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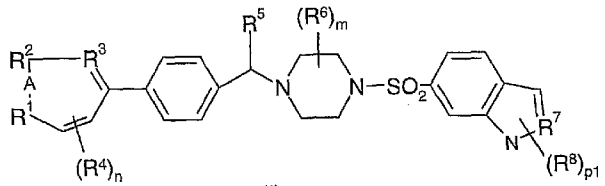
(54) Title: HETEROCYCLIC SULFONAMIDE DERIVATIVES AS INHIBITORS OF FACTOR XA



(I)

(57) Abstract: The invention relates to compounds of formula (I), wherein R^1, R^2 and R^3 are independently selected from carbon and nitrogen, and where at least one of R^1, R^2 and R^3 is nitrogen; A is a single bond or a double bond; n is 0, 1, 2 or 3; each R^4 is independently selected from hydrogen, C_{1-3} alkyl, hydroxy, oxo and thioxo; R^5 is hydrogen or oxo; m is 0, 1, 2 or 3; each R^6 is independently selected from hydrogen, C_{1-5}alkyl, oxo, carboxy, cyano, tetrazolyl, hydroxy C_{1-5} alkyl, carboxy C_{1-5} alkyl, C_{1-5} alkylcarboxy, C_{1-5}alkoxyoxo C_{1-5} alkyl, carbamoyl, C_{1-5} alkylcarbamoyl, di(C_{1-5} alkyl) carbamoyl, $-CONR^{80}(CH_2)_xS(O)_pR^9$, $-CONH(CH_2)_qNR^{10}R^{11}$, $-C_{1-5}$alkyl-Y, $-COOCHR^{17}R^{18}$ and $-CONR^{17}R^{18}$; R^7 is carbon or nitrogen; p1 is 0, 1 or 2; each R^8 is independently selected from hydrogen and halogen; or a pharmaceutically acceptable salt thereof, said compounds possess antithrombotic and anticoagulant properties and are accordingly useful in methods of treatment of humans or animals. The invention also relates to processes for the preparation of the compounds, to their use, to pharmaceutical compositions comprising them, to their use in the manufacture of medicaments for use in the production of an antithrombotic or anticoagulant effect, and to combinations comprising them.

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HETEROCYCLIC SULFONAMIDE DERIVATIVES AS INHIBITORS OF FACTOR Xa

The invention relates to novel heterocyclic derivatives, or pharmaceutically-acceptable salts thereof, which possess antithrombotic and anticoagulant properties and are accordingly useful in methods of treatment of humans or animals. The invention also relates to processes for the preparation of the heterocyclic derivatives, to their use, to pharmaceutical compositions comprising them, to their use in the manufacture of medicaments for use in the production of an antithrombotic or anticoagulant effect, and to combinations comprising them.

The antithrombotic and anticoagulant effect produced by the compounds of the invention is believed to be attributable to their strong inhibitory effect against the activated coagulation protease known as Factor Xa. Factor Xa is one of a cascade of proteases involved in the complex process of blood coagulation. The protease known, as thrombin is the final protease in the cascade and Factor Xa is the preceding protease, which cleaves prothrombin to generate thrombin.

Certain compounds are known to possess Factor Xa inhibitory properties and the field has been reviewed by B.-Y. Zhu, R. M. Scarborough, Current Opinion in Cardiovascular, Pulmonary & Renal Investigational Drugs, 1999, 1(1), 63-88. Thus it is known that two proteins, one known as recombinant antistasin (r-ATS) and the other known as recombinant tick anticoagulant protein (r-TAP), are specific direct Factor Xa inhibitors which possess antithrombotic properties in various animal models of thrombotic disease.

It is also known that certain non-peptidic compounds possess Factor Xa inhibitory properties. Of the low molecular weight inhibitors mentioned in the review by B.-Y. Zhu and R. M. Scarborough, many inhibitors possess a strongly basic group such as an amidinophenyl or amidinonaphthyl group.

We have now found that certain heterocyclic derivatives possess Factor Xa inhibitory activity. Many of the compounds of the present invention also possess the advantage of being selective Factor Xa inhibitors, that is the enzyme Factor Xa is inhibited strongly at concentrations of test compound which do not inhibit or which inhibit to a lesser extent the enzyme thrombin which is also a member of the blood coagulation enzymatic cascade.

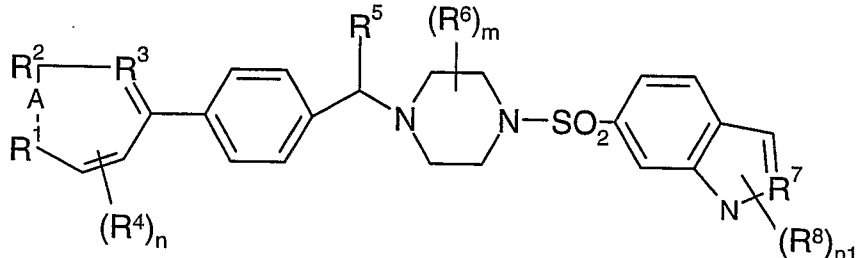
The compounds of the present invention possess activity useful in the treatment or prevention of a variety of medical disorders where anticoagulant therapy is indicated, for

example in the treatment or prevention of thrombotic conditions such as coronary artery and cerebrovascular disease. Further examples of such medical disorders include various cardiovascular and cerebrovascular conditions such as myocardial infarction, the rupture of atherosclerotic plaques, venous or arterial thrombosis, coagulation syndromes, vascular injury including reocclusion and restenosis following angioplasty and coronary artery bypass surgery, thrombus formation after the application of blood vessel operative techniques or after general surgery such as hip replacement surgery, the introduction of artificial heart valves or on the recirculation of blood, cerebral infarction, cerebral thrombosis, stroke, cerebral embolism, pulmonary embolism, ischemia and angina (including unstable angina).

The compounds of the invention are also useful as inhibitors of blood coagulation in an *ex vivo* situation such as, for example, the storage of whole blood or other biological samples suspected to contain Factor Xa and in which coagulation is detrimental.

WO 98/21188 describes a range of Factor Xa inhibitors. Further particular examples of this type of compound including 1-(5-chloroindol-2-ylsulphonyl)-4-[4-(6-oxo-1H-pyridazin-3-yl) benzoyl]piperazine are described in WO 99/57113. The applicants have found however, that by further derivatising the compounds of this type, enhanced properties may be obtained.

The present invention provides a compound of formula (I)



(I)

wherein R^1, R^2 and R^3 are independently selected from carbon and nitrogen, and where at least one of R^1, R^2 and R^3 is nitrogen

A is a single bond or a double bond;

n is 0, 1, 2 or 3;

each R^4 is independently selected from hydrogen, C_{1-3}alkyl, hydroxy, oxo and thioxo;

R^5 is hydrogen or oxo;

m is 0, 1, 2 or 3;

each R^6 is independently selected from hydrogen, C_{1-5}alkyl, oxo, carboxy, cyano, tetrazolyl, hydroxyC_{1-5}alkyl, carboxyC_{1-5}alkyl, C_{1-5}alkylcarboxy, C_{1-5}alkoxyoxoC_{1-5}alkyl, carbamoyl, C_{1-5}alkylcarbamoyl, di(C_{1-5}alkyl)carbamoyl, $-CONR^{80}(CH_2)_xS(O)_pR^9$, $-CONH(CH_2)_qNR^{10}R^{11}$, $-C_{1-5}$alkyl-Y^1, $-COOCHR^{17}R^{18}$ and $-CON\ R^{17}\ R^{18}$,

wherein x represents an integer 0 to 4;

p is 0, 1 or 2;

q represents an integer 2 to 4;

R^{80} represents hydrogen or C_{1-3}alkyl;

R^9 represents C_{1-5}alkyl or phenyl; or

R^{80} and R^9 may together form a C_{1-5}alkylene group;

R^{10} and R^{11} independently represent hydrogen, C_{1-5}alkyl, phenyl, C_{1-5}alkylphenyl, $S(O)_pR^9$, COR^{12} or a 5- or 6-membered monocyclic heteroaryl ring containing up to 3 heteroatoms selected from nitrogen, oxygen and sulphur;

R^{12} represents hydrogen, C_{1-5}alkyl or phenyl;

Y^1 represents $S(O)_pR^9$, $NHS(O)_2R^9$, $NHCOR^{13}$, $O(CH_2)_rR^{14}$, azetidino, pyrrolidin-1-yl, piperidino, morpholino, thiamorpholino, 1-oxothiamorpholino, 1,1-dioxothiamorpholino, piperazin-1-yl or C_{1-5}alkylamino,

R^{13} represents C_{1-5}alkyl, phenyl or C_{1-5}alkylphenyl;

r represents an integer 1 to 4;

when r represents an integer 2 to 4, R^{14} represents hydroxy, C_{1-5}alkylalkoxy, carboxy, C_{1-5}alkoxycarbonyl, $S(O)_pR^9$ or $NR^{15}R^{16}$; and when r represents 1, R^{14} represents carboxy or C_{1-5}alkoxycarbonyl;

wherein any phenyl group within R^6 is independently substituted by 0, 1 or 2 substituents selected from halogeno, trifluoromethyl, cyano, C_{1-5}alkyl and C_{1-5}alkoxy;

R^{15} and R^{16} independently represent hydrogen or C_{1-5}alkyl;

R^{17} and R^{18} are independently selected from hydrogen, C_{1-6}alkyl, C_{4-7}cycloalkyl, C_{2-6}alkenyl, R^{17} and R^{18} may form along with the carbon to which they are attached a 4- ,5- , 6- or 7- membered carbocyclic ring which contains 0, 1 or 2 heteroatoms selected from nitrogen, oxygen and sulphur, or R^{17} and R^{18} may form along with the nitrogen to which they are attached a 4- ,5- , 6- or 7- membered heterocyclic ring which contain in addition to the nitrogen atom present 0, 1 or 2 additional heteroatoms selected from nitrogen, oxygen

and sulphur, wherein each R^{17}, R^{18} or any of said rings formed by R^{17} and R^{18} is independently substituted by 0, 1 or 2 substituents selected from hydroxy, amino, carboxy, C_{1-5}alkoxycarbonyl, oxo, C_{1-5}alkyl, hydroxyC_{1-5}alkyl, C_{1-5}alkoxyC_{1-5}alkyl, carboxyC_{1-5}alkyl, C_{1-5}alkoxyoxoC_{1-6}alkyl, and carbamoylC_{1-5}alkyl;

R^7 is carbon or nitrogen;

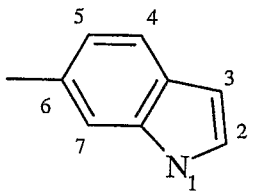
p1 is 0, 1 or 2; and

each R^8 is independently selected from hydrogen and halogen;

or a pharmaceutically acceptable salt thereof.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. An analogous convention applies to other generic terms.

