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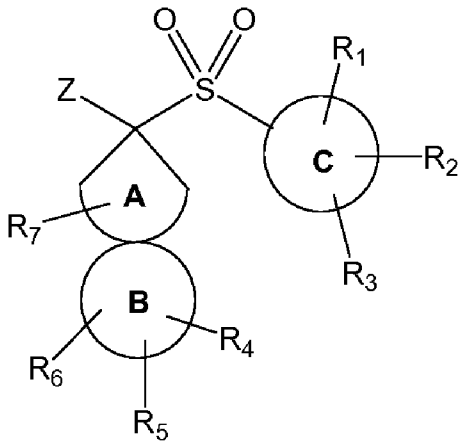

(I)

(57) Abstract: It relates to spirocyclic compounds of formula (I), or pharmaceutically or veterinary acceptable salts thereof, or any stereoisomers either of the compounds of formula (I) or of their pharmaceutically or veterinary acceptable salts, wherein A and B form a spirocyclic ring system wherein the spiro atom connecting A and B is a carbon atom and wherein A is a known 3-to 8-membered carbocyclic or heterocyclic monocyclic ring or a known 6-to 18- membered carbocyclic or heterocyclic polycyclic ring system; B is a known 4- to 7-membered carbocyclic or heterocyclic monocyclic ring; C is phenyl or a known 5-to 6-membered heteroaromatic ring; and Z and R^1-R^7 are as defined herein. It also relates to pharmaceutical or veterinary compositions containing them, and to their use in medicine, in particular as antifibrinolytic and antihemorrhagic agents.

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New antifibrinolytic compounds

The present invention relates to spirocyclic compounds of formula (I), to a process for their preparation, as well as to the intermediates used in this process. It also relates to pharmaceutical or veterinary compositions containing them, and to their use in medicine, in particular as antifibrinolytic and antihemorrhagic agents.

BACKGROUND ART

The haemostatic system is responsible for maintaining circulatory fluidity and for preventing haemorrhage in response to vascular injury. Physiological hemostasis is controlled by mechanisms of coagulation and the formation of fibrin and by those favouring the degradation of fibrin (fibrinolysis).

Hyperfibrinolytic states caused by congenital or acquired conditions predispose to important haemorrhagic complications, often requiring transfusions and the need for re-exploration having a detrimental effect on patient outcome. Hemorhage is responsible for almost 50% of deaths occurring within 24 hours of traumatic injury and for up to 80% of intraoperative trauma mortality. In western countries about one third of in-hospital deaths due to trauma is caused by abnormal blood loss which is an important contributory factor for other causes of death, particularly multi-organ failure, requiring massive blood transfusion. Failure to start appropriate early management in bleeding trauma patients is a leading cause of preventable death from trauma. Post-partum hemorrhage (PPH) is another leading cause of death in the developing world, accounting for 25% of maternal deaths, and rose in the the developed world from 1.5% in 1999 to 4.1% in 2009. The risk of haemorrhage can also be important in cardiovascular patients on anti-coagulant therapy. Pharmacological approaches are an important part of multimodal therapy aiming to reducing bleeding and transfusion in order to reverse specific defects associated with such states; among them, the role of fibrinolysis inhibitors is growing.

It is well known that subjects who bleed excessively in association with surgery or major trauma and need blood transfusions develop more complications than those who do not experience any bleeding. However,

moderate bleeding requiring the administration of human blood products may lead to complications associated with the risk of transferring human viruses. Extensive bleeding requiring massive blood transfusions may lead to the development of multiple organ failure including lung or kidney function. Therefore, a major goal in surgery as well as in the treatment of major tissue damage is to avoid or minimise bleeding in order to ensure the formation of stable and solid haemostatic plugs that are not easily dissolved by fibrinolytic enzymes. Furthermore, it is of importance to ensure quick and effective formation of such plugs or clots.

Antifibrinolytic agents are widely used in major surgery to prevent fibrinolysis and reduce blood loss. Currently two synthetic lysine analogs, epsilon-aminocaproic acid (EACA) and tranexamic acid (TXA), are the only antifibrinolytics commercially avaliable to control bleeding. These agents competitively inhibit activation of plasminogen to plasmin, an enzyme that degrades fibrin clots, fibrinogen and other plasma proteins.
However, there are some concerns with these currently available antifibrinolytic agents due to the potential risk of thrombotic complications.

Peiqiang Huang, *et al.,* Synthetic Communications, 1991, 21 (22), 2369-2376 Describes the chemical synthesis of the compound 1-[7-(phenylsulfonyl)-1,4-dioxaspiro[4.5]dec-7-yl]-2-propen-1-one. Any use of this compound is not disclosed.

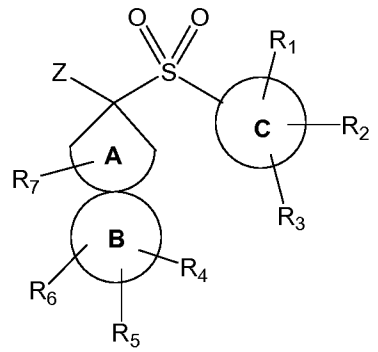
There is still a need for improved treatment of subjects experiencing bleeding episodes, including those due to surgery, trauma, or other forms of tissue damage, as well as in clinical scenarios characterized by excessive fibrinolysis.

SUMMARY OF THE INVENTION

Inventors have conceived and produced a novel series of spirocyclic compounds that shows good antifibrinolytic and antihemorrhagic properties. In particular, the spirocyclic compounds which comprise spirocyclic ring system containing a carbon atom (spiro atom) attached to Z and a sulfonyl group, show a significant delay in the lysis time in a thromboelastometry assay. In addition, the spirocyclic compounds of the invention also show an important

reduction of the bleeding time in vivo animal models as it will be shown in detail in the examples. These characteristics of the compounds of the invention allow a rapid cessation of hemorrhage; favor an effective formation of plugs or clots; have a sustained action (persistence of the clot and prevention of hemorrhage) and aid in minimizing the adverse effects related to other antifibrinolytic/antihemorrhagic treatments having risk of thrombotic complications.

Therefore, a first aspect of the invention relates to a compound of formula (I), or a pharmaceutically or veterinary acceptable salt thereof, or any stereoisomer either of the compound of formula (I) or of its pharmaceutically or veterinary acceptable salt



(I)

wherein

A and B form a spirocyclic ring system wherein the spiro atom connecting A and B is a carbon atom and wherein

A is a known 3- to 8-membered carbocyclic or heterocyclic monocyclic ring, saturated or partially unsaturated; or alternatively

A is a known 6- to 18-membered carbocyclic or heterocyclic polycyclic ring system, saturated, partially unsaturated, or partially aromatic; and

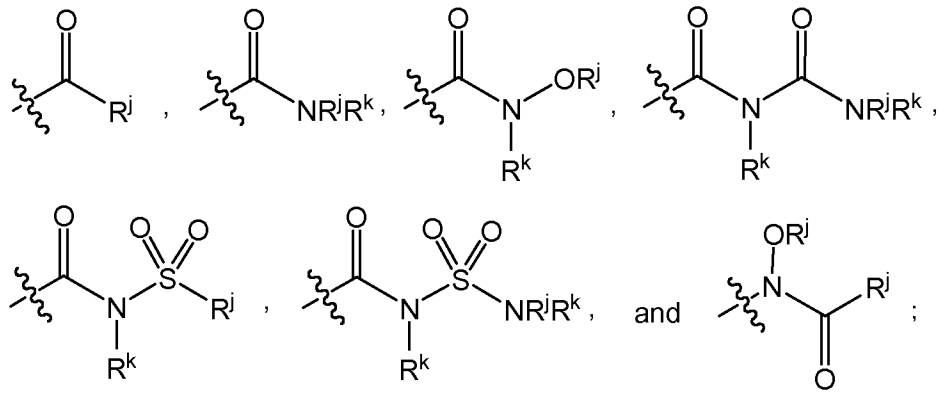
B is a known 4- to 7-membered carbocyclic or heterocyclic monocyclic ring, saturated or partially unsaturated;

C is phenyl or a known 5- to 6-membered heteroaromatic ring;

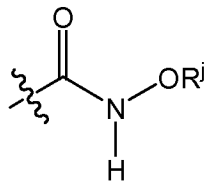
R_1-R_3 are independently selected from H, halogen, -NO_2, -CN, R^a, -$OR^{a'}$, -$OC(Y)R^{a'}$, -$OC(Y)OR^{a'}$, -$OC(Y)NR^bR^{a'}$, -$OSO_2OR^{a'}$, -$NR^bR^{a'}$, -$NR^bC(Y)R^{a'}$, -$NR^bC(Y)OR^{a'}$, -$NR^bC(Y)NR^bR^{a'}$, -$NR^bS(O)_2R^{a'}$, -$NR^bSO_2NR^bR^{a'}$, -$SR^{a'}$, -$S(O)R^{a'}$, -$S(O)OR^{a'}$, -$SO_2R^{a'}$,-$SO_2(OR^{a'})$, -$SO_2NR^bR^{a'}$, -$SC(Y)NR^bR^{a'}$, -$C(Y)R^{a'}$, -$C(Y)OR^{a'}$, -$C(Y)NR^bR^{a'}$, -$C(Y)NR^bOR^{a'}$, and -$C(O)NR^bSO_2R^{a'}$;

R_4-R_7 are independently selected from halogen, -NO_2, -CN, R^c, -OR^c, -NR^dR^c, -$NR^dC(Y)R^c$, -$NR^dC(Y)OR^c$, -$NR^dC(Y)NR^dR^c$, -$NR^dS(O)_2R^c$, -$NR^dSO_2NR^dR^c$, -SR^c, -$S(O)R^c$, -$S(O)OR^c$, -SO_2R^c, -$SO_2R(OR^c)$, -$SO_2NR^dR^c$, -$SC(Y)NR^dR^c$, -$C(Y)R^c$, -$C(Y)OR^c$, -$C(Y)NR^dR^c$, -$C(Y)NR^dOR^c$,and -$C(O)NR^dSO_2R^c$;

Z is selected from the group consisting of R^j, -C(O)OPh,



with the proviso that Z is other than



R^a is a saturated or unsaturated (C_1-C_{12})alkyl optionally substituted with one or more substituents R^e and/or one Cy^1; or alternatively R^a is Cy^2;
wherein Cy^1 and Cy^2 are independently optionally substituted with: one Cy^3 and/or one or more substituents R^e, and/or one or more saturated or unsaturated (C_1-C_6)alkyl groups optionally substituted with one or more substituents R^e and/or one Cy^3; and
wherein any Cy^3 is optionally substituted with one or more substituents independently selected from R^e and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more substituents R^e;

each $R^{a'}$ and R^b are independently H or R^a;

R^c and each R^d are independently selected from H, Cy^4, and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more substituents R^h and/or one Cy^5;
wherein Cy^4 and Cy^5 are optionally substituted with one or more substituents independently selected from R^h and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more substituents R^h;

each R^e is independently selected from halogen, $-NO_2$, -CN, $-OR^f$, $-OC(Y)R^f$, $-OC(Y)OR^f$, $-OC(Y)NR^gR^f$, $-NR^gR^f$, $-NR^gC(Y)R^f$, $-NR^gC(Y)OR^f$, $-NR^gC(Y)NR^gR^f$, $-NR^gS(O)_2R^f$, $-NR^gSO_2NR^gR^f$, $-SR^f$, $-S(O)R^f$, $-S(O)OR^f$, $-SO_2R^f$, $-SO_2(OR^f)$, $-SO_2NR^gR^f$, $-SC(Y)NR^gR^f$, $-C(Y)R^f$, $-C(Y)OR^f$, $-C(Y)NR^gR^f$, $-C(Y)NR^gOR^f$ and $-C(O)NR^gSO_2R^f$;

R^f and each R^g are independently selected from H, Cy^6, and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more substituents R^h and/or one Cy^7;
wherein Cy^6 is optionally substituted with: one Cy^7, and/or one or more substituents R^h, and/or one or more saturated or unsaturated (C_1-C_6)alkyl groups optionally substituted with one or more substituents R^h and/or one Cy^7; and
wherein any Cy^7 is optionally substituted with one or more substituents independently selected from R^h and (C_1-C_4)alkyl optionally substituted with one or more substituents R^h;

each R^h is independently selected from halogen, $-NO_2$, -CN, $-OR^i$, $-OC(O)R^i$, $-OC(O)OR^i$, $-OC(O)NR^iR^i$, $-NR^iR^i$, $-NR^iC(O)R^i$, $-NR^iC(O)OR^i$, $-NR^iC(O)NR^iR^i$, $-NR^iS(O)_2R^i$, $-NR^iSO_2NR^iR^i$, $-SR^i$, $-S(O)R^i$, $-SO_2R^i$, $-SO_2(OR^i)$, $-SO_2NR^iR^i$, $-C(O)R^i$, $-C(O)OR^i$, $-C(O)NR^iR^i$, and $-C(O)NR^iOR^i$;

each R^i is independently H or -(C_1-C_4)alkyl optionally substituted with one or more halogen atoms;

R^j and each R^k are independently selected from H, Cy^8, and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more substituents R^h and/or one Cy^9;

wherein Cy^8 is optionally substituted with one or more substituents independently selected from R^h, Cy^9, and saturated or unsaturated $(C_1\text{-}C_6)$alkyl optionally substituted with one or more substituents R^h; and wherein Cy^9 is optionally substituted with one or more substituents independently selected from R^h and saturated or unsaturated $(C_1\text{-}C_6)$alkyl optionally substituted with one or more substituents R^h;

Y is O, S, or NR^g;

Cy^1, Cy^2, Cy^4 and Cy^6 are independently a C or N-attached known ring system selected from 3- to 8-membered carbocyclic or heterocyclic monocyclic ring, saturated or partially unsaturated; phenyl; 5- or 6-membered heteroaromatic ring; and 6- to 18-membered carbocyclic or heterocyclic polycyclic ring system, saturated, partially unsaturated, aromatic or partially aromatic;

Cy^3, Cy^5, Cy^7, Cy^8 and Cy^9 are independently a C or N-attached known ring system selected from 3- to 8-membered carbocyclic or heterocyclic monocyclic ring, saturated or partially unsaturated; phenyl; and 5- or 6-membered heteroaromatic ring;

wherein in the carbocyclic rings all ring members are carbon atoms; and in the heterocyclic and heteroaromatic rings one or more ring members are selected from N, O, and S; and wherein in all saturated or partially unsaturated rings one or two members of the rings are optionally C(O) and/or C(NH) and/or C[N$(C_1\text{-}C_4)$alkyl];

with the proviso that the compound of formula (I) is other than 1-[7-(phenylsulfonyl)-1,4-dioxaspiro[4.5]dec-7-yl]-2-propen-1-one.

Another aspect of the invention relates to a pharmaceutical or veterinary composition which comprises an effective amount of a compound of formula (I) as defined above, or a pharmaceutically or veterinary acceptable salt thereof, or any stereoisomer either of the compound of formula (I) or of its pharmaceutically or veterinary acceptable salt, together with one or more pharmaceutically or veterinary acceptable excipients or carriers.

As previously described, the compounds of the invention are useful as antifibrinolytic and antihemorrhagic agents. Therefore, another aspect of the invention relates to a compound of formula (I) as defined above, or a pharmaceutically or veterinary acceptable salt thereof, or any stereoisomer either of the compound of formula (I) or of its pharmaceutically or veterinary acceptable salt, for use as a medicament.

Another aspect of the invention relates to a compound of formula (I) as defined above, or a pharmaceutically or veterinary acceptable salt thereof, or any stereoisomer either of the compound of formula (I) or of its pharmaceutically or veterinary acceptable salt, for use as antifibrinolytic and antihemorrhagic agent. Thus, this aspect relates to the use of a compound of formula (I) as defined above, or a pharmaceutically or veterinary acceptable salt thereof, or any stereoisomer either of the compound of formula (I) or of its pharmaceutically or veterinary acceptable salt, for the manufacture of a medicament for use as antifibrinolytic and antihemorrhagic agent; and may also be formulated as a method for the treatment and/or prevention of hyperfibrinolysis and/or hemorrhages comprising administering an effective amount of the previously defined compound of formula (I), or a pharmaceutically or veterinary acceptable salt thereof, or any stereoisomer either of the compound of formula (I) or of its pharmaceutically or veterinary acceptable salt, and one or more pharmaceutically or veterinary acceptable excipients or carriers, in a subject in need thereof, including a human.

DETAILED DESCRIPTION OF THE INVENTION

All terms as used herein in this application, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. Other more specific definitions for certain terms as used in the present application are as set forth below and are intended to apply uniformly through-out the specification and claims unless an otherwise expressly set out definition provides a broader definition.

For the purposes o the present invention, in the spirocyclic ring system formed by the ring system A and ring system B, the spiro atom connecting A and B is a carbon atom.

The term “carbocyclic” ring system refers to a known ring system wherein all the ring members are carbon atoms. The term “heterocyclic” ring system refers to a known ring system wherein one or more of the ring members, preferably 1, 2, 3, or 4 ring members, are selected from N, O, and S, where chemically possible. Unless otherwise specified, the “heterocyclic” ring system may be attached to the rest of the molecule through a C or a N atom. Both the carbocyclic and heterocyclic rings can be saturated or partially unsaturated, and may be unsubstituted or substituted as described herein, being the susbstituents placed on any available position.

According to the present invention, the term "polycyclic" ring refers to a ring system which is formed by two, three or four rings which can be fused, bridged-fused, spiro-fused or can contain different types of fusion. For the purposes of the present invention, in "fused" rings the fusion occurs through one bond which is common to two adjoining rings; in "bridged-fused" rings the fusion occurs through a sequence of atoms (bridgehead) which is common to two rings; and in "spiro-fused" rings, the fusion occurs through only one atom (spiro atom), preferably a carbon atom, which is common to two adjoining rings (including bridged rings).

The polycyclic ring system can be saturated, partially unsaturated, aromatic (except in the case of ring system A) or partially aromatic; and may be unsubstituted or substituted as described herein, being the susbstituents placed on any available position.

The term "heteroaromatic" ring refers to a known aromatic ring system, wherein one or more of the ring members, preferably 1, 2, 3, or 4 ring members, are selected from N, O, and S where chemically possible. The heteroaromatic ring and phenyl may be unsubstituted or substituted as described herein, being the susbstituents placed on any available position.

The term "known" ring system as used herein refers to a ring system which is chemically feasible and is known in the art and so intends to exclude those ring systems that are not chemically possible.

For the purposes of the present invention, in all saturated or partially unsaturated rings, one or two members of the rings are optionally C(O) and/or C(NH) and/or C[N(C_1-C_4)alkyl].

The term saturated or unsaturated (C_1-C_n)alkyl refers to a saturated branched or linear hydrocarbon chain which contains from 1 to n carbon atoms. When the (C_1-C_n)alkyl is saturated it contains only single bonds. When the (C_1-C_n)alkyl is unsaturated it contains one or two double bonds and/or one or two triple bonds. The saturated or unsaturated (C_1-C_n)alkyl may be substituted or unsubstituted as described herein.

A halogen substituent means fluoro, chloro, bromo or iodo.

In the embodiments of the invention referring to the compounds of formula (I), where the substitution or unsubstitution of a certain group is not specified, e.g. either by indicating a certain substitution for that group or by indicating that the group is unsubstituted, it has to be understood that the possible substitution of this group is the one as in the definition of formula (I).

"Protective group" (PG) refers to a grouping of atoms that when attached to a reactive group in a molecule masks, reduces or prevents that reactivity.

The expression “substituted with one or more" means that a group can be substituted with one or more, preferably with 1, 2, 3 or 4 substituents, provided that this group has enough positions susceptible of being substituted.

For the purposes of the invention, room temperature is 20-25 ºC.

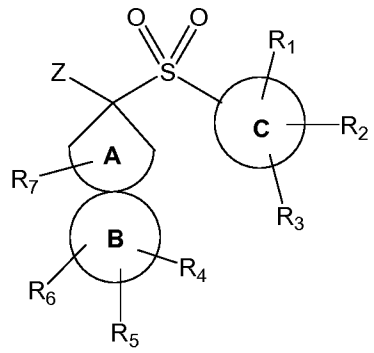
As mentioned above, a first aspect of the invention relates to compounds of formula (I) or pharmaceutically or veterinary acceptable salts thereof, or any stereoisomer either of the compound of formula (I) or of its pharmaceutically or veterinary acceptable salt. There is no limitation on the type of salt that can be used, provided that these are pharmaceutically or veterinary acceptable when they are used for therapeutic purposes. The term "pharmaceutically or veterinary acceptable salts", embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases.

The preparation of pharmaceutically or veterinary acceptable salts of the compounds of formula (I) can be carried out by methods known in the art. For instance, they can be prepared from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods. Generally, such salts are, for example, prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate pharmaceutically or veterinary acceptable base or acid in water or in an organic solvent or in a mixture of them. The compounds of formula (I) and their salts may differ in some physical properties but they are equivalent for the purposes of the present invention.

The compounds of the invention may be in crystalline form either as free solvation compounds or as solvates (e.g. hydrates) and it is intended that both forms are within the scope of the present invention. Methods of solvation are generally known within the art. In general, the solvated forms with pharmaceutically or veterinary acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated form for the purposes of the invention.

Some compounds of formula (I) can have chiral centres that can give rise to various stereoisomers. The present invention relates to each of these stereoisomers and also mixtures thereof. Moreover, some of the compounds of the present invention can show cis/trans isomers. The present invention relates to each of the geometric isomers and mixtures thereof.

