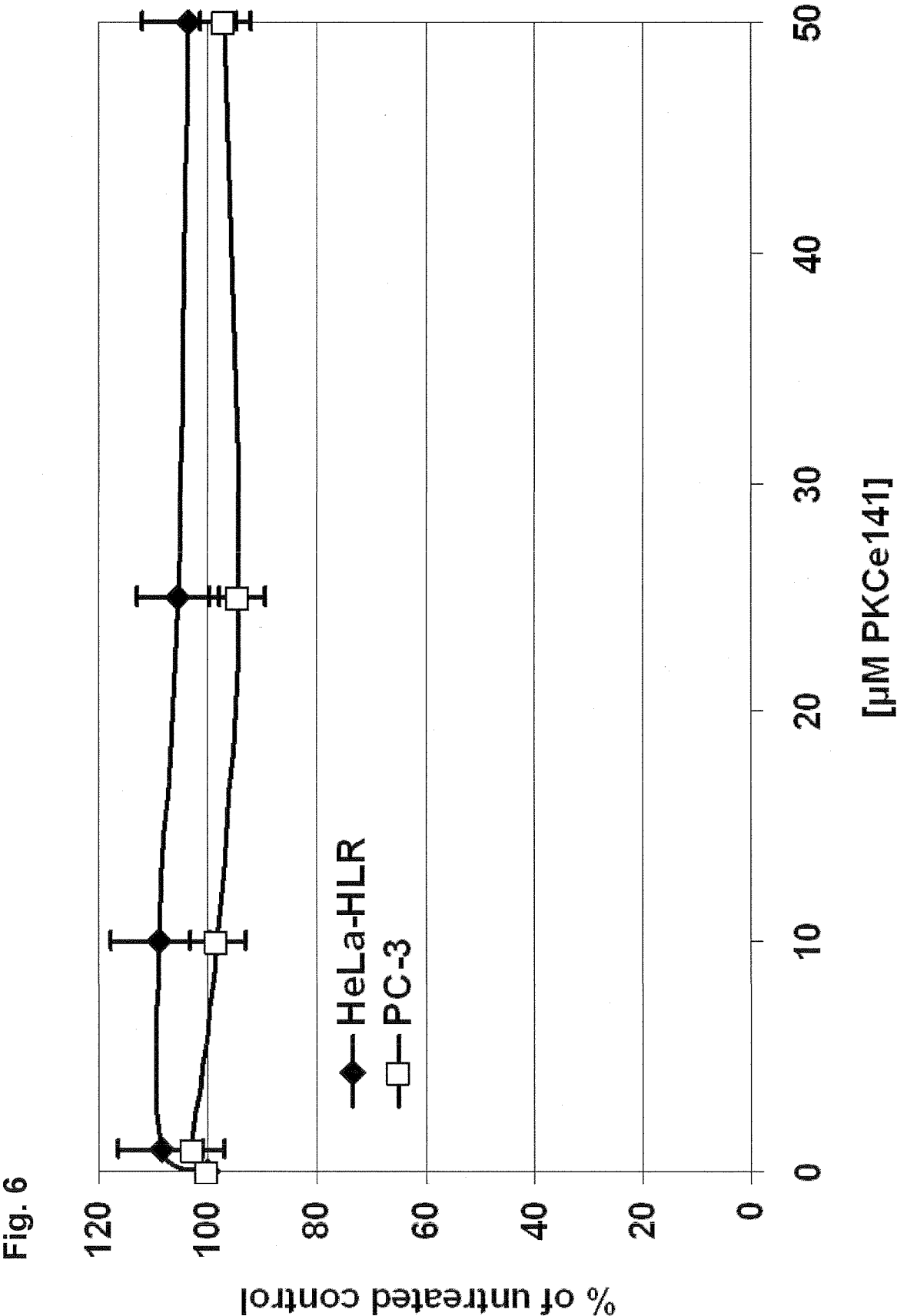