For the avoidance of doubt, the atoms of the indolyl ring appearing in formula (I) is numbered as drawn below:



6-indolyl

It is to be understood that certain of the compounds of the formula (I) defined above can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms, which possess Factor Xa inhibitory activity.

It is further to be understood that, insofar as certain of the compounds of the formula (I) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention encompasses any such optically active or racemic form which possesses Factor Xa inhibitory activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form.

Further, "tautomer" or "tautomerism" refers to the coexistence of two (or more) compounds that differ from each other only in the position of one (or more) mobile atoms and in electron distribution, i.e. different tautomeric forms. An example may be keto-enol tautomers.

Moreover, it is also to be understood that, insofar as certain of the compounds of the formula (I) defined above may exist in various tautomeric forms, the invention encompasses any such tautomeric forms which possesses Factor Xa inhibitory activity.

Compounds of the invention are potent inhibitors of Factor Xa, and may have improved selectivity over oxido squalene cyclase, better solubility and/or less cytochrome P 450 (CYP_{450}) inhibition and/or Caco2-permeability than some related compounds. Caco2 is a cell line which mimics transport over the gut wall.

Suitable values in the compound of formula (I):

for halogen:	fluoro, chloro, bromo, iodo;
for C_{1-3}alkyl (also as in e.g. oxoC_{1-3}alkyl):	methyl, ethyl, propyl, isopropyl;
for C_{1-4}alkyl (also as in e.g. oxoC_{1-4}alkyl):	methyl, ethyl, propyl, isopropyl, n-butyl, secbutyl, isobutyl, tertbutyl;
for C_{1-5}alkyl (also as in e.g. oxoC_{1-5}alkyl):	C_{1-4}alkyl (as above), C_{1-3}alkyl (as above), n-butyl, isobutyl, pentyl, 2-pentyl, 3-pentyl, 2-methyl-1-butyl, isopentyl, neopentyl, 3-methyl-2-butyl, 2-methyl-2-butyl;
for C_{1-3}alkoxy:	methoxy, ethoxy, propoxy, isopropoxy;
for C_{1-4}alkoxy:	C_{1-3}alkoxy (as above), n-butoxy, secbutoxy, isobutoxy, terbutoxy;
for C_{1-5}alkoxy:	C_{1-4}alkoxy (as above), C_{1-3}alkoxy (as above), pentoxy, 2-pentoxy, 3-pentoxy, 2-methyl-1-butoxy, isopentoxy, neopentoxy, 3-methyl-2-butoxy, 2-methyl-2-butoxy;

for 4- , 5- , 6- or 7- membered heterocyclic ring: azetidine, pyrrolidine, morpholine, piperazine, azepane, [1,4]-diazepane, tetrahydro-pyran, or piperidin.

Moreover, the term "oxido" denotes a $^{-}$O-group (ion) and the term "carbamoyl" denotes a H_2N-C(O)-group.

In an embodiment of the invention a compound of formula (I) is disclosed wherein one or two of R^1, R^2 and R^3 is/are nitrogen.

A further embodiment of the invention discloses a compound of formula (I) wherein both R^2 and R^3 are nitrogen.

In a further embodiment of the invention a compound of formula (I) is disclosed wherein R^1 is nitrogen.

In still a further embodiment of the invention a compound of formula (I) is disclosed wherein A is a single bond.

In even a further embodiment of the invention a compound of formula (I) is disclosed wherein A is a double bond

A further embodiment of the invention discloses a compound of formula (I) where one of R^4 is oxo.

In a further embodiment of the invention a compound of formula (I) is disclosed wherein said R^4 being oxo is positioned at R^1.

In still a further embodiment of the invention a compound of formula (I) is disclosed where one of R^4 is C_{1-3}alkyl, e.g methyl.

In even a further embodiment of the invention a compound of formula (I) is disclosed where one or two of R^4 is/are hydrogen.

In a further embodiment of the invention a compound of formula (I) is disclosed where one of R^4 is hydroxy.

In still a further embodiment of the invention a compound of formula (I) is disclosed wherein R^5 is oxo.

In a further embodiment of the invention a compound of formula (I) is disclosed wherein each R^6 is independently selected from hydrogen, C_{1-5}alkyl, oxo, carboxy, cyano, tetrazolyl, hydroxyC_{1-5}alkyl, carboxyC_{1-5}alkyl, C_{1-5}alkylcarboxy, C_{1-5}alkoxyoxoC_{1-5}alkyl, carbamoyl, C_{1-5}alkylcarbamoyl, di(C_{1-5}alkyl)carbamoyl, $-CONR^{80}(CH_2)_xS(O)_pR^9$, $-CONH(CH_2)_qNR^{10}R^{11}$, $-C_{1-5}$alkyl-Y^1, $-COOCHR^{17}R^{18}$ and $-CON\ R^{17}\ R^{18}$.

In still a further embodiment of the invention a compound of formula (I) is disclosed wherein each R^6 is independently selected from hydrogen, C_{1-5}alkyl, oxo, carboxy, C_{1-5}alkyl, carboxyC_{1-5}alkyl, C_{1-5}alkylcarboxy, C_{1-5}alkoxyoxoC_{1-5}alkyl, $-C_{1-5}$alkyl-Y^1 and $-COOCHR^{17}R^{18}$.

In even a further embodiment of the invention a compound of formula (I) is disclosed wherein each R^6 is independently selected from hydrogen, C_{1-5}alkyl and oxo.

In a further embodiment of the invention a compound of formula (I) is disclosed wherein R^5 is hydrogen and at least one of R^6 is oxo.

In still a further embodiment of the invention a compound of formula (I) is disclosed wherein each R^6 is hydrogen.

In even a further embodiment of the invention a compound of formula (I) is disclosed wherein R^7 is carbon.

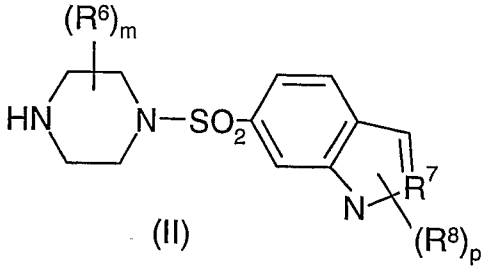
In a further embodiment of the invention a compound of formula (I) is disclosed wherein R^7 is nitrogen.

A further embodiment of the invention discloses a compound of formula (I) wherein at least one of R^8 is halogen, e.g. chloro or bromo.

In a further embodiment of the invention a compound of formula (I) is disclosed wherein each R^8 is hydrogen.

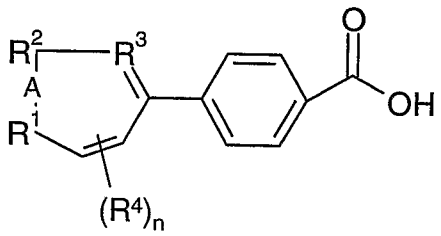
A further embodiment of the invention discloses a compound of formula (I) which is
6-{4-[4-(3-Chloro-1H-indazole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2H-pyridazin-3-one,
6-{4-[4-(3-Bromo-1H-indazole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2H-pyridazin-3-one,
6-{4-[4-(3-Bromo-1H-indole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2-methyl-2H-pyridazin-3-one,
6-{4-[4-(3-Chloro-1H-indole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2-methyl-2H-pyridazin-3-one,
6-{4-[4-(1H-Indole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2-methyl-2H-pyridazin-3-one,
[4-(3-Chloro-1H-indole-6-sulfonyl)-piperazin-1-yl]-[4-(6-hydroxy-pyridazin-3-yl)-phenyl]-methanone,
[4-(6-Hydroxy-pyridazin-3-yl)-phenyl]-[4-(1H-indole-6-sulfonyl)-piperazin-1-yl]-methanone,
[4-(3-Chloro-1H-indole-6-sulfonyl)-piperazin-1-yl]-(4-pyridin-4-yl-phenyl)-methanone,
[4-(1H-Indole-6-sulfonyl)-piperazin-1-yl]-(4-pyridin-4-yl-phenyl)-methanone or
6-{4-[S)-4-(3-chloro-1H-indole-6-sulfonyl)-2-methyl-6-sulfonyl)
-2-methyl-6-oxo-piperazin-1-ylmethyl]-phenyl}-2-methyl-2H-pyridazin-3-one.

For instance, the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt thereof, which comprises the reaction, conveniently in the presence of a suitable base, of an amine of formula (II) or a salt thereof,



(II)

with an acid of the formula (III),



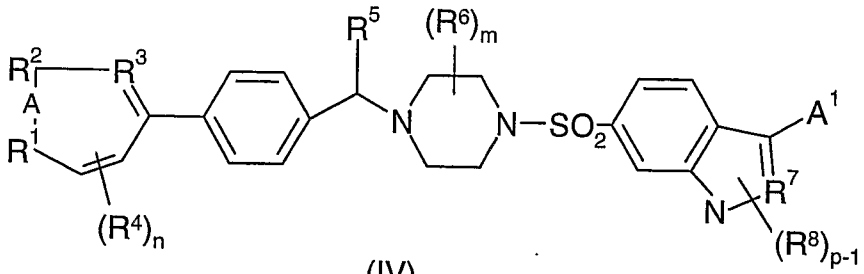
(III)

wherein R groups and A, n, p, p1 and m are as defined above in relation to formula (I), or a reactive derivative thereof.