Diastereoisomers can be separated by conventional techniques such as chromatography or fractional crystallization. Optical isomers can be resolved by conventional techniques of optical resolution to give optically pure isomers. This resolution can be carried out on any chiral synthetic intermediate or on products of general formula (I). Optically pure isomers can also be individually obtained using enantiospecific synthesis.
In one embodiment, optionally in combination with any of the embodiments of the invention, the invention relates to a compound of formula (I), or a pharmaceutically or veterinary acceptable salt thereof, or any stereoisomer either of the compound of formula (I) or of its pharmaceutically or veterinary acceptable salt



(I)

wherein

A and B form a spirocyclic ring system wherein the spiro atom connecting A and B is a carbon atom and wherein

A is a known 3- to 8-membered carbocyclic or heterocyclic monocyclic ring, saturated or partially unsaturated; or alternatively

A is a known 6- to 18-membered carbocyclic or heterocyclic polycyclic ring system, saturated, partially unsaturated, or partially aromatic; and

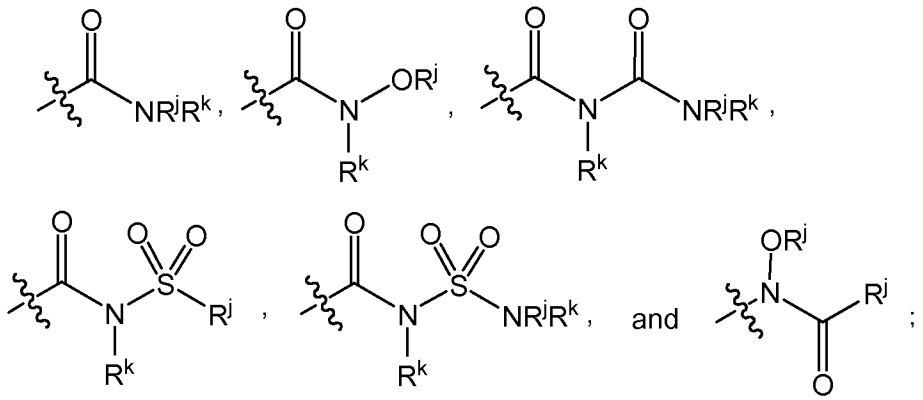
B is a known 4- to 7-membered carbocyclic or heterocyclic monocyclic ring, saturated or partially unsaturated;

C is phenyl or a known 5- to 6-membered heteroaromatic ring;

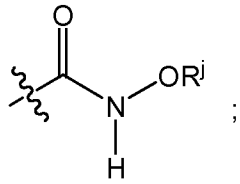
R_1-R_3 are independently selected from H, halogen, -NO_2, -CN, R^a, -$OR^{a'}$, -$OC(Y)R^{a'}$, -$OC(Y)OR^{a'}$, -$OC(Y)NR^bR^{a'}$, -$OSO_2OR^{a'}$, -$NR^bR^{a'}$, -$NR^bC(Y)R^{a'}$, -$NR^bC(Y)OR^{a'}$, -$NR^bC(Y)NR^bR^{a'}$, -$NR^bS(O)_2R^{a'}$, -$NR^bSO_2NR^bR^{a'}$, -$SR^{a'}$, -$S(O)R^{a'}$, -$S(O)OR^{a'}$, -$SO_2R^{a'}$,-$SO_2(OR^{a'})$, -$SO_2NR^bR^{a'}$, -$SC(Y)NR^bR^{a'}$, -$C(Y)R^{a'}$, -$C(Y)OR^{a'}$, -$C(Y)NR^bR^{a'}$, -$C(Y)NR^bOR^{a'}$, and -$C(O)NR^bSO_2R^{a'}$;

R_4-R_7 are independently selected from halogen, -NO_2, -CN, R^c, -OR^c, -NR^dR^c, -$NR^dC(Y)R^c$, -$NR^dC(Y)OR^c$, -$NR^dC(Y)NR^dR^c$, -$NR^dS(O)_2R^c$, -$NR^dSO_2NR^dR^c$, -SR^c, -$S(O)R^c$, -$S(O)OR^c$, -SO_2R^c, -$SO_2R(OR^c)$, -$SO_2NR^dR^c$, -$SC(Y)NR^dR^c$, -$C(Y)R^c$, -$C(Y)OR^c$, -$C(Y)NR^dR^c$, -$C(Y)NR^dOR^c$,and -$C(O)NR^dSO_2R^c$;

Z is selected from the group consisting of R^j, -C(O)OPh,



with the proviso that Z is other than



R^a is a saturated or unsaturated (C_1-C_{12})alkyl optionally substituted with one or more substituents R^e and/or one Cy^1; or alternatively R^a is Cy^2;
wherein Cy^1 and Cy^2 are independently optionally substituted with: one Cy^3 and/or one or more substituents R^e, and/or one or more saturated or unsaturated (C_1-C_6)alkyl groups optionally substituted with one or more substituents R^e and/or one Cy^3; and
wherein any Cy^3 is optionally substituted with one or more substituents independently selected from R^e and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more substituents R^e;

each $R^{a'}$ and R^b are independently H or R^a;

R^c and each R^d are independently selected from H, Cy^4, and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more substituents R^h and/or one Cy^5;
wherein Cy^4 and Cy^5 are optionally substituted with one or more substituents independently selected from R^h and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more substituents R^h;

each R^e is independently selected from halogen, $-NO_2$, -CN, $-OR^f$, $-OC(Y)R^f$, $-OC(Y)OR^f$, $-OC(Y)NR^gR^f$, $-NR^gR^f$, $-NR^gC(Y)R^f$, $-NR^gC(Y)OR^f$, $-NR^gC(Y)NR^gR^f$, $-NR^gS(O)_2R^f$, $-NR^gSO_2NR^gR^f$, $-SR^f$, $-S(O)R^f$, $-S(O)OR^f$, $-SO_2R^f$, $-SO_2(OR^f)$,

$-SO_2NR^gR^f$, $-SC(Y)NR^gR^f$, $-C(Y)R^f$, $-C(Y)OR^f$, $-C(Y)NR^gR^f$, $-C(Y)NR^gOR^f$ and $-C(O)NR^gSO_2R^f$;

R^f and each R^g are independently selected from H, Cy^6, and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more substituents R^h and/or one Cy^7;
wherein Cy^6 is optionally substituted with: one Cy^7, and/or one or more substituents R^h, and/or one or more saturated or unsaturated (C_1-C_6)alkyl groups optionally substituted with one or more substituents R^h and/or one Cy^7; and
wherein any Cy^7 is optionally substituted with one or more substituents independently selected from R^h and (C_1-C_4)alkyl optionally substituted with one or more substituents R^h;

each R^h is independently selected from halogen, $-NO_2$, -CN, $-OR^i$, $-OC(O)R^i$, $-OC(O)OR^i$, $-OC(O)NR^iR^i$, $-NR^iR^i$, $-NR^iC(O)R^i$, $-NR^iC(O)OR^i$, $-NR^iC(O)NR^iR^i$, $-NR^iS(O)_2R^i$, $-NR^iSO_2NR^iR^i$, $-SR^i$, $-S(O)R^i$, $-SO_2R^i$, $-SO_2(OR^i)$, $-SO_2NR^iR^i$, $-C(O)R^i$, $-C(O)OR^i$, $-C(O)NR^iR^i$, and $-C(O)NR^iOR^i$;

each R^i is independently H or $-(C_1-C_4)$alkyl optionally substituted with one or more halogen atoms;

R^j and each R^k are independently selected from H, Cy^8, and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more substituents R^h and/or one Cy^9;
wherein Cy^8 is optionally substituted with one or more substituents independently selected from R^h, Cy^9, and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more substituents R^h; and
wherein Cy^9 is optionally substituted with one or more substituents independently selected from R^h and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more substituents R^h;

Y is O, S, or NR^g;

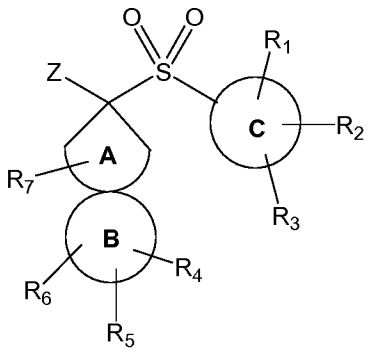
Cy^1, Cy^2, Cy^4 and Cy^6 are independently a C or N-attached known ring system selected from 3- to 8-membered carbocyclic or heterocyclic monocyclic ring, saturated or partially unsaturated; phenyl; 5- or 6-membered heteroaromatic

ring; and 6- to 18-membered carbocyclic or heterocyclic polycyclic ring system, saturated, partially unsaturated, aromatic or partially aromatic;

Cy^3, Cy^5, Cy^7, Cy^8 and Cy^9 are independently a C or N-attached known ring system selected from 3- to 8-membered carbocyclic or heterocyclic monocyclic ring, saturated or partially unsaturated; phenyl; and 5- or 6-membered heteroaromatic ring; and

wherein in the carbocyclic rings all ring members are carbon atoms; and in the heterocyclic and heteroaromatic rings one or more ring members are selected from N, O, and S; and wherein in all saturated or partially unsaturated rings one or two members of the rings are optionally C(O) and/or C(NH) and/or C[N(C_1-C_4)alkyl].

The invention also relates to a compound of formula (I), or a pharmaceutically or veterinary acceptable salt thereof, or any stereoisomer either of the compound of formula (I) or of its pharmaceutically or veterinary acceptable salt

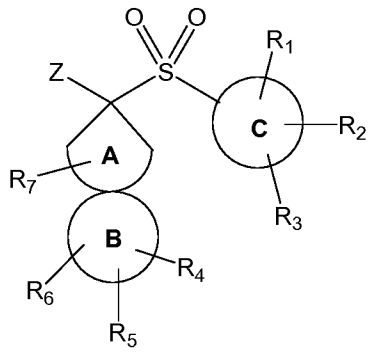


(I)

wherein A, B, C, R_1-R_7 are as defined above and Z is -C(O)OCy^{10}, wherein Cy^{10} is a Cy^8 as defined above with the proviso that Cy^{10} is not p-methoxyphenyl. More particularly, Cy^{10} is selected from phenyl and 5- or 6-membered heteroaromatic ring and may be optionally substituted as defined above with the proviso that Cy^{10} is not p-methoxyphenyl.

In another embodiment, optionally in combination with any of the embodiments of the invention, the invention relates to a compound of formula (I), or a pharmaceutically or veterinary acceptable salt thereof, or any

stereoisomer either of the compound of formula (I) or of its pharmaceutically or veterinary acceptable salt



(I)

wherein

A and B form a spirocyclic ring system wherein the spiro atom connecting A and B is a carbon atom and wherein

A is a known 3- to 8-membered carbocyclic or heterocyclic monocyclic ring, saturated or partially unsaturated; or alternatively

A is a known 6- to 18-membered carbocyclic or heterocyclic polycyclic ring system, saturated, partially unsaturated, or partially aromatic; and

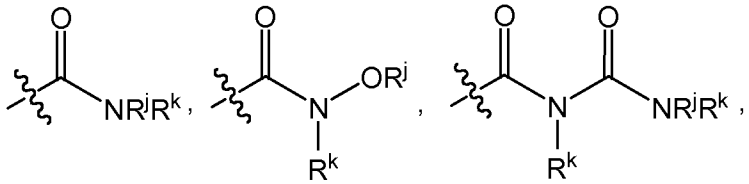
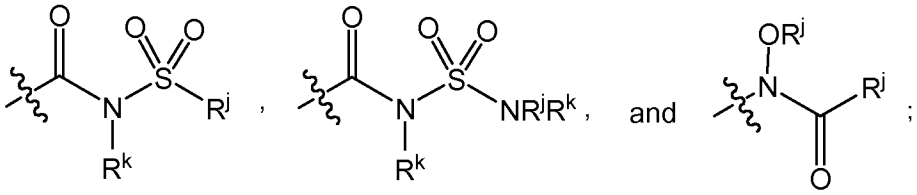
B is a known 4- to 7-membered carbocyclic or heterocyclic monocyclic ring, saturated or partially unsaturated;

C is phenyl or a known 5- to 6-membered heteroaromatic ring;

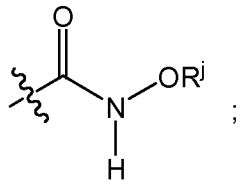
R_1-R_3 are independently selected from H, halogen, -NO_2, -CN, R^a, -$OR^{a'}$, -$OC(Y)R^{a'}$, -$OC(Y)OR^{a'}$, -$OC(Y)NR^bR^{a'}$, -$OSO_2OR^{a'}$, -$NR^bR^{a'}$, -$NR^bC(Y)R^{a'}$, -$NR^bC(Y)OR^{a'}$, -$NR^bC(Y)NR^bR^{a'}$, -$NR^bS(O)_2R^{a'}$, -$NR^bSO_2NR^bR^{a'}$, -$SR^{a'}$, -$S(O)R^{a'}$, -$S(O)OR^{a'}$, -$SO_2R^{a'}$,-$SO_2(OR^{a'})$, -$SO_2NR^bR^{a'}$, -$SC(Y)NR^bR^{a'}$, -$C(Y)R^{a'}$, -$C(Y)OR^{a'}$, -$C(Y)NR^bR^{a'}$, -$C(Y)NR^bOR^{a'}$, and -$C(O)NR^bSO_2R^{a'}$;

R_4-R_7 are independently selected from halogen, -NO_2, -CN, R^c, -OR^c, -NR^dR^c, -$NR^dC(Y)R^c$, -$NR^dC(Y)OR^c$, -$NR^dC(Y)NR^dR^c$, -$NR^dS(O)_2R^c$, -$NR^dSO_2NR^dR^c$, -SR^c, -$S(O)R^c$, -$S(O)OR^c$, -SO_2R^c, -$SO_2R(OR^c)$, -$SO_2NR^dR^c$, -$SC(Y)NR^dR^c$, -$C(Y)R^c$, -$C(Y)OR^c$, -$C(Y)NR^dR^c$, -$C(Y)NR^dOR^c$,and -$C(O)NR^dSO_2R^c$;

Z is selected from the group consisting of R^j

with the proviso that Z is other than



R^a is a saturated or unsaturated (C_1-C_{12})alkyl optionally substituted with one or more substituents R^e and/or one Cy^1; or alternatively R^a is Cy^2;
wherein Cy^1 and Cy^2 are independently optionally substituted with: one Cy^3 and/or one or more substituents R^e, and/or one or more saturated or unsaturated (C_1-C_6)alkyl groups optionally substituted with one or more substituents R^e and/or one Cy^3; and
wherein any Cy^3 is optionally substituted with one or more substituents independently selected from R^e and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more substituents R^e;

each $R^{a'}$ and R^b are independently H or R^a;

R^c and each R^d are independently selected from H, Cy^4, and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more substituents R^h and/or one Cy^5;
wherein Cy^4 and Cy^5 are optionally substituted with one or more substituents independently selected from R^h and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more substituents R^h;

each R^e is independently selected from halogen, $-NO_2$, -CN, $-OR^f$, $-OC(Y)R^f$, $-OC(Y)OR^f$, $-OC(Y)NR^gR^f$, $-NR^gR^f$, $-NR^gC(Y)R^f$, $-NR^gC(Y)OR^f$, $-NR^gC(Y)NR^gR^f$,

$-NR^gS(O)_2R^f$, $-NR^gSO_2NR^gR^f$, $-SR^f$, $-S(O)R^f$, $-S(O)OR^f$, $-SO_2R^f$, $-SO_2(OR^f)$, $-SO_2NR^gR^f$, $-SC(Y)NR^gR^f$, $-C(Y)R^f$, $-C(Y)OR^f$, $-C(Y)NR^gR^f$, $-C(Y)NR^gOR^f$ and $-C(O)NR^gSO_2R^f$;

R^f and each R^g are independently selected from H, Cy^6, and saturated or unsaturated $(C_1$-$C_6)$alkyl optionally substituted with one or more substituents R^h and/or one Cy^7;
wherein Cy^6 is optionally substituted with: one Cy^7, and/or one or more substituents R^h, and/or one or more saturated or unsaturated $(C_1$-$C_6)$alkyl groups optionally substituted with one or more substituents R^h and/or one Cy^7; and
wherein any Cy^7 is optionally substituted with one or more substituents independently selected from R^h and $(C_1$-$C_4)$alkyl optionally substituted with one or more substituents R^h;

each R^h is independently selected from halogen, $-NO_2$, -CN, $-OR^i$, $-OC(O)R^i$, $-OC(O)OR^i$, $-OC(O)NR^iR^i$, $-NR^iR^i$, $-NR^iC(O)R^i$, $-NR^iC(O)OR^i$, $-NR^iC(O)NR^iR^i$, $-NR^iS(O)_2R^i$, $-NR^iSO_2NR^iR^i$, $-SR^i$, $-S(O)R^i$, $-SO_2R^i$, $-SO_2(OR^i)$, $-SO_2NR^iR^i$, $-C(O)R^i$, $-C(O)OR^i$, $-C(O)NR^iR^i$, and $-C(O)NR^iOR^i$;

each R^i is independently H or $-(C_1$-$C_4)$alkyl optionally substituted with one or more halogen atoms;

R^j and each R^k are independently selected from H, Cy^8, and saturated or unsaturated $(C_1$-$C_6)$alkyl optionally substituted with one or more substituents R^h and/or one Cy^9;
wherein Cy^8 is optionally substituted with one or more substituents independently selected from R^h, Cy^9, and saturated or unsaturated $(C_1$-$C_6)$alkyl optionally substituted with one or more substituents R^h; and
wherein Cy^9 is optionally substituted with one or more substituents independently selected from R^h and saturated or unsaturated $(C_1$-$C_6)$alkyl optionally substituted with one or more substituents R^h;

Y is O, S, or NR^g;

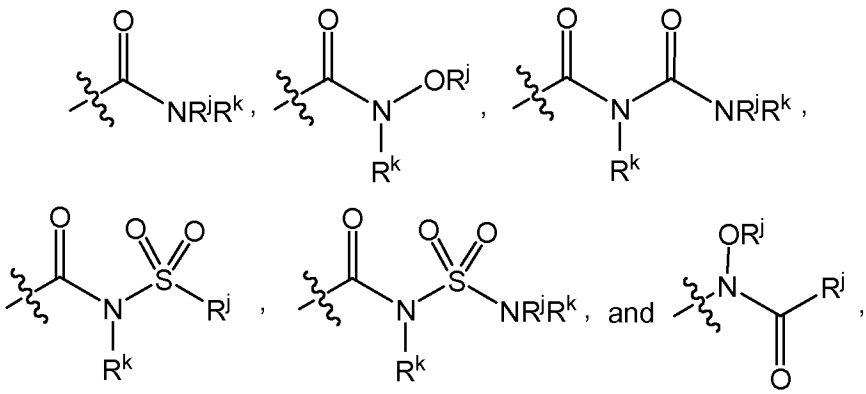
Cy^1, Cy^2, Cy^4 and Cy^6 are independently a C or N-attached known ring system selected from 3- to 8-membered carbocyclic or heterocyclic monocyclic ring,

saturated or partially unsaturated; phenyl; 5- or 6-membered heteroaromatic ring; and 6- to 18-membered carbocyclic or heterocyclic polycyclic ring system, saturated, partially unsaturated, aromatic or partially aromatic;

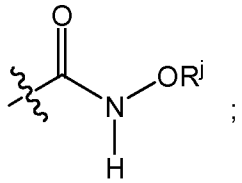
Cy^3, Cy^5, Cy^7, Cy^8 and Cy^9 are independently a C or N-attached known ring system selected from 3- to 8-membered carbocyclic or heterocyclic monocyclic ring, saturated or partially unsaturated; phenyl; and 5- or 6-membered heteroaromatic ring; and

wherein in the carbocyclic rings all ring members are carbon atoms; and in the heterocyclic and heteroaromatic rings one or more ring members are selected from N, O, and S; and wherein in all saturated or partially unsaturated rings one or two members of the rings are optionally C(O) and/or C(NH) and/or C[N(C_1-C_4)alkyl].

In one embodiment, optionally in combination with any of the embodiments of the invention, Z is selected from the group consisting of R^j,



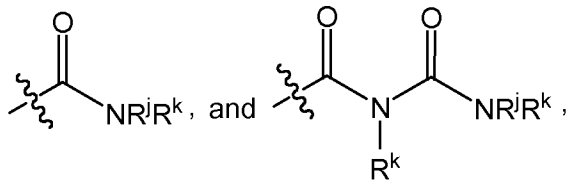
with the proviso that Z is other than



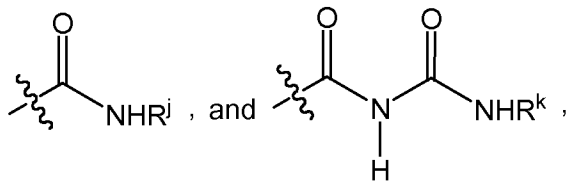
;

wherein R^k is H or -(C_1-C_4)alkyl optionally substituted with one or more halogen atoms.

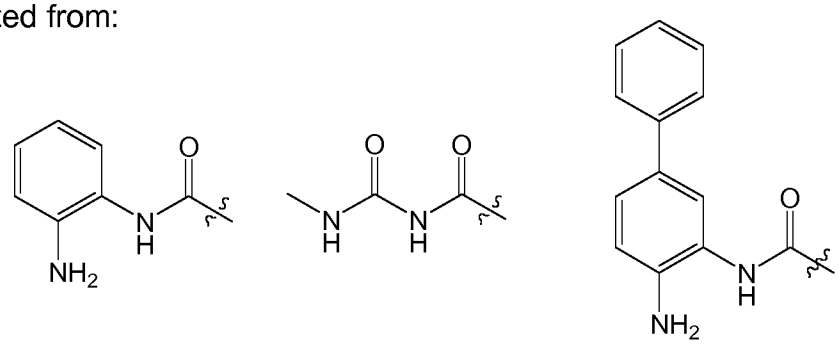
In another embodiment, optionally in combination with any of the embodiments below, the invention refers to a compound of formula (I) as previously defined, wherein Z is selected from the group consisting of



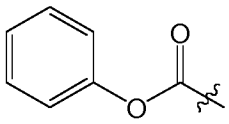
more particularly Z is selected from the group consisting of



wherein R^j and R^k are independently selected from Cy^8, and saturated or unsaturated $(C_1\text{-}C_6)$alkyl; more particulary R^j is Cy^8, more particularly phenyl, and R^k is saturated or unsaturated $(C_1\text{-}C_6)$alkyl. Even more particularly Z is selected from:



In another embodiment, optionally in combination with any of the embodiments of the invention, Z is -C(O)OPh, i.e.:



In another embodiment, optionally in combination with any of the embodiments above or below, the invention refers to a compound of formula (I) as defined above, wherein A is a known 3- to 8-membered carbocyclic or heterocyclic monocyclic ring or a known 6- to 10-membered carbocyclic or heterocyclic bicyclic ring system.

More particularly, A is a monocyclic ring selected from a 3- to 6-membered carbocyclic ring, and a 5- to 6-membered heterocyclic ring.

In another embodiment, optionally in combination with any of the embodiments above or below, A is a carbocyclic monocyclic ring; or a polycyclic ring system, preferably a bicyclic ring system, wherein the ring containing the spiro atom attached to Z and the sulfonyl group is a carbocyclic ring.

In another embodiment, optionally in combination with any of the embodiments above or below, A is selected from cyclopropane, cyclobutane, cyclopentane, cyclohexane, tetrahydrofuran, pyrrolidine, bicyclo[2.2.1]heptane, 2,3-dihydro-1H-indene, hexahydropyrrolizin-3-one, and 4-azaspiro[4.4]nonane.

In another embodiment, optionally in combination with any of the embodiments above or below, A is unsubstituted, i.e. R_7 is H, and more particularly, A is selected from unsubstituted cyclopropane, unsubtituted cyclopentane, and unsubtituted cyclohexane.

In another embodiment, optionally in combination with any of the embodiments above or below, the invention refers to a compound of formula (I) as previously defined, wherein B is a 6- to 7-membered carbocyclic or heterocyclic monocyclic ring.

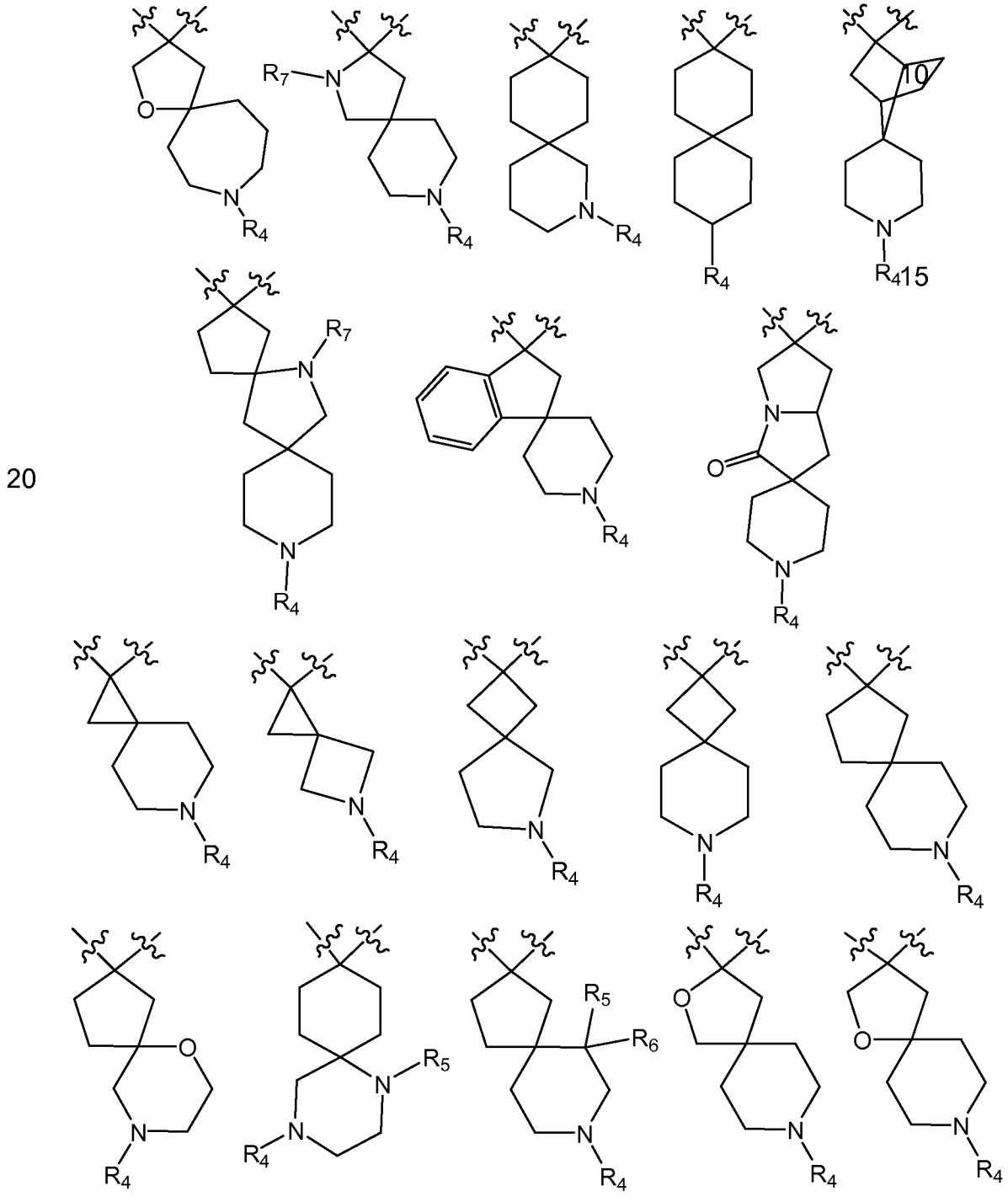
In another embodiment, optionally in combination with any of the embodiments above or below, B is a saturated monocyclic ring, carbocyclic or heterocyclic, wherein at least one of the ring members of the heterocyclic ring is NR_4.