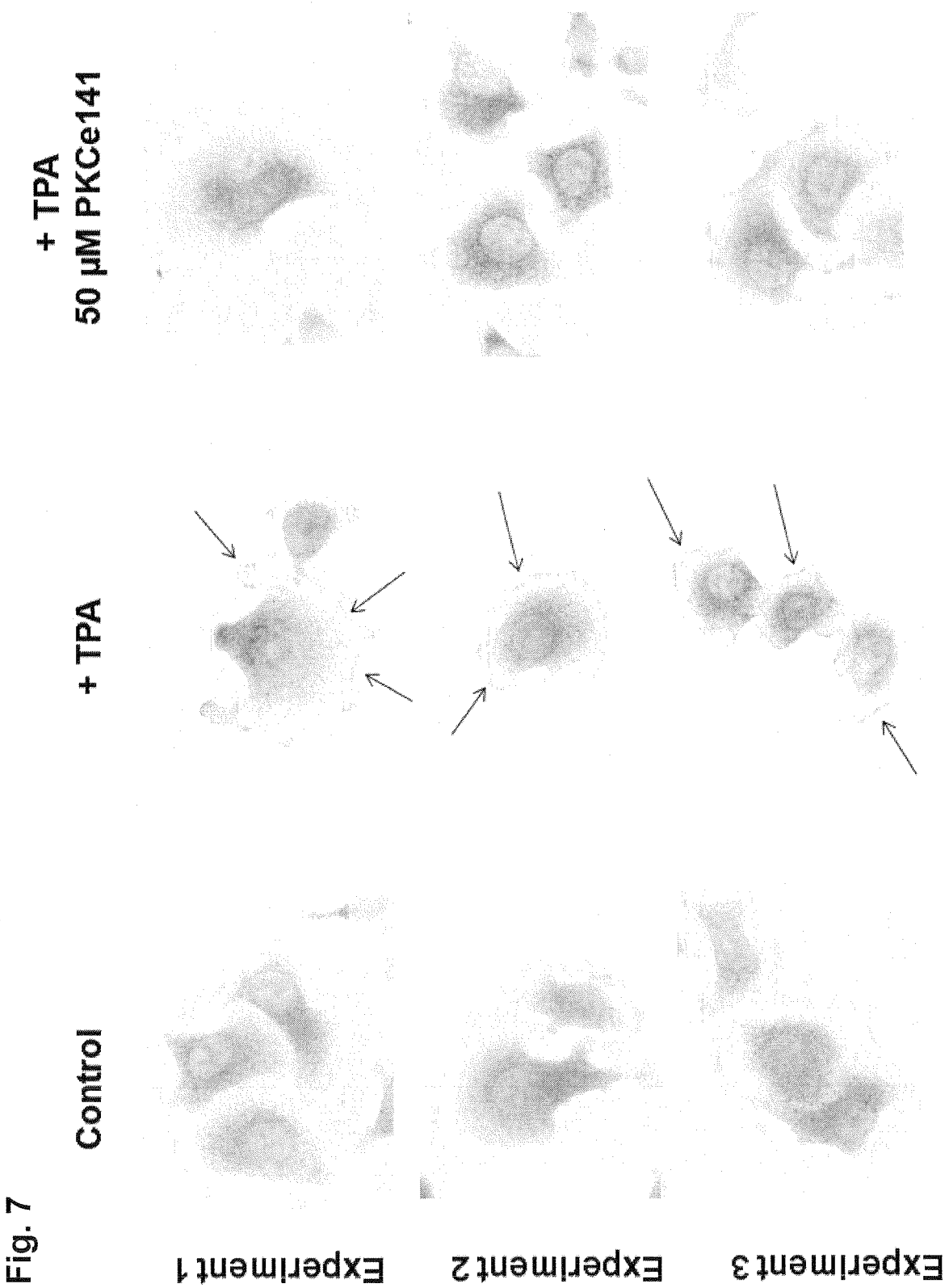


