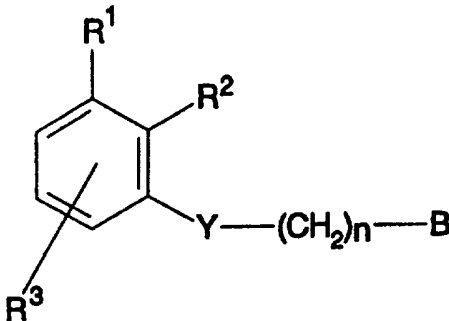




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<p>(21) International Application Number: PCT/SE97/01150</p> <p>(22) International Filing Date: 26 June 1997 (26.06.97)</p> <p>(30) Priority Data: 9602646-3 4 July 1996 (04.07.96) SE</p> <p>(71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).</p> <p>(72) Inventor; and (75) Inventor/Applicant (for US only): ANTONSSON, Thomas [SE/SE]; Torkels väg, PI 3503, S-437 34 Lindome (SE).</p> <p>(74) Agents: PÅRUP, Mats et al.; Astra Aktiebolag, Patent Dept., S-151 85 Södertälje (SE).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>
<p>(54) Title: NEW AMIDINO DERIVATIVES AND THEIR USE AS THROMBIN INHIBITORS</p> <p>(57) Abstract</p> <p>There are provided compounds of formula (I), wherein R¹, R², R³, Y, n and B have meanings given in the description which are useful as competitive inhibitors of trypsin-like proteases, such as thrombin, and in particular in the treatment of conditions where inhibition of thrombin is required (e.g. thrombosis) or as anticoagulants.</p> <div style="display: flex; align-items: center; justify-content: center;">  <div style="margin-left: 20px;">(I)</div> </div>		

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NEW AMIDINO DERIVATIVES AND THEIR USE AS THROMBIN INHIBITORS

Field of the Invention

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This invention relates to novel pharmaceutically useful compounds, in particular competitive inhibitors of trypsin-like serine proteases, especially thrombin, their use as medicaments, pharmaceutical compositions containing them and synthetic routes to their production.

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Background

Blood coagulation is the key process involved in both haemostasis (i.e. the prevention of blood loss from a damaged vessel) and thrombosis (i.e. the formation of a blood clot in a blood vessel, sometimes leading to vessel obstruction).

Coagulation is the result of a complex series of enzymatic reactions. One of the ultimate steps in this series of reactions is the conversion of the proenzyme prothrombin to the active enzyme thrombin.

Thrombin is known to play a central role in coagulation. It activates platelets, leading to platelet aggregation, converts fibrinogen into fibrin monomers, which polymerise spontaneously into fibrin polymers, and activates factor XIII, which in turn crosslinks the polymers to form insoluble fibrin. Furthermore, thrombin activates factor V and factor VIII leading to a "positive feedback" generation of thrombin from prothrombin.

By inhibiting the aggregation of platelets and the formation and crosslinking of fibrin, effective inhibitors of thrombin would therefore be expected to

30

exhibit antithrombotic activity. In addition, antithrombotic activity would be expected to be enhanced by effective inhibition of the positive feedback mechanism.

5 Prior Art

The early development of low molecular weight inhibitors of thrombin has been described by Claesson in *Blood Coagul. Fibrinol.* (1994) 5, 411.

- 10 Blombäck *et al* (in *J. Clin. Lab. Invest.* 24, suppl. 107, 59, (1969)) reported thrombin inhibitors based on the amino acid sequence situated around the cleavage site for the fibrinogen A α chain. Of the amino acid sequences discussed, these authors suggested the tripeptide sequence Phe-Val-Arg (P9-P2-P1, hereinafter referred to as the P3-P2-P1 sequence) would be the most
15 effective inhibitor.

Thrombin inhibitors based on dipeptidyl derivatives with an α,ω -aminoalkyl guanidine in the P1-position are known from US Patent N° 4,346,078 and International Patent Application WO 93/11152. Similar, structurally related,
20 dipeptidyl derivatives have also been reported. For example International Patent Application WO 94/29336 discloses compounds with, for example, aminomethyl benzamidines, cyclic aminoalkyl amidines and cyclic aminoalkyl guanidines in the P1-position; European Patent Application 0 648 780, discloses compounds with, for example, cyclic aminoalkyl guanidines
25 in the P1-position.

Thrombin inhibitors based on peptidyl derivatives, also having cyclic aminoalkyl guanidines (e.g. either 3- or 4- aminomethyl-1-amidinopiperidine) in the P1-position are known from European Patent
30 Applications 0 468 231, 0 559 046 and 0 641 779.

Thrombin inhibitors based on tripeptidyl derivatives with arginine aldehyde in the P1-position were first disclosed in European Patent Application 0 185 390.

5 More recently, arginine aldehyde-based peptidyl derivatives, modified in the P3-position, have been reported. For example, International Patent Application WO 93/18060 discloses hydroxy acids, European Patent Application 0 526 877 des-amino acids, and European Patent Application 0 542 525 O-methyl mandelic acids in the P3-position.