In another embodiment, optionally in combination with any of the embodiments above or below, B is selected from cyclohexane, piperidine, morpholine, azepane, piperazine, pyrrolidine, and azetidine.

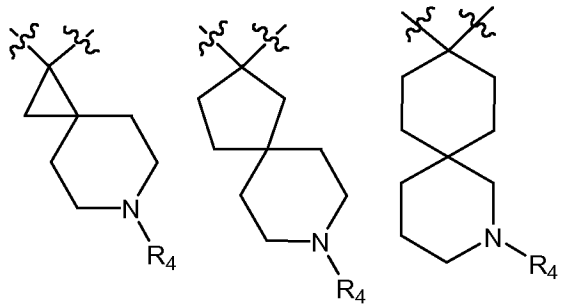
More particularly, B is piperidine, morpholine, azepane, pyrrolidine, and azetidine, even more particularly piperidine, wherein in all these rings one of the ring members is NR_4, wherein R_4 is R^c, more particularly R_4 is H or -

(C_1-C_4)alkyl optionally substituted with one or more halogen atoms, and is placed on the N atom of these rings, and R_5-R_6 are H.

In another embodiment, optionally in combination with any of the embodiments above or below, the invention refers to a compound of formula (I) as previously defined, wherein A and B form a spirocyclic ring system selected from the group consisting of:



More particularly, A and B form a spirocyclic ring system selected from:



wherein R_4 is R^c, more particularly R_4 is H or -(C_1-C_4)alkyl optionally substituted with one or more halogen atoms.

In another embodiment, optionally in combination with any of the embodiments above or below, the invention refers to a compound of formula (I) as previously defined, wherein C is phenyl, more particularly, C is phenyl substituted with R^1 at the orto, meta or para position, and R_2 and R_3 are independently selected from H, halogen, R^a, -$OR^{a'}$,and -$NR^bR^{a'}$; wherein R^a, $R^{a'}$ and R^b in R_2 and R_3 are independently selected from H and -(C_1-C_4)alkyl optionally substituted with one or more halogen atoms. More particularly, C is phenyl substituted with R_1 at the orto, meta or para position and R_2 and R_3 are H.

In another embodiment, optionally in combination with any of the embodiments above or below, C is phenyl substituted with R^1 at the meta position, and R_2 at the para position, R_3 being H, or alternatively, C is phenyl substituted with R^1 at the para position, and R_2 at the meta position, R_3 being H; wherein R_2 is selected from H, halogen, R^a, -$OR^{a'}$,and -$NR^bR^{a'}$; and R^a, $R^{a'}$and R^b in R_2 are independently selected from H and -(C_1-C_4)alkyl optionally substituted with one or more halogen atoms.

In another embodiment, optionally in combination with any of the embodiments above or below, the invention refers to a compound of formula (I) as previously defined, wherein in R^b (relating to R_1-R_3), Cy^1 and Cy^2 are independently optionally substituted with one or more substituents selected from R^e and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more substituents R^e; and Cy^6 is optionally substituted with one or more substituents independently selected from R^h and saturated or

unsaturated (C_1-C_6)alkyl optionally substituted as previously defined, more particularly with one or more substituents R^h.

In a more particular embodiment, optionally in combination with any of the embodiments above or below, the invention refers to a compound of formula (I) as previously defined, wherein R^b (relating to R_1-R_3) is H and saturated or unsaturated (C_1-C_{12})alkyl optionally substituted with one or more substituents R^e; more particularly wherein in R^e, R^f and each R^g are independently selected from H and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more fluorine atoms.

In another embodiment, optionally in combination with any of the embodiments above or below, the invention refers to a compound of formula (I) as previously defined, wherein in R_1-R_3, R^e is selected from halogen, $-NO_2$, -CN, $-OR^f$, $-OC(O)R^f$, $-OC(O)OR^f$, $-OC(O)NR^gR^f$, $-NR^gR^f$, $-NR^gC(O)R^f$, $-NR^gC(O)OR^f$, $-NR^gC(O)NR^gR^f$, $-NR^gS(O)_2R^f$, $-SR^f$, $-S(O)R^f$, $-SO_2R^f$, $-SO_2NR^gR^f$, $-C(O)R^f$, $-C(O)OR^f$, $-C(O)NR^gR^f$, and $-C(O)NR^gOR^f$.

In another embodiment, optionally in combination with any of the embodiments above or below, the invention refers to a compound of formula (I) as previously defined, wherein in R_1-R_3, R^f and each R^g are independently selected from H and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more fluorine atoms.

In another embodiment, optionally in combination with any of the embodiments above or below, the invention refers to a compound of formula (I) as previously defined, wherein in R_1-R_3, Cy^1 and Cy^2 are independently optionally substituted with one or more substituents selected from R^e and saturated or unsaturated (C_1-C_6)alkyl optionally substituted as previously defined; and Cy^6 is optionally substituted with one or more substituents independently selected from R^h and saturated or unsaturated (C_1-C_6)alkyl optionally substituted as previously defined.

In another embodiment, optionally in combination with any of the embodiments above or below, the invention refers to a compound of formula (I) as previously defined, wherein R_1-R_3 are independently selected from H, halogen, $-NO_2$, -CN, R^a, $-OR^{a'}$, $-OC(O)R^{a'}$, $-OC(O)OR^{a'}$, $-OC(O)NR^bR^{a'}$,

$-NR^bR^{a'}$, $-NR^bC(O)R^{a'}$, $-NR^bC(O)OR^{a'}$, $-NR^bC(O)NR^bR^{a'}$, $-NR^bS(O)_2R^{a'}$, $-SR^{a'}$, $-S(O)R^{a'}$, $-SO_2R^{a'}$, $-SO_2NR^bR^{a'}$, $-C(O)R^{a'}$, $-C(O)OR^{a'}$, $-C(O)NR^bR^{a'}$, and $-C(O)NR^bOR^{a'}$.

In another embodiment, optionally in combination with any of the embodiments above or below, the invention refers to a compound of formula (I) as previously defined, wherein in R_4-R_7, R^h is selected from halogen, $-NO_2$, -CN, $-OR^i$, $-OC(O)R^i$, $-OC(O)OR^i$, $-OC(O)NR^iR^i$, $-NR^iR^i$, $-NR^iC(O)R^i$, $-NR^iC(O)OR^i$, $-NR^iC(O)NR^iR^i$, $-NR^iS(O)_2R^i$, $-SR^i$, $-S(O)R^i$, $-SO_2R^i$, $-SO_2NR^iR^i$, $-C(O)R^i$, $-C(O)OR^i$, and $-C(O)NR^iR^i$.

In another embodiment, optionally in combination with any of the embodiments above or below, the invention refers to a compound of formula (I) as previously defined, wherein R_4-R_7 are independently selected from halogen, $-NO_2$, -CN, R^c, $-OR^c$, $-NR^dR^c$, $-NR^dC(O)R^c$, $-NR^dC(O)OR^c$, $-NR^dC(O)NR^dR^c$, $-NR^dS(O)_2R^c$, $-SR^c$, $-S(O)R^c$, $-SO_2R^c$, $-SO_2NR^dR^c$, $-C(O)R^c$, $-C(O)OR^c$, and $-C(O)NR^dR^c$.

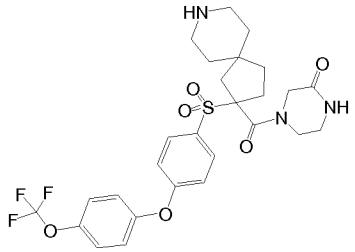
In another embodiment, optionally in combination with any of the embodiments above or below, the invention refers to a compound of formula (I) as previously defined, wherein R_2 and R_3 are independently selected from H, halogen, R^a, $-OR^{a'}$,and $-NR^bR^{a'}$; and R_5-R_7 are independently selected from H, halogen, R^c, $-OR^c$, and $-NR^dR^c$, wherein in R_2-R_3 and R_5-R_7, R^a, $R^{a'}$, R^b, R^c and R^d are independently selected from H and $-(C_1$-$C_4)$alkyl optionally substituted with one or more fluorine atoms.

In another embodiment, optionally in combination with any of the embodiments above or below, the invention refers to a compound of formula (I) as previously defined, wherein R_1 is selected from H, halogen, $-NO_2$, -CN, R^a, $-OR^{a'}$, $-OR^{a'}$, $-OC(O)R^{a'}$, $-OC(O)OR^{a'}$, $-OC(O)NR^bR^{a'}$, $-NR^bR^{a'}$, $-NR^bC(O)R^{a'}$, $-NR^bC(O)OR^{a'}$, $-NR^bC(O)NR^bR^{a'}$, $-NR^bS(O)_2R^{a'}$, $-SR^{a'}$, $-S(O)R^{a'}$, $-SO_2R^{a'}$, $-SO_2NR^bR^{a'}$, $-C(O)R^{a'}$, $-C(O)OR^{a'}$, $-C(O)NR^bR^{a'}$, and $-C(O)NR^bOR^{a'}$; R_4 is selected from halogen, $-NO_2$, -CN, R^c, $-OR^c$, $-NR^dR^c$, $-NR^dC(O)R^c$, $-NR^dC(O)OR^c$, $-NR^dC(O)NR^dR^c$, $-NR^dS(O)_2R^c$, $-SR^c$, $-S(O)R^c$, $-SO_2R^c$, $-SO_2NR^dR^c$, $-C(O)R^c$, $-C(O)OR^c$, and $-C(O)NR^dR^c$; and R_2, R_3, and R_5-R_7 are independently selected from H, halogen, $-(C_1$-$C_4)$alkyl, -OH, $-O[(C_1$-$C_4)$alkyl],

-NH_2, -NH[(C_1-C_4)alkyl], -N[(C_1-C_4)alkyl]$_2$, wherein each (C_1-C_4)alkyl is independently optionally substituted with one or more fluorine atoms.

The present invention also relates to the combination of any of the specific embodiments defined above for any of the variables A, B, C, Z, and R_1-R_7.

In another embodiment of the invention, the compound of formula (I) is selected from the group consisting of:



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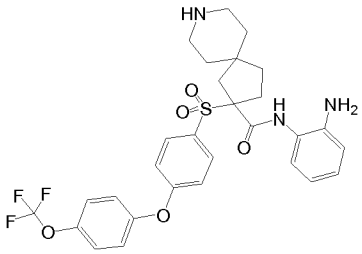

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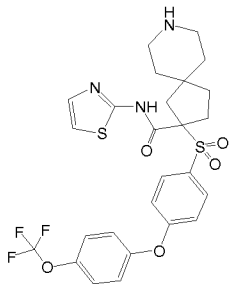

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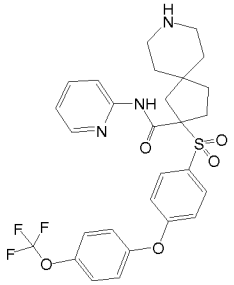

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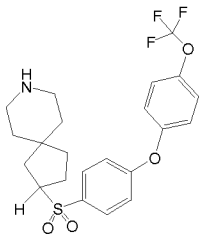

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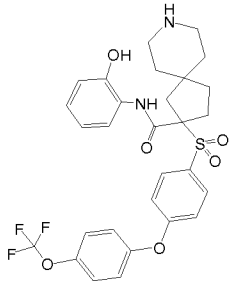

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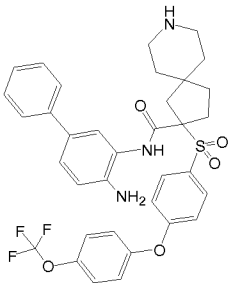

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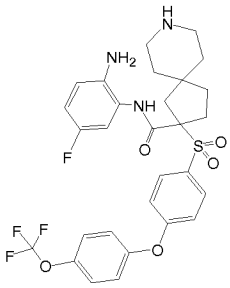

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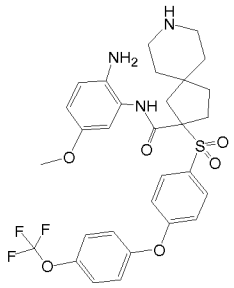

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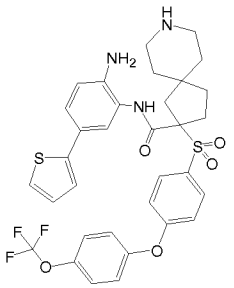

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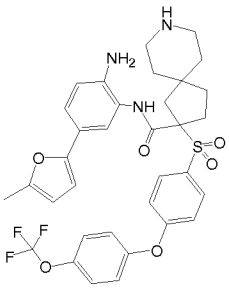

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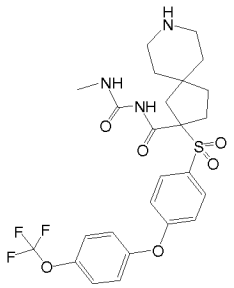

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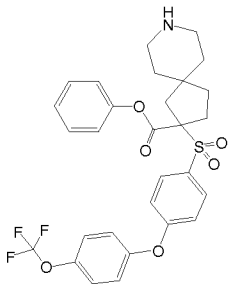

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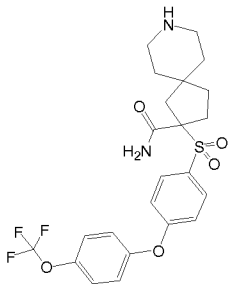

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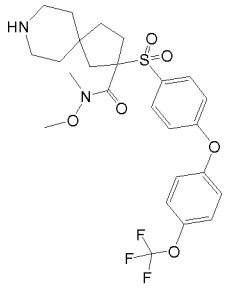

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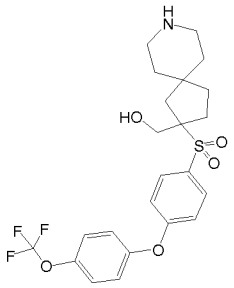

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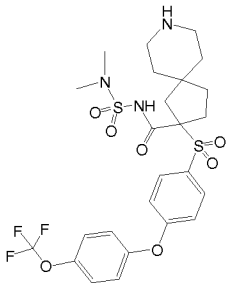

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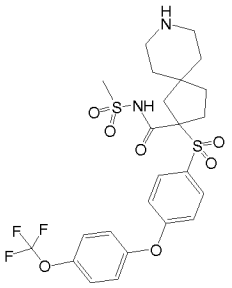

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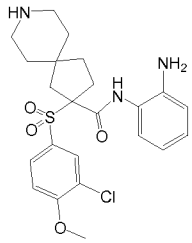

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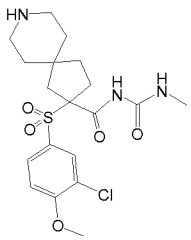

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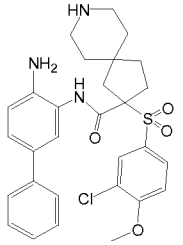

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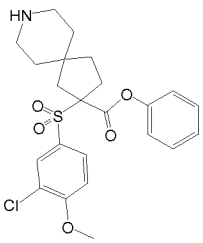

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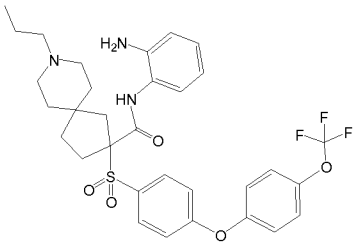

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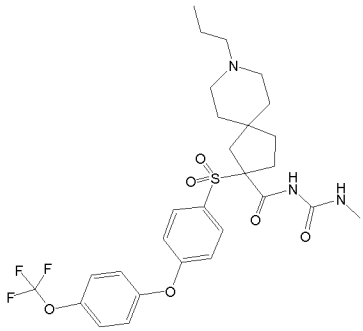

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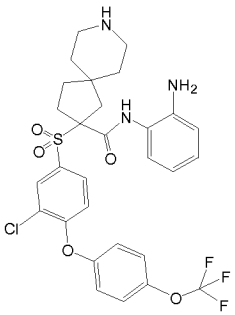

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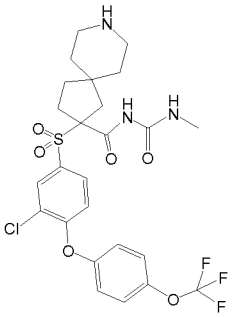

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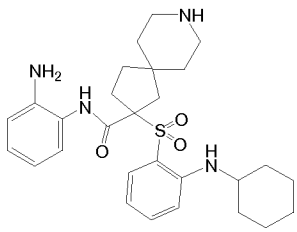

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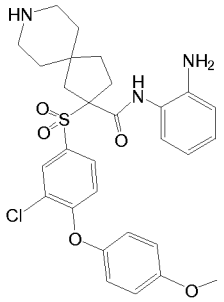

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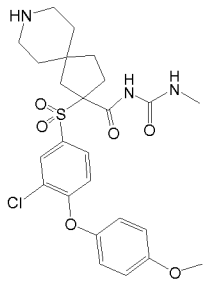

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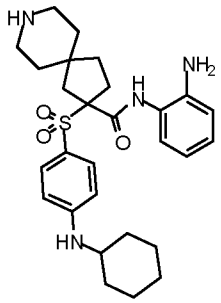

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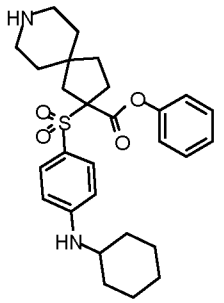

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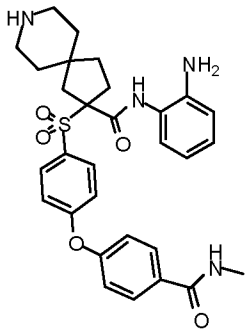

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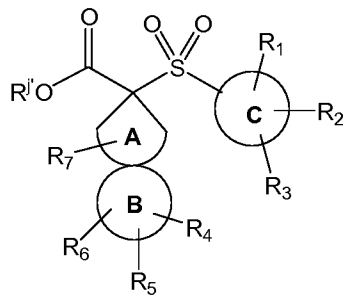
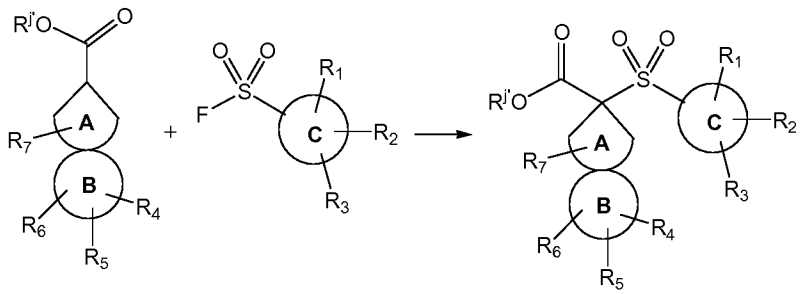
Processes for the preparation of compounds of formula (I) are also part of the invention as well as intermediates used in these processes.

Compounds of formula (IA),



(IA)

wherein A, B, C, R_1-R_7 are as defined for the compounds of formula (I) and $R^{j'}$ is an R^j as defined for the compounds of formula (I) other than H, can be obtained by coupling a compound of formula (III) with a compound of formula (IV):

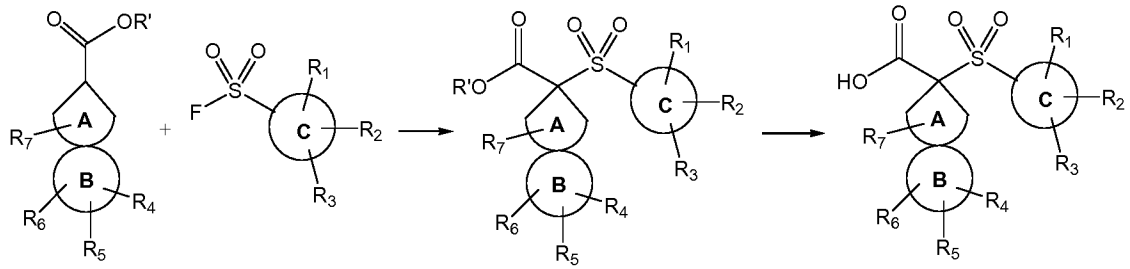


(III) (IV) (IA)

Scheme 1

wherein A, B, C, and R_1-R_7 are as previously defined for the compounds of formula (I). This conversion is carried out in the presence of a base, such as lithium diisopropylamide (LDA), in a suitable solvent, such as tetrahydrofuran, and at a suitable temperature, preferably -78 ºC.

Compounds of formula (IA'), wherein A, B, C, and R_1-R_7 are as previously defined for the compounds of formula (I), can generally be obtained by coupling a compound of formula (III') with a compound of formula (IV), and removing the protective group in the resulting compound as shown in the following scheme:



(III') (IV) (IA')

Scheme 2

wherein A, B, C and R_1-R_7 are as previously defined and R' is a carboxy protective group. Representative carboxy protective groups include alkyl, aryl or benzyl esters, sylil esters, amides or hydrazides. For example, the carboxy protective group is (C_1-C_6)alkyl, benzyl, p-methoxyphenyl, trimethylsilyl, or [2-(Trimethylsilyl)-ethoxy]methyl (SEM).

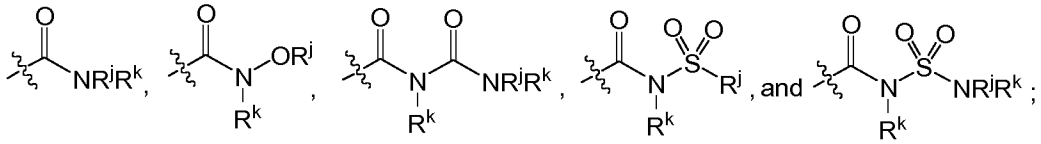
The first conversion may be carried out under the reaction conditions mentioned above. The removal of the carboxy protective group is carried out by standard methods well-known in the art as described for example in T. W.

Green and P. G. M. Wuts, Protective Groups in Organic Chemistry (Wiley, 3rd ed. 1999, Chapter 5, pp. 369-451). For example, when the carboxy protective group is (C_1-C_6)alkyl, the deprotection is carried out in basic medium, such as with LiOH in a suitable solvent, such as tetrahydrofuran-methanol.

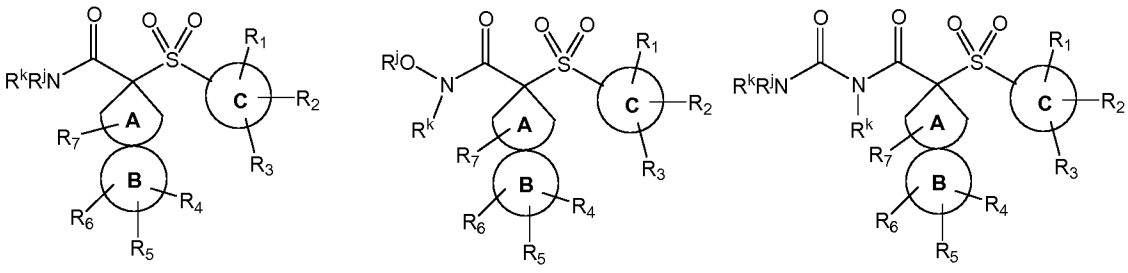
Alternatively, a compound of formula (IA) may also be obtained by reacting a compound of formula (IA') with a compound of formula $R^{j'}$-X, wherein X is halogen and $R^{j'}$ is R^j other than H, in the presence of a base, such as K_2CO_3, and in a suitable solvent, such as dimethylformamide.

Alternatively, a compound of formula (IA) may be obtained by reacting a compound of formula (IA') with $(COCl)_2$ in the presence of a suitable solvent, such as dichloromethane and dimethylformamide; and then reacting the acyl chloride intermediate with $R^{j'}$-X, in the presence of a base, such as triethylamine, and in a suitable solvent such as dichloromethane.