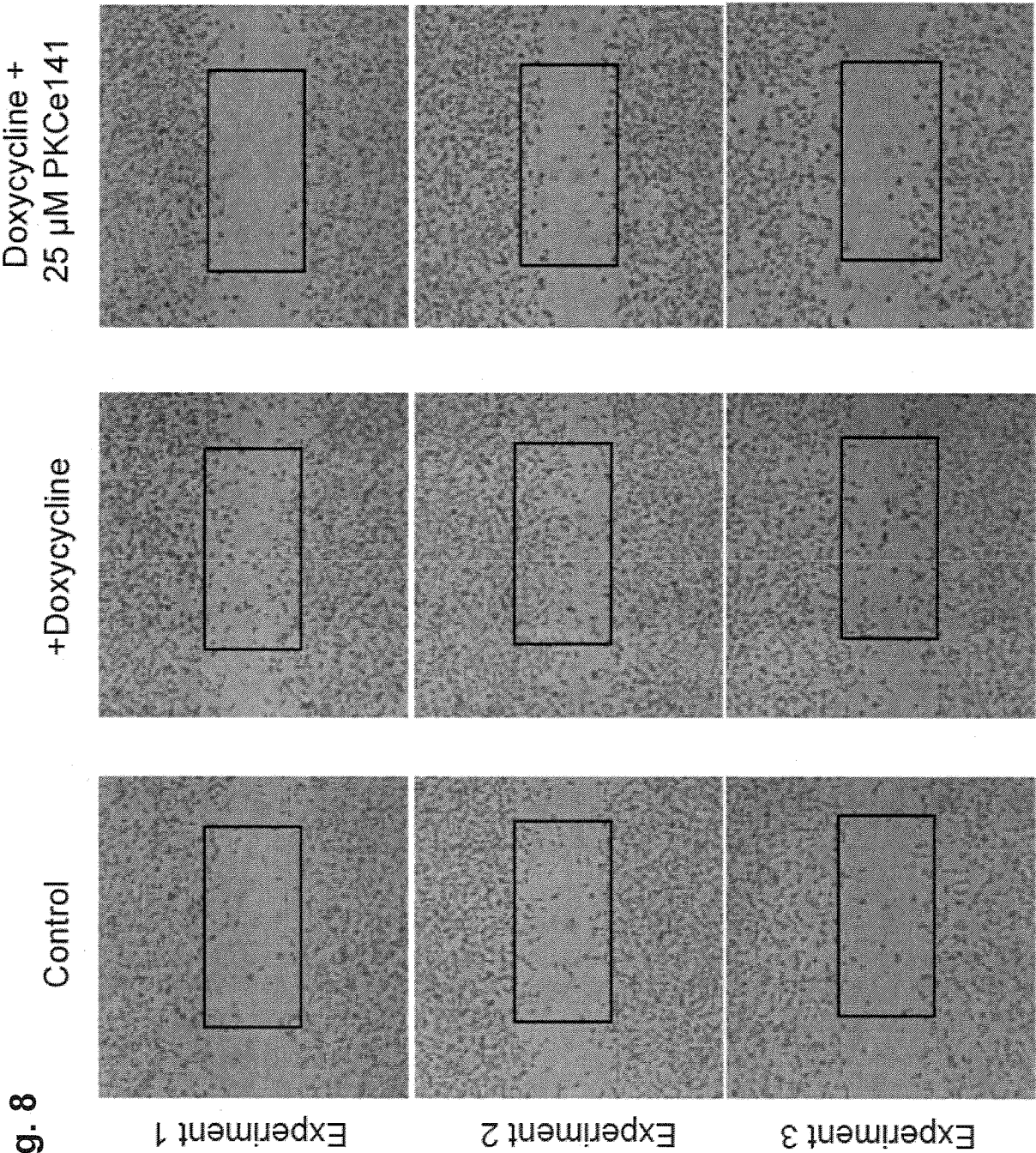
Fig. 4 (cont.)
B)