10

Inhibitors of serine proteases (e.g. thrombin) based on electrophilic ketones in the P1-position are also known. For example, European Patent Application 0 195 212 discloses peptidyl α -keto esters and amides, European Patent Application 0 362 002 fluoroalkylamide ketones, European Patent
15 Application 0 364 344 α,β,δ -triketocompounds, and European Patent Application 0 530 167 α -alkoxy ketone derivatives of arginine in the P1-position.

Other, structurally different, inhibitors of trypsin-like serine proteases based
20 on C-terminal boronic acid derivatives of arginine and isothiuronium analogues thereof are known from European Patent Application 0 293 881.

More recently, thrombin inhibitors based on peptidyl derivatives have been disclosed in European Patent Application 0 669 317 and International Patent
25 Applications WO 95/35309, WO 95/23609 and WO 94/29336.

Moreover, achiral thrombin inhibitors based on aminopyridine and aminopyridazine derivatives have recently been disclosed in International Patent Applications WO 94/20467, WO 96/06832 and WO 96/06849. Other
30 achiral thrombin inhibitors have more recently been disclosed in Bioorg.

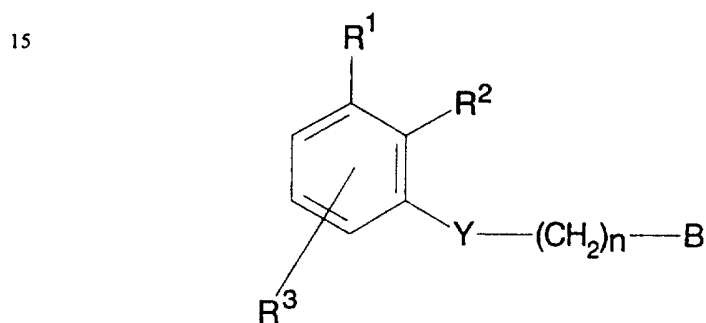
Med. Chem. Lett. 7, 1283 (1997).

However, there remains a need for effective inhibitors of trypsin-like serine proteases, such as thrombin. There is a particular need for compounds which
 5 are both orally bioavailable and selective in inhibiting thrombin over other serine proteases. Compounds which exhibit competitive inhibitory activity towards thrombin would be expected to be especially useful as anticoagulants and therefore in the therapeutic treatment of thrombosis and related disorders.

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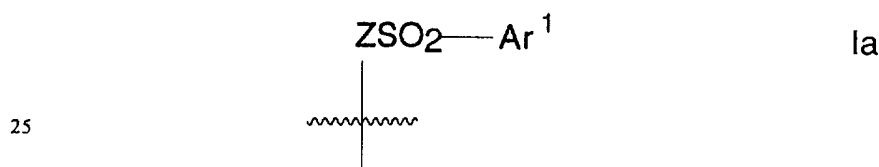
Disclosure of the Invention

According to the invention there is provided a compound of formula I,



wherein

one of R¹ and R² represents a structural fragment of formula Ia



and the other represents R⁴;

Z represents O or N(R⁵);

R³ represents one or more optional substituents selected from OH, halo,
 30 cyano, nitro, C(O)OR⁶, C₁-₆ alkoxy or C₁-₆ alkyl (which two latter groups are

optionally substituted and/or terminated by one or more halo or hydroxy group) or $N(R^7)R^8$;

R^4 represents H, OH, halo, cyano, nitro, $C(O)OR^6$, C_{1-6} alkoxy or C_{1-6} alkyl (which two latter groups are optionally substituted and/or terminated by one or more halo or hydroxy group) or $N(R^7)R^8$;

Ar^1 represents phenyl, C_{1-3} alkylphenyl, C_{1-3} alkylidiphenyl, C_{3-7} cycloalkyl, C_{1-3} -alkyl- C_{3-7} -cycloalkyl, C_{1-3} -alkyl-di- C_{3-7} -cycloalkyl, naphthyl, C_{1-3} alkyl naphthyl, thienyl, imidazolyl or isoxazolyl, all of which may be substituted by one or more substituent selected from OH, halo, cyano, nitro, $C(O)OR^6$, C_{1-6} alkoxy or C_{1-6} alkyl (which two latter groups are optionally substituted and/or terminated by one or more halo or hydroxy group) or $N(R^7)R^8$;

R^5 represents H, C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl (which three latter groups are optionally substituted and/or terminated by one or more substituent selected from OH, halo, cyano, nitro, $C(O)OR^9$, $C(O)N(R^{10})R^{11}$, $P(O)(R^{12})R^{13}$, $P(O)(OR^{14})OR^{15}$, $S(O)_2(R^{16})R^{17}$, $S(O)_2N(R^{18})R^{19}$, C_{1-6} alkoxy or C_{1-6} alkyl (which two latter groups are optionally substituted and/or terminated by one or more halo or hydroxy group) or $N(R^{20})R^{21}$);

Y represents O, S, $S(O)$, $S(O)_2$ or $N(R^{22})$;