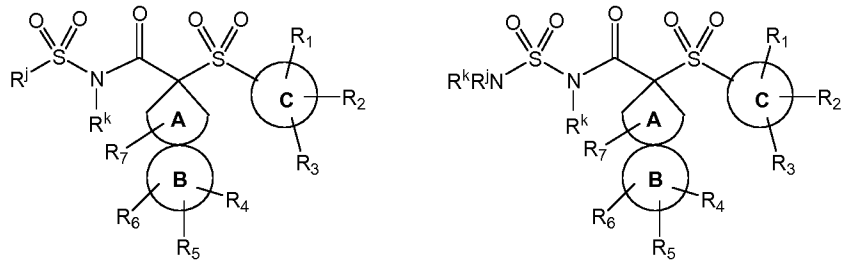
Compounds of formula (I) wherein Z is selected from the group consisting of:



i.e. compounds of formula (IB), (IC), (ID), (IE), and (IF), respectively,

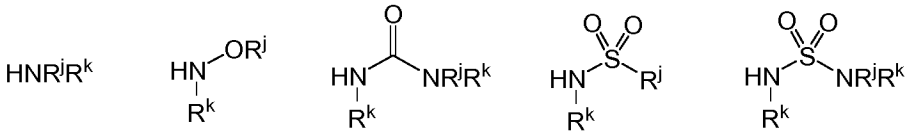


(IB) (IC) (ID)



(IE) (IF)

can generally be obtained from the compounds of formula (IA') with a suitable reagent of formula (VI), (VII), (VIII), (IX), (X), respectively,

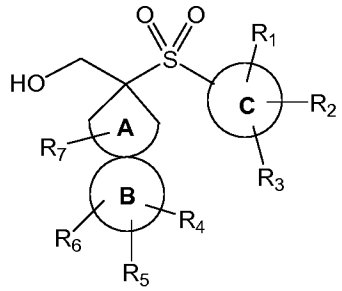


(VI) (VII) (VIII) (IX) (X)

wherein R^j and R^k are as previously defined. These conversions may be carried out in the presence of an activating agent, such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl) and hydroxybenzotriazole (HOBt), or pentafluorophenol (PFP) and N,N'-diisopropylcarbodiimide (DIC) in the presence of dimethylaminopyridine (DMAP), or (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), preferably in the presence of a base, such as N-methylmorpholine (NMM) or N,N'-diisopropylethylamine (DIEA), in a suitable solvent, such as dichloromethane, chloroform or dimethylformamide, at a temperature comprised from room temperature to the temperature of the boiling point of the solvent.

Alternatively, a compound of formula (IB), (IC), (ID), (IE), or (IF) may be obtained by reacting a compound of formula (IA') with $(COCl)_2$ as mentioned above; and then reacting the acyl chloride intermediate with a suitable reagent of formula (VI), (VII), (VIII), (IX), or (X), respectively, in the presence of a base, such as triethylamine, and in a suitable solvent such as dichloromethane.

Compounds of formula (I) wherein Z is $-CH_2OH$, i.e. compounds of formula (IG)

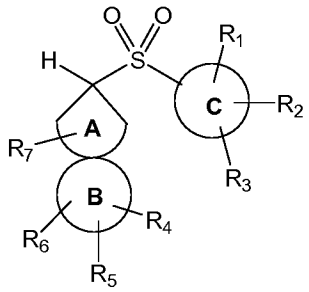


(IG)

can generally be obtained by reacting a compound of formula (IA') with a reducing agent, such as $NaBH_4$ in a suitable solvent, such as methanol and tetrahydrofuran.

Compounds of formula (I) wherein Z is H; i.e. compounds of formula (IH)

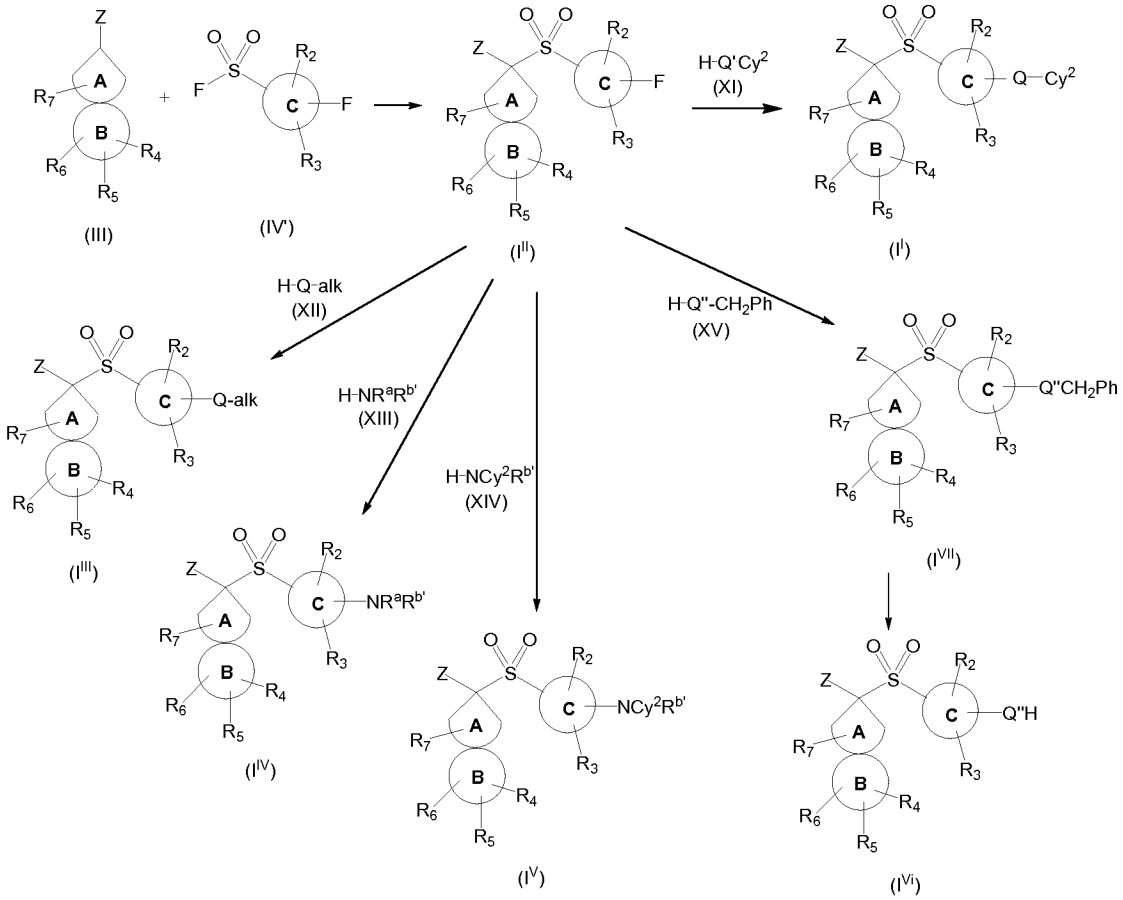
(IH)



(IH)

can generally be obtained by reacting a compound of formula (IA) with an alkylating agent, such as benzyl halide in the presence of a base, such as K_2CO_3, in a suitable solvent, such as dimethylformamide, and then reacting the obtained compound with a compound of formula H-Q-R, wherein Q is O, S or SO_2, R is phenyl or a 5- to 6- membered heteroaryl or a 3- to 7- heterocyclic or carbocyclic aliphatic ring or a hydrocarbon chain which can be optionally substituted, in the presence of a base, such as Cs_2CO_3, in a suitable solvent, such as dimethylformamide, at preferably heating.

Additionally, compounds of formula (I) may be converted into other compounds of formula (I) as shown in the Scheme below:



Scheme 3

Thus, a compound of formula (I), wherein R^1 is Q-Cy^2, Q is O, S, SO or SO_2 and Cy^2 is as defined above (i.e. a compound of formula (I^I)), may be obtained by reacting a compound of formula (III), wherein A, B, R_4-R_7 and Z are as previously defined, with a compound of formula (IV') to give a compound (I^{II}) under the reaction conditions mentioned above. Then, the obtained compound (I^{II}) is reacted with a compound of formula H-Q'-Cy^2 (XI), wherein Q' is O or S, to give a compound of formula (I^I). This latter reaction is carried out in the presence of a base, such as cesium carbonate, optionally in a suitable solvent or without solvent, and preferably heating.

Further, a compound of formula (I^I) wherein Q is S can be oxidized to a compound of formula (I^I) wherein Q is SO or SO_2 in the presence of an oxidizing agent, such as m-chloroperbenzoic acid, in a suitable solvent, such as dichlorormethane, and preferably at room temperature.

Additionally, a compound of formula (I), wherein R^1 is Q-alk, Q is O or S, and alk is saturated or unsaturated -(C_1-C_{12})alkyl optionally substituted (i.e. a compound of formula (I^{III})) may be obtained by reacting a compound of formula (I^{II}) with a compound of formula H-Q-alk (XII) in the presence of a base, such as NaH or cesium carbonate, optionally in a suitable solvent, such as dimethylformamide, or without solvent, and preferably heating.

A compound of formula (I), wherein R^1 is -$NR^bR^{a'}$, R^b is saturated or unsaturated -(C_1-C_{12})alkyl optionally substituted and $R^{a'}$ is H or saturated or unsaturated -(C_1-C_{12})alkyl optionally substituted (i.e. a compound of formula (I^{IV})) may be obtained by reacting a compound of formula (I^{II}) with a compound of formula H-$NR^bR^{a'}$ (XIII), optionally in a suitable solvent or without solvent, and preferably heating.

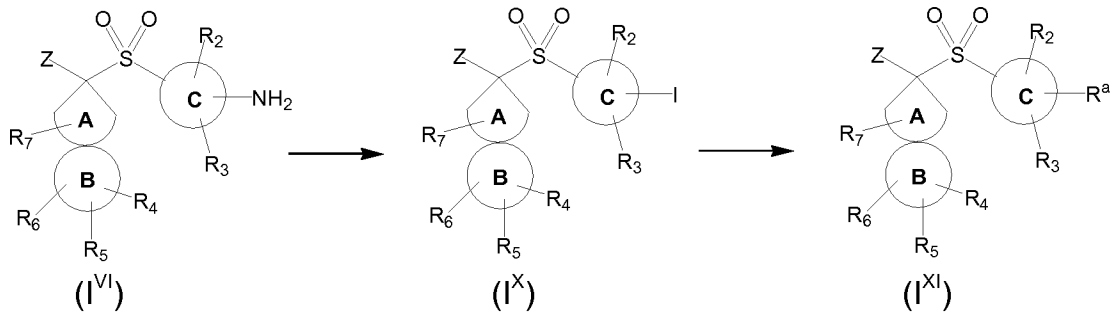
A compound of formula (I), wherein R^1 is -$NCy^2R^{a'}$ and Cy^2 is an optionally substituted aromatic, heteroaromatic or aliphatic ring (i.e. a compound of formula (I^V)) may be obtained by reacting a compound of formula (I^{II}) with a compound of formula H-$NCy^2R^{a'}$ (XIV), optionally in a suitable solvent or without solvent, and preferably heating.

A compound of formula (I), wherein R^1 is -$NR^bC(Y)R^{a'}$, -$NR^bC(Y)OR^{a'}$, -$NR^bC(Y)NR^bR^a$, -$NR^bS(O)_2R^{a'}$, -$NR^bSO_2NR^bR^{a'}$ (i.e. a compound of formula (I^{VIII})) may be obtained by reacting a compound of formula (I^{II}) with a compound of formula H-Q''-CH_2Ph (XV), wherein Q'' is NH, preferably heating, to give a compound of formula (I^{VII}), which can be hydrogenated in the presence of Pd/C to give a compound of formula (I^{VI}), wherein Q'' is NH. This compound can be reacted for example with an acyl halide in the presence of a base, such as triethylamine, in a suitable solvent, such as tetrahydrofuran, at a temperature comprised from room temperature to the reflux temperature of the solvent, to give an amide; or with an isocyanate to give a urea.

A compound of formula (I), wherein R^1 is -$OC(Y)R^{a'}$ (i.e. compound of formula (I^{IX})) may be obtained by reacting a compound of formula (I^{II}) with a compound of formula H-Q''-CH_2Ph (XV), wherein Q'' is O, in the presence of a base, such as NaH, in a suitable solvent, such as tetrahydrofuran, to give a compound of formula (I^{VII}) which can be hydrogenated in the presence of Pd/C to give a compound of formula (I^{VI}), wherein Q'' is O. This compound

can be reacted for example with an acyl halide in the presence of a base, such as triethylamine, in a suitable solvent, preferably at room temperature to give an ester.

A compound of formula (I), wherein R^1 is R^a (i.e. a compound of formula (I^{XII})) may be obtained by reacting a compound of formula (I^{VI}), wherein Q'' is NH,



(I^{VI}) (I^{X}) (I^{XI})

Scheme 4

with potassium iodide and $NaNO_2$ in a suitable solvent, such as acetonitrile and then an acid, such as concentrated HCl, is added to give a compound of formula (I^X). This compound can be reacted for example with boronic acid derivatives in the presence of a palladium catalyst (Suzuki coupling) to give a compound of formula (I^{XI}).

The same type of reactions shown above for R_1 can be aplied to R_2-R_7. Alternatively, the reactions described above can be carried out in a different order. Thus, the reactions for obtaining different substitution R_1-R_7 on any of the rings A-C can be carried out directly on the compounds of formula (I), or on precursors thereof, which are later on converted into compounds of formula (I).

The compounds of formulas (III), (III'), (IV), (IV'), and (VI) to (XV) are commercially available or can be obtained by conventional synthetic processes.

The present invention also relates to a pharmaceutical or veterinary composition comprising an effective amount of a compound of formula (I) as defined above, or a pharmaceutically or veterinary acceptable salt thereof, or any stereoisomer either of the compound of formula (I) or of its

pharmaceutically or veterinary acceptable salt, together with pharmaceutically or veterinary acceptable excipients or carriers.

The expression "effective amount" as used herein, refers to the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disease which is addressed. The specific dose of the compound of the invention to obtain a therapeutic benefit may vary depending on the particular circumstances of the individual patient including, among others, the size, weight, age and sex of the patient, the nature and stage of the disease, the aggressiveness of the disease, and the route of administration. For example, a dose of from about 0.01 to about 300 mg/kg may be used.

The expression "pharmaceutically or veterinary acceptable excipients or carriers" refers to pharmaceutically or veterinary acceptable materials, compositions or vehicles. Each component must be pharmaceutically or veterinary acceptable in the sense of being compatible with the other ingredients of the pharmaceutical or veterinary composition. It must also be suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity or other problems or complications commensurate with a reasonable benefit/risk ratio.

The election of the pharmaceutical or veterinary formulation will depend upon the nature of the active compound and its route of administration. Any route of administration may be used, for example oral, parenteral and topical administration.

For example, the pharmaceutical or veterinary composition may be formulated for oral administration and may contain one or more physiologically compatible carriers or excipients, in solid or liquid form. These preparations may contain conventional ingredients such as binding agents, fillers, lubricants, and acceptable wetting agents.

The pharmaceutical or veterinary composition may be formulated for parenteral administration in combination with conventional injectable liquid carriers, such as water or suitable alcohols. Conventional pharmaceutical or

veterinary excipients for injection, such as stabilizing agents, solubilizing agents, and buffers, may be included in such compositions. These pharmaceutical or veterinary compositions may be injected intramuscularly, intraperitoneally, or intravenously.

The pharmaceutical or veterinary composition may be formulated for topical administration. Formulations include creams, lotions, gels, powders, solutions and patches wherein the compound is dispersed or dissolved in suitable excipients. The topical compositions of the invention may be administered by means of a carrier material, which can be a solid support. Thus, it also forms part of the invention a topical composition comprising a carrier material, which can be a solid support. Illustrative, non-limiting examples of solid supports include intelligent textiles, dressings, coatings, sponges, band-aids, sanitary pads, compresses, plasters, etc. The manufacture of such compositions can be obtained by conventional methods, for example, by mixing the combinations of the invention and the material carrier.

The pharmaceutical or veterinary compositions may be in any form, including, among others, tablets, pellets, capsules, aqueous or oily solutions, suspensions, emulsions, or dry powdered forms suitable for reconstitution with water or other suitable liquid medium before use, for immediate or retarded release.

The appropriate excipients and/or carriers, and their amounts, can readily be determined by those skilled in the art according to the type of formulation being prepared.

The compounds of the present invention are useful as antihemorrhagic and antifibrinolytic agents and can be used in a broad range of therapeutic applications. In surgery, antifibrinolytic agents, in addition to reducing post-operative hemorrhage, can diminish blood transfusion and other hemoderivative requirements for example in heart, liver and orthopedic surgery, and also in the setting of oncologic surgery in organs rich in fibrinolysis activators (prostate, uterus). In trauma patients antifibrinolytic agents can reduce all-cause mortality and death due to bleeding. Further, the antifibrinolytic agents of the invention can also be used to control bleeding in thrombolytic therapy, e.g. in cases of acute heart attack and ischemic stroke,

and major or intracraneal hemorrhages. Moreover, the antifibrinolytic agents of the invention are useful in the treatment of menorrhage in women associated with congenital or acquired coagulopathies, as well as in post-partum haemorrhage, and in the treatment of hemorrhages of gastrointestinal and urologic origin, including prostatectomy. In addition they can be useful in the treatment of local hemorrhages, e.g. after teeth extraction, in particular in patients with congenital coagulopathies, such as hemophilia and von willebrand disease.

Throughout the description and claims the word "comprise" and variations of thereof, are not intended to exclude other technical features, additives, components, or steps. Furthermore, the word “comprise” encompasses the case of “consisting of”. Additional objects, advantages and features of the invention will become apparent to those skilled in the art upon examination of the description or may be learned by practice of the invention. The following examples are provided by way of illustration, and they are not intended to be limiting of the present invention. Furthermore, the present invention covers all possible combinations of particular and preferred embodiments described herein.

EXAMPLES

General Procedure for Prep-HPLC purification method:

The HPLC measurement was performed using Gilson 281 from 233 pump (binary), an autosampler, and a UV detector. The fractions was detected by LC-MS. The MS detector was configured with an electrospray ionization source. The source temperature was maintained at 300-350 ºC.

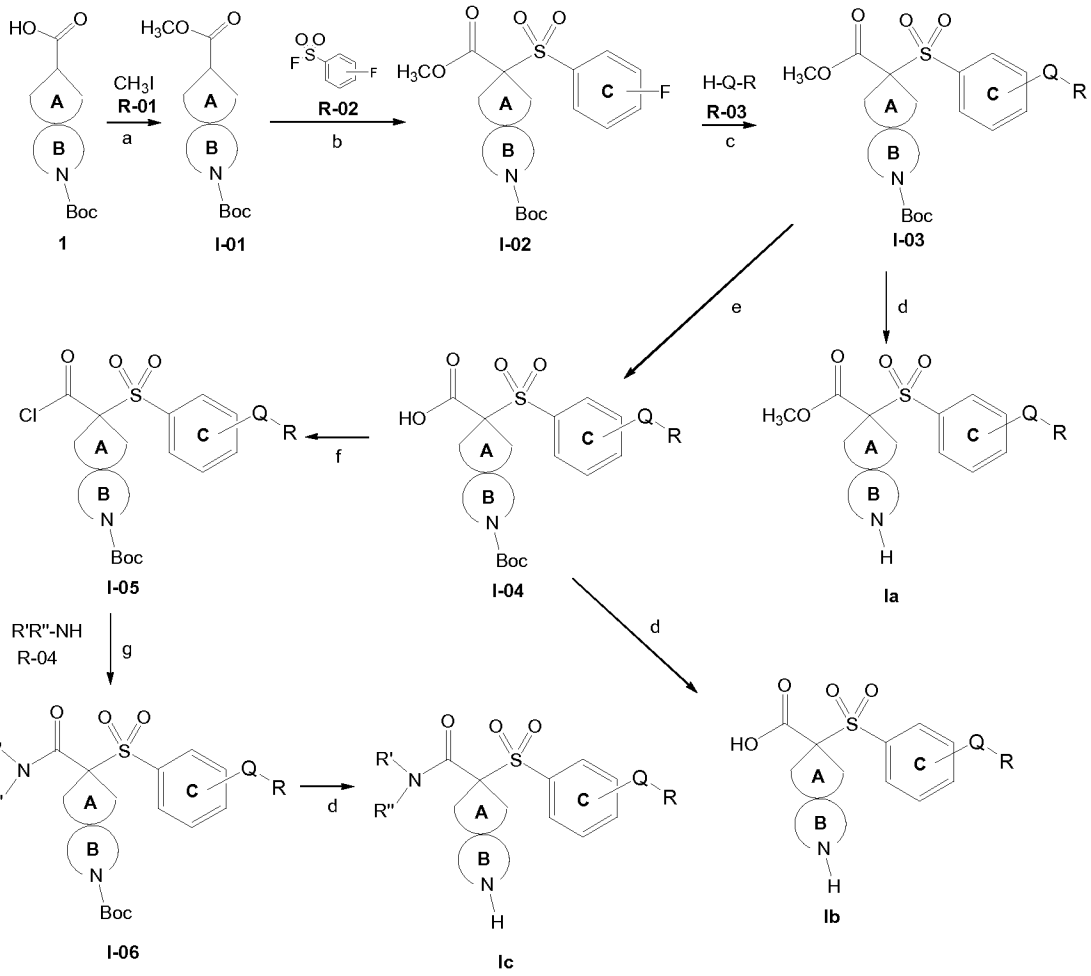
Method 1

Reverse phase HPLC was carried out on Luna C18 (100×30 mm; 4um). Solvent A: water with 0.075% trifluoroacetic acid; Solvent B: acetonitrile with 0.075% trifluoroacetic acid. Gradient: At room temperature, 20% of B to 40% of B within 6 min at 25 mL/min; then 40% B at 25 mL/min over 2 min, UV detector.

The following abbreviations have been used in the examples:
ACN: acetonitrile

Boc: tert-butoxycarbonyl
BOP: (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
DIC: *N,N'*-Diisopropylcarbodiimide
DIEA: N,N-Diisopropylethylamine
DMAP: dimethylaminopyridine
DMF: dimethylformamide
DMSO: dimethylsulfoxide
EA/EtOAc: ethyl acetate
EDC.HCl: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
Et_3N: triethylamine
HOBt: Hydroxybenzotriazole
LDA Lithium diisopropylamide
MeOH: methanol
NMM: N-Methylmorpholine
PE: Petroleum ether
PFP: pentafluorophenol
r.t.: room temperature
Rt: retention time
THF: tetrahydrofuran
TLC: Thin Layer Chromatography

Synthetic route 1(a)



Conditions: a. K_2CO_3 (2 eq) and R-01 (1.5 eq) in DMF, r.t. for 2 hours; b. LDA (1.25 M) in THF, 1 hour at -78 ºC; then, R-02 (2 eq), 1 hour at -78 ºC and finally r.t. overnight; c. R-03 (1.2 eq) and Cs_2CO_3 (1.5 eq) in DMF, μW at 120 ºC, 1h; d. HCl/EtOAc, r.t. for 2 hours; e. $LiOH.H_2O$ (10 eq) in THF/MeOH/H_2O (3/3/2), r.t.; f. $(COCl)_2$ (3 eq) in CH_2Cl_2 and DMF at -5 ºC; then, r.t. for 3 hours; g. R-04 (1.2 eq) and Et_3N (4 eq) in CH_2Cl_2 at -0 ºC; then r.t. overnight.

In the scheme above Q is O, S or SO_2, R is phenyl or a 5- to 6- membered heteroaryl or a 3- to 7- heterocyclic or carbocyclic aliphatic ring or a hydrocarbon chain which can be optionally substituted, R' and R'' are independently phenyl or a 5- to 6- membered heteroaryl or a 3- to 7- heterocyclic or carbocyclic aliphatic ring or a hydrocarbon chain which can be optionally substituted or hydrogen.

Preparation of intermediate I-01a: 8-tert-butoxycarbonyl-8-azaspiro[4.5]decane-3-carboxylic acid methyl ester

To a solution of 8-tert-butoxycarbonyl-8-azaspiro[4.5]decane-3-carboxylic acid (20 g, 0.071 mol), commercially available from Wuxi Apptec, in DMF (200mL) was added K_2CO_3 (18.59 g, 2 eq), then compound CH_3I (14.34 g, 1.5 eq) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. After TLC (PE/EA 5:1) showed the starting material was consumed, the mixture was quenched with water and extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated to give the crude compound 8-tert-butoxycarbonyl-8-azaspiro[4.5]decane-3-carboxylic acid methyl ester (20.38 g, 97.09%) as a pale yellow oil which was used for the next step without further purification. ESI-MS (M+1): 298 calc. for $C_{16}H_{27}NO_4$.

Preparation of reagent R-02a: 4-Fluorobenzenesulfonyl fluoride

To a solution of compound 4-Fluorobenzenesulfonyl chloride (50 g, 0.256 mol) in ACN (500 mL) was added KF (74.36 g, 5 eq) and 18-crown-6 (2 g) at r.t., then the mixture was stirred at r.t. overnight. The mixture was detected by LC-MS, then saturated aqueous $NaHCO_3$ was added and the mixture was extracted with EtOAc, the organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, concentrated to give the crude compound 4-Fluorobenzenesulfonyl fluoride (46.70 g) as pale yellow oil which was used for the next step without further purification. ESI-MS (M+1): 179 calc. for $C_6H_4F_2O_2S$.