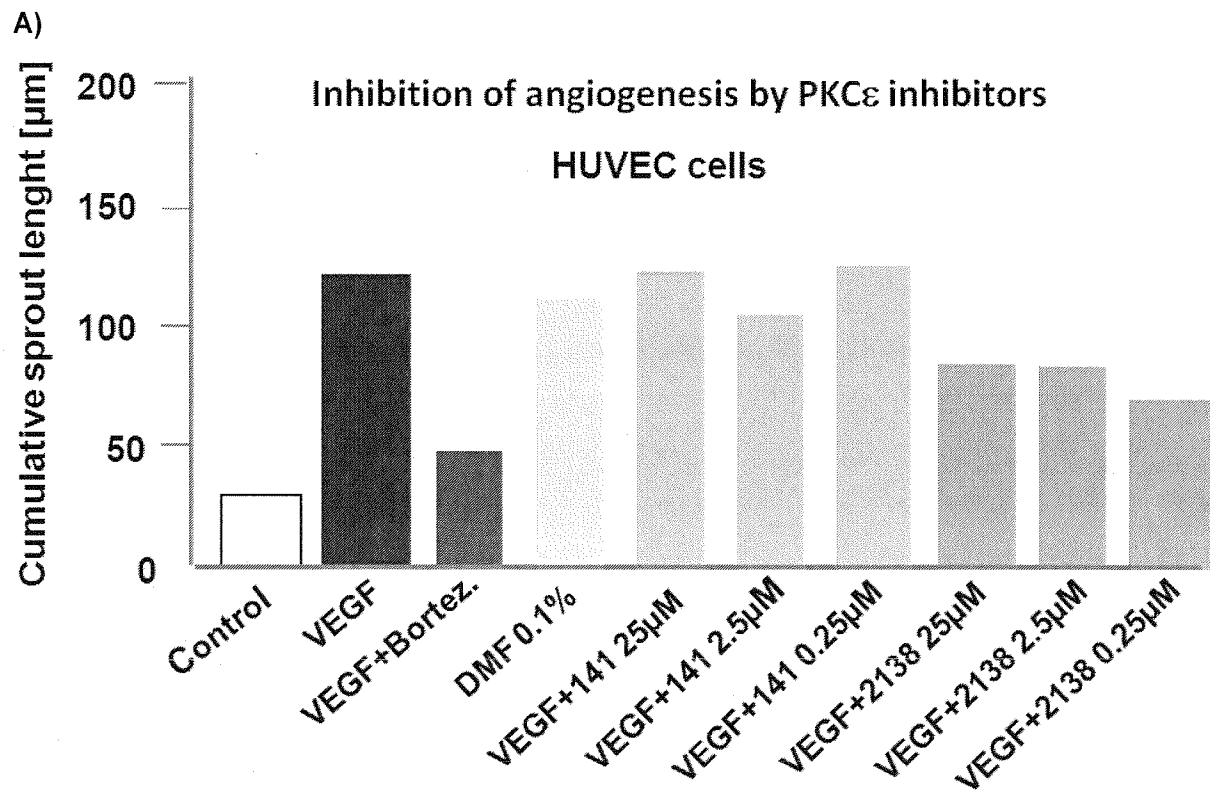






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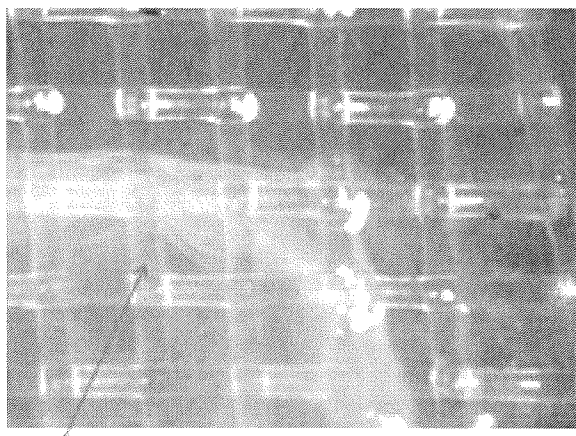
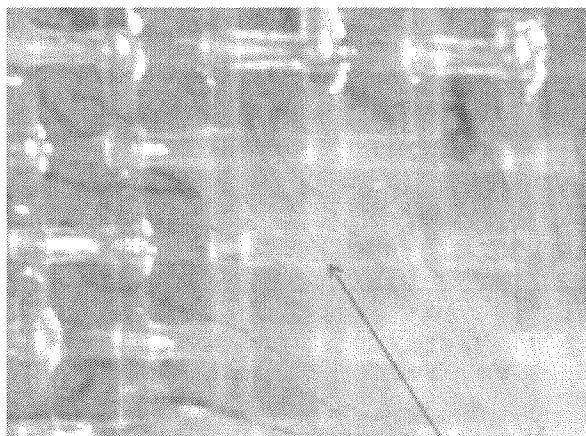
Fig. 9



B)