A suitable reactive derivative of an acid of the formula (III) is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid with a chloroformate such as isobutyl chloroformate or with an activated amide such as 1,1'-carbonyldiimidazole; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol, an ester such as pentafluorophenyl trifluoroacetate or an alcohol such as *N*-hydroxybenzotriazole or *N*-hydroxysuccinimide; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as *N,N'*-dicyclohexylcarbodiimide or *N*-(3-dimethylaminopropyl)-*N'*-ethyl-carbodiimide.

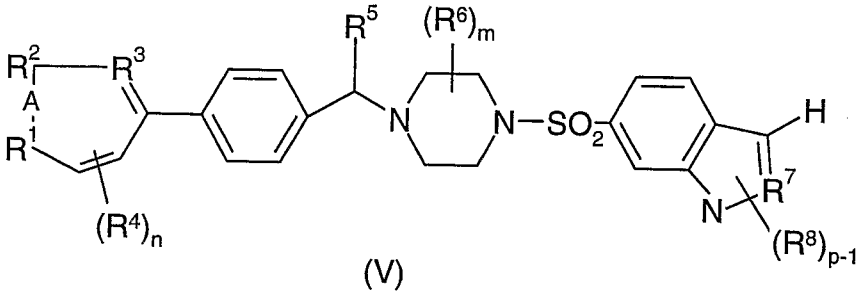
The reaction is conveniently carried out in the presence of a suitable base such as, for example, an alkali or alkaline earth metal carbonate, also preferably carried out in a suitable inert solvent or diluent, for example methylene chloride, and at a temperature in the range, for example, -78 °C to 150 °C, conveniently at or near ambient temperature.

Compounds of formula (IV) are suitably prepared by reacting a compound of formula (V),



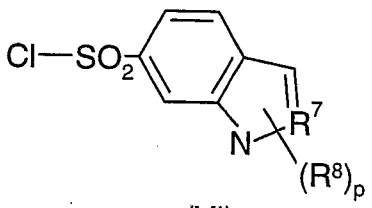
(IV)

wherein R groups, n, p, p1 and m are as defined above in relation to formula (I) and A^1 is halogen, with corresponding halogen succinimide in an inert solvent like dichloromethane or *N,N*-dimethylformamide at a temperature in the range -50 °C – 100 °C, conveniently at or near ambient temperature.



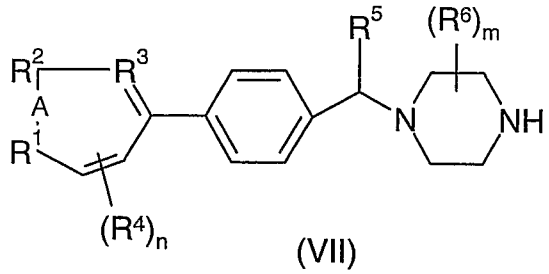
(V)

Alternatively, compounds of formula (I) are prepared by reaction a sulfonyl chloride derivative of formula (VI),



(VI)

with an amine of formula (VII) or a salt thereof,



(VII)

wherein the R-groups, A, n and m are as defined above in relation to formula (I).

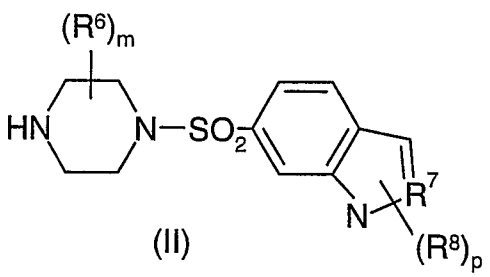
This reaction is carried out using a base such as *N,N*-dimethyl aminopyridine, diisopropylethyl amine in inert solvents, typically dichloromethane and *N,N*-dimethylformamide at a temperature in the range -50 °C – 100 °C, conveniently at or near ambient temperature.

When a pharmaceutically-acceptable salt of a compound of the formula (I) is required, it may be obtained, for example, by reaction of said compound with a suitable acid or base using a conventional procedure.

When an optically active form of a compound of the formula (I) is required, it may be obtained, for example, by carrying out one of the aforesaid procedures using an optically active starting material or by resolution of a racemic form of said compound using a conventional procedure, for example by the formation of diastereomeric salts, use of chromatographic techniques, conversion using stereospecific enzymatic processes, or by addition of temporary extra chiral group to aid separation.

The invention also relates to a process for preparing a compound of formula (I) which process comprises either

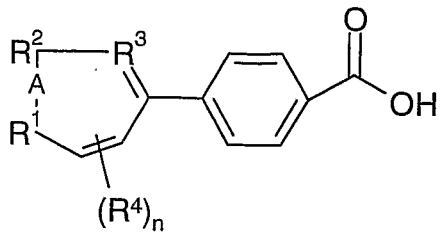
(a) reacting an amine of formula (II),



(II)

or a salt thereof,

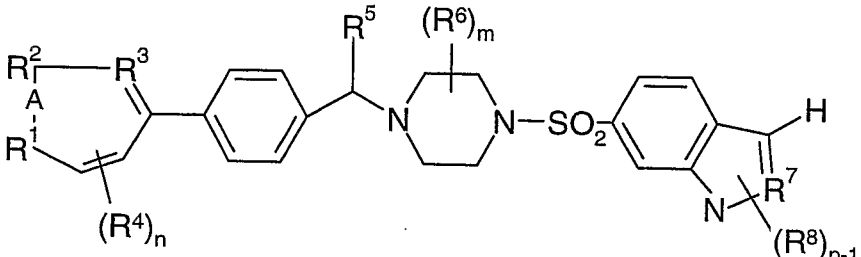
with an acid of the formula (III),



(III)

(b)

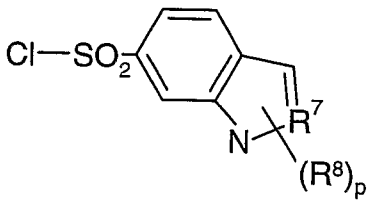
reacting a compound of formula (V),



(V)

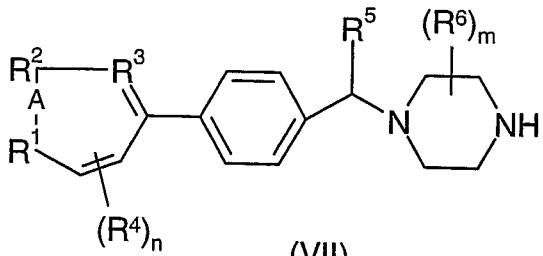
with corresponding halogen succinimide; or

(c) reacting a sulfonyl chloride derivative of formula (VI),



(VI)

with an amine of formula (VII) or a salt thereof.



(VII)

As stated previously, the compounds of the formula (I) are inhibitors of the enzyme Factor Xa. The effects of this inhibition may be demonstrated using one or more of the standard procedures set out hereinafter:-

a) Measurement of Factor Xa Inhibition

The FXa inhibitor potency was measured with a chromogenic substrate method, in a Plato 3300 robotic microplate processor (Rosys AG, CH-8634 Hombrechtikon, Switzerland), using 96-well, half-volume microtiter plates (Costar, Cambridge, MA, USA; Cat No 3690). Stock solutions of test substance in DMSO (72 µL), 10 mmol/L, alternatively 1 mmol/L were diluted serially 1:3 (24 + 48 µL) with DMSO to obtain ten different concentrations, which were analyzed as samples in the assay, together with controls and blanks. As control sample melagatran was analysed. The dilutions of each test substance were analyzed consecutively, row-wise on the microtiter plate, with wash-cycles between substances to avoid cross-contamination. First 2 µL of test sample or DMSO for the blank were added, followed by 124 µL of assay buffer (0.05 mol/L Tris-hydrochloric acid pH 7.4 at 37 °C, 5 mM $CaCl_2$, ionic strength 0.15 adjusted with NaCl, 0.1 % bovine serum albumin, ICN Biomedicals, Inc, USA, 1g/L) and 12 µL of chromogenic substrate solution (S-2765, Chromogenix, Mölndal, Sweden) and finally 12 µL of FXa solution (human FXa, Haematologic Technologies Inc., Essec Junction, Vermont, USA), in buffer, was added, and the samples were mixed. The final assay concentrations were: test substance 0.0068-133, respectively 0.00068-13.3 µmol/L, S-2765 0.40 mmol/L (K_M = 0.25 mmol/L) and FXa 0.1 nmol/L. The linear absorbance increase at 405 nm during 40 min incubation at 37 °C was used for calculation of percent inhibition for the test samples, as compared to references without inhibitor and/ or enzyme. The IC_{50}-value, corresponding to the inhibitor concentration, which caused 50 % inhibition of the FXa activity, was calculated by fitting the data to a three-parameter equation by Microsoft XLfit.

b) Measurement of Thrombin Inhibition

The thrombin inhibitor potency was measured with a chromogenic substrate method developed in-house in principle as described in a) for FXa but using instead 0.3 mM of the chromogenic substrate solution S-2366 (Chromogenix, Mölndal, Sweden) and 0.1 nmol/L human thrombin (Haematologic Technologies Inc., Essec Junction, Vermont, USA).

c) Measurement of Anticoagulant Activity

An *in vitro* assay whereby human blood is collected and added directly to a sodium citrate solution (3.2 g/100 mL, 9 parts blood to 1 part citrate solution). Plasma is prepared by centrifugation (1000 g, 15 minutes) and stored at –80 °C.) and an aliquot was rapidly thawed at 37 °C on the day of the experiment and kept on ice before addition to the coagulometer cups. Conventional prothrombin time (PT) tests are carried out in the presence of various concentrations of a test compound and the concentration of test compound required to double the clotting time is determined. Thromborel ® S (Dade Behring, Liederbach, Germany) was reconstituted with 10 mL water. This solution was kept at 4 °C and was used within one week. Before the experiment the solution was kept at 37 °C for at least 30 minutes before start of the experiment. A ball coagulation timer KC 10A from Heinrich Amelung GmbH. (Lemgo, Germany) was used to study if the compounds could prevent coagulation in human plasma. The time for 50 µl plasma with compound to coagulate after addition of 100 µl Thromborel S, the Prothrombin Time or PT_i, is compared with the time it takes for pure plasma to coagulate, PT_0. With this technique the change in viscosity in the stirred solution is used to define clotting. The IC_{50} is calculated from the curve of PT_i/PT_o versus the inhibitor concentration in plasma, *id est* three times the final assay concentration.

d) An *in vivo* Measurement of Antithrombotic Activity

The abdoman is opened and the caval vein exposed. The thrombotic stimulus is partial stasis to the caval vein and a piece of filter paper soaked with ferric chloride and superimposed to the external surface of the vein. Thrombus size is determined as the thrombus wet weight at the end of the experiment. (Ref Thromb. Res. 2002;107:163-168).