R^{10} and R^{11} independently represent H, OR^{23} , $C(O)R^{24}$, $OC(O)R^{25}$, $C(O)OR^{26}$, C_{1-4} alkyl, (which latter group is optionally substituted and/or terminated by one or more substituent selected from C_{1-4} alkyl, OR^{27} , $N(R^{28})R^{29}$, $C(O)OR^{30}$, $C(O)N(R^{31})R^{32}$, $P(O)(R^{33})R^{34}$, $P(O)(OR^{35})OR^{36}$ and $S(O)_2N(R^{37})R^{38}$),

$-(CH_2CH_2O)_pR^{39}$ or, together with the nitrogen atom to which they are attached, form a C_{4-7} nitrogen-containing, aromatic or non-aromatic, ring which ring may contain a further heteroatom or group (as appropriate) selected from O, S and $N(R^{40})$ and may further be substituted by one or more substituent selected from $C(O)R^{41}$, $C(O)OR^{42}$ or $C(O)N(R^{43})R^{44}$;

R^{28} , R^{29} , R^{30} , R^{31} , R^{32} and R^{40} independently represent H or C_{1-6} alkyl, which latter group is optionally substituted and/or terminated by one or more

substituent selected from $C(O)R^{45}$, $C(O)OR^{46}$ or $C(O)N(R^{47})R^{48}$;

at each occurrence, R^6 , R^7 and R^8 independently represent H or C_{1-4} alkyl;

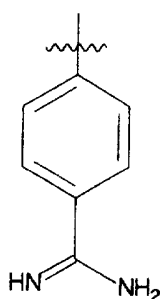
R^9 , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{33} , R^{34} , R^{35} , R^{36} , R^{37} , R^{38} , R^{39} , R^{41} , R^{42} , R^{43} , R^{44} , R^{45} , R^{46} , R^{47} and R^{48}

5 independently represent H or C_{1-4} alkyl;

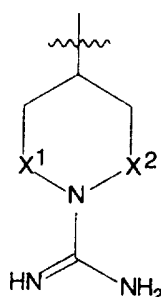
n represents 0, 1, 2, 3 or 4;

p represents 1, 2, 3, 4, 5 or 6; and

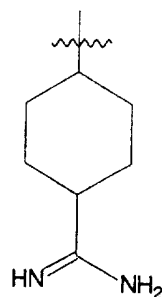
B represents a structural fragment of formula Ib, Ic, Id or Ie



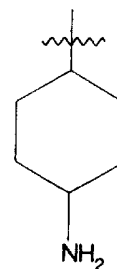
Ib



Ic



Id



Ie

wherein

10 X^1 and X^2 independently represent a single bond or CH_2 ;

or a pharmaceutically acceptable salt thereof (hereinafter referred to as "the compounds of the invention").

The compounds of the invention may exhibit tautomerism. All tautomeric
15 forms and mixtures thereof are included within the scope of the invention.

The compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. All diastereoisomers may be separated using conventional techniques, e.g.
20 chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds

using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means (e.g. HPLC, chromatography over silica). All stereoisomers are included within the scope of the invention.

Alkyl groups which $R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}$ and R^{48} may represent; the alkyl part of alkylphenyl, alkylidiphenyl, alkylcycloalkyl, alkylidicycloalkyl and alkyl naphthyl groups which Ar^1 may represent; the alkyl part of alkylphenyl groups which R^5 may represent; and alkoxy groups which R^3 and R^4 may represent, may be linear or branched, saturated or unsaturated, cyclic or acyclic. When Ar^1, R^5, R^{10} or R^{11} are substituted or terminated (as appropriate) by alkyl or alkoxy, such substituents may be linear or branched, saturated or unsaturated, cyclic or acyclic.

Halo groups which R^3 and R^4 may represent include fluoro, chloro, bromo and iodo. When Ar^1 and R^5 are substituted by halo, such substituents include fluoro, chloro, bromo and iodo.

The wavy lines on the carbon atom in the fragments of formulae Ia, Ib, Ic, Id and Ie signify the bond position of the fragment.

Abbreviations are listed at the end of this specification.

According to a further aspect of the invention there is provided a compound of formula I, as hereinbefore defined, provided that:

- (a) R^1 represents a structural fragment of formula Ia and R^2 represents R^4 ;
- (b) Ar^1 represents optionally substituted phenyl;
- (c) R^5 is not substituted by $P(O)(OR^{14})OR^{15}$, $S(O)_2(R^{16})R^{17}$ or $S(O)_2N(R^{18})R^{19}$;
- 5 (d) R^{10} and/or R^{11} represent H or unsubstituted C_{1-4} alkyl;
- (e) Y represents O, S or $N(R^5)$;
- (f) B represents a structural fragment of formula Ib, Ic or Id.

According to a further aspect of the invention there is provided a compound
 10 of formula I, as hereinbefore defined, provided that:

- (a) R^2 represents a structural fragment of formula Ia and R^1 represents R^4 ;
- (b) Ar^1 does not represent optionally substituted phenyl;
- (c) R^5 is substituted by $P(O)(OR^{14})OR^{15}$, $S(O)_2(R^{16})R^{17}$ or $S(O)_2N(R^{18})R^{19}$;
- (d) R^{10} and/or R^{11} do not represent H or unsubstituted C_{1-4} alkyl;
- 15 (e) Y represents $S(O)$ or $S(O)_2$;
- (f) B represents a structural fragment of formula Ie.