DMSO + 10 ng VEGF

10 ng 141 + 10 ng VEGF



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Fig. 10

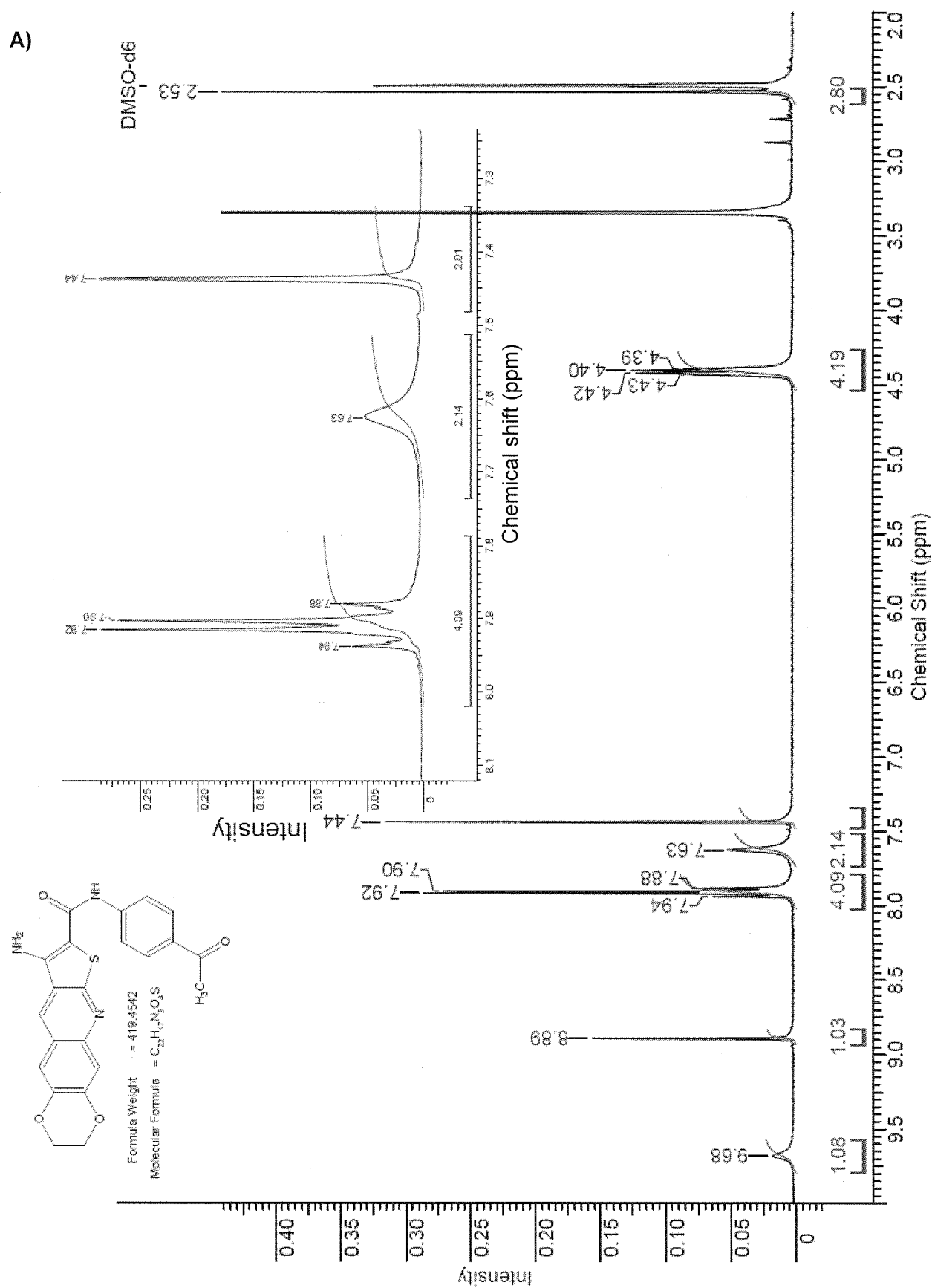
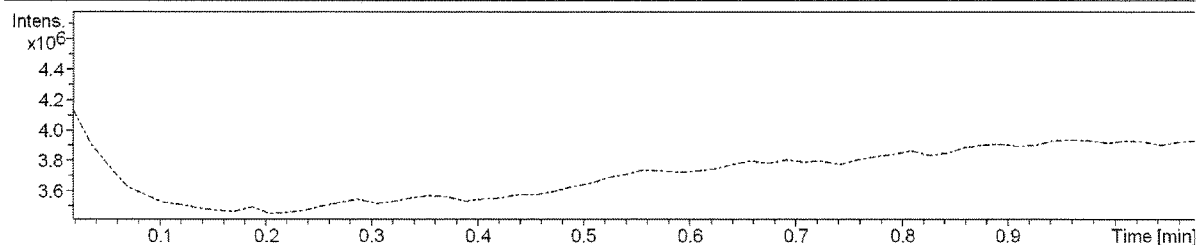