When tested in the above mentioned screen a) Measurement of Factor Xa Inhibition, the compounds of the Examples gave IC_{50} values for inhibition of Factor Xa activity of less than 10 µM, indicating that the compounds of the invention are expected to possess useful therapeutic properties.

Specimen results are shown in the following Table:

Compound	Factor Xa IC_{50} value (nM)
Example 10	0.5

A feature of the invention is a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in medical therapy.

According to a further feature of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

The composition may be in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use, for example a cream, ointment, gel or aqueous or oily solution or suspension; for nasal use, for example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example as a finely divided powder such as a dry powder, a microcrystalline form or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oily solution or suspension. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The amount of active ingredient (that is a compound of the formula (I), or a pharmaceutically-acceptable salt thereof) that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient.

According to a further feature of the invention there is provided a compound of formula (I), or a pharmaceutically-acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

The invention also includes the use of such an active ingredient (i.e. a compound of the formula (I), or a pharmaceutically-acceptable salt thereof) in the production of a medicament for use in:-

(i) producing a Factor Xa inhibitory effect;

(ii) producing an anticoagulant effect;

(iii) producing an antithrombotic effect;

(iv) treating a Factor Xa mediated disease or medical condition;

(v) treating a thrombosis mediated disease or medical condition;

(vi) treating coagulation disorders; and/or

(vii) treating thrombosis or embolism involving Factor Xa mediated coagulation.

The invention also includes a method of producing an effect as defined hereinbefore or treating a disease or disorder as defined hereinbefore which comprises administering to a warm-blooded animal requiring such treatment an effective amount of an active ingredient as defined hereinbefore.

The size of the dose for therapeutic or prophylactic purposes of a compound of the formula (I) will naturally vary according to the nature and severity of the medical condition, the age and sex of the animal or patient being treated and the route of administration, according to well known principles of medicine. As mentioned above, compounds of the formula (I) are useful in the treatment or prevention of a variety of medical disorders where anticoagulant therapy is indicated. In using a compound of the formula (I) for such a purpose, it will generally be administered so that a daily oral dose in the range, for example, 0.5 to 100 mg/kg body weight/day is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed, for example a dose for intravenous administration in the range, for example, 0.01 to 10 mg/kg body weight/day will generally be used. For preferred and especially preferred compounds of the invention, in general, lower doses will be employed, for example a daily dose in the range, for example, 0.1 to 10 mg/kg body weight/day. In general a preferred dose range for either oral or parenteral administration would be 0.01 to 10 mg/kg body weight/day.

Although the compounds of formula (I) are primarily of value as therapeutic or prophylactic agents for use in warm-blooded animals including man, they are also useful

whenever it is required to produce an anticoagulant effect, for example during the *ex vivo* storage of whole blood or in the development of biological tests for compounds having anticoagulant properties.

The compounds of the invention may be administered as a sole therapy or they may be administered in conjunction with other pharmacologically active agents such as a thrombolytic agent, for example tissue plasminogen activator or derivatives thereof or streptokinase. The compounds of the invention may also be administered with, for example, a known platelet aggregation inhibitor (for example aspirin, a thromboxane antagonist or a thromboxane synthase inhibitor), a known hypolipidaemic agent or a known anti-hypertensive agent.

The compounds of the invention may also be combined and/or co-administered with any antithrombotic agent(s) with a different mechanism of action, such as one or more of the following: the anticoagulants unfractionated heparin, low molecular weight heparin, other heparin derivatives, synthetic heparin derivatives (e.g. fondaparinux), vitamin K antagonists, synthetic or biotechnological inhibitors of other coagulation factors than FXa (e.g. synthetic thrombin, FVIIa, FXIa and FIXa inhibitors, and rNAPc2), the antiplatelet agents acetylsalicylic acid, ticlopidine and clopidogrel; thromboxane receptor and/or synthetase inhibitors; fibrinogen receptor antagonists; prostacyclin mimetics; phosphodiesterase inhibitors; ADP-receptor (P2X1, P2Y1, P2Y12 [P2T]) antagonists; and inhibitors of carboxypeptidase U (CPU or TAFIa) and inhibitors of plasminogen activator inhibitor-1 (PAI-1).

The compounds of the invention may further be combined and/or co-administered with thrombolytics such as one or more of tissue plasminogen activator (natural, recombinant or modified), streptokinase, urokinase, prourokinase, anisoylated plasminogen-streptokinase activator complex (APSAC), animal salivary gland plasminogen activators, and the like, in the treatment of thrombotic diseases, in particular myocardial infarction.

The invention further relates to a combination comprising a compound of formula (I) and any antithrombotic agent(s) with a different mechanism of action. Said antithrombotic agent(s) may be, for example, one or more of the following: the anticoagulants

unfractionated heparin, low molecular weight heparin, other heparin derivatives, synthetic heparin derivatives (e.g. fondaparinux), vitamin K antagonists, synthetic or biotechnological inhibitors of other coagulation factors than FXa (e.g. synthetic thrombin, FVIIa, FXIa and FIXa inhibitors, and rNAPc2), the antiplatelet agents acetylsalicylic acid, ticlopidine and clopidogrel; thromboxane receptor and/or synthetase inhibitors; fibrinogen receptor antagonists; prostacyclin mimetics; phosphodiesterase inhibitors; ADP-receptor (P2X1, P2Y1, P2Y12 [P2T]) antagonists; and inhibitors of carboxypeptidase U (CPU or TAFIa) and inhibitors of plasminogen activator inhibitor-1 (PAI-1).

Moreover, the invention further relates to a combination comprising a compound of formula (I) and thrombolytics, e.g. one or more of tissue plasminogen activator (natural, recombinant or modified), streptokinase, urokinase, prourokinase, anisoylated plasminogen-streptokinase activator complex (APSAC), animal salivary gland plasminogen activators.

Further, the invention also relates to a combination comprising a compound of formula (I) and thrombolytics, e.g. one or more of tissue plasminogen activator (natural, recombinant or modified), streptokinase, urokinase, prourokinase, anisoylated plasminogen-streptokinase activator complex (APSAC), animal salivary gland plasminogen activators, and the like, in the treatment of thrombotic diseases, in particular myocardial infarction.

The invention will now be illustrated in the following Examples in which, unless otherwise stated:-

(i) Yields are given for illustration only and are not necessarily the maximum attainable. Single node microwave irradiation was performed using either an Emrys Optimizer or a Smith Creator from Personal Chemistry. All solvents and reagents were used as purchased without purification unless noted.;

(ii) The end-products have satisfactory high resolution mass spectral (HRMS) data as analysed on a Micromass QTof Micro spectrometer equipped with an Agilent 1100 LC system high performance liquid chromatography (HPLC). The spectrometer was continually calibrated with leucine enkephaline $C_{28}H_{37}N_5O_7$ (m/z 556.2771) . MS

conditions: Electrospray ionization, positive mode, capillary voltage 2.3 kV and desolvation temperature 150 °C. Accurate mass was determined for positive ionization using leucine enkephaline (m/z 556.2771) as lock mass. Structures were confirmed by ^{1}H nuclear magnetic resonance (^{1}H NMR) spectra which were obtained with either a Varian Unity *plus* or a Varian Inova spectrometer operating at 400, 500 and 600 MHz respectively. Chemical shift values were measured on the delta scale; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; sept, septet; m, multiplet.;

(iii) Isolated intermediates were generally characterised as the end products with the exception of HRMS data.;

(iv) Preparative reversed phase HPLC was performed using a Waters Prep LC 2000 with UV detection equipped with a 25 cm x 2 cm or 30 x 5 cm C8 or C18 columns from Kromasil. Preparative chiral resolution using HPLC was performed using a Gilson 306 with UV detection equipped with either a Ciralpak AS (25 x 2 cm) (ester separations), a Chiralpak AD (25 x 2 cm) (amide separations) or a Chirobiotic R (25 x 2 cm) (carboxylic acid separation) column using 100 % methanol or methanol / acetic acid / triethyl amine 100 / 0.1 / 0.05. All chiral separations were performed at 40 °C.

Example 1

6-{4-[4-(3-Chloro-1H-indazole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2H-pyridazin-3-one

A) 4-(3-Amino-4-methyl-benzenesulfonyl)-piperazine-1-carboxylic acid tert-butyl ester

To a solution of 4-(4-methyl-3-nitro-benzenesulfonyl)-piperazine-1-carboxylic acid tert-butyl ester (0.96 g, 2.5 mmol) in tetrahydrofuran (14 mL) and methanol (14 mL) was added Raney nickel (1 spoonful). Hydrazine monohydrate (2 mL) was added dropwise, keeping the internal temperature at 45 °C. After stirring for 1 hour, the reaction mixture was diluted with tetrahydrofuran and methanol. The catalyst was filtered off, and the solution evaporated to dryness to give 0.89 g (quantitative yield) of the sub-title compound.

^{1}H NMR (300 MHz, chloroform-d as solvent and internal reference) δ (ppm) 1.40 (s, 9H), 2.27 (s, 3H), 2.89 - 3.02 (m, 4H), 3.44 - 3.55 (m, 4H), 7.09 - 7.17 (m, 2H), 7.22 (d, 1H, J = 7.9 Hz).