When B represents a structural fragment of formula Ib, Id, Ie or Ic in which
 latter fragment X^1 and X^2 both represent CH_2 , preferred compounds of the
 20 invention include those wherein n represents 2.

Preferred compounds of formula I include those wherein:

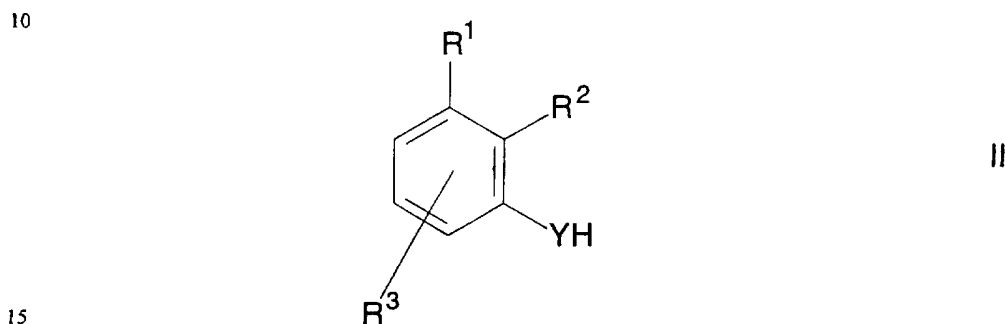
- R^1 represents a structural fragment of formula Ia and R^2 represents R^4 ;
- Z represents O or $N(R^5)$, in which latter case R^5 represents C_{1-6} alkyl
- 25 substituted by $C(O)N(R^{10})R^{11}$;
- R^3 is not present, or represents methyl, chloro or methoxy;
- Ar^1 represents substituted phenyl;
- Y represents O;
- n represents 2;
- 30 B represents a structural fragment of formula Ib.

Preferred compounds of the invention include the compounds of Examples 1 to 55.

Preparation

According to the invention there is also provided a process for the preparation of compounds of formula I which comprises:

(a) reaction of a compound of formula II,

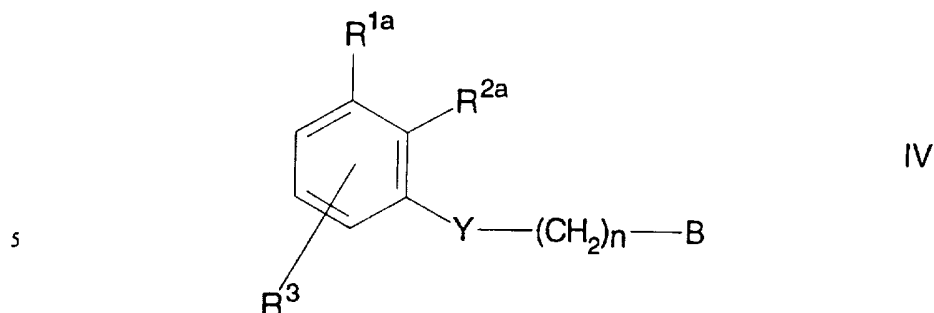


wherein R¹, R², R³ and Y are as hereinbefore defined with a compound of formula III,



wherein L¹ represents a suitable leaving group (e.g. chloro, bromo, iodo, mesylate, triflate or arylsulfonate) and n and B are as hereinbefore defined, for example between 0 and 100°C in the presence of a suitable base (e.g. potassium carbonate or triethylamine) and an appropriate solvent (e.g. acetonitrile, tetrahydrofuran or dimethylformamide);

(b) reaction of a compound of formula IV,

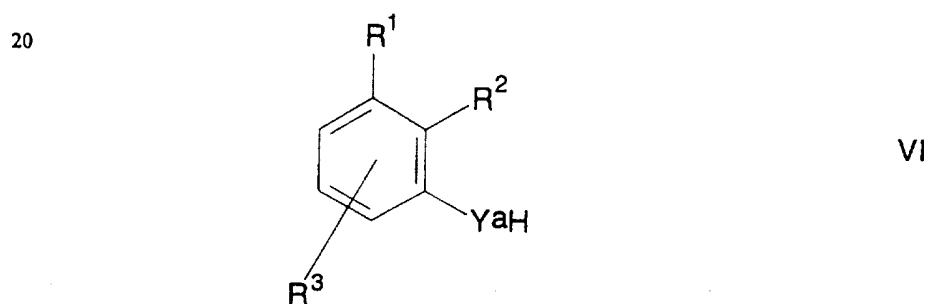


wherein one of R^{1a} and R^{2a} represents ZH and the other represents R^4 , and Z, R^3 , R^4 , Y, n and B are as hereinbefore defined with a compound of
 10 formula V,



wherein L^2 is a suitable leaving group (e.g. chloro) and Ar^I is as hereinbefore defined, under conditions which are well known to those skilled in the art, for example in the presence of a suitable base (e.g. pyridine or
 15 sodium bicarbonate) and, if appropriate, a suitable organic solvent;