Fig. 10 (cont.)

B)

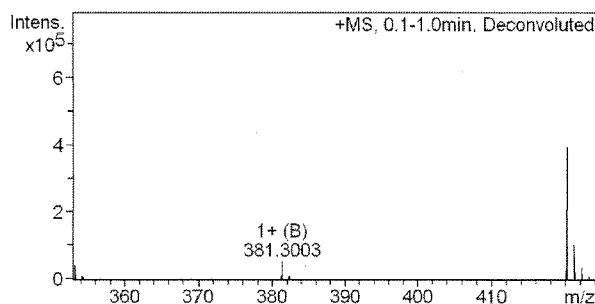
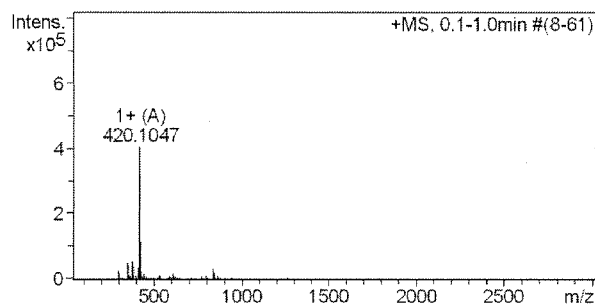
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	550.0 Vpp	Set Divert Valve	Source



#	RT [min]	Area	Int. Type	Intens.	S/N	Chromatogram	Max. m/z
n.a.	0.6	n.a.	Average spectrum	n.a.	n.a.	n.a.	420.1047

+MS, 0.1-1.0min #(8-61)



#	m/z	Res.	S/N	I	I %	#	m/z	Res.	S/N	I	I %
1	303.0467	7683	220.9	27006	6.6	1	353.2692			48429	11.9
2	353.2692	8012	331.2	48429	11.9	2	381.3003			54374	13.4
3	381.3003	8570	369.9	54375	13.4	3	420.1041			406959	100.0
4	413.2689	8722	238.7	35375	8.7						
5	420.1047	8224	2754.1	406960	100.0						
6	421.1073	8473	701.2	103752	25.5						
7	422.1047	8704	227.2	33728	8.3						
8	609.8194	9603	129.9	18658	4.6						
9	839.2041	11229	205.6	33450	8.2						
10	840.2083	11168	104.8	17207	4.2						

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/063723

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4743 C07D495/04 C07D495/14 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 A61K 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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	FLORIAN RECHFELD ET AL: "Thienoquinolines as Novel Disruptors of the PKC[epsilon]/RACK2 Protein-Protein Interaction", JOURNAL OF MEDICINAL CHEMISTRY, vol. 57, no. 8, 24 April 2014 (2014-04-24), pages 3235-3246, XP055143375, ISSN: 0022-2623, DOI: 10.1021/jm401605c the whole document ----- -/--	1,2,4-9, 11-14



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"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

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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

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"&" document member of the same patent family