B) 4-(1H-Indazole-6-sulfonyl)-piperazine-1-carboxylic acid tert-butyl ester

To a solution of 4-(3-amino-4-methyl-benzenesulfonyl)-piperazine-1-carboxylic acid tert-butyl ester (0.86 g, 2.5 mmol) from step A in acetic acid (16 mL) and water (4 mL) was added a solution of sodium nitrite (0.24 g, 3.0 mmol) in water (1.5 mL) at 0 °C dropwise. The reaction mixture was stirred for 95 minutes at 0 °C, and then 90 minutes at room temperature. The reaction mixture was then neutralised with a solution of sodium hydroxide (11 g) in water (40 mL) at 0 °C. The solids formed were filtered, washed with water and air dried. The crude product was purified by column chromatography on silica gel using first dichloromethane / ethyl acetate (100 : 10 and 100 : 20) and then dichloromethane / methanol (100 : 10) as eluent to give 0.72 g (82 %) of the sub-title compound.

^{1}H NMR (300 MHz, methanol-d_4 as solvent and internal reference): 1.38 (s, 9H), 2.95 - 3.04 (m, 4H), 3.43 - 3.54 (m, 4H), 7.50 (dd, 1H, J = 1.5, 8.6 Hz), 7.98 - 8.05 (m, 2H), 8.21 (s, 1H).

C) 6-(Piperazine-1-sulfonyl)-1H-indazole dihydrochloride

To a solution of 4-(1H-indazole-6-sulfonyl)-piperazine-1-carboxylic acid tert-butyl ester (0.750 g, 2.05 mmol) from step B in ethanol (10 mL) was added saturated ethanolic hydrogen chloride (21 mL) at 0 °C dropwise. After stirring for 90 minutes at room temperature, the solution was evaporated to dryness to give 0.70 g (98 %) of the sub-title compound.

^{1}H NMR (500 MHz, methanol-d_4 as solvent and internal reference) δ (ppm) 3.30 - 3.39 (m, 8H), 7.56 (d, 1H, J = 8.6 Hz), 8.07 (d, 1H, J = 8.6 Hz), 8.12 (s, 1H), 8.27 (d, 1H, J = 3.9 Hz).

D) 6-{4-[4-(1H-Indazole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2H-pyridazin-3-one

To a mixture of 4-(6-oxo-1,6-dihydro-pyridazin-3-yl)-benzoic acid (90 mg, 0.36 mmol), and 6-(piperazine-1-sulfonyl)-1H-indazole dihydrochloride (121 mg, 0.36 mmol) from step C in anhydrous *N,N*-dimethylformamide (2 mL) was added diisopropylethylamine (207 mg, 1.6 mmol) and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (154 mg, 0.48 mmol) under argon. After stirring for 2.5 hours at room temperature, the reaction flask was cooled to 0 °C and the reaction mixture was quenched by adding water. The solids obtained were filtered, washed with water, ether, and purified by column chromatography on silica gel using dichloromethane / methanol (100 : 5 and 100 : 10) as eluent to give 34 mg (21 %) of the sub-title compound.

^{1}H NMR (500 MHz, acetic acid-d_4 as solvent and internal reference) δ (ppm) 3.00 - 3.30 (m, 4H), 3.50 - 4.00 (m, 4H), 7.33 (d, 1H, J = 9.3 Hz), 7.44 (d, 2H, J = 5.9 Hz), 7.53 (d,

1H, J = 5.5 Hz), 7.92 (d, 2H, J = 5.9 Hz), 8.02 (d, 1H, J = 6.3 Hz), 8.07 (d, 1H, J = 9.7 Hz), 8.18 (s, 1H), 8.30 (broad s, 1H).

E)

To a solution of 6-{4-[4-(1H-indazole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2H-pyridazin-3-one (20 mg, 0.04 mmol) from step D in anhydrous *N,N*-dimethylformamide (1 mL) was added *N*-chlorosuccinimide (14 mg, 0.10 mmol) under argon. After stirring for 3.5 hours, the reaction flask was cooled to 0 °C and the reaction mixture was quenched by adding water. The solids formed were filtered, washed with water and dried *in vacuo*. The crude product was purified by column chromatography on silica gel using dichloromethane / methanol (100 : 5) as eluent to give 8 mg (37 %) of the title compound.

^{1}H NMR (300 MHz, methanol-d_4 as solvent and internal reference) δ (ppm) 2.90 - 3.24 (m, 4H), 3.48 - 4.00 (m, 4H), 7.05 (d, 1H, J = 9.9 Hz), 7.41 (d, 2H, J = 8.6 Hz), 7.52 (dd, 1H, J = 1.3, 8.6 Hz), 7.66 (s, 1H), 7.83 - 8.00 (m, 4H).

HRMS (ESI+) calc. $[M+H]^+$ 499.0950, found 499.0895.

Example 2

6-{4-[4-(3-Bromo-1H-indazole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2H-pyridazin-3-one

To a solution of 6-{4-[4-(1H-Indazole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2H-pyridazin-3-one (14 mg, 0.030 mmol) in anhydrous *N,N*-dimethylformamide (1 mL) was added *N*-bromosuccinimide (6 mg, 0.03 mmol) under argon. After stirring the reaction mixture for 75 minutes, the reaction flask was cooled to 0 °C and the reaction mixture was quenched by adding water. The solids formed were filtered, washed with water, ether and dried *in vacuo*. The crude product was purified by column chromatography on silica gel using dichloromethane / methanol (100 : 5) as eluent to give 12 mg (73 %) of the title compound.

^{1}H NMR (500 MHz, methanol-d_4 as solvent and internal reference) δ (ppm) 2.96 - 3.24 (m, 4H), 3.46 - 3.94 (m, 4H), 7.05 (d, 1H, *J* = 9.9 Hz), 7.43 (d, 2H, *J* = 8.3 Hz), 7.57 (d, 1H, *J* = 8.6 Hz), 7.83 (d, 1H, *J* = 8.6 Hz), 7.90 (d, 2H, *J* = 8.3 Hz), 8.01 (d, 1H, *J* = 9.9), 8.02 (s, 1H).

HRMS (ESI+) calc. $[M+H]^+$ 543.0444, found 543.0423.

Example 3

6-{4-[4-(3-Bromo-1H-indole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2-methyl-2H-pyridazin-3-one

To a solution of 6-{4-[4-(1H-indole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2-methyl-2H-pyridazin-3-one (75 mg, 0.16 mmol) in anhydrous dichloromethane (1.5 mL) was added *N*-bromosuccinimide (29 mg, 0.17 mmol) under argon. After stirring the reaction mixture for 35 minutes, the reaction flask was cooled to 0 °C and the reaction mixture was quenched by adding water. Dichloromethane was added. The organic layer was separated, washed with sodium bicarbonate (aq. satd.), dried and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane / methanol (100 : 3) as eluent to give 55 mg (63 %) of the title compound.

^{1}H NMR (500 MHz, chloroform-d as solvent and internal reference) δ (ppm) 2.79 - 3.21 (m, 4H), 2.45 - 3.90 (m, 4H), 3.90 (s, 3H), 7.06 (d, 1H, *J* = 9.6 Hz), 7.41 (d, 2H, *J* = 8.3 Hz), 7.45 (d, 1H, *J* = 2.5 Hz), 7.50 (dd, 1H, *J* = 1.3, 8.3 Hz), 7.66 - 7.73 (m, 2H), 7.81 (d, 2H. *J* = 8.3 Hz), 7.89 (s, 1H), 9.85 (s, 1H).

HRMS (ESI+) calc. $[M+H]^+$ 556.0648, found 556.0661.

Example 4

6-{4-[4-(3-Chloro-1H-indole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2-methyl-2H-pyridazin-3-one

The title compound was prepared from 6-{4-[4-(1H-indole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2-methyl-2H-pyridazin-3-one according to the procedure for step E of example 1 in 115 mg (89 %) isolated yield.

^{1}H NMR (500 MHz, methanol-d_4 as solvent and internal reference) δ (ppm) 2.91 - 3.20 (m, 4H), 3.50 - 3.88 (m, 4H), 3.88 (s, 3H), 7.06 (d, 1H, J = 9.6 Hz), 7.43 (d, 2H, J = 8.3 Hz), 7.49 (dd, 1H, J = 1.6, 8.3 Hz), 7.53 (d, 1H, J = 2.1 Hz), 7.73 (d, 1H, J = 8.3 Hz), 7.87 (s, 1H), 7.92 (d, 2H, J = 8.3 Hz), 7.97 (d, 1H, J = 9.6 Hz).

HRMS (ESI+) calc. $[M+H]^+$ 512.1154, found 512.1184.

Example 5

6-{4-[4-(1H-Indole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2-methyl-2H-pyridazin-3-one

The title compound was prepared from 6-(piperazine-1-sulfonyl)-1H-indole and 4-(1-methyl-6-oxo-1,6-dihydro-pyridazin-3-yl)-benzoic acid according to the procedure for step D of example 1 in 274 mg (56 %) isolated yield.

^{1}H NMR (500 MHz, methanol-d_4 as solvent and internal reference) δ (ppm) 2.88 - 3.20 (m, 4H), 3.42 - 3.82 (m, 4H), 3.82 (s, 3H), 6.59 (dd, 1H, J = 1.0, 3.1 Hz), 7.03 (d, 1H, J = 9.9 Hz), 7.34 - 7.41 (m, 3H), 7.49 (d, 1H, J = 3.1 Hz), 7.73 (d, 1H, J = 8.3 Hz), 7.83 - 7.92 (m, 4H).

HRMS (ESI+) calc. $[M+H]^+$ 478.1543, found 478.1569.

Example 6

6-{4-[4-(3-Chloro-1H-indole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2H-pyridazin-3-one

The title compound was prepared from 6-{4-[4-(1H-indole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2H-pyridazin-3-one according to the procedure for step E of example 1 in 40 mg (59 %) isolated yield.