(c) for compounds of formula I in which Y represents O or S, reaction of a compound of formula VI,



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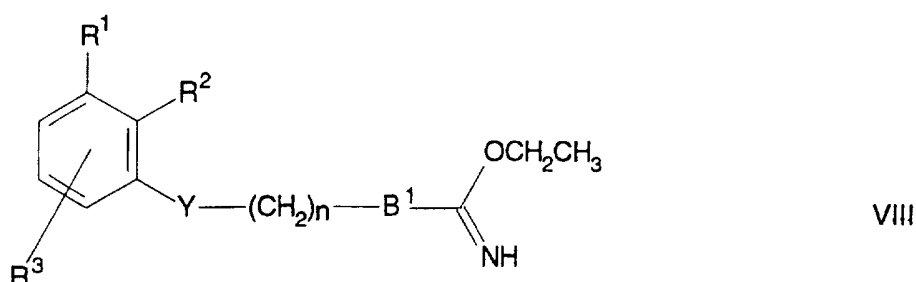
wherein Y^a represents O or S and R^1 , R^2 and R^3 are as hereinbefore defined with a compound of formula VII,



wherein n and B are as hereinbefore defined, for example at or below room
 30 temperature in the presence of an appropriate coupling system (e.g.

diethylazodicarboxylate and triphenylphosphine) and a suitable organic solvent (e.g. tetrahydrofuran);

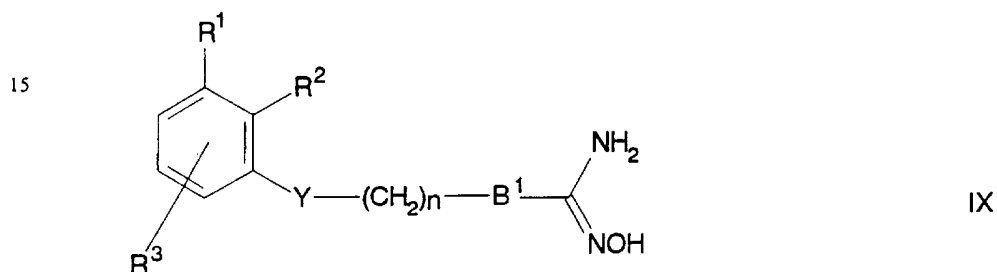
(d) for compounds of formula I wherein B represents a structural fragment
5 of formula Ib or Id, reaction of a compound of formula VIII,



wherein B¹ represents 1,4-phenylene or 1,4-cyclohexylene and R¹, R², R³, Y and n are as hereinbefore defined with ammonia gas for example at room temperature in the presence of a suitable organic solvent (e.g. methanol or ethanol);

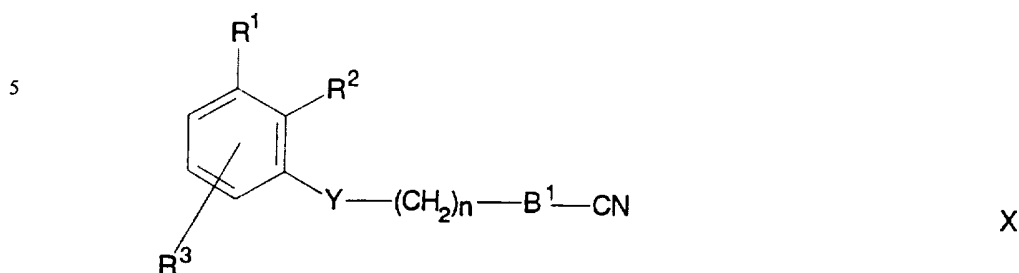
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(e) for compounds of formula I wherein B represents a structural fragment
of formula Ib or Id, reduction of a compound of formula IX,



15
20 wherein R¹, R², R³, Y, n and B¹ are as hereinbefore defined in the presence of a suitable reducing agent (for example by catalytic hydrogenation in the presence of e.g. Pd/C or TiCl₃) and an appropriate organic solvent;

(f) for compounds of formula I wherein B represents a structural fragment of formula Ib or Id, reaction of a compound of formula X,



10 wherein R^1 , R^2 , R^3 , Y, n and B^1 are as hereinbefore defined with ammonium chloride, for example under reflux in the presence of a suitable catalyst (e.g. trimethyl aluminium) and an appropriate organic solvent (e.g. toluene);

(g) for compounds of formula I wherein Y represents $S(O)$ or $S(O)_2$,
 15 oxidation of a corresponding compound of formula I wherein Y represents S in the presence of an appropriate quantity of a suitable oxidising agent (e.g. *m*-chloroperbenzoic acid or sodium periodate) and an appropriate organic solvent;

20 (h) for compounds of formula I wherein Z represents $N(R^5)$ and R^5 represents optionally substituted C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl, reaction of a corresponding compound of formula I wherein Z represents NH with a compound of formula XI,



25 wherein R^{5a} represents optionally substituted C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl and L^2 is as hereinbefore defined, for example in the presence of suitable base (e.g. sodium hydride or potassium carbonate) and an appropriate organic solvent (e.g. DMF);