Preparation of intermediate I-02a: 8-tert-butoxycarbonyl-3-(4-fluorophenylsulfonyl)-8-azaspiro[4.5]decane-3-carboxylic acid methyl ester

To a solution of compound I-01a (18.38 g, 0.062 mol) in THF (200mL) was added LDA (102 mL, 1.25 M) at -78ºC. After stirring at -78 ºC for 1h, the compound 4-Fluorobenzenesulfonyl fluoride (22.23 g, 2 eq) was added to the solution, the reaction was stirred at -78 ºC for 1 hour, and then the mixture was stirred at r.t. overnight. After TLC (PE/EA 5:1) showed the starting material was consumed, the mixture was quenched with aqueous NH_4Cl and extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated to give the crude product which was purified by column chromatography (eluting with EA/PE= 100:1 to 10: 1) to give pure compound I-02a (18.94 g, 67.03%) as a pale yellow oil. ESI-MS (M+1): 456 calc. for $C_{22}H_{30}FNO_6S$.

Preparation of intermediate I-03a: 8-tert-butoxycarbonyl-3-[4-(4-(trifluoromethoxy)phenoxy)phenylsulfonyl]-8-azaspiro[4.5]decane-3-carboxylic acid methyl ester

To a suspension of compound I-02a (2.5 g, 5.5 mmol) and p-trifluoromethoxyphenol (1.17 g, 6.6 mmol, R-03) in DMF (40 mL) was added Cs2CO3 (3.26 g, 10 mmol). The sealed vial was irradiated in the microwave on a Biotage Smith Synthesis at 120 ºC for 1 hrs. The resulting mixture was cooled to room temperature and water wa s added. The organic layer was separated and the aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure to afford the desired crude product which was purified by column to give the compound I-03a (2.8 g, 83%). ESI-MS (M-55): 558.2 calc. for C29H34F3NO8S.

Preparation of intermediate I-04a: 8-tert-butoxycarbonyl-3-[4-(4-(trifluoromethoxy)phenoxy)phenylsulfonyl]-8-azaspiro[4.5]decane-3-carboxylic acid

To a solution of compound I-03a (2.8 g, 4.57 mmol) in THF/MeOH/H2O (3/3/2, 64 mL) was added LiOH.H2O (2.0g, 10 eq). The resulting mixture was stirred at r.t. for 8 hrs, after TLC (PE/EA 5:1) showed the staring materials were consumed completely, then the mixture was diluted with water and adjusted pH to 3~4 with 1N HCl and the mixture was extracted with EtOAc, washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude product I-04a (2.7 g, 98%) as a pale yellow oil which was used directly in the next step.

Preparation of intermediate I-05a: tert-butyl 3-chlorocarbonyl-3-[4-(4-(trifluoromethoxy)phenoxy)phenylsulfonyl]-8-azaspiro[4.5]decane-8-carboxylate

To a solution of compound I-04a (1.5 g, 2.5 mmol) in CH2Cl2 (40 mL) was added $(COCl)_2$ (1.01 g, 8 mmol) and DMF (0.1 mL) at -5 ºC under N2. The mixture was stirred at r.t. for 3 hrs. The mixture was concentrated under vacuo to give the crude intermediate I-05a (1.4 g, crude) used directly in next step.

Preparation of intermediate I-06a: tert-butyl 3-[[2-(tert-butoxycarbonylamino)-5-fluoro-phenyl]carbamoyl]-3-[4-(4-(trifluoromethoxy)phenoxy)phenylsulfonyl]-8-azaspiro[4.5]decane-8-carboxylate

The crude intermediate I-05a (150 mg, 0.25 mmol) in CH2Cl2 (10 mL) was added to a solution of compound Et3N (101 mg, 1.0 mmol) and tert-butyl N-(2-amino-4-fluoro-phenyl)carbamate (68 mg, 0.3 mmol, R-04) dissolved in CH2Cl2 (40 mL) at 0 ºC under N2. The resulting mixture was stirred at r.t. overnight until TLC showed the starting material was consumed completely, then water was added and the mixture was extracted with CH2Cl2, the organic layer was washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude product which was purified by prep-TLC to give the compound I-06a (125 mg, 62%). ESI-MS (M-155): 652.2 calc. for C39H45F4N3O9S.

Preparation of compound 1-09: N-(2-amino-5-fluoro-phenyl)-3-[4-(4-(trifluoromethoxy)phenoxy)phenylsulfonyl]-8-azaspiro[4.5]decane-3-carboxamide

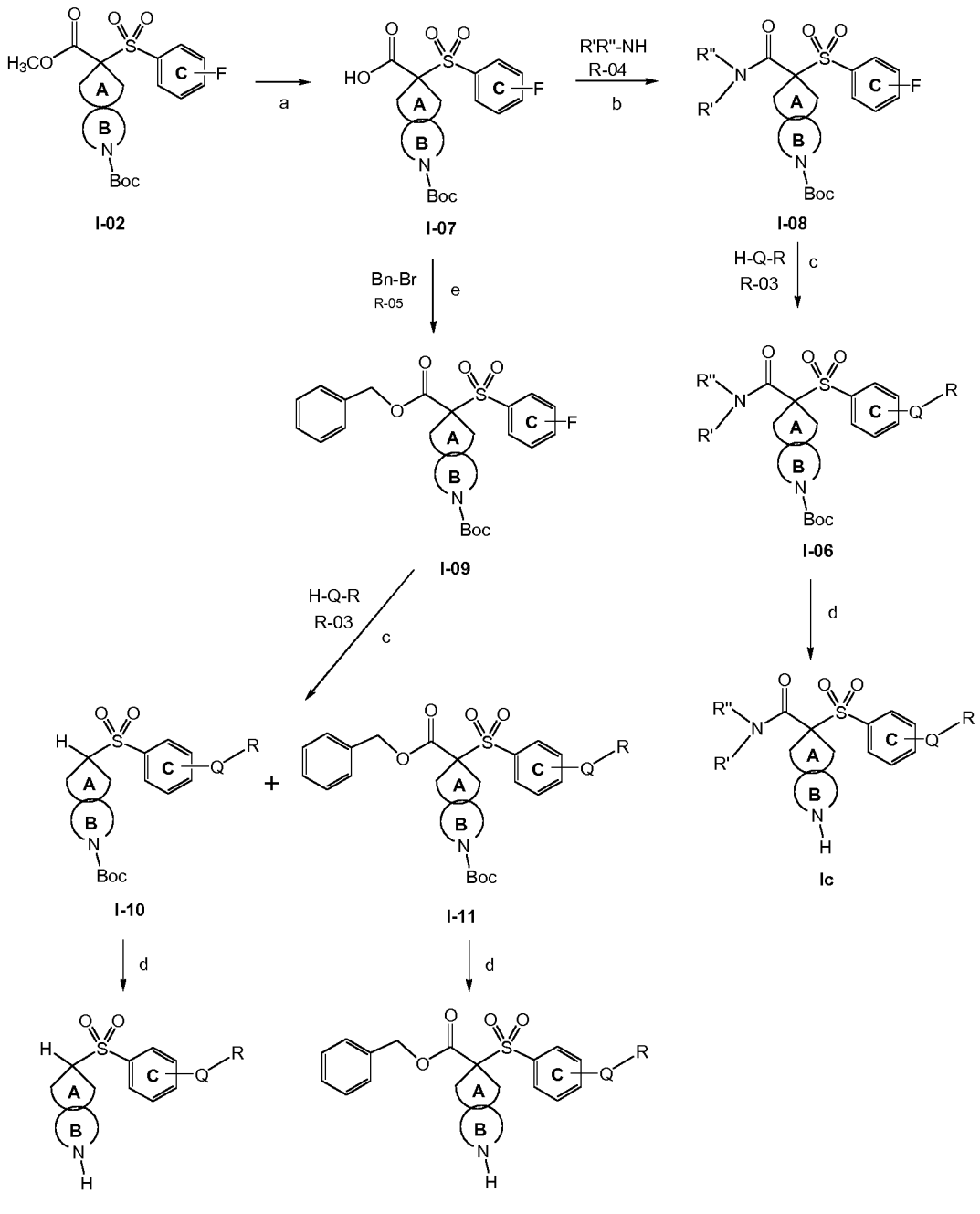
A solution of compound intermediate I-06a (125 mg, 0.15 mmol) in HCl/EtOAc (1.0 M, 15 mL) was stirred at room temperature for 2 hr, then concentrated to give the crude compound which was purified by prep-HPLC (General procedure, Method 1) to obtained pure compound 1-09 (33.7 mg, 37%) as a white solid. ESI-MS (M+1): 608.1 calc. for C29H29F4N3O5S. Rt is 3.05.

Following the same synthetic route 1a, and using the same reagents as for compound 1-09 unless otherwise indicated in the table below, the following compounds were obtained:

Example	Rt	$[M+1]^+$	LC-MS Method	Starting materials
Reference compound 1-11 (**Ia**)	3.04	514.2	1	p-trifluoromethoxyphenol (R-03)
Reference compound 1-12 (**Ib**)	2.71	500.1	1	p-trifluoromethoxyphenol (R-03)
1-08 (**Ic**)	3.42	666.2	1	p-trifluoromethoxyphenol (R-03) and tert butyl N-(2-amino-4-phenyl phenyl)carbamate (R-04)
1-10 (**Ic**)	2.70	620.3	1	p-trifluoromethoxyphenol (R-03) and tert-butyl N-(2-amino-4-methoxy-phenyl)carbamate (R-04)

Example	Rt	$[M+1]^+$	LC-MS Method	Starting materials
1-13 (**Ic**)	3.41	672.1	1	p-trifluoromethoxyphenol (R-03) and tert-butyl N-[2-amino-4-(2-thienyl)phenyl]carbamate (R-04)
1-14 (**Ic**)	3.36	670.2	1	p-trifluoromethoxyphenol (R-03) and tert-butyl N-[2-amino-4-(5-methyl-2-furyl)phenyl]carbamate (R-04)
1-15 (**Ic**)	2.90	556.1	1	p-trifluoromethoxyphenol (R-03) and methylurea (R-04)
1-17 (**Ic**)	2.70	499.1	1	p-trifluoromethoxyphenol (R-03) and ammonium hydroxide (R-04)
1-18 (**Ic**)	2.93	543.1	1	p-trifluoromethoxyphenol (R-03) and N-methoxymethanamine (R-04)

Synthetic route 1(b)



Conditions: a. $LiOH.H_2O$ (10 eq) in THF/MeOH/H_2O (3/3/2), r.t.; b. R-04 (2 eq), BOP (2 eq) and DIEA (2 eq) in DMF at 80 ºC overnight; c. R-03 (3 eq) and Cs_2CO_3 (3 eq) in DMF at 80 ºC overnight; d. HCl/dioxane, r.t. for 1 hour; e. K_2CO_3 (2.5 eq) and R-05 (1.5 eq) in DMF, r.t. for 10 hours.

In the scheme above Q is O, S or SO_2, R is phenyl or a 5- to 6- membered heteroaryl or a 3- to 7- heterocyclic or carbocyclic aliphatic ring or a hydrocarbon chain which can be optionally substituted, R' and R'' are independently phenyl or a 5- to 6- membered heteroaryl or a 3- to 7- heterocyclic or carbocyclic aliphatic ring or a hydrocarbon chain which can be optionally substituted or hydrogen.

Preparation of intermediate I-07a: 8-tert-butoxycarbonyl-3-(4-fluorophenyl)sulfonyl-8-azaspiro[4.5]decane-3-carboxylic acid

To a suspension of compound I-02a (2.5 g, 5.5 mmol) in THF/MeOH/H2O (3/3/2, 64 mL) was added LiOH.H2O (2.0g, 10 eq). The resulting mixture was stirred at r.t. for 8 hrs, after TLC (PE/EA 5:1) showed the staring materials were consumed completely, then the mixture was diluted with water and adjusted pH to 3~4 with 1N HCl and the mixture was extracted with EtOAc, washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude product I-07a (2.4 g, 98%) as a pale yellow oil which was used directly in the next step.

Preparation of intermediate I-09a: Benzyl tert-butyl 3-(4-fluorophenyl)sulfonyl-8-azaspiro[4.5]decane-3,8-dicarboxylate

To a solution of intermediate I-07a (1.5 g, 3.4 mmol) in DMF (50 mL) was added K2CO3 (1.17 g, 8.5 mmol), then compound BnBr (0.70 g, 4.1 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 10 hrs. After TLC showed the starting material was consumed, the mixture was quenched with water and extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude compound I-09a (1.6 g, 88.6%) as pale yellow oil which was used for the next step without further purification.

Preparation of intermediates I-10a and I-11a: tert-butyl 3-[4-[4-(trifluoro-methoxy)phenoxy]phenyl]sulfonyl-8-azaspiro[4.5]decane-8-carboxylate and benzyl tert-butyl 3-[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl-8-azaspiro[4.5]decane-3,8-dicarboxylate

To a solution of intermediate I-09a (1.4 g, 2.64 mmol) in DMF (20 mL) was added compound p-trifluoromethoxyphenol (0.71 g, 4.0 mmol, R-03) and Cs2CO3 (2.61 g, 8.0 mmol), then the reaction mixture was stirred at 80 ºC under microwave for 1 hr. After TLC showed the starting material was consumed, the mixture was quenched with water and extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude compound which was purified by column to give compound I-11a (1.1 g, 60%) ESI-MS (M+1): 689.2 calc. for C35H38F3NO8S and by-product compound I-10a (150 mg, 10%) ESI-MS (M+1): 556.2 calc. for C27H32F3NO6S.

Preparation of reference compound 1-05: Benzyl 3-[4-[4-(trifluoromethoxy)phenoxy]-phenyl]sulfonyl-8-azaspiro[4.5]decane-3-carboxylate.

A solution of intermediate I-11a (80 mg, 0.12 mmol) in HCl/EtOAc (1.0 M, 10 mL) was stirred at r.t for 4 hr, then concentrated to give the crude product which was purified by prep-HPLC (General procedure, Method 1) to obtained pure compound 1-05 (8.0 mg, 11.3 %) as white solid. ESI-MS (M+1): 590.1 calc. for C30H30F3NO6S. Rt is 3.35.

Preparation of compound 1-06: 3-[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl-8-azaspiro[4.5]decane.

A solution of intermediate I-10a (150 mg, 0.27 mmol) in HCl/EtOAc (1.0 M, 20 mL) was stirred at r.t for 1 hr, then concentrated to give the crude product which was purified by prep-HPLC (General procedure, Method 1) to obtained pure compound 1-06 (53.4mg, 43.5%) as white solid. ESI-MS (M+1): 456.1 calc. for C22H24F3NO4S. Rt is 2.84.

Preparation of intermediate I-08a: tert-butyl 3-(4-fluorophenyl)sulfonyl-3-(thiazol-2-ylcarbamoyl)-8-azaspiro[4.5]decane-8-carboxylate

To a solution of intermediate I-07a (50 mg, 0.11 mmol) and thiazol-2-amine (25 mg, 0.22 mmol, R-04) in DMF (10 mL) was added BOP (97 mg, 0.22 mmol) and DIEA (29 mg, 0.22 mmol) at r.t, then the mixture was stirred at 80 ºC overnight. The mixture was quenched with aqueous water and extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude product which was purified by prep-TLC to give the intermediate I-08a (40 mg, 70%) as a pale yellow solid. ESI-MS (M+1): 524.2; calc. for C24H30FN3O5S2.

Preparation of intermediate I-06i: tert-butyl 3-(thiazol-2-ylcarbamoyl)-3-[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl-8-azaspiro[4.5]decane-8-carboxylate.

To a solution of intermediate I-08a (40 mg, 0.076 mmol), p-trifluoromethoxyphenol (41 mg, 0.23 mmol, R-03) and Cs2CO3 (75 mg, 0.23 mmol) in DMF (5 mL) were stirred at 80 ºC overnight. The mixture was quenched with aqueous water and extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na2SO4, concentrated to give

the crude product which was purified by prep-TLC to give the intermediate I-06i (30 mg, 57%) as a pale yellow solid. ESI-MS (M+1): 682.2; calc. for C31H34F3N3O7S2.

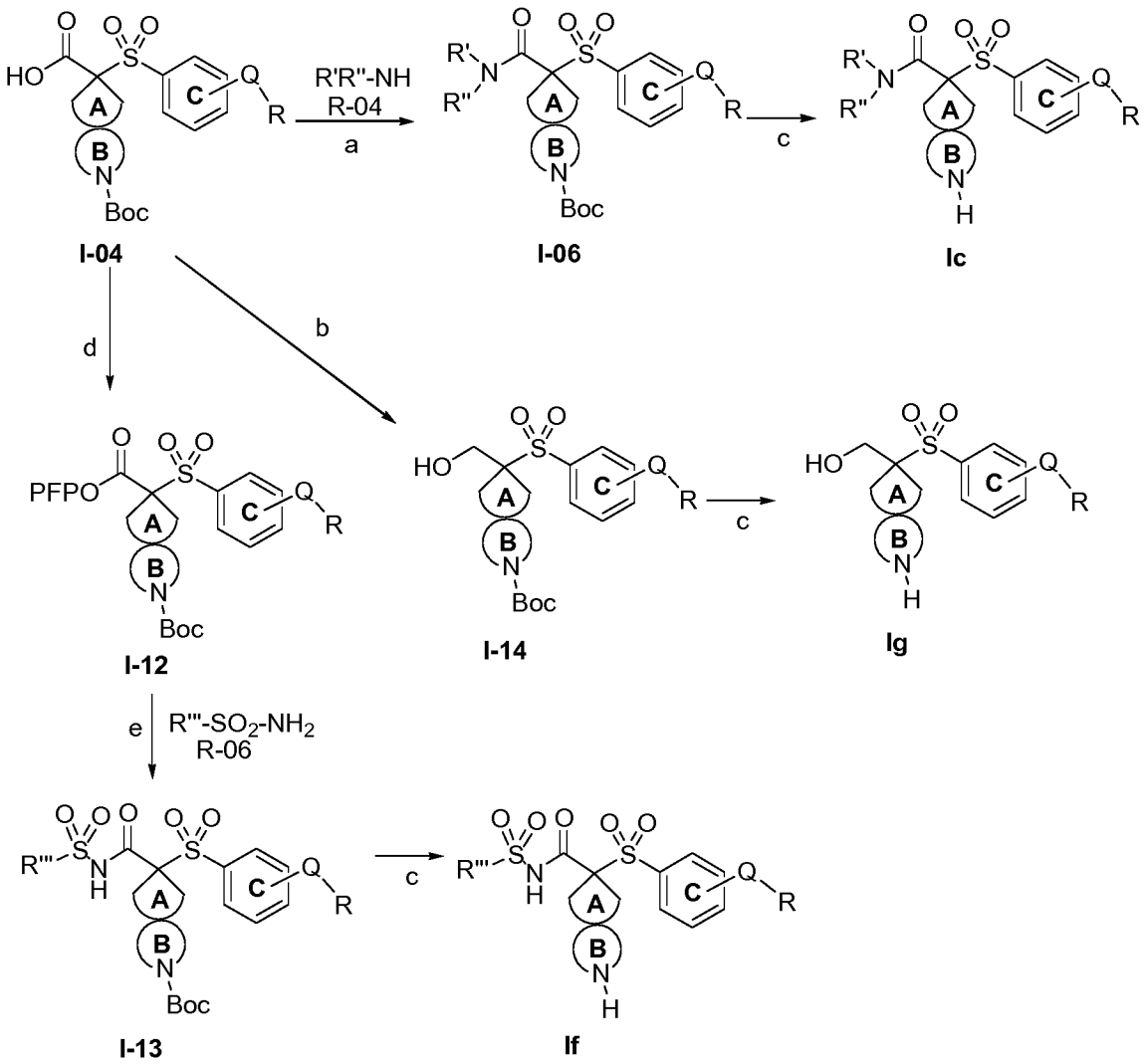
Preparation of compound 1-03: N-thiazol-2-yl-3-[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl-8-azaspiro[4.5]decane-3-carboxamide.

A solution of intermediate I-06i (30 mg, 0.044 mmol) in HCl/dioxane (10 mL) was stirred at r.t for 1 h, then concentrated to give the crude product which was purified by prep-HPLC (General procedure, Method 1) to obtained pure compound 1-03 (10.9 mg, 44 %) as a yellow oil. ESI-MS (M+1): 582.2 calc. for C26H26F3N3O5S2. Rt is 3.02.

Following the same synthetic route 1b, and using the same reagents as for compound 1-03 unless otherwise indicated in the table below, the following compounds were obtained:

Example	Rt	$[M+1]^+$	LC-MS Method	Starting materials
1-04 (**Ic**)	3.04	576.3	1	pyridin-2-amine (R-04) and p-trifluoromethoxyphenol (R-03)

Synthetic route 1(c)



Conditions: a. EDC.HCl (2 eq), HOBt (2 eq), R-04 (2 eq) and NMM (3 eq) in DMF at r.t. overnight; b. $NaBH_4$ (3 eq) in MeOH and THF at 60 ºC overnight; c. HCl/EtOAc, r.t. for 2 hours; d. DIC (1.5 eq) and PFP (1.1 eq) in CH_2Cl_2, r.t. overnight; e. DIEA (2.5 eq), DMAP (0.4 eq) and R-06 (2 eq)) in CH_2Cl_2 at 50 ºC overnight.

In the scheme above Q is O, S or SO_2, R is phenyl or a 5- to 6- membered heteroaryl or a 3- to 7- heterocyclic or carbocyclic aliphatic ring or a hydrocarbon chain which can be optionally substituted, R' and R'' are independently phenyl or a 5- to 6- membered heteroaryl or a 3- to 7- heterocyclic or carbocyclic aliphatic ring or a hydrocarbon chain which can be optionally substituted or hydrogen and R''' is hydrocarbon chain which can be optionally substituted or an amine (secondary or tertiary)

Preparation of intermediate I-12a: 8-tert-butyl 3-(2,3,4,5,6-pentafluorophenyl) 3-[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl-8-azaspiro[4.5]decane-3,8-dicarboxylate.

To a solution of the intermediate I-04a (800 mg, 1.34 mmol) in CH2Cl2 (50 mL) was added DIC (277 mg, 2.2 mmol), pentafluorophenol (270 mg, 1.47 mmol). The resulting mixture was stirred at r.t. overnight until TLC showed the starting material was consumed completely, then quenched with water and extracted with CH2Cl2, the organic layer was washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude compound which was purified by column chromatography to give pure compound I-12a (890 mg, 89%) as a pale yellow oil. ESI-MS (M-55): 710.1; calc. for C34H31F8NO8S.

Preparation of intermediate I-13a: tert-butyl 3-(dimethylsulfamoylcarbamoyl)-3-[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl-8-azaspiro[4.5]decane-8-carboxylate

To a solution of compound intermediate I-12a (100 mg, 0.13 mmol) in CH2Cl2 (20 mL) was added DIEA (43 mg, 0.33 mmol), DMAP (7 mg, 0.05 mmol) and compound [methyl(sulfamoyl)amino]methane (32 mg, 0.25 mmol, R-06). The mixture was stirred at 50 ºC overnight until LC-MS showed the starting material was consumed completely, then quenched with water and extracted with CH2Cl2, the organic layer was washed with brine, dried over anhydrous Na2SO4, concentrated to give intermediate I-13a (95 mg, crude) used directly in next step. ESI-MS (M-55): 649.9; calc. for C30H38F3N3O9S2.

Preparation of compound 1-20: N-(dimethylsulfamoyl)-3-[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl-8-azaspiro[4.5]decane-3-carboxamide

A solution of intermediate I-13a (95 mg, 0.13 mmol) in HCl/EtOAc (1M, 15 mL) was stirred at room temperature for 2 hrs, then concentrated to give the crude compound which was purified by prep-HPLC (General procedure, Method 1) to obtained pure compound 1-20 (22.8 mg, 29%) as a white solid. ESI-MS (M+1): 606.1 calc. for C25H30F3N3O7S2. Rt is 2.99.

Preparation of intermediate I-06k: tert-butyl 3-(3-oxopiperazine-1-carbonyl)-3-[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl-8-azaspiro[4.5]decane-8-carboxylate

To a solution of intermediate I-04a (60 mg, 0.1 mmol) in DMF (10 mL) was added EDC.HCl (38 mg, 0.2 mmol), HOBt (27 mg, 0.2 mmol), piperazin-2-one (20 mg, 0.2 mmol, R-04) and NMM (30 mg, 0.3 mmol) at room temperature, then the mixture was stirred at room temperature overnight. The mixture was quenched with aqueous water and extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude product which was purified by prep-TLC to give the intermediate I-06k (30 mg, 50%) as a pale yellow solid. ESI-MS (M+1): 682.2; calc. for C32H38F3N3O8S.