^{1}H NMR (500 MHz, methanol-d_4 as solvent and internal reference) δ (ppm) 2.90 - 3.22 (m, 4H), 3.50 - 3.92 (m, 4H), 7.06 (d, 1H, J = 9.9 Hz), 7.43 (d, 2H, J = 8.3 Hz), 7.49 (dd, 1H, J = 1.6, 8.3 Hz), 7.53 (s, 1H), 7.74 (d, 1H, J = 8.6 Hz), 7.89 (d, 1H, J = 1.0 Hz), 7.91 (d, 2H, J = 8.3 Hz), 7.99 (d, 1H, J = 9.9 Hz).

HRMS (ESI+) calc. $[M+H]^+$ 498.0997, found 498.1006.

Example 7

6-{4-[4-(1H-Indole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2H-pyridazin-3-one

The title compound was prepared from 4-(6-oxo-1,6-dihydro-pyridazin-3-yl)-benzoic acid and 6-(piperazine-1-sulfonyl)-1H-indole hydrochloride according to the procedure for step D of example 1 in 144 mg (41 %) isolated yield.

^{1}H NMR (500 MHz, dimethyl sulfoxide-d_6 as solvent and internal reference) δ (ppm) 2.80 - 3.10 (m, 4H), 3.40 - 3.82 (m, 4H), 6.63 (d, 1H, J = 2.6 Hz), 7.01 (d, 1H, J = 9.9 Hz), 7.33 (dd, 1H, J = 1.3, 8.3 Hz), 7.43 (d, 2H, J = 8.3 Hz), 7.70 (s, 1H), 7.79 (d, 1H, J = 8.3 Hz), 7.81 (s, 1H), 7.87 (d, 2H, J = 8.0 Hz), 8.05 (d, 1H, J = 9.9 Hz), 11.68 (s, 1H), 13.28 (s, 1H).

HRMS (ESI+) calc. $[M+H]^+$ 464.1387, found 464.1391.

Example 8

[4-(3-Chloro-1H-indole-6-sulfonyl)-piperazin-1-yl]-(4-pyridin-4-yl-phenyl)-methanone

A solution of [4-(1H-indole-6-sulfonyl)-piperazin-1-yl]-(4-pyridin-4-yl-phenyl)-methanone (30 mg, 0.067 mmol) in dry *N,N*-dimethylformamide (1 mL) was treated at room temperature with *N*-chlorosuccinimide (40 mg, 0.30 mmol). Additional *N*-chlorosuccinimide was added after 30 minutes (35 mg, 0.26 mmol) and after 1.5 hours (45 mg, 0.34 mmol) and reaction mixture was stirred for a further 3 hours. The reaction was quenched by the addition of crushed ice and the subsequent addition of Na_2SO_3 (s) after 15 minutes. The formed solid material was filtered off and washed with water and diethyl ether. The aqueous filtrate was extracted with dichloromethane and the organic phase was dried (sodium sulfate) and concentrated. The evaporated residue plus the filtered material was subjected to flash column chromatography (dichloromethane / methanol 100 : 4) to give 11 mg (34 %) of the title compound.

^{1}H NMR (300 MHz, methanol-d_4 as solvent and internal reference) δ(ppm) 2.99 - 3.18 (m, 4H), 3.50 - 3.94 (m, 4H), 7.45 - 7.51 (m, 3H), 7.57 (s, 1H), 7.69 - 7.82 (m, 5H), 7.90 (s, 1H), 8.58 - 8.62 (m, 2H).

HRMS (ESI+) calc. $[M+H]^+$ 481.1095, found 481.1108.

Example 9

[4-(1H-Indole-6-sulfonyl)-piperazin-1-yl]-(4-pyridin-4-yl-phenyl)-methanone

To a suspension of 6-(piperazine-1-sulfonyl)-1H-indole hydrochloride (200 mg, 0.663 mmol) and 4-pyridin-4-yl-benzoic acid (139 mg, 0.698 mmol) in dry *N,N*-dimethylformamide (3 mL) at room temperature was added *N,N*-diisopropylethyl-amine (289 µL, 1.66 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (277 mg, 0.862 mmol). The reaction mixture was stirred at room temperature for 1 hour and then concentrated *in vacuo*. The residue was subjected to flash

column chromatography (dichloromethane/methanol 100 : 3) to give 130 mg (44 %) of the title compound.

^{1}H NMR (300 MHz, methanol-d_4 as solvent and internal reference) δ (ppm) 2.96 - 3.14 (m, 4H), 3.48 - 3.90 (m, 4H), 6.61 (s, 1H), 7.38 - 7.48 (m, 3H), 7.53 (s, 1H), 7.70 (d, 2H, J = 4.9 Hz), 7.74 - 7.81 (m, 3H), 7.88 (s, 1H), 8.59 (d, 2H, J = 5.0 Hz).

HRMS (ESI+) calc. $[M+H]^+$ 447.1485, found 447.1465

Example 10

6-{4-[S)-4-(3-chloro-1H-indole-6-sulfonyl)-2-methyl-6-sulfonyl) -2-methyl-6-oxo-piperazin-1-ylmethyl]-phenyl}-2-methyl-2H-pyridazin-3-one

A) ((S)-2-Amino-propyl)-carbamic acid tert-butyl ester

To a solution of trietylamine (0.95 mL, 6.8 mmol) in 15 mL ethanol was added (s)-(-)-diaminopropane (252 mg, 74.1 mmol). The reaction mixture was stirred under reflux over night. Solvent was evaporated. Water was added and the pH was adjusted to pH 3 by addition of 2 M hydrochloric acid followed by extraction with dichloromethane. The aqueous phase was made alkaline by addition of 2 M sodium hydroxide and extracted with dichloromethane. The organic phase was dried over magnesium sulfate and dried *in vacuo* over night to give the sub-title compound (211 mg, 36 % yield) and the by-product ((S)-2-amino-1-methyl-ethyl)-carbamic acid tert-butyl ester in a 3 : 1 mixture according to NMR.

^{1}H NMR (400 MHz; chloroform-d as solvent and internal reference) δ(ppm) 1.09 (d, 3H, J = 6.5 Hz), 1.45 (s, 9H), 2.91 (m, 1H), 3.04 (m, 1H), 3.16 (m, 1H)

B) 4-(1-Methyl-6-oxo-1,6-dihydro-pyridazin-3-yl)benzaldehyde

To a solution mixture containing 1,2-dimethoxyethane : ethanol : water 7 : 3 : 2 (5 mL) was added-formylboronic acid (250 mg, 1.67 mmol), 6-chloro-2-methyl-2H-pyridazin-3-

one (421 mg, 1.67 mmol), caesium carbonate (543 mg, 1.67 mg) and benzylbis(triphenylphosphine)palladium(II)chloride (101 mg, 0.133 mmol). The reaction mixture is heated in a micro wave oven at 150 °C for 10 minutes. The mixture was filtered and concentrated. Purification by flash chromatography with a gradient from heptane / ethyl acetate (1 : 1) to ethyl acetate / triethylamine (5 %) gave 946 mg of the sub-title compound (88 % yield).

^{1}H NMR (400 MHz, methanol-d_4 as solvent and internal reference) δ(ppm) 3.89 (s, 3H), 8.01 (m, 2H), 8.09 (m, 4H), 10.04 (s, 1H)

C) {(S)-2-[4-(1-Methyl-6-oxo-1,6-dihydro-pyridazin-3-yl)-benzylamino]-propyl}-carbamic acid tert-butyl ester

To a solution of 4-(1-methyl-6-oxo-1,6-dihydro-pyridazin-3-yl)benzaldehyde (300 mg, 1.40 mmol) from step B in dry dichloromethane was added ((S)-2-amino-propyl)carbamic acid tert-butyl ester (211 mg, 1.21 mmol) from step A. Acetic acid (160 µL, 2.80 mmol) was added dropwise under stirring followed by addition of sodium triacetoxyborohydride (712 mg, 3.36 mmol) and stirring over night at room temperature. Purification by preparative HPLC gave a mixture of products with the sub-title compound (120 mg, 23 %) being the major product. The material was used directly in the next step.

D) ((S)-2-{(2-Chloro-acetyl) -[4-(1-methyl-6-oxo-1,6- dihydro-pyridazin-3-yl)-benzylamino]-propyl}-carbamic acid tert-butyl ester

A solution of {(S)-2-[4-(1-methyl-6-oxo-1,6-dihydro-pyridazin-3-yl)-benzylamino]-propyl}-carbamic acid tert-butyl ester (120 mg, 0.322 mmol) from step C in dichloromethane is cooled in an ice bath and triethylamine (80 µL, 0.55 mmol) was added. Bromoacetyl chloride (76 mg, 0.48 mmol) in dichloromethane was added and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated *in vacuo* and the crude was purified by preparative HPLC to give a mixture of products with the sub-title compound being the major product (130 mg, 81 % yield) which was used further in the next step.

E) N-((S)-2-Amino-1-methyl-ethyl)-2-chloro-N-[4-(1-methyl-6-oxo-1,6-dihydro-pyridazin-3-yl)-benzyl]-acetamide

A solution of ((S)-2-{(2-chloro-acetyl)-[4-(1-methyl-6-oxo-1,6-dihydro-pyridazin-3-yl)-benzylamino]-propyl}-carbamic acid tert-butyl ester (217 mg, 0.440 mmol) from step D in methanol (5 mL) was cooled on an ice bath and methanol saturated with hydrochloric acid (3 mL) is added dropwise. The reaction mixture was stirred at room temperature for 1 hour and then concentrated and dried *in vacuo*. The crude sub-title product was used without further purification.

F) 2-Methyl-6-[4-(S)-2-methyl-6-oxo-piperazin-1-ylmethyl)-phenyl]-2H-pyridazin-3-one

A solution of *N*-((S)-2-amino-1-methyl-ethyl)-2-chloro-*N*-[4-(1-methyl-6-oxo-1,6-dihydro-pyridazin-3-yl)-benzyl]-acetamide (173 mg, 0.440 mmol) from step E in *N,N*-dimethyl-formamide (4 mL) is cooled in an ice bath and triethylamine (150 µL, 1.08 mmol) is added dropwise. The reaction mixture is stirred at room temperature for 48 hours. Methylene chloride and water was added at 0 °C. The organic layer was separated, dried over magnesium sulfate, filtered, concentrated and dried *in vacuo*. Purification by flash chromatography, toluene / ethyl acetate (1 : 1) gave pure sub-title product (136 mg, 99 %).