30 (i) for compounds of formula I wherein Z represents $N(R^5)$ and R^5 represents

C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl, all of which are substituted and/or terminated by $C(O)N(R^{10})R^{11}$, reaction of a corresponding compound of formula I wherein R^5 represents C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl, all of which are substituted and/or terminated, by $C(O)OR^9$, wherein R^9 is as
 5 hereinbefore defined, with a compound of formula XII,



wherein R^{10} and R^{11} are as hereinbefore defined, for example (in the case where R^9 represents H) in the presence of suitable a coupling system (e.g. DCC/HOBt or EDC/HOBt) and an appropriate organic solvent (e.g. DMF
 10 or acetonitrile); or (in the case where R^9 represents C_{1-4} alkyl) at room temperature in the presence of an appropriate organic solvent (e.g. MeOH or acetonitrile);

(j) for compounds of formula I wherein Z represents $N(R^5)$ and R^5 represents
 15 C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl, all of which are substituted and/or terminated by $C(O)OH$, hydrolysis of a corresponding compound of formula I wherein R^5 represents C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl, all of which are substituted and/or terminated by $C(O)OR^9$ and R^9 represents C_{1-4} alkyl under conditions which are well known to those skilled in the art; or

20

(k) for compounds of formula I wherein Z represents $N(R^5)$ and R^5 represents $(CH_2)_2C(O)OR^9$ and R^9 is as hereinbefore defined, reaction of a corresponding compound of formula I wherein R^5 represents H with a compound of formula XIII,

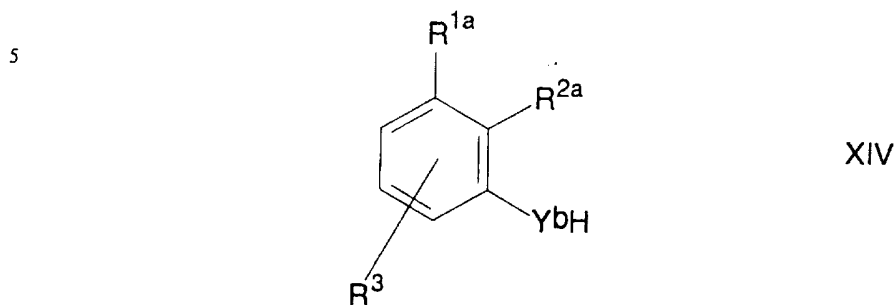


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wherein R^9 is as hereinbefore defined, for example by refluxing in the presence of a catalytic amount of an appropriate organic acid (e.g. acetic acid).

30 Compounds of formulae II and VI are commercially available, are known in

the literature or are available using known techniques. For example compounds of formulae II and VI may be prepared by reaction of a compound of formula XIV,



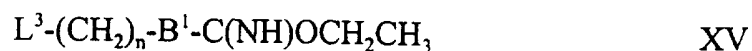
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wherein Y^b represents Y or Y^a as appropriate and R^{1a}, R^{2a} and R³ are as hereinbefore defined with a compound of formula V as hereinbefore defined, for example under similar conditions to those described hereinbefore for synthesis of compounds of formula I (process (b)).

15

Compounds of formulae III and VII are commercially available, are known in the literature or are available using known techniques. For example compounds of formulae III and VII wherein B represents a structural fragment of formula Ib or Id may be prepared by reaction of a

20 corresponding compound of formula XV,



wherein L³ represents L¹ or OH as appropriate and n and B¹ are as hereinbefore defined with ammonia gas for example under similar conditions to those described hereinbefore for synthesis of compounds of formula I

25 (process (d)).

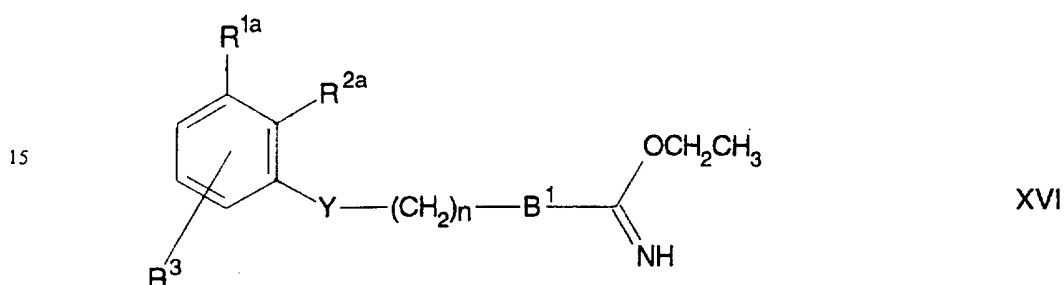
Compounds of formula IV may be prepared by reaction of a compound of formula XIV wherein Y^b represents Y and Y is as hereinbefore defined with a compound of formula III as hereinbefore defined, for example under

30 similar conditions to those described hereinbefore for synthesis of

compounds of formula I (process (a)).