Preparation of compound 1-01: 4-[3-[4-[4-(trifluoromethoxy)phenoxy]-phenyl]sulfonyl-8-azaspiro[4.5]decane-3-carbonyl]piperazin-2-one

A solution of intermediate I-06k (30 mg, 0.044 mmol) in HCl/dioxane (10 mL) was stirred at r.t for 1 hr, then concentrated to give the crude product which was purified by prep-HPLC (General procedure, Method 1) to obtained pure compound 1-01 (10.5 mg, 42 %) as a yellow oil. ESI-MS (M+1): 582.2 calc. for C27H30F3N3O6S. Rt is 2.64.

Preparation of intermediate I-14a: tert-butyl 3-(hydroxymethyl)-3-[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl-8-azaspiro[4.5]decane-8-carboxylate

To a solution of the intermediate I-04a (160 mg, 0.267 mmol), NaBH4 (80 mg, 0.9 mmol) and MeOH (2 mL) in THF (5 mL) was stirred at 60 ºC for overnight. The mixture was quenched with aqueous water and extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude product which was purified by the column chromatography to give the intermediate I-14a (75 mg, 50%) as a pale yellow oil. ESI-MS (M-55): 531.2; calc. for C28H34F3NO7S.

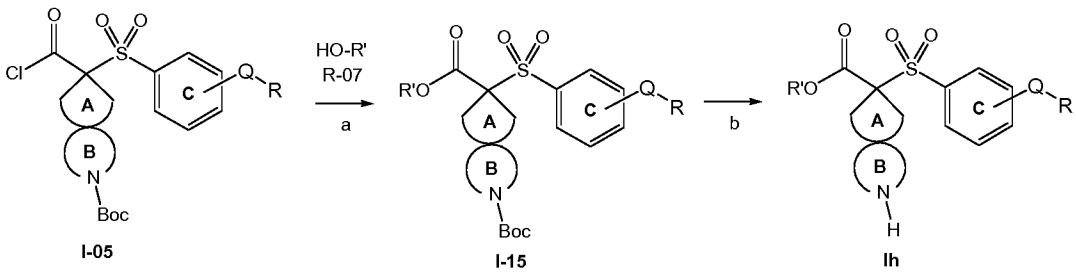
Preparation of compound 1-19: [3-[4-[4-(trifluoromethoxy)phenoxy]phenyl]-sulfonyl-8-azaspiro[4.5]decan-3-yl]methanol

A solution of intermediate I-14a (75 mg, 0.13 mmol) in EtOAc/dioxane (10 mL) was stirred at r.t for 1 h, then concentrated to give the crude product which was purified by prep-HPLC (General procedure, Method 1) to obtained pure compound 1-19 (43.2 mg, 65 %) as a yellow oil. ESI-MS (M+1): 486.2 calc. for C23H26F3NO5S. Rt is 2.65.

Following the same synthetic route 1c, and using the same reagents as for compounds 1-01 or 1-20 unless otherwise indicated in the table below, the following compounds were obtained:

Example	Rt	$[M+1]^+$	LC-MS Method	Starting materials
1-21 (**If**)	2.78	577.1	1	p-trifluoromethoxyphenol (R-03) and methanesulfonamide (R-06)
1-02 (**Ic**)	2.97	590.3	1	trifluoromethoxyphenol (R-03) and benzene-1,2-diamine (R-04)
1-07 (**Ic**)	3.08	591.3	1	trifluoromethoxyphenol (R-03) and 2-aminophenol (R-04)
1-35 (**Ic**)	2.07	563.2	1	4-hydroxy-N-methylbenzamide (R-03) and benzene-1,2-diamine (R-04)

Synthetic route 1(d)



Conditions: a. R-07 (1.2 eq) and Et_3N (4 eq) in CH_2Cl_2 at 0 ºC; then overnight at r.t.; b. HCl/EtOAc, r.t. for 2 hours.

In the scheme above Q is O, S or SO_2, R is phenyl or a 5- to 6- membered heteroaryl or a 3- to 7- heterocyclic or carbocyclic aliphatic ring or a hydrocarbon chain which can be optionally substituted, R' is phenyl or a 5- to 6- membered heteroaryl or a 3- to 7- heterocyclic or carbocyclic aliphatic ring or a hydrocarbon chain which can be optionally substituted or hydrogen.

Preparation of intermediate I-15a: 8-tert-butyl 3-phenyl 3-[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl-8-azaspiro[4.5]decane-3,8-dicarboxylate

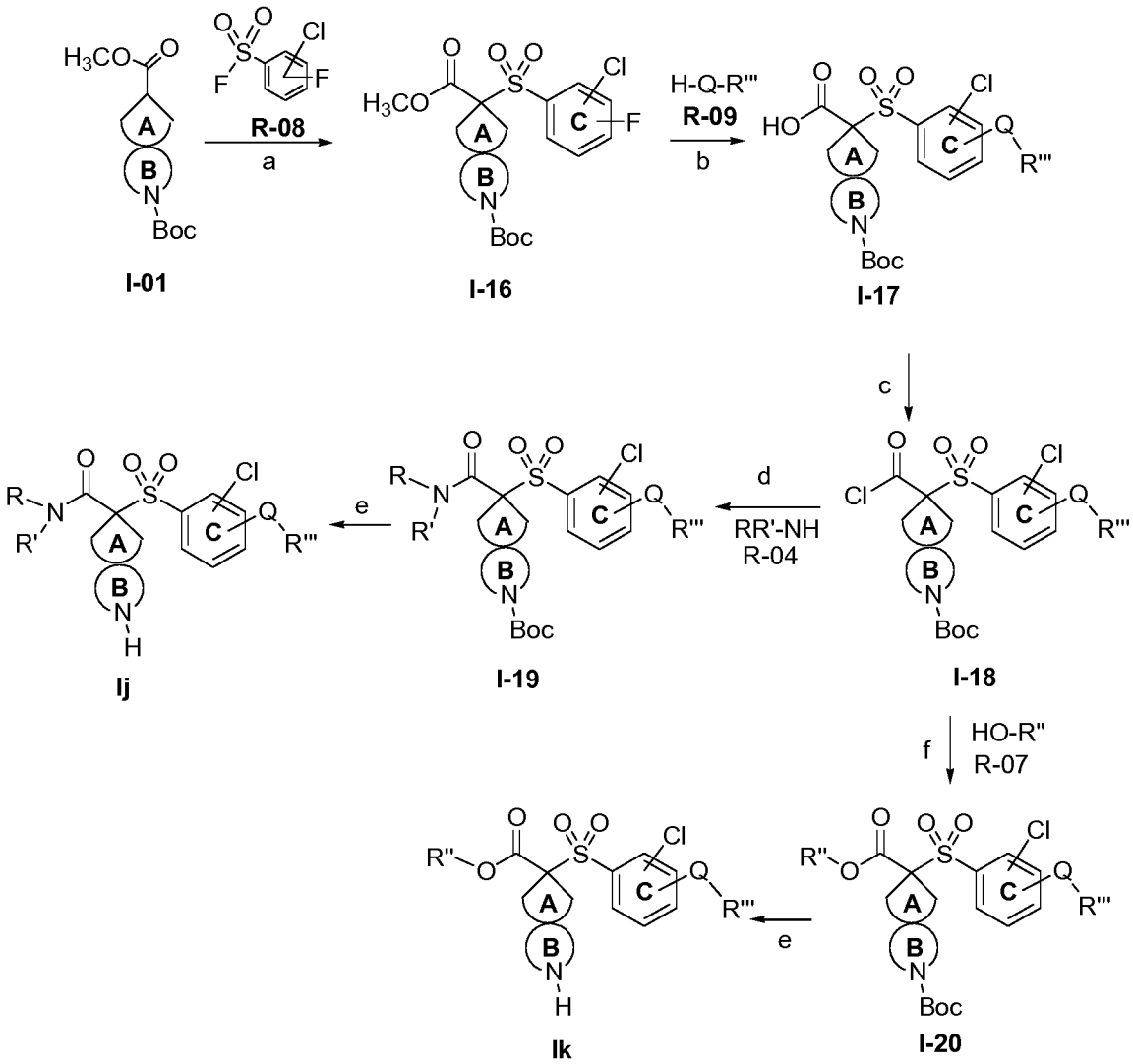
The crude intermediate I-05a (150 mg, 0.25 mmol) in CH2Cl2 (10 mL) was added to a solution of compound Et3N (101 mg, 1.0 mmol) and phenol (30 mg, 0.3 mmol, R-07) dissolved in CH2Cl2 (40 mL) at 0 ºC under N2. The resulting mixture was stirred at r.t. overnight until TLC showed the starting material was consumed completely, then water was added and the mixture was extracted with CH2Cl2, the organic layer was washed with brine, dried

over anhydrous Na2SO4, concentrated to give the crude product which was purified by prep-TLC to give the intermediate I-15a (125 mg, 74%). ESI-MS (M-55): 620.2 calc. for C34H36F3NO8S.

Preparation of compound 1-16: phenyl 3-[4-[4-(trifluoromethoxy)phenoxy]-phenyl]sulfonyl-8-azaspiro[4.5]decane-3-carboxylate

A solution of intermediate I-15a (125 mg, 0.185 mmol) in HCl/EtOAc (1.0 M, 15 mL) was stirred at room temperature for 2 hr, then concentrated to give the crude compound which was purified by prep-HPLC (General procedure, Method 1) to obtained pure compound 1-16 (21.9 mg, 20.6%) as a white solid. ESI-MS (M+1): 576.1 calc. for C29H28F3NO6S. Rt is 3.36.

Synthetic route 1(e)



Conditions: a. LDA (1.25 M) in THF, 1 hour at -78 ºC; then, R-08 (1.4 eq), 1 hour at -78 ºC and finally r.t. overnight; b. $LiOH.H_2O$ (10 eq) in $THF/H_2O/MeOH$ (R-09) (3/2/3), r.t.; c. $(COCl)_2$ (3 eq) in CH_2Cl_2

and DMF at -5 ºC; then, r.t. for 3 hours; d. R-04 (1 eq) and Et_3N (3 eq) in CH_2Cl_2 at 0 ºC; then overnight at r.t.; e. HCl/EtOAc, r.t. for 2 hours; f. R-07 (1.3 eq) and Et_3N (3 eq) in CH_2Cl_2 at 0 ºC; then overnight at r.t.

In the scheme above Q is O, S, SO_2 or NH, R and R' are independently phenyl or a 5- to 6- membered heteroaryl or a 3- to 7- heterocyclic or carbocyclic aliphatic ring or a hydrocarbon chain which can be optionally substituted or hydrogen, R'' is phenyl or a 5- to 6- membered heteroaryl or a 3- to 7- heterocyclic or carbocyclic aliphatic ring or a hydrocarbon chain which can be optionally substituted or hydrogen and R''' is hydrocarbon chain which can be optionally substituted.

Preparation of reagent R-08a: 3-chloro-4-fluorobenzenesulfonyl fluoride

To a solution of the commercially available 3-chloro-4-fluorobenzenesulfonyl chloride (7g, 30mmol) in CH3CN (40 mL) was added KF (7 g, 120 mmol) and 18-crown-6 (0.5 g), then the mixture was stirred at room temperature overnight. The mixture was quenched with aqueous water and extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude product which was purified by column to give the reagent R-12a (4.2 g, 95.5%) as a pale yellow solid. ESI-MS (M+1): 213.2 calc. for C6H3ClF2O2S.

Preparation of intermediate I-16a: 8-tert-butyl 3-methyl 3-(3-chloro-4-fluoro-phenyl)sulfonyl-8-azaspiro[4.5]decane-3,8-dicarboxylate.

To a solution of compound I-01a (4.8 g, 16.2 mmol) in THF (30 mL) was added LDA (20 mL, 1.25 N, 24 mmol) at -70 ºC. After stirring at -70 ºC for 2 hrs, the reagent R-08a (4.68 g, 22 mmol) was added to the solution, the reaction was stirred at -70 ºC for 1 hour, and then the mixture was stirred at r.t overnight. After TLC showed the starting material was consumed, the mixture was quenched with aqueous NH4Cl and extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude product which was purified by column chromatography to give pure intermediate I-16a (3.6 g, 45.4%) as a pale yellow oil. ESI-MS (M-55): 434.1 calc. for C22H29ClFNO6S.

Preparation of intermediate I-17a: 8-tert-butoxycarbonyl-3-(3-chloro-4-methoxy-phenyl)sulfonyl-8-azaspiro[4.5]decane-3-carboxylic acid.

To a solution of intermediate I-16a (450 mg, 0.92 mmol) in THF/H2O/MeOH (R-09) (3/2/3, 32 mL) was added LiOH.H2O (430 mg, 10 eq). The resulting mixture was stirred at r.t. for 4 hrs, after TLC showed the staring materials were consumed completely, then the mixture was diluted with water and adjusted pH to 3~4 with 1 N HCl and the mixture was extracted with EtOAc, washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude product I-17a (360 mg, 80%) as a pale yellow oil which was used in the next step. ESI-MS (M-55): 432.2; calc. for C22H30ClNO7S.

Preparation of intermediate I-18a: tert-butyl 3-chlorocarbonyl-3-(3-chloro-4-methoxy-phenyl)sulfonyl-8-azaspiro[4.5]decane-8-carboxylate

To a solution of intermediate I-17a (360 mg, 0.74 mmol) in CH2Cl2 (40 mL) was added (COCl)2 (380 mg, 3 mmol) and DMF (0.2 mL) at -5 ºC under N2. The mixture was stirred at r.t. for 3 hrs. The mixture was concentrated under vacuo to give the crude intermediate I-18a (400 mg, crude) used directly in next step.

Preparation of intermediate I-19a: tert-butyl 3-[(2-aminophenyl)carbamoyl]-3-(3-chloro-4-methoxy-phenyl)sulfonyl-8-azaspiro[4.5]decane-8-carboxylate

The crude intermediate I-18a (100 mg, 0.19 mmol) in CH2Cl2 (10 mL) was added to a solution of compound Et3N (61 mg, 0.6 mmol) and benzene-1,2-diamine (22 mg, 0.2 mmol, R-04) dissolved in CH2Cl2 (40 mL) at 0 ºC under N2. The resulting mixture was stirred at r.t. overnight until TLC showed the starting material was consumed completely, then water was added and the mixture was extracted with CH2Cl2, the organic layer was washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude intermediate I-19a (122 mg, ~100%). ESI-MS (M-55): 522.1 calc. for C28H36ClN3O6S.

Preparation of compound 1-22: N-(2-aminophenyl)-3-(3-chloro-4-methoxy-phenyl)sulfonyl-8-azaspiro[4.5]decane-3-carboxamide

A solution of intermediate I-19a (122 mg, 0.19 mmol) in HCl/EtOAc (1.0 M, 25 mL) was stirred at room temperature for 2 hrs, then concentrated to give the crude compound which was purified by prep-HPLC (General procedure, Method 1) to obtained pure compound 1-22 (10.8 mg, 12%) as a white solid. ESI-MS (M+1): 478.1 calc. for C23H28ClN3O4S. Rt is 2.23.

Preparation of intermediate I-20a: 8-tert-butyl 3-phenyl 3-(3-chloro-4-methoxy-phenyl)sulfonyl-8-azaspiro[4.5]decane-3,8-dicarboxylate

The crude intermediate I-18a (100 mg, 0.19 mmol) in CH2Cl2 (10 mL) was added to a solution of compound Et3N (61 mg, 0.6 mmol) and phenol (25 mg, 0.26 mmol, R-07) dissolved in CH2Cl2 (40 mL) at 0 ºC under N2. The resulting mixture was stirred at r.t. overnight until TLC showed the starting material was consumed completely, then water was added and the mixture was extracted with CH2Cl2, the organic layer was washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude intermediate I-20a (113 mg, ~100%). ESI-MS (M-55): 508.1 calc. for C28H34ClNO7S.

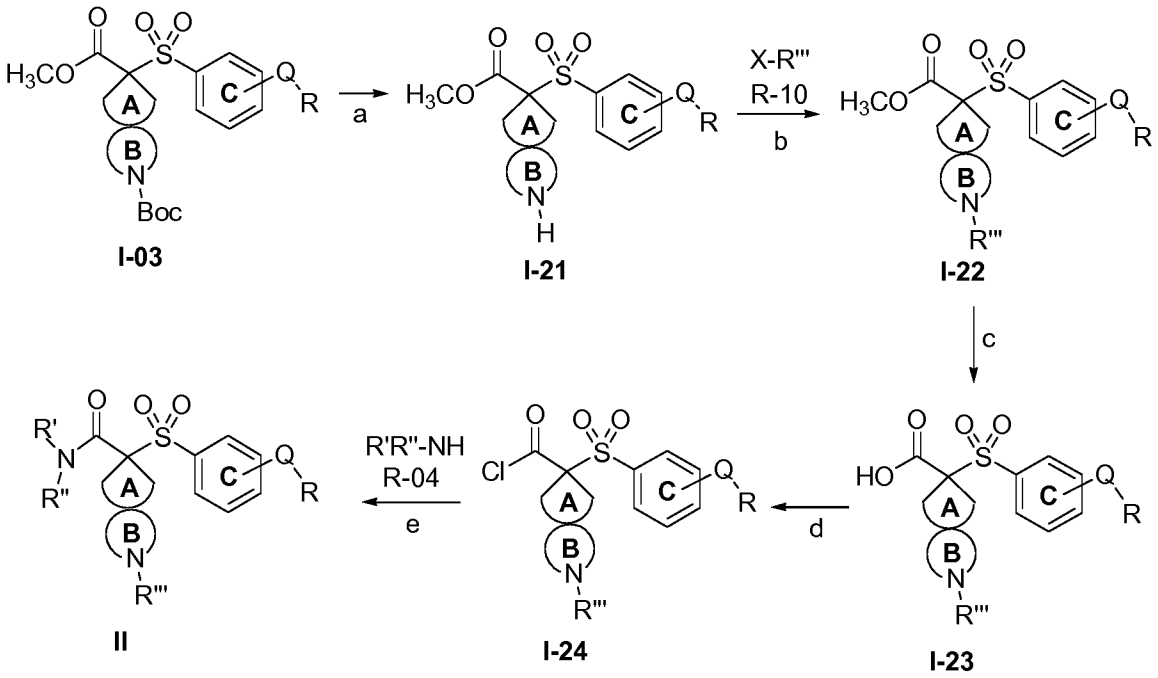
Preparation of compound 1-25: phenyl 3-(3-chloro-4-methoxy-phenyl)sulfonyl-8-azaspiro[4.5]decane-3-carboxylate

A solution of intermediate I-20a (113 mg, 0.19 mmol) in HCl/EtOAc (1.0 M, 25 mL) was stirred at room temperature for 2 hrs, then concentrated to give the crude compound which was purified by prep-HPLC (General procedure, Method 1) to obtained pure compound 1-25 (29.1 mg, 33%) as a white solid. ESI-MS (M+1):464.1 calc. for C23H26ClNO5S. Rt is 2.68.

Following the same synthetic route 1e, and using the same reagents as for compound 1-25 unless otherwise indicated in the table below, the following compounds were obtained:

Example	Rt	$[M+1]^+$	LC-MS Method	Starting materials
1-23 (**Ij**)	2.01	444.0	1	methanol (R-09) and methylurea (R-04)
1-24 (**Ij**)	2.75	554.1	1	methanol (R-09) and tert butyl N-(2-amino-4-phenyl phenyl)carbamate (R-04)

Synthetic route 1(f)



Conditions: a. HCl/EtOAc, r.t. for 2 hours; b. K_2CO_3 (2 eq) and R-10 (1 eq) in CH_3CN, r.t. for 1 hour; c. $LiOH.H_2O$ (10 eq) in THF/MeOH/H_2O (3/3/2), r.t.; d. $(COCl)_2$ (3 eq) in CH_2Cl_2 and DMF at -5 ºC; then, r.t. for 3 hours; e. R-04 (1.2 eq) and Et_3N (3 eq) in CH_2Cl_2 at 0 ºC; then overnight at r.t.

In the scheme above Q is O, S or SO_2, R is phenyl or a 5- to 6- membered heteroaryl or a 3- to 7- heterocyclic or carbocyclic aliphatic ring or a hydrocarbon chain which can be optionally substituted, R' and R'' are independently phenyl or a 5- to 6- membered heteroaryl or a 3- to 7- heterocyclic or carbocyclic aliphatic ring or a hydrocarbon chain which can be optionally substituted or hydrogen and R''' is phenyl or a 5- to 6- membered heteroaryl or a 3- to 7- heterocyclic or carbocyclic aliphatic ring or a hydrocarbon chain which can be optionally substituted.

Preparation of intermediate I-21a: methyl 3-[4-[4-(trifluoromethoxy)phenoxy]-phenyl]sulfonyl-8-azaspiro[4.5]decane-3-carboxylate

A solution of compound I-03a (500 mg, 0.81 mmol) in HCl/EtOAc (1 M, 20 mL) was stirred at room temperature for 2 hrs, then concentrated to give the crude intermediate I-21a (406 mg, 97.0%) as a white solid. ESI-MS (M+1): 514.1 calc. for C24H26F3NO6S.

Preparation of intermediate I-22a: methyl 8-propyl-3-[4-[4-(trifluoromethoxy)-phenoxy]phenyl]sulfonyl-8-azaspiro[4.5]decane-3-carboxylate

A solution of intermediate I-21a (400 mg, 0.78 mmol) in CH3CN (20 mL) was added K2CO3 (214 mg, 1.56 mmol), 1-bromopropane (98.5 mg, 0.80 mmol, R-10). The resulting mixture was stirred at r.t. for 1 h. After TLC showed the staring materials were consumed completely, the mixture was diluted with EtOAc, washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude product which was purified by prep-TLC to give the intermediate 1-22a (400 mg, 92.0%). ESI-MS (M+1): 556.2 calc. for C27H32F3NO6S.

Preparation of intermediate I-23a: 8-propyl-3-[4-[4-(trifluoromethoxy)phenoxy]-phenyl]sulfonyl-8-azaspiro[4.5]decane-3-carboxylic acid

To a solution of intermediate I-22a (400 mg, 0.72 mmol) in THF/MeOH/H2O (3/3/2, 8 mL) was added LiOH.H2O (303 mg, 10 eq). The resulting mixture was stirred at r.t. for 8 hrs, after TLC showed the staring materials were consumed completely, then the mixture was diluted with water and adjusted pH to 3~4 with 1N HCl and the mixture was extracted with EtOAc, washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude product I-23a (200 mg, 51.4%) as a pale yellow solid which was used directly in the next step. ESI-MS (M+1): 542.2; calc. for C26H30F3NO6S.

Preparation of intermediate I-24a: 8-propyl-3-[4-[4-(trifluoromethoxy)phenoxy]-phenyl]sulfonyl-8-azaspiro[4.5]decane-3-carbonyl chloride

To a solution of intermediate I-23a (200 mg, 0.37 mmol) in CH2Cl2 (10 mL) was added (COCl)2 (188 mg, 1.48 mmol) and DMF (0.1 mL) at -5 ºC under N2. The mixture was stirred at r.t. for 3 hrs. The mixture was concentrated under vacuo to give the crude intermediate I-24a (200 mg, crude) used directly in next step.