Date of the actual completion of the international search

10 October 2014

Date of mailing of the international search report

20/10/2014

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Fax: (+31-70) 340-3016

Authorized officer

Garabatos-Perera, J

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2014/063723

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	P. GRUBER ET AL: "Barbituric acid derivative BAS 02104951 inhibits PKC , PKC , PKC /RACK2 interaction, Elk-1 phosphorylation in HeLa and PKC and translocation in PC3 cells following TPA-induction", JOURNAL OF BIOCHEMISTRY, vol. 149, no. 3, 1 March 2011 (2011-03-01) , pages 331-336, XP055084145, ISSN: 0021-924X, DOI: 10.1093/jb/mvq147 abstract page 331, left-hand column, line 1 - right-hand column, paragraph 1 figure 1; compound BAS 02104951 -----	1-17
A	SANAM R ET AL: "Combined pharmacophore and structure-guided studies to identify diverse HSP90 inhibitors", JOURNAL OF MOLECULAR GRAPHICS AND MODELLING, ELSEVIER SCIENCE, NEW YORK, NY, US, vol. 28, no. 6, 26 February 2010 (2010-02-26), pages 472-477, XP026875379, ISSN: 1093-3263 [retrieved on 2009-11-24] abstract page 472, left-hand column, line 1 - page 473, left-hand column, paragraph 1 page 476; table 2; compound 7 -----	1-17
A	US 2011/077250 A1 (RYDER SEAN [US]) 31 March 2011 (2011-03-31) abstract paragraphs [0072] - [0073] paragraph [0199] figure 73; compound 17508839 -----	1-17
A	WO 2013/033037 A2 (UNIV CALIFORNIA [US]; RENSLO ADAM R [US]; GALLARDO-GODOY ALEJANDRA [US]) 7 March 2013 (2013-03-07) abstract claims 42,43,77 -----	1-17
A	CN 102 757 447 A (UNIV BEIJING) 31 October 2012 (2012-10-31) abstract compounds: 338431-65-5 (present compound 1e), 351359-78-9 (present compound 1f), 552819-38-2 (present compound 1c), 602291-11-2 (present compound 1i), 602293-00-5 (present compound 1b); page 16 - page 45; tables ----- -/--	1-17

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2014/063723

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	A. D. PILLAI ET AL: "A Cell-Based High-Throughput Screen Validates the Plasmodial Surface Anion Channel As an Antimalarial Target", MOLECULAR PHARMACOLOGY, vol. 77, no. 5, 1 May 2010 (2010-05-01), pages 724-733, XP055022753, ISSN: 0026-895X, DOI: 10.1124/mol.109.062711 abstract page 729; figure 3b page 728; table 1; compound 3 -----	1-17
A	US 2013/129677 A1 (DAI DONGCHENG [US] ET AL) 23 May 2013 (2013-05-23) abstract page 77; compound 364 -----	1-17
A	RU 2 371 444 C1 (IVASHCHENKO ANDREJ ALEKSANDROV [RU]; ALLA KHEMLLS [US]) 27 October 2009 (2009-10-27) the whole document see for example compounds: 933235-90-6, 933235-97-3, 933237-56-0, 1192320-38-9 -----	1-17
A	WO 92/03427 A1 (YOSHITOMI PHARMACEUTICAL [JP]; JAPAN TOBACCO INC [JP]) 5 March 1992 (1992-03-05) abstract compound: 142221-63-4 -----	1-17
A	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 25 May 2001 (2001-05-25), Chemical Library Supplier: AsInEx: XP002715019, retrieved from STN accession no. 338433-13-9 Database accession no. 338433-13-9 the whole document -----	1-17
A	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 27 April 2001 (2001-04-27), Chemical Library Supplier: AsInEx: XP002715020, retrieved from STN accession no. 333330-11-3 Database accession no. 333330-11-3 the whole document ----- -/--	1-17

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2014/063723

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2013/123071 A1 (CLEAVE BIOSCIENCES INC [US]) 22 August 2013 (2013-08-22) abstract page 49; compounds 154-156 claims	1,2,4-9, 11-14
E	----- WO 2014/116859 A1 (UNIV CHICAGO [US]) 31 July 2014 (2014-07-31) abstract page 21; compounds LC-40 claims -----	1,2,4-9, 11-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2014/063723

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2011077250 A1	31-03-2011	US 2011077250 A1	31-03-2011
		WO 2010151799 A2	29-12-2010

WO 2013033037 A2	07-03-2013	NONE	

CN 102757447 A	31-10-2012	NONE	

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WO 2013123071 A1	22-08-2013	NONE	

WO 2014116859 A1	31-07-2014	NONE	