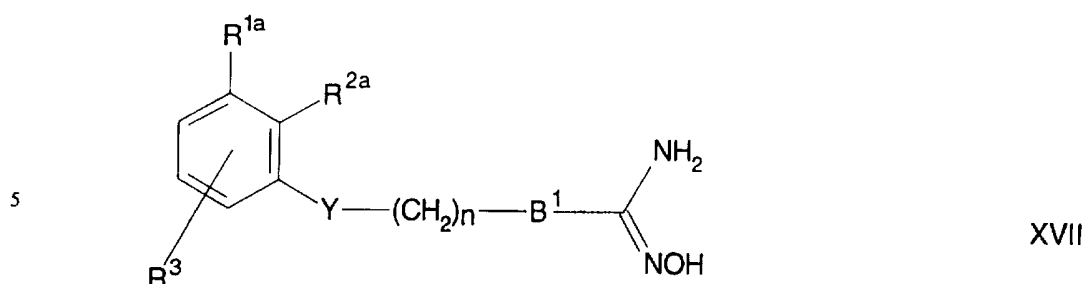
Compounds of formula IV in which Y represents O or S may alternatively be prepared by reaction of a compound of formula XIV wherein Y^b represents Y^a and Y^a is as hereinbefore defined with a compound of formula VII, for example under similar conditions to those described hereinbefore for synthesis of compounds of formula I (process (c)).

Compounds of formula IV in which B represents a structural fragment of formula Ib or Id may alternatively be prepared by reaction of a compound of formula XVI,



wherein R^{1a}, R^{2a}, R³, Y, n and B¹ are as hereinbefore defined with ammonia gas for example under similar conditions to those described hereinbefore for synthesis of compounds of formula I (process (d)).

Compounds of formula IV in which B represents a structural fragment of formula Ib or Id may alternatively be prepared by reduction of a compound of formula XVII,



wherein R^{1a} , R^{2a} , R^3 , Y, n and B^1 are as hereinbefore defined, under similar conditions to those described hereinbefore for synthesis of compounds of formula I (process (e)).

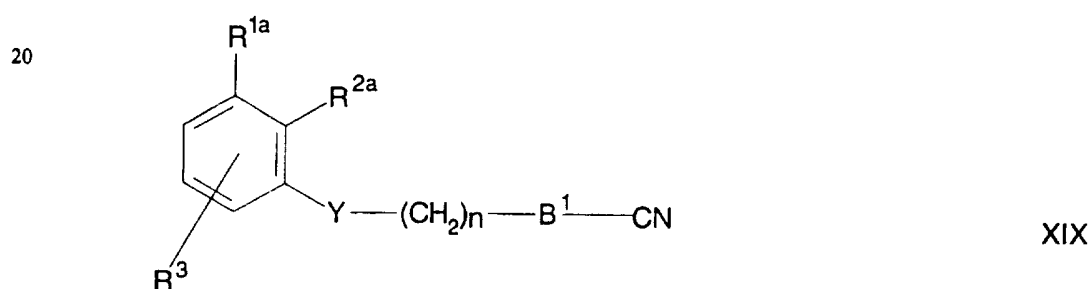
10

Compounds of formulae VIII, XV and XVI may be prepared by reaction of a corresponding cyanobenzene of formula X as hereinbefore defined (for a compound of formula VIII), a corresponding cyanobenzene of formula

15 XVIII,



wherein L^3 , n and B^1 are as hereinbefore defined (for a compound of formula XV), or a corresponding cyanobenzene of formula XIX,



25 wherein R^{1a} , R^{2a} , R^3 , Y, n and B^1 are as hereinbefore defined (for a compound of formula XVI), with HCl(g) and ethanol, for example at or below room temperature (e.g. 0°C).

Compounds of formula IX and XVII may be prepared by reaction of a

30 compound of formula X or XIX as hereinbefore defined (as appropriate)

with hydroxylamine, for example at or around 40°C in the presence of a suitable base (e.g. triethylamine) and an appropriate organic solvent (e.g. ethanol).

- 5 Compounds of formula X may be prepared by reaction of a compound of formula XIX as hereinbefore defined with a compound of formula V as hereinbefore defined for example under similar conditions to those described hereinbefore for synthesis of compounds of formulae I (process (b)), II and VI.

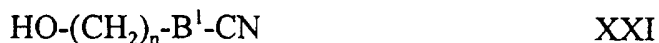
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Compounds of formula X may alternatively be prepared by reaction of a compound of formula II as hereinbefore defined with a compound of formula XX



- 15 wherein L^1 , n and B^1 are as hereinbefore defined, for example under similar conditions to those described hereinbefore for synthesis of compounds of formula I (process (a)).

- Compounds of formula X wherein Y represent O or S may alternatively be prepared by reaction of a compound of formula VI as hereinbefore defined with a compound of formula XXI



- wherein n and B^1 are as hereinbefore defined, for example under similar conditions to those described hereinbefore for synthesis of compounds of formula I (process (c)).

- Compounds of formula XIX may be prepared by reaction of a compound of formula XIV wherein Y^b represents Y and Y is as hereinbefore defined with a compound of formula XX as hereinbefore defined, for example under similar conditions to those described hereinbefore for synthesis of

30

compounds of formula I (process (a)).