Preparation of compound 1-26: N-(2-aminophenyl)-8-propyl-3-[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl-8-azaspiro[4.5]decane-3-carboxamide

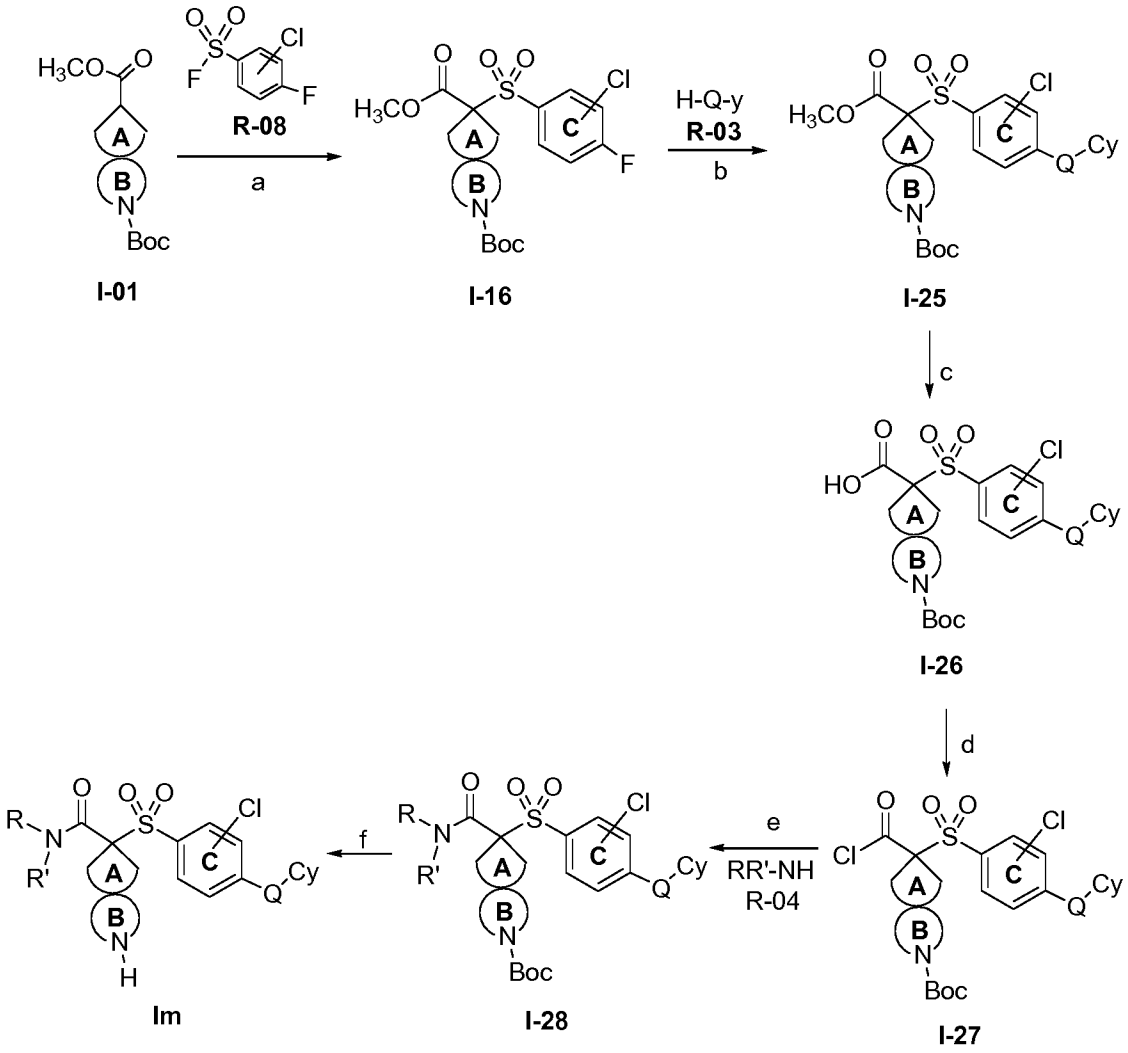
The crude intermediate I-24a (100 mg, 0.18 mmol) in CH2Cl2 (2 mL) was added to a solution of compound Et3N (54.2 mg, 0.54 mmol) and benzene-1,2-diamine (23.2 mg, 0.22 mmol, R-04) dissolved in CH2Cl2 (10 mL) at 0 ºC under N2. The resulting mixture was stirred at r.t. overnight until TLC showed

the starting material was consumed completely, then water was added and the mixture was extracted with CH2Cl2, the organic layer was washed with brine, dried over anhydrous Na2SO4, then concentrated to give the crude compound which was purified by prep-HPLC (General procedure, Method 1) to obtained pure compound 1-26 (51 mg, 45.1%) as a yellow solid. ESI-MS (M+1): 632.2 calc. for C32H36F3N3O5S. Rt is 3.29.

Following the same synthetic route 1f, and using the same reagents as for compound 1-26 unless otherwise indicated in the table below, the following compounds were obtained:

Example	Rt	$[M+1]^+$	LC-MS Method	Starting materials
1-27 (**II**)	2.99	598.1	1	p-trifluoromethoxyphenol (R-03) and methylurea (R-04)

Synthetic route 1(g)



Conditions: a. LDA (1.25 M) in THF, 1 hour at -78 ºC; then, R-08 (1.4 eq), 1 hour at -78 ºC and finally r.t. overnight; b. R-03 (1.2 eq) and Cs_2CO_3 (1.5 eq) in DMF, μW at 120 ºC, 1h; c. $LiOH.H_2O$ (10 eq) in $THF/H_2O/MeOH$ (R-09) (3/2/3), r.t.; d. $(COCl)_2$ (3 eq) in CH_2Cl_2 and DMF at -5 ºC; then, r.t. for 3 hours; e. R-04 (1 eq) and Et_3N (3 eq) in CH_2Cl_2 at 0 ºC; then overnight at r.t.; f. HCl/EtOAc, r.t. for 2 hours.

In the scheme above Q is O, S or SO_2, Cy is phenyl or a 5- to 6- membered heteroaryl and can be optionally substituted, R and R' are independently phenyl or a 5- to 6- membered heteroaryl or a 3- to 7- heterocyclic or carbocyclic aliphatic ring or a hydrocarbon chain which can be optionally substituted or hydrogen.

Preparation of intermediate I-25a: 8-tert-butyl 3-methyl 3-[3-chloro-4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl-8-azaspiro[4.5]decane-3,8-dicarboxylate

A solution of intermediate I-16a (100 mg, 0.2 mmol) in DMF (5 mL) was added the commercially available reagent p-trifluoromethoxyphenol (72.8 mg, 0.4 mmol, R-03), Cs2CO3 (196 mg, 0.6 mmol). The resulting mixture was stirred at 80 ºC for 40 mins by MW. After TLC showed the staring materials were consumed completely, and the mixture was extracted with EtOAc, washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude product I-25a (80 mg, 61.5%) which was purified by prep-TLC as a yellow solid. ESI-MS (M+1): 648.1 calc. for C29H33ClF3NO8S.

Preparation of intermediate I-26a: 8-tert-butoxycarbonyl-3-[3-chloro-4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl-8-azaspiro[4.5]decane-3-carboxylic acid

To a solution of intermediate I-25a (425 mg, 0.66 mmol) in THF/MeOH/H2O (9/9/6, 24 mL) was added LiOH.H2O (28 mg, 10 eq). The resulting mixture was stirred at r.t. for 8 hrs, after TLC showed the staring materials were consumed completely, then the mixture was diluted with water and adjusted pH to 3~4 with 1N HCl and the mixture was extracted with EtOAc, washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude product I-26a (400 mg, 94.1%) as a pale yellow solid which was used directly in the next step. ESI-MS (M+1): 635.1 calc. for C28H31ClF3NO8S.

Preparation of intermediate I-27a: tert-butyl 3-chlorocarbonyl-3-[3-chloro-4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl-8-azaspiro[4.5]decane-8-carboxylate.

To a solution of intermediate I-26a (160 mg, 0.25 mmol) in CH2Cl2 (10 mL) was added (COCl)2 (128 mg, 1.01 mmol) and DMF (0.1 mL) at -5 ºC under N2. The mixture was stirred at r.t. for 3 hrs. The mixture was concentrated under vacuo to give the crude intermediate I-27a (160 mg, crude) used directly in next step.

Preparation of intermediate I-28a: tert-butyl 3-[(2-aminophenyl)carbamoyl]-3-[3-chloro-4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl-8-azaspiro[4.5]decane-8-carboxylate

The crude intermediate I-27a (80 mg, 0.12 mmol) in CH2Cl2 (2 mL) was added to a solution of Et3N (37 mg, 0.37 mmol) and benzene-1,2-diamine (16 mg, 0.15 mmol, R-04) dissolved in CH2Cl2 (10 mL) at 0 ºC under N2. The resulting mixture was stirred at r.t. overnight until TLC showed the starting

material was consumed completely, then water was added and the mixture was extracted with CH2Cl2, the organic layer was washed with brine, dried over anhydrous Na2SO4, then concentrated to give the crude compound which was purified by prep-TLC to obtained pure intermediate I-28a (30 mg, 34.4%) as a yellow solid. ESI-MS (M+1): 725.1.calc. for C34H37ClF3N3O7S.

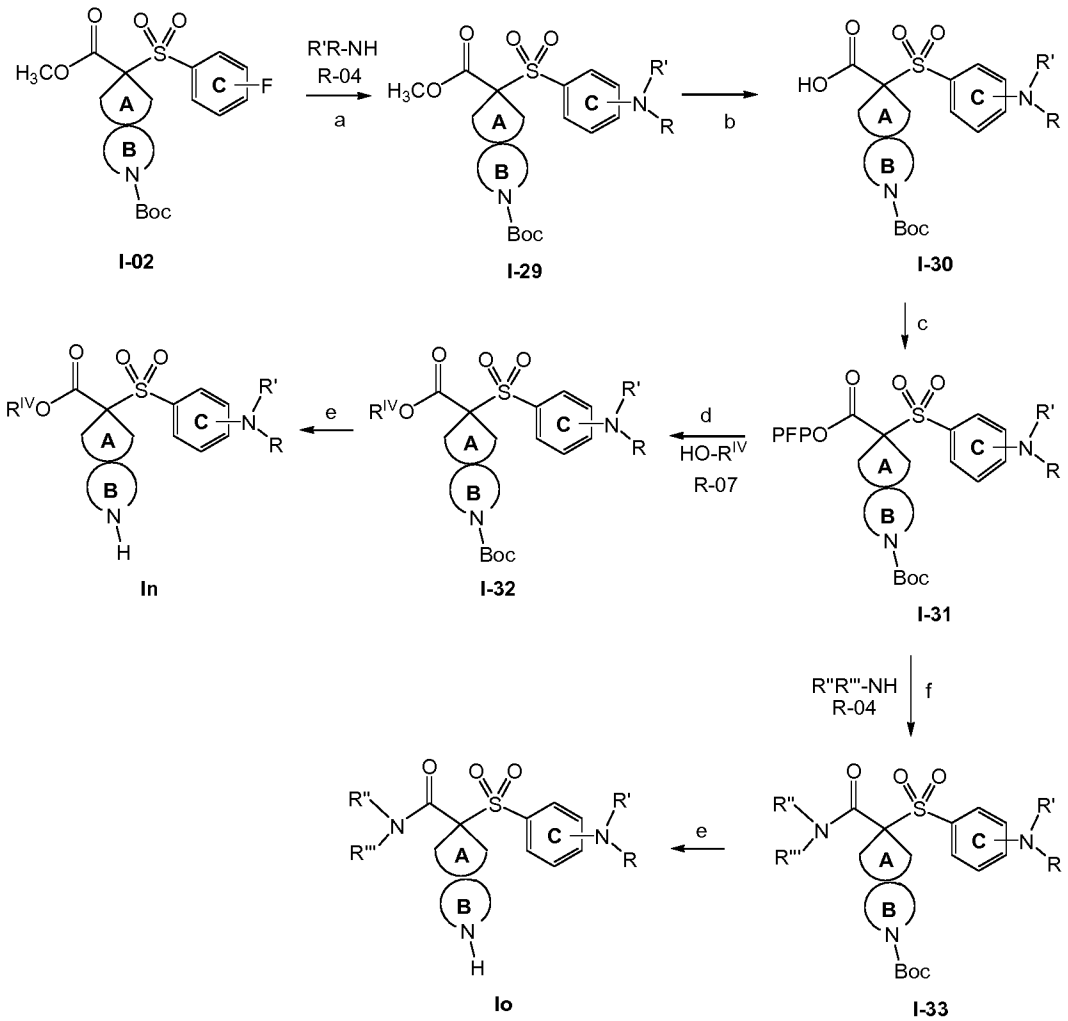
Preparation of compound 1-28: N-(2-aminophenyl)-3-[3-chloro-4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl-8-azaspiro[4.5]decane-3-carboxamide

A solution of intermediate I-28a (80 mg, 0.12 mmol) in HCl/EtOAc (1 M, 10 mL) was stirred at room temperature for 2 hrs, then concentrated to give the crude compound which was purified by prep-HPLC (General procedure, Method 1) to obtained pure compound 1-28 (6 mg, 10%) as a yellow solid. ESI-MS (M+1):624.1 calc. for C29H29ClF3N3O5S. Rt is 3.03.

Following the same synthetic route 1g, and using the same reagents as for compound 1-28 unless otherwise indicated in the table below, the following compounds were obtained:

Example	Rt	$[M+1]^+$	LC-MS Method	Starting materials
1-29 (**Im**)	2.83	590.1	1	p-trifluoromethoxyphenol (R-03) and methylurea (R-04)
1-31 (**Im**)	2.85	570.2	1	p-methoxyphenol (R-03) and benzene-1,2-diamine (R-04)
1-32 (**Im**)	2.57	536.1	1	p-methoxyphenol (R-03) and methylurea (R-04)

Synthetic route 1(h)



Conditions: a. R-04 (10 eq), overnight at 80 ºC; b. $LiOH.H_2O$ (10 eq) in $THF/H_2O/MeOH$ (R-09) (3/2/3), r.t.; c. DIC (1.5 eq) and PFP (1.1 eq) in CH_2Cl_2, at 0ºC for 3 hours; d. R-07 (1.3 eq) and Et_3N (3 eq) in CH_2Cl_2 at 0 ºC; then overnight at r.t. e. HCl/EtOAc, r.t. for 2 hours; f. DIEA (1.5 eq), DMAP (1 eq) and R-04 (1 eq)) in DMF at 60 ºC overnight.

In the scheme above R, R', R'', R''' and R^{IV} are independently phenyl or a 5- to 6- membered heteroaryl or a 3- to 7- heterocyclic or carbocyclic aliphatic ring or a hydrocarbon chain which can be optionally substituted or hydrogen.

Preparation of reagent R-02b: 4-Fluorobenzenesulfonyl fluoride.

To a solution of compound 2-Fluorobenzenesulfonyl chloride (4 g, 20 mmol) and KF (3.5 g, 60 mol), 18-crown-6 (1 g) in ACN (50 mL) was stirred at r.t overnight. The mixture was quenched with aqueous H2O and extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude product which was purified by column chromatography to give pure compound 150-1 (4 g, 89%) as a pale yellow oil. GC-MS (M+1): 179 calc. for C6H4F2O2S.

Preparation of intermediate I-02b: 8-tert-butyl 3-methyl 3-(2-fluorophenyl)sulfonyl-8-azaspiro[4.5]decane-3,8-dicarboxylate.

To a solution of intermediate I-01a (1.1 g, 3.7 mmol) in THF (10 mL) was added LDA (4.2 mL, 1.25 M, 5.2 mmol) at -78 ºC. After stirring at-78 ºC for 2 h, the reagent R-02b (0.93 g, 5.2 mmol) was added to the solution, the reaction was stirred at -78 ºC for 1 hour, and then the mixture was stirred at r.t overnight. After TLC showed the starting material was consumed, the mixture was quenched with aqueous NH4Cl and extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude product which was purified by column chromatography to give pure intermediate I-02b (615 g, 39%) as a pale yellow oil. ESI-MS (M-55): 400.1 calc. for C22H30FNO6S.

Preparation of intermediate I-29a: 8-tert-butyl 3-methyl 3-[2-(cyclohexylamino)phenyl]sulfonyl-8-azaspiro[4.5]decane-3,8-dicarboxylate.

The intermediate I-02b (615 mg, 1.35 mmol) was dissolved in cyclohexylamine (1.36 g, 13.5 mmol, R-04). The solution was stirred at 85 ºC overnight. The mixture was quenched with aqueous water and extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude product which was purified by prep-TLC to give the intermediate I-29a (450 mg, 62%) as a pale yellow solid. ESI-MS (M-55): 480.1; calc. for C28H42N2O6S.

Preparation of intermediate I-30a: 8-tert-butoxycarbonyl-3-[2-(cyclohexylamino)phenyl]sulfonyl-8-azaspiro[4.5]decane-3-carboxylic acid.

To a solution of intermediate I-29a (450 g, 0.85 mmol) in THF/MeOH/H2O (9/9/6, 24 mL) was added LiOH.H2O (357 mg, 10 eq). The resulting mixture was stirred at r.t for 6 hrs, after TLC showed the staring materials were consumed completely, then the mixture was diluted with water and adjusted pH to 2-3 with 1N HCl and the mixture was extracted with EtOAc, washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude intermediate I-30a (400 mg, 91%) as a pale yellow oil which was used in the next step. ESI-MS (M-55): 465.2; calc. for C27H40N2O6S.

Preparation of intermediate I-31a: 8-tert-butyl 3-(2,3,4,5,6-pentafluorophenyl) 3-[2-(cyclohexylamino)phenyl]sulfonyl-8-azaspiro[4.5]decane-3,8-dicarboxylate

To a solution of intermediate I-30a (150 mg, 0.29 mmol) and pentafluorophenol (50 mg, 0.32 mmol) in CH2Cl2 (10 mL) was added DIC (60 mg, 0.48 mmol) at 0 ºC under N2. The mixture was stirred at 0 ºC for 3 hrs. After TLC showed the staring materials were consumed completely, and the mixture was extracted with EtOAc, washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude intermediate I-31a (170 mg, 96 %) which was purified by prep-TLC as a yellow solid. ESI-MS (M-55): 631.1 calc. for C33H39F5N2O6S.

Preparation of intermediate I-33a: tert-butyl 3-[(2-aminophenyl)carbamoyl]-3-[2-(cyclohexylamino)phenyl]sulfonyl-8-azaspiro[4.5]decane-8-carboxylate

To a solution of intermediate I-31a (140 mg, 0.24 mmol) in DMF (5 mL) was added DMAP (40 mg, 0.26 mmol), DIEA (50 mg, 0.38 mmol) and benzene-1,2-diamine (28 mg, 0.25 mmol, R-04) at r.t, then the mixture was stirred at 60 ºC overnight. The mixture was quenched with aqueous water and extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude product which was purified by prep-TLC to give the intermediate I-33a (60 mg, 42%) as a pale yellow solid. ESI-MS (M+1): 611.2; calc. for C33H46N4O5S.

Preparation of compound 1-30: N-(2-aminophenyl)-3-[2-(cyclohexylamino)phenyl]sulfonyl-8-azaspiro[4.5]decane-3-carboxamide

A solution of compound intermediate I-33a (60 mg, 0.1 mmol) in EtOAc/dioxane (10 mL) was stirred at r.t for 1 h, then concentrated to give the crude product which was purified by prep-HPLC (General procedure, Method 1) to obtained pure compound 1-30 (9.1 mg, 18 %) as a yellow solid. ESI-MS (M+1): 511.2 calc. for C28H38N4O3S. Rt is 2.83.

Preparation of intermediate I-32a: 8-tert-butyl 3-phenyl 3-[4-(cyclohexylamino)phenyl]sulfonyl-8-azaspiro[4.5]decane-3,8-dicarboxylate.

To a solution of intermediate I-31a (70 mg, 0.1 mmol) in DMF (5 mL) was added phenol (19 mg, 0.2 mmol, R-07), DMAP (14 mg, 0.11 mmol) and DIEA (14 mg, 0.11 mmol) at r.t, then the mixture was stirred at 60 ºC overnight. The mixture was quenched with aqueous water and extracted with EtOAc, the

organic layer was washed with brine, dried over anhydrous Na2SO4, concentrated to give the crude product which was purified by prep-TLC to give the intermediate I-32a (35 mg, 58.3%) as a pale yellow solid. ESI-MS (M-55): 541.2, calc. for C33H44N2O6S.

Preparation of compound 1-34: phenyl 3-[4-(cyclohexylamino)phenyl]sulfonyl-8-azaspiro[4.5]decane-3-carboxylate

A solution of intermediate I-32a (35 mg, 0.06 mmol) in HCl/EtOAc (1 M, 5 mL) was stirred at room temperature for 2 hrs, then concentrated to give the crude compound which was purified by prep-HPLC (General procedure, Method 1) to obtained pure compound 1-34 (8 mg, 26.7%) as a yellow solid. ESI-MS (M+1):497.2 calc. for C28H36N2O4S. Rt is 3.17.

Following the same synthetic route 1h, and using the same reagents as for compounds 1-30 or 1-34 unless otherwise indicated in the table below, the following compounds were obtained:

Example	Rt	$[M+1]^+$	LC-MS Method	Starting materials
1-33 (**Io**)	2.83	511.3	1	cyclohexylamine (R-04) and benzene-1,2-diamine (R-04)

Synthesized compounds are obtained as racemic mixtures. Corresponding isomers are purified by supercritical fluid chromatography (SFC) to obtain two enantiomers from each racemic compound.

Antifibrinolytic effect on whole blood clot formation and lysis

Thromboelastometry is a viscoelastometric method for haemostasis testing in whole blood. TEM® measures the interactions of coagulation factors, inhibitors and cellular components during the phases of clotting and subsequent lysis over time. The rheological conditions of this method mimic the sluggish flow of blood in veins.

Detection method:

Blood samples were obtained between 8-9 a.m. from healthy volunteers and mice in tubes containing citrate solution (0.129 M sodium citrate, Vacutainer BD) and ROTEM tests were performed following the technical details of the ROTEM® analyser (Pentapharm GmbH, Munich, Germany). A modification of

in-tem test as described below was used for the examination of antifibrinolytic effects of tested compounds and its interaction with platelets in citrated blood. Kits: START-TEM assay as a recalcification reagent (ref#503-01) and IN-TEM assay for activation of intrinsic coagulation pathway (ref #503-02).

Procedure:

In a pre-warmed cuvette and holder 1 µL of tPA (150,000 U/mL, Actylise), 20 µL of start-tem reagent ($CaCl_2$), 20 µL of in-tem reagent (activators of coagulation system), 3 µL of DMSO (control) or tested compounds (CMs) in DMSO and 300 µL of citrated blood pre-warmed were pipetted. The cup holder containing the sample mixture was placed immediately on the appropriate channel. The measurement was recorded for 60 min to allow clot formation and lysis.

Table 1 shows the results in human blood as effective concentration to delay lysis time by 50% (EC_{50LT}); where, $EC_{50LT} \geq 25$ µM (+),10 µM $\leq EC_{50LT} < 25$ µM (++), 1 µM $\leq EC_{50LT} < 10$ µM (+++), $EC_{50LT} < 1$ µM (++++) at all the assayed concentrations (1000-0.2 µM).

Example	EC_{50LT}	Example	EC_{50LT}
TXA	+++	1-20	+
1-01	+++	1-21	+
1-02	++++	1-22	+++
1-03	+	1-23	+
1-04	+	1-24	++
1-06	+	1-25	+++
1-07	+	1-26	++++
1-08	++++	1-27	+
1-09	+	1-28	+++
1-10	+++	1-29	+++
1-13	++++	1-30	+++
1-14	+	1-31	+
1-15	++++	1-32	+++
1-16	++++	1-33	++++
1-17	+++	1-34	+
1-18	+++	1-35	+++
1-19	+		

Table 1

Table 2 shows the results in mice blood as effective concentration to delay lysis time by 50% (EC_{50LT}); where, EC_{50LT} ≥10μM (+),1 μM ≤ EC_{50LT} < 10μM (++),1 nM ≤ EC_{50LT} < 1 μM (+++) and EC_{50LT} < 1 nM (++++) for all the assayed concentrations (1000-0.2 μM).

Example	EC_{50LT}
TXA	+++
1-15	++
1-26	+++

Table 2

As observed in the tables above (Tables 1 and 2), compounds of the invention show significant delay in the lysis time, in many cases higher than TXA.

Antifibrinolytic effect *in vivo* (tail bleeding assay)

Bleeding time was evaluated in 2 months old wild-type C57Bl6 (n=10) mice by removing the tail tip. Mice (20-25 g) were anaesthetized with 2.5% isoflurane and maintained at 37 ºC on heating pads. The hemostatic efficacy was evaluated in a hyperfibrinolytic bleeding model.

Hyperfibrinolytic bleeding model, consisted in injection of 0.5 mg/kg tPA into the ocular plexus to prolong bleeding time due to excessive fibrinolysis. First, the femoral vein was exposed and cannulated with a saline-filled polyurethane catheter (Microcannula 72-9030, Harvard Apparatus) for agents administration. The catheter was connected to a syringe pump (AL-1000, WPI) for the infusion of 200 μL (10% bolus, 90% perfusion during 40 minutes) of tested agents. Then, tPA (0.5 mg/kg) was injected into the ocular plexus and five minutes after tPA administration, saline or the different compounds was infused through the femoral catheter to ensure systemic distribution of all the agents. Reference compounds, TXA and Aprotinin, were administered at 300 and 10 mg/Kg respectively; however, all compounds of the invention were administered at 1 mg/Kg. Five minutes later, 5 mm of tail tip were removed using a scalpel blade and the tail tip bathed in 1 mL of sterile saline at 37 ºC. The time of bleeding was defined as the interval between initial transections and the visual cessation of bleeding, that was measured up to 30

minutes. A value of 30 min was assigned to those animals bleeding longer than the observation period. Table 3 shows the results reporting bleeding time (BT); where BT ≥ 20 minutes (+),10 minutes ≤ BT < 20 minutes (++), 5 minutes ≤ BT < 10 minutes (+++) and BT < 5 minutes (++++). Bleeding time was determined in wild type mice (C57/BI6), where n ≥ 10 per assayed compound; therefore, BT is reported as a mean value - in the case of saline, BT is reported as mean±ESM.