^{1}H NMR (400 MHz, chloroform-d as solvent and internal reference) δ(ppm) 1.38 (d, 3H), 2.82 (dd, 2H), 3.07 (dd, 2H), 3.18 (m, 1H), 3.45 (m, 1H), 3.83 (s, 3H) 4.38 (d, 2H), 5.12 (d, 2H), 7.04 (d, 1H), 7.40 (d, 1H), 7.83 (d, 2H), 8.02 (d, 1H)

G) 6-{4-[S)-4-(1-Benzenesulfonyl-3-chloro-1H-indole-6-sulfonyl)-2-methyl-6-sulfonyl)-2-methyl-6-oxo-piperazin-1-ylmethyl]-phenyl}-2-methyl-2H-pyridazin-3-one

2-Methyl-6-[4-(S)-2-methyl-6-oxo-piperazin-1-ylmethyl)-phenyl]-2H-pyridazin-3-one (70 mg, 0.22 mmol) from step F was dissolved in dichloromethane and cooled to 0 °C. Triethylamine (23 mg, 0.22 mmol) and 1-benzenesulfonyl-3-chloro-1H-indole-6-sulfonyl chloride (105 mg, 0.27 mmol) dissolved in dichloromethane was added. The reaction was

stirred at room temperature for 4 hours. Dichloromethane and water was added. The organic phase was washed with water, brine, dried over magnesium sulfate and evaporated. The crude was purified by preparative HPLC to give the sub-title product as a white powder after evaporation and freeze drying (60 mg, 40 % yield).

^{1}H NMR (400 MHz, chloroform-d as solvent and internal reference) δ(ppm) 1.38 (d, 3H, *J* = 6.3 Hz), 2.77 (m, 1H), 3.40 (d, 1H, *J* = 16.5 Hz), 3.49 (m, 2H), 4.0 (d, 1H, *J* = 15.0 Hz), 4.11 (d, 1H, *J* = 16.5 Hz), 5.27 (d, 1H, *J* = 15 Hz), 5.30 (s, 3H), 7.01 (d, 1H, *J* = 9.6 Hz), 7.25 (d, 2H, *J* = 8.1), 7.50 - 7.54 (m, 2H), 7.54 - 7.64 (m, 2H), 7.67 - 7.74 (m, 4H), 7.78 (s, 1H), 7.91 - 7.94 (m, 2H), 8.44 (s, 1H)

H)

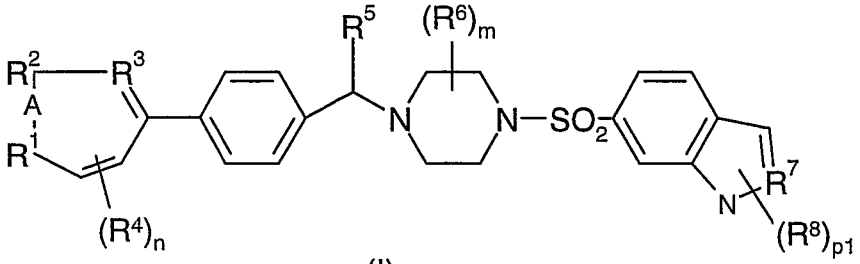
To 6-{4-[S)-4-(1-benzenesulfonyl-3-chloro-1H-indole-6-sulfonyl)-2-methyl-6-sulfonyl)-2-methyl-6-oxo-piperazin-1-ylmethyl]-phenyl}-2-methyl-2H-pyridazin-3-one (60 mg, 0.09 mmol) from step G in tetrahydrofuran was added tetrabutylammonium fluoride (28 mg, 0.09 mmol, 1 M in tetrahydrofuran). The mixture was heated in a microwave oven (5 minutes, 100 °C). Dichloromethane and water was added. The organic phase was washed with water, brine, dried over magnesium sulfate and evaporated. The crude was purified by preparative HPLC to give the title product (35 mg, 74 %).

^{1}H NMR (400 MHz, chloroform-d as solvent and internal reference) δ(ppm) 1.38 (d, 3H, *J* = 6.1 Hz), 2.8 (m, 1H), 3.49 (m, 3H), 3.85 (s, 3H), 4.02 (d, 1H, *J* = 15.0 Hz), 4.11 (d, 1H, *J* = 16.0 Hz), 5.24 (d, 1H, *J* = 15.0 Hz), 6.99 (d, 1H, *J* = 9.7 Hz), 7.22 (d, 2H, *J* = 8.3), 7.39 (d, 1H, *J* = 2.6 Hz), 7.50 (dd, 1H, *J* = 1.5, 8.5 Hz), 7.62 (d, 1H, H = 9.7), 7.67 (d, 2H, *J* = 8.3 Hz), 7.75 (d, 1H, *J* = 8.5), 7.94 (d, 1H, *J* = 1.0 Hz), 9.69 (s, 1 H).

HRMS (ESI+) calc. $[M+H]^+$ 526.1310, found 526.1322.

CLAIMS

1. A compound of formula (I)



(I)

wherein R^1, R^2 and R^3 are independently selected from carbon and nitrogen, and where at least one of R^1, R^2 and R^3 is nitrogen;

A is a single bond or a double bond;

n is 0, 1, 2 or 3;

each R^4 is independently selected from hydrogen, C_{1-3}alkyl, hydroxy, oxo and thioxo;

R^5 is hydrogen or oxo;

m is 0, 1, 2 or 3;

each R^6 is independently selected from hydrogen, C_{1-5}alkyl, oxo, carboxy, cyano, tetrazolyl, hydroxyC_{1-5}alkyl, carboxyC_{1-5}alkyl, C_{1-5}alkylcarboxy, C_{1-5}alkoxyoxoC_{1-5}alkyl, carbamoyl, C_{1-5}alkylcarbamoyl, di(C_{1-5}alkyl)carbamoyl, $-CONR^{80}(CH_2)_xS(O)_pR^9$, $-CONH(CH_2)_qNR^{10}R^{11}$, $-C_{1-5}$alkyl-Y^1, $-COOCHR^{17}R^{18}$ and $-CON\ R^{17}\ R^{18}$,

wherein x represents an integer 0 to 4;

p is 0, 1 or 2;

q represents an integer 2 to 4;

R^{80} represents hydrogen or C_{1-3}alkyl;

R^9 represents C_{1-5}alkyl or phenyl; or

R^{80} and R^9 may together form a C_{1-5}alkylene group;

R^{10} and R^{11} independently represent hydrogen, C_{1-5}alkyl, phenyl, C_{1-5}alkylphenyl, $S(O)_pR^9$, COR^{12} or a 5- or 6-membered monocyclic heteroaryl ring containing up to 3 heteroatoms selected from nitrogen, oxygen and sulphur;

R^{12} represents hydrogen, C_{1-5}alkyl or phenyl;

Y^1 represents $S(O)_pR^9$, $NHS(O)_2R^9$, $NHCOR^{13}$, $O(CH_2)_rR^{14}$, azetidino, pyrrolidin-1-yl, piperidino, morpholino, thiamorpholino, 1-oxothiamorpholino, 1,1-dioxothiamorpholino, piperazin-1-yl or C_{1-5}alkylamino,

R^{13} represents C_{1-5}alkyl, phenyl or C_{1-5}alkylphenyl;

r represents an integer 1 to 4;

when r represents an integer 2 to 4, R^{14} represents hydroxy, C_{1-5}alkylalkoxy, carboxy, C_{1-5}alkoxycarbonyl, $S(O)_pR^9$ or $NR^{15}R^{16}$; and when r represents 1, R^{14} represents carboxy or C_{1-5}alkoxycarbonyl;

wherein any phenyl group within R^6 is independently substituted by 0, 1 or 2 substituents selected from halogeno, trifluoromethyl, cyano, C_{1-5}alkyl and C_{1-5}alkoxy;

R^{15} and R^{16} independently represent hydrogen or C_{1-5}alkyl;

R^{17} and R^{18} are independently selected from hydrogen, C_{1-6}alkyl, C_{4-7}cycloalkyl, C_{2-6}alkenyl, R^{17} and R^{18} may form along with the carbon to which they are attached a 4- ,5- , 6- or 7- membered carbocyclic ring which contains 0, 1 or 2 heteroatoms selected from nitrogen, oxygen and sulphur, or R^{17} and R^{18} may form along with the nitrogen to which they are attached a 4- ,5- , 6- or 7- membered heterocyclic ring which contain in addition to the nitrogen atom present 0, 1 or 2 additional heteroatoms selected from nitrogen, oxygen and sulphur, wherein each R^{17}, R^{18} or any of said rings formed by R^{17} and R^{18} is independently substituted by 0, 1 or 2 substituents selected from hydroxy, amino, carboxy, C_{1-5}alkoxycarbonyl, oxo, C_{1-5}alkyl, hydroxyC_{1-5}alkyl, C_{1-5}alkoxyC_{1-5}alkyl, carboxyC_{1-5}alkyl, C_{1-5}alkoxyoxoC_{1-6}alkyl, and carbamoylC_{1-5}alkyl;

R^7 is carbon or nitrogen;

p1 is 0, 1 or 2; and

each R^8 is independently selected from hydrogen and halogen;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein one or two of R^1, R^2 and R^3 is/are nitrogen.
3. A compound according to claim 1 wherein both R^2 and R^3 are nitrogen.
4. A compound according to claim 1 wherein R^1 is nitrogen.
5. A compound according to anyone of claims 1 to 4 wherein A is a single bond.
6. A compound according to anyone of claims 1 to 4 wherein A is a double bond
7. A compound according to anyone of claims 1 to 5 where one of R^4 is oxo.
8. A compound according to claim 7 wherein said R^4 being oxo is positioned at R^1.

9. A compound according to anyone of claims 1 to 8 where one of R^4 is C_{1-3}alkyl, e.g methyl.

10. A compound according to anyone of claims 1 to 9 where one or two of R^4 is/are hydrogen.

11. A compound according to anyone of claims 1 to 5 where one of R^4 is hydroxy.

12. A compound according to anyone of claims 1 to 11 wherein R^5 is oxo.

13. A compound according to anyone of claims 1 to 12 wherein each R^6 is independently selected from hydrogen, C_{1-5}alkyl, oxo, carboxy, cyano, tetrazolyl, hydroxyC_{1-5}alkyl, carboxyC_{1-5}alkyl, C_{1-5}alkylcarboxy, C_{1-5}alkoxyoxoC_{1-5}alkyl, carbamoyl, C_{1-5}alkylcarbamoyl, di(C_{1-5}alkyl)carbamoyl, $-CONR^{80}(CH_2)_xS(O)_pR^9$, $-CONH(CH_2)_qNR^{10}R^{11}$, $-C_{1-5}$alkyl-Y^1, $-COOCHR^{17}R^{18}$ and $-CON\,R^{17}\,R^{18}$.

14. A compound according to anyone of claims 1 to 13 wherein each R^6 is independently selected from hydrogen, C_{1-5}alkyl, oxo, carboxy, C_{1-5}alkyl, carboxyC_{1-5}alkyl, C_{1-5}alkylcarboxy, C_{1-5}alkoxyoxoC_{1-5}alkyl, $-C_{1-5}$alkyl-Y^1 and $-COOCHR^{17}R^{18}$.

15. A compound according to anyone of claims 1 to 14 wherein each R^6 is independently selected from hydrogen, C_{1-5}alkyl and oxo.

16. A compound according to anyone of claims 1 to 15 wherein R^5 is hydrogen and at least one of R^6 is oxo.

17. A compound according to anyone of claims 1 to 15 wherein each R^6 is hydrogen.

18. A compound according to anyone of claims 1 to 17 wherein R^7 is carbon.

19. A compound according to anyone of claims 1 to 17 wherein R^7 is nitrogen.

20. A compound according to anyone of claims 1 to 19 wherein at least one of R^8 is halogen, e.g. chloro or bromo.

21. A compound according to anyone of claims 1 to 19 wherein each R^8 is hydrogen.

22. A compound according to claim 1 which is

6-{4-[4-(3-Chloro-1H-indazole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2H-pyridazin-3-one,

6-{4-[4-(3-Bromo-1H-indazole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2H-pyridazin-3-one,

6-{4-[4-(3-Bromo-1H-indole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2-methyl-2H-pyridazin-3-one,

6-{4-[4-(3-Chloro-1H-indole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2-methyl-2H-pyridazin-3-one,

6-{4-[4-(1H-Indole-6-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2-methyl-2H-pyridazin-3-one,

[4-(3-Chloro-1H-indole-6-sulfonyl)-piperazin-1-yl]-[4-(6-hydroxy-pyridazin-3-yl)-phenyl]-methanone,

[4-(6-Hydroxy-pyridazin-3-yl)-phenyl]-[4-(1H-indole-6-sulfonyl)-piperazin-1-yl]-methanone,

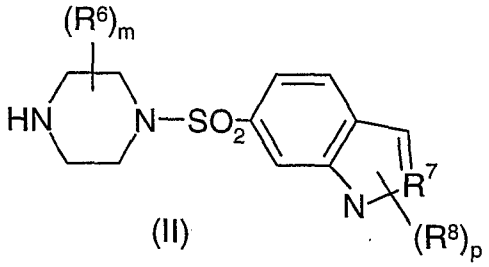
[4-(3-Chloro-1H-indole-6-sulfonyl)-piperazin-1-yl]-(4-pyridin-4-yl-phenyl)-methanone,

[4-(1H-Indole-6-sulfonyl)-piperazin-1-yl]-(4-pyridin-4-yl-phenyl)-methanone or

6-{4-[S)-4-(3-chloro-1H-indole-6-sulfonyl)-2-methyl-6-sulfonyl)-2-methyl-6-oxo-piperazin-1-ylmethyl]-phenyl}-2-methyl-2H-pyridazin-3-one.

23. A process for preparing a compound of formula (I) as defined in claim 1 which process comprises either

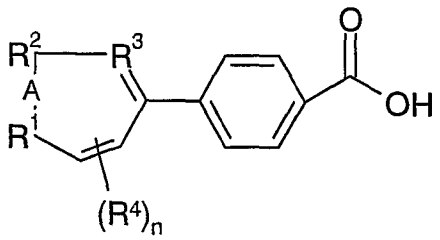
(a) reacting an amine of formula (II),



(II)

or a salt thereof,

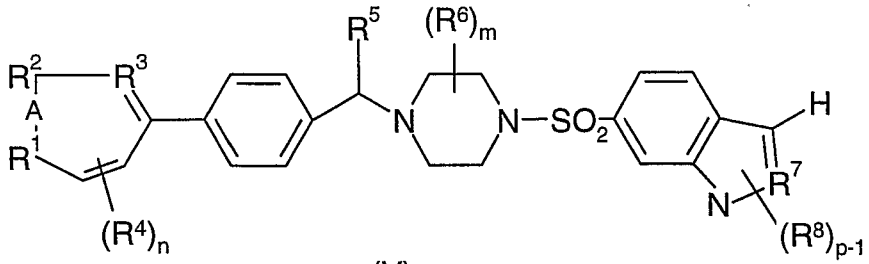
with an acid of the formula (III);



(III)

(b)

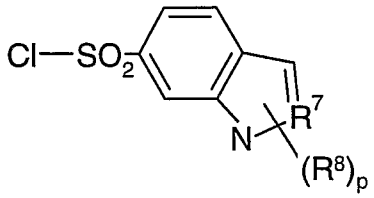
reacting a compound of formula (V),



(V)

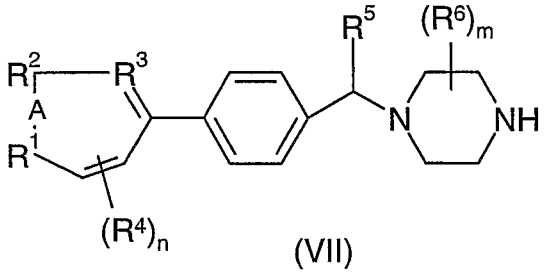
with corresponding halogen succinimide; or

(c) reacting a sulfonyl chloride derivative of formula (VI),



(VI)

with an amine of formula (VII) or a salt thereof.



(VII)

24. A compound of formula (I), as defined in any claim from 1 to 22, or a pharmaceutically-acceptable salt thereof for use in medical therapy.

25. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically-acceptable salt thereof, as defined in any claim from 1 to 22, with a pharmaceutically-acceptable diluent or carrier.

26. Use of a compound of formula (I), as defined in any claim from 1 to 22, or a pharmaceutically-acceptable salt thereof, in the preparation of a medicament for use in a method of treating a Factor Xa mediated disease or condition.

27. A method of treating a Factor Xa mediated disease or condition in a warm-blooded animal comprising administering an effective amount of a compound of formula (I), as defined in any claim from 1 to 22, or a pharmaceutically-acceptable salt thereof.

28. A combination comprising a compound of formula (I), as defined in any claim from 1 to 22, or a pharmaceutically-acceptable salt thereof, and any antithrombotic agent(s) with a different mechanism of action, wherein said antithrombotic agent(s) may be, for example, one or more of the following: the anticoagulants unfractionated heparin, low molecular weight heparin, other heparin derivatives, synthetic heparin derivatives (e.g. fondaparinux), vitamin K antagonists, synthetic or biotechnological inhibitors of other coagulation factors than FXa (e.g. synthetic thrombin, FVIIa, FXIa and FIXa inhibitors, and rNAPc2), the antiplatelet agents acetylsalicylic acid, ticlopidine and clopidogrel; thromboxane receptor and/or synthetase inhibitors; fibrinogen receptor antagonists; prostacyclin mimetics; phosphodiesterase inhibitors; ADP-receptor (P2X1, P2Y1, P2Y12 [P2T]) antagonists; and inhibitors of carboxypeptidase U (CPU or TAFIa) and inhibitors of plasminogen activator inhibitor-1 (PAI-1).

29. A combination comprising a compound of formula (I), as defined in any claim from 1 to 22, or a pharmaceutically-acceptable salt thereof, and thrombolytics, e.g. one or more of tissue plasminogen activator (natural, recombinant or modified), streptokinase, urokinase, prourokinase, anisoylated plasminogen-streptokinase activator complex (APSAC), animal salivary gland plasminogen activators.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000839

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
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)

IPC: C07D

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

SE,DK,FI,NO classes as above

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

EPO-INTERNAL, WPI DATA, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9957113 A1 (ZENECA LIMITED), 11 November 1999 (11.11.1999), abstract; example 1,3-5,7-11; page 26, compounds 1-3; page 28, compounds 14-16, 18; page 29, compound 24 --	1-29
X	WO 9957099 A1 (ZENECA LIMITED), 11 November 1999 (11.11.1999), abstract; examples 5-6; page 26, compounds 7,13; page 27, compounds 15; page 28, compound 22; page 29, compound 29 --	1-29
X	WO 0195931 A1 (ASTRAZENECA AB), 20 December 2001 (20.12.2001), abstract; example 1 --	1-29

[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
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"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
4 October 2006	09 -10- 2006
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson/MP Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000839

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 27
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 27 relates to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic

.../...

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Box II.1

methods /Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000839

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 0078749 A1 (ASTRAZENECA UK LIMITED), 28 December 2000 (28.12.2000), abstract; claim 1	1-29
X	WO 0117990 A1 (ASTRAZENECA UK LIMITED), 15 March 2001 (15.03.2001), abstract; example 1	1-29
X	WO 9854164 A1 (TAKEDA CHEMICAL INDUSTRIES, LTD.), 3 December 1998 (03.12.1998), abstract; examples	1-29
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