Example	BT
Saline	28.9±0.7
TXA	++**
Aprotinin	++**
1-15	+*
1-26	++++**††
1-33	+++**

*p<0.05;**p<0.01 vs saline; †p<0.05; ††p<0.01 vs TXA

Table 3

As shown in table 3, tested compounds of the invention show a significant reduction of the bleeding time. In all the cases the dose of tested compounds was lower than TXA or Aprotinin doses.

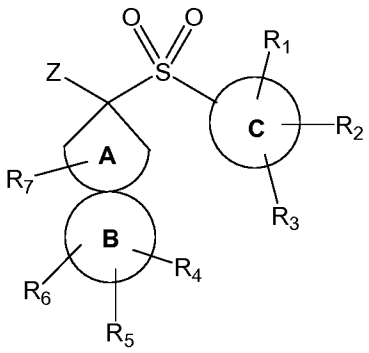
REFERENCES CITED IN THE APPLICATION

Green and P. G. M. Wuts, Protective Groups in Organic Chemistry, Wiley, 3rd ed. 1999, Chapter 5, pp. 369-451.

Peiqiang Huang, *et al.,* Synthetic Communications, 1991, 21 (22), 2369-2376.

CLAIMS

1. A compound of formula (I), or a pharmaceutically or veterinary acceptable salt thereof, or any stereoisomer either of the compound of formula (I) or of its pharmaceutically or veterinary acceptable salt



(I)

wherein

A and B form a spirocyclic ring system wherein the spiro atom connecting A and B is a carbon atom and wherein

A is a known 3- to 8-membered carbocyclic or heterocyclic monocyclic ring, saturated or partially unsaturated; or alternatively

A is a known 6- to 18-membered carbocyclic or heterocyclic polycyclic ring system, saturated, partially unsaturated, or partially aromatic; and

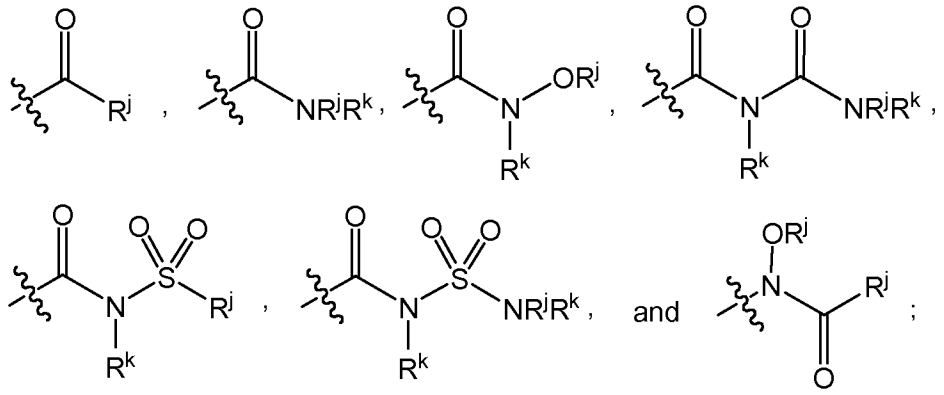
B is a known 4- to 7-membered carbocyclic or heterocyclic monocyclic ring, saturated or partially unsaturated;

C is phenyl or a known 5- to 6-membered heteroaromatic ring;

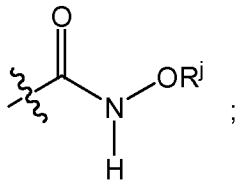
R_1-R_3 are independently selected from H, halogen, -NO_2, -CN, R^a, -$OR^{a'}$, -$OC(Y)R^{a'}$, -$OC(Y)OR^{a'}$, -$OC(Y)NR^bR^{a'}$, -$OSO_2OR^{a'}$, -$NR^bR^{a'}$, -$NR^bC(Y)R^{a'}$, -$NR^bC(Y)OR^{a'}$, -$NR^bC(Y)NR^bR^{a'}$, -$NR^bS(O)_2R^{a'}$, -$NR^bSO_2NR^bR^{a'}$, -$SR^{a'}$, -$S(O)R^{a'}$, -$S(O)OR^{a'}$, -$SO_2R^{a'}$,-$SO_2(OR^{a'})$, -$SO_2NR^bR^{a'}$, -$SC(Y)NR^bR^{a'}$, -$C(Y)R^{a'}$, -$C(Y)OR^{a'}$, -$C(Y)NR^bR^{a'}$, -$C(Y)NR^bOR^{a'}$, and -$C(O)NR^bSO_2R^{a'}$;

R_4-R_7 are independently selected from halogen, -NO_2, -CN, R^c, -OR^c, -NR^dR^c, -$NR^dC(Y)R^c$, -$NR^dC(Y)OR^c$, -$NR^dC(Y)NR^dR^c$, -$NR^dS(O)_2R^c$, -$NR^dSO_2NR^dR^c$, -SR^c, -$S(O)R^c$, -$S(O)OR^c$, -SO_2R^c, -$SO_2R(OR^c)$, -$SO_2NR^dR^c$, -$SC(Y)NR^dR^c$, -$C(Y)R^c$, -$C(Y)OR^c$, -$C(Y)NR^dR^c$, -$C(Y)NR^dOR^c$,and -$C(O)NR^dSO_2R^c$;

Z is selected from the group consisting of R^j, -C(O)OPh,



with the proviso that Z is other than



R^a is a saturated or unsaturated (C_1-C_{12})alkyl optionally substituted with one or more substituents R^e and/or one Cy^1; or alternatively R^a is Cy^2;
wherein Cy^1 and Cy^2 are independently optionally substituted with: one Cy^3 and/or one or more substituents R^e, and/or one or more saturated or unsaturated (C_1-C_6)alkyl groups optionally substituted with one or more substituents R^e and/or one Cy^3; and
wherein any Cy^3 is optionally substituted with one or more substituents independently selected from R^e and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more substituents R^e;

each $R^{a'}$ and R^b are independently H or R^a;

R^c and each R^d are independently selected from H, Cy^4, and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more substituents R^h and/or one Cy^5;

wherein Cy^4 and Cy^5 are optionally substituted with one or more substituents independently selected from R^h and saturated or unsaturated $(C_1\text{-}C_6)$alkyl optionally substituted with one or more substituents R^h;

each R^e is independently selected from halogen, $-NO_2$, -CN, $-OR^f$, $-OC(Y)R^f$, $-OC(Y)OR^f$, $-OC(Y)NR^gR^f$, $-NR^gR^f$, $-NR^gC(Y)R^f$, $-NR^gC(Y)OR^f$, $-NR^gC(Y)NR^gR^f$, $-NR^gS(O)_2R^f$, $-NR^gSO_2NR^gR^f$, $-SR^f$, $-S(O)R^f$, $-S(O)OR^f$, $-SO_2R^f$, $-SO_2(OR^f)$, $-SO_2NR^gR^f$, $-SC(Y)NR^gR^f$, $-C(Y)R^f$, $-C(Y)OR^f$, $-C(Y)NR^gR^f$, $-C(Y)NR^gOR^f$ and $-C(O)NR^gSO_2R^f$;

R^f and each R^g are independently selected from H, Cy^6, and saturated or unsaturated $(C_1\text{-}C_6)$alkyl optionally substituted with one or more substituents R^h and/or one Cy^7;
wherein Cy^6 is optionally substituted with: one Cy^7, and/or one or more substituents R^h, and/or one or more saturated or unsaturated $(C_1\text{-}C_6)$alkyl groups optionally substituted with one or more substituents R^h and/or one Cy^7; and
wherein any Cy^7 is optionally substituted with one or more substituents independently selected from R^h and $(C_1\text{-}C_4)$alkyl optionally substituted with one or more substituents R^h;

each R^h is independently selected from halogen, $-NO_2$, -CN, $-OR^i$, $-OC(O)R^i$, $-OC(O)OR^i$, $-OC(O)NR^iR^i$, $-NR^iR^i$, $-NR^iC(O)R^i$, $-NR^iC(O)OR^i$, $-NR^iC(O)NR^iR^i$, $-NR^iS(O)_2R^i$, $-NR^iSO_2NR^iR^i$, $-SR^i$, $-S(O)R^i$, $-SO_2R^i$, $-SO_2(OR^i)$, $-SO_2NR^iR^i$, $-C(O)R^i$, $-C(O)OR^i$, $-C(O)NR^iR^i$, and $-C(O)NR^iOR^i$;

each R^i is independently H or $-(C_1\text{-}C_4)$alkyl optionally substituted with one or more halogen atoms;

R^j and each R^k are independently selected from H, Cy^8, and saturated or unsaturated $(C_1\text{-}C_6)$alkyl optionally substituted with one or more substituents R^h and/or one Cy^9;
wherein Cy^8 is optionally substituted with one or more substituents independently selected from R^h, Cy^9, and saturated or unsaturated $(C_1\text{-}C_6)$alkyl optionally substituted with one or more substituents R^h; and

wherein Cy^9 is optionally substituted with one or more substituents independently selected from R^h and saturated or unsaturated $(C_1\text{-}C_6)$alkyl optionally substituted with one or more substituents R^h;

Y is O, S, or NR^g;

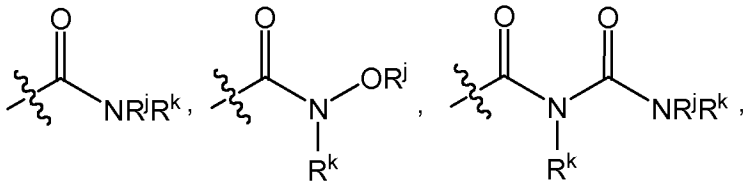
Cy^1, Cy^2, Cy^4 and Cy^6 are independently a C or N-attached known ring system selected from 3- to 8-membered carbocyclic or heterocyclic monocyclic ring, saturated or partially unsaturated; phenyl; 5- or 6-membered heteroaromatic ring; and 6- to 18-membered carbocyclic or heterocyclic polycyclic ring system, saturated, partially unsaturated, aromatic or partially aromatic;

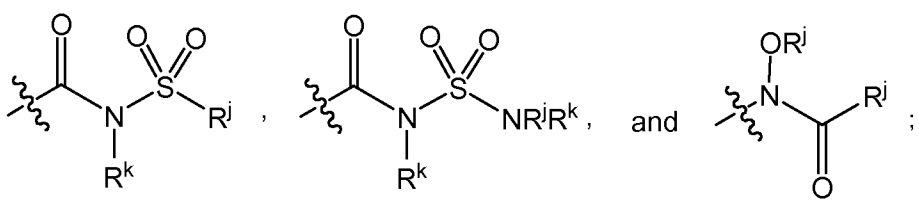
Cy^3, Cy^5, Cy^7, Cy^8 and Cy^9 are independently a C or N-attached known ring system selected from 3- to 8-membered carbocyclic or heterocyclic monocyclic ring, saturated or partially unsaturated; phenyl; and 5- or 6-membered heteroaromatic ring;

wherein in the carbocyclic rings all ring members are carbon atoms; and in the heterocyclic and heteroaromatic rings one or more ring members are selected from N, O, and S; and wherein in all saturated or partially unsaturated rings one or two members of the rings are optionally C(O) and/or C(NH) and/or C[N$(C_1\text{-}C_4)$alkyl];

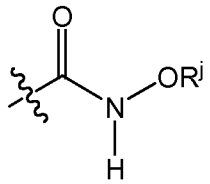
with the proviso that the compound of formula (I) is other than 1-[7-(phenylsulfonyl)-1,4-dioxaspiro[4.5]dec-7-yl]-2-propen-1-one.

2. The compound of formula (I) according to claim 1, wherein Z is selected from the group consisting of R^j,





with the proviso that Z is other than



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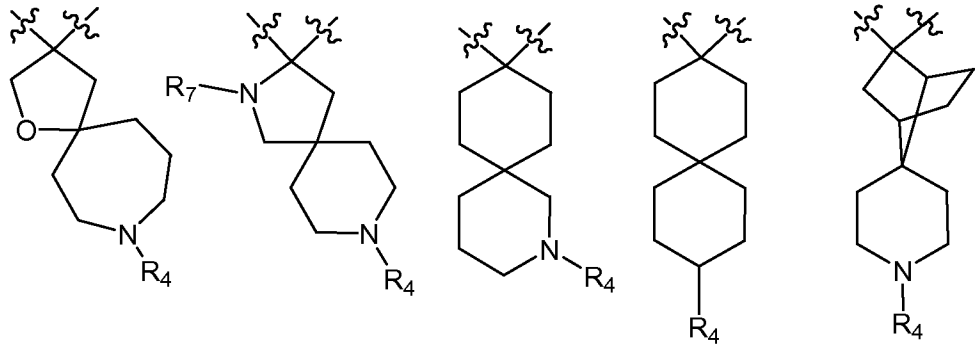
3. The compound of formula (I) according to claim 2, wherein Z is selected from the group consisting of -C(O)NR^{j}R^k, and -C(O)NR^{k}C(O)NR^{j}R^k.

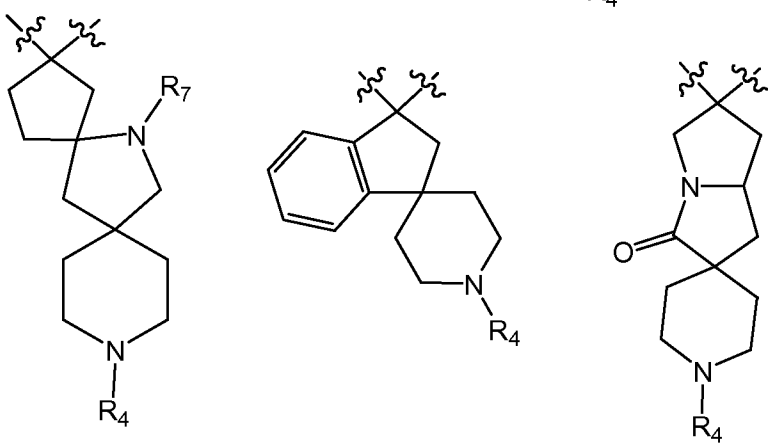
4. The compound of formula (I) according to any of the claims 2-3, wherein A is a known 3- to 8-membered carbocyclic or heterocyclic monocyclic ring or a known 6- to 10-membered carbocyclic or heterocyclic bicyclic ring system.

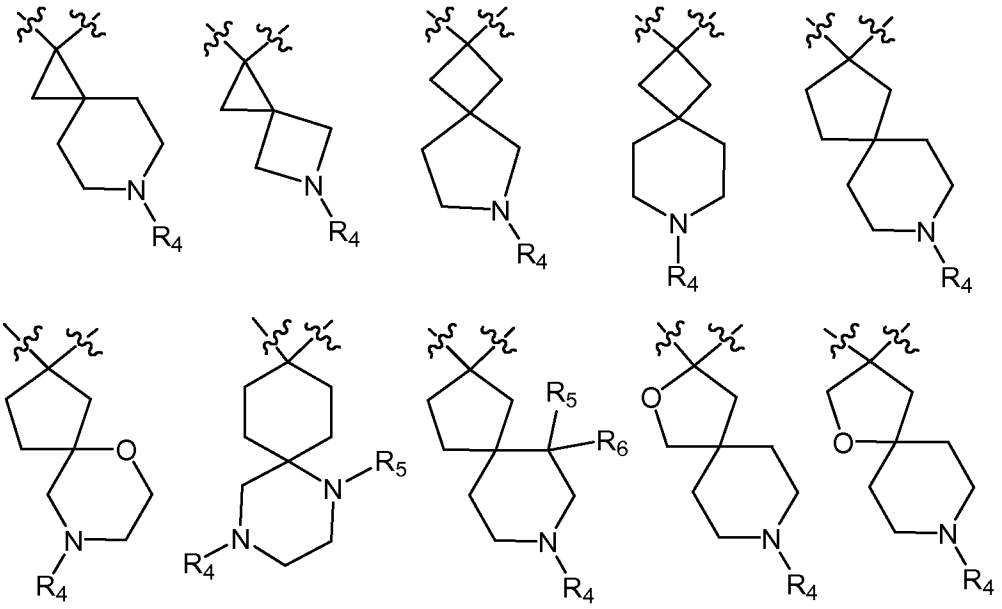
5. The compound of formula (I) according to claim 4, wherein A is a monocyclic ring selected from a 3- to 6-membered carbocyclic ring and a 5- to 6-membered heterocyclic ring.

6. The compound of formula (I) according to any of the claims 2-5, wherein B is a 6- to 7-membered carbocyclic or heterocyclic monocyclic ring.

7. The compound of formula (I) according to any of the claims 2-6, wherein A and B form a spirocyclic ring system selected from the group consisting of:







8. The compound of formula (I) according to any of the claims 2-7, wherein C is phenyl.

9. The compound of formula (I) according to any of the claims 2-8, wherein in R_1-R_3, R^f and each R^g are independently selected from H and saturated or unsaturated (C_1-C_6)alkyl optionally substituted with one or more fluorine atoms.

10. The compound of formula (I) according to any of the claims 2-9, wherein in R_1-R_3, Cy^1 and Cy^2 are independently optionally substituted with one or more substituents selected from R^e and saturated or unsaturated (C_1-C_6)alkyl optionally substituted; and Cy^6 is optionally substituted with one or more substituents independently selected from R^h and saturated or unsaturated (C_1-C_6)alkyl optionally substituted.

11. The compound of formula (I) according to any of the claims 2-10, wherein R_1-R_3 are independently selected from H, halogen, -NO_2, -CN, R^a, -$OR^{a'}$, -$OC(O)R^{a'}$, -$OC(O)OR^{a'}$, -$OC(O)NR^bR^{a'}$, -$NR^bR^{a'}$, -$NR^bC(O)R^{a'}$, -$NR^bC(O)OR^{a'}$, -$NR^bC(O)NR^bR^{a'}$, -$NR^bS(O)_2R^{a'}$, -$SR^{a'}$, -$S(O)R^{a'}$, -$SO_2R^{a'}$, -$SO_2NR^bR^{a'}$, -$C(O)R^{a'}$, -$C(O)OR^{a'}$, -$C(O)NR^bR^{a'}$, and -$C(O)NR^bOR^{a'}$.

12. The compound of formula (I) according to any of the claims 2-11, wherein R_4-R_7 are independently selected from halogen, -NO_2, -CN, R^c, -OR^c, -NR^dR^c,

$-NR^dC(O)R^c$, $-NR^dC(O)OR^c$, $-NR^dC(O)NR^dR^c$, $-NR^dS(O)_2R^c$, $-SR^c$, $-S(O)R^c$, $-SO_2R^c$, $-SO_2NR^dR^c$, $-C(O)R^c$, $-C(O)OR^c$, and $-C(O)NR^dR^c$.

13. The compound of formula (I) according to any of the claims 2-12, wherein R_2 and R_3 are independently selected from H, halogen, R^a, $-OR^{a'}$, and $-NR^bR^{a'}$; and R_5-R_7 are independently selected from H, halogen, R^c, $-OR^c$, and $-NR^dR^c$, wherein R^a, $R^{a'}$, R^b, R^c and R^d are independently selected from H and $-(C_1$-$C_4)$alkyl optionally substituted with one or more fluorine atoms.

14. A pharmaceutical or veterinary composition which comprises an effective amount of a compound of formula (I) as defined in any of the claims 1-13, or a pharmaceutically or veterinary acceptable salt thereof, or any stereoisomer either of the compound of formula (I) or of its pharmaceutically or veterinary acceptable salt, together with one or more pharmaceutically or veterinary acceptable excipients or carriers.

15. A compound of formula (I) according to any of the claims 1-13, or a pharmaceutically or veterinary acceptable salt thereof, or any stereoisomer either of the compound of formula (I) or of its pharmaceutically or veterinary acceptable salt, for use as a medicament.

16. A compound of formula (I) according to any of the claims 1-13, or a pharmaceutically or veterinary acceptable salt thereof, or any stereoisomer either of the compound of formula (I) or of its pharmaceutically or veterinary acceptable salt, for use as antifibrinolytic and antihemorrhagic agent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/050270

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C317/44 C07D221/20 C07D401/12 C07D409/12 C07D417/12
A61K31/438 A61P7/04
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)
C07C 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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	C.J. DUNN, ET AL.: "Tranexamic acid: a review of its use in surgery and other indications", DRUGS, vol. 57, no. 6, June 1999 (1999-06), pages 1005-1032, XP002231741, Adis International Ltd, NZ ISSN: 0012-6667, DOI: 10.2165/00003495-199957060-00017 page 1006	1-16

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

"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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 March 2015	02/04/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	English, Russell

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	D.L.J. CLIVE, ET AL.: "A route to linear, bridged or spiro polycyclic compounds: sequential use of the intermolecular Diels-Alder reaction and radical cyclisation", JOURNAL OF ORGANIC CHEMISTRY, vol. 55, no. 6, March 1990 (1990-03), pages 1786-1792, XP055177790, American Chemical Society, Washington, DC, US ISSN: 0022-3263, DOI: 10.1021/jo00293a022 compound 8c ----- Y. GAONI: "Preparation of ring-substituted (arylsulfonyl)cyclopropanes and (arylsulfonyl)bicyclobutanes from gamma,delta-epoxy sulfones", JOURNAL OF ORGANIC CHEMISTRY, vol. 47, no. 13, June 1982 (1982-06), pages 2564-2571, XP055177791, American Chemical Society, Washington, DC, US ISSN: 0022-3263, DOI: 10.1021/jo00134a012 compounds 3g, 3h ----- Y. GAONI, ET AL.: "Bridgehead reactivity, nucleophilic and radical additions, and lithium aluminum hydride reduction of 1-(arylsulfonyl)bicyclobutanes: general access to substituted, functionalised cyclobutanes", JOURNAL OF ORGANIC CHEMISTRY, vol. 50, no. 16, August 1985 (1985-08), pages 2948-2957, XP055177800, American Chemical Society, Washington, DC, US ISSN: 0022-3263, DOI: 10.1021/jo00216a028 compounds 30; page 2956, right-hand column, lines 57-62 ----- D. TANNER, ET AL.: "Stereocontrolled synthesis of the spirocyclic alkaloid (+/-)-nitramine", TETRAHEDRON LETTERS, vol. 29, no. 49, 1988, pages 6493-6495, XP055177792, Elsevier Science Publishers, Amsterdam, NL ISSN: 0040-4039, DOI: 10.1016/s0040-4039(00)82382-5 compound 5 ----- -/--	1,2,4,5, 9,11-13 1,2,4-6, 8,9, 11-13 1,2,4,5, 8,9, 11-13 1,2,4-6, 9,11,12

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WEIFENG SHI, ET AL.: "Stereoselective intramolecular 1,3 C-H insertion in Rh(II) carbene reactions", ORGANIC LETTERS, vol. 7, no. 14, 16 June 2005 (2005-06-16), pages 3103-3106, XP055177803, American Chemical Society, Washington, DC, US ISSN: 1523-7060, DOI: 10.1021/ol0511301 compounds 8a, 8b	1,2,4-6, 9,11,12
X	J. GOLINSKI, ET AL.: "Reactions of organic anions; part LXXXIV. A convenient method for synthesis of 1-chloro-, 1,1-dichloro- and 1,2-epoxyalkanesulfonamides", SYNTHESIS, vol. 1978, no. 11, 1978, pages 823-825, XP055168558, Georg Thieme Verlag, Stuttgart, DE ISSN: 0039-7881, DOI: 10.1055/s-1978-24899 compound 5e	1,2,4-6, 9,11-13

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	T. YOSHIDA, ET AL.: "A new procedure for desulfonylation: preparation of beta-substituted alpha,beta-unsaturated ketones and aldehydes", CHEMISTRY LETTERS, no. 2, 1982, pages 165-168, XP055178047, ISSN: 0366-7022, DOI: 10.1246/cl.1982.165 table: starting materials and intermediates in runs 1-6	1,2,4-6, 9,11-13
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X	US 2009/131419 A1 (J.L. CASTRO PINEIRO,, ET AL.) 21 May 2009 (2009-05-21) table, paragraph [0104], 4th entry; paragraphs [0116] - [0117]; examples 89, 147	1,2,4-6, 11-15

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Information on patent family members

International application No
PCT/EP2015/050270

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