Compounds of formula XIX wherein Y represents O or S may be prepared by reaction of a compound of formula XIV wherein Y^b represents Y^a and Y^a is as hereinbefore defined with a compound of formula XXI as hereinbefore defined, for example under similar conditions to those described hereinbefore for synthesis of compounds of formula I (process (c)).

Compounds of formulae II, IV, VI, VIII, IX, X, XIV, XVI, XVII and XIX wherein Z represents N(R⁵) and R⁵ represents optionally substituted C₁₋₆ alkyl, phenyl or C₁₋₃ alkylphenyl, may be prepared by reaction of a corresponding compound of formula II, IV, VI, VIII, IX, X, XIV, XVI, XVII or XIX (as appropriate) wherein Z represents NH with a compound of formula XI as hereinbefore defined, for example under similar conditions to those described hereinbefore for synthesis of compounds of formula I (process (h)).

Compounds of formulae II, IV, VI, VIII, IX, X, XIV, XVI, XVII and XIX wherein Z represents N(R⁵) and R⁵ represents C₁₋₆ alkyl, phenyl or C₁₋₃ alkylphenyl substituted and/or terminated, in all three cases, by C(O)N(R¹⁰)R¹¹ may alternatively be prepared by reaction of a corresponding compound of formula II, IV, VI, VIII, IX, X, XIV, XVI, XVII or XIX (as appropriate) wherein R⁵ represents C₁₋₆ alkyl, phenyl or C₁₋₃ alkylphenyl substituted and/or terminated, in all three cases, by C(O)OR⁹, wherein R⁹ is as hereinbefore defined, with a compound of formula XII as hereinbefore defined, for example under similar conditions to those described hereinbefore for synthesis of compounds of formula I (process (i)).

Compounds of formulae II, IV, VI, VIII, IX, X, XIV, XVI, XVII and XIX wherein Z represents N(R⁵) and R⁵ represents C₁₋₆ alkyl, phenyl or C₁₋₃

alkylphenyl substituted and/or terminated, in all three cases, by C(O)OH may alternatively be prepared by hydrolysis of a corresponding compound of formula II, IV, VI, VIII, IX, X, XIV, XVI, XVII or XIX (as appropriate) wherein R⁵ represents C₁₋₆ alkyl, phenyl or C₁₋₃ alkylphenyl substituted
5 and/or terminated, in all three cases, by C(O)OR⁹ and R⁹ represents C₁₋₄ alkyl under conditions which are well known to those skilled in the art.

Compounds of formulae II, IV, VI, VIII, IX, X, XIV, XVI, XVII and XIX wherein Z represents N(R⁵) and R⁵ represents (CH₂)₂C(O)OR⁹ and R⁹ is as
10 hereinbefore defined, may alternatively be prepared by reaction of a corresponding compound of formula II, IV, VI, VIII, IX, X, XIV, XVI, XVII or XIX (as appropriate) wherein R⁵ represents H with a compound of formula XIII as hereinbefore defined, for example under similar conditions to those described hereinbefore for synthesis of compounds of formula I
15 (process (k)).

Compounds of formulae V, XI, XII, XIII, XIV, XVIII, XX and XXI are either commercially available, are well known in the literature, or are available using known techniques. For example compounds of formula XIV
20 wherein R^{1a} and/or R^{2a} represent NH₂ may be prepared by reduction of the corresponding nitrobenzene under conditions which are well known to those skilled in the art. Similarly, compounds of formula XIV wherein R^{1a} and/or R^{2a} represent OH may be prepared by hydrolysis of a corresponding alkoxybenzene under conditions which are well known to those skilled in the
25 art. Compounds of formulae IV, XVI, XVII and XIX wherein R^{1a} and/or R^{2a} represent NH₂ or OH may also be prepared from the corresponding nitrobenzene or alkoxybenzene (as appropriate) in accordance with these techniques.

30 Substituents on the aromatic and/or non-aromatic, carbocyclic and/or

heterocyclic ring(s) in compounds of formulae I, II, IV, V, VI, VIII, IX, X, XI, XII, XIV, XVI, XVII and XIX may be interconverted by techniques well known to those skilled in the art.

- 5 The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

It will be appreciated by those skilled in the art that in the process described above the functional groups of intermediate compounds may need to be
10 protected by protecting groups.

Functional groups which it is desirable to protect include hydroxy, amino, amidino, guanidino and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl and diarylalkylsilyl groups (e.g. *t*-
15 butyldimethylsilyl, *t*-butyldiphenylsilyl or trimethylsilyl) and tetrahydropyranyl. Suitable protecting groups for hydroxy groups, which groups are attached to adjacent carbon atoms include O,O'-isopropylidene. Suitable protecting groups for amino, amidino and guanidino include *t*-butyloxycarbonyl or benzyloxycarbonyl. Amidino and guanidino nitrogens
20 may be either mono- or diprotected. Suitable protecting groups for carboxylic acid include C₁₋₆ alkyl or benzyl esters.

The protection and deprotection of functional groups may take place before or after a reaction step.

25

Protecting groups may be removed in accordance with techniques which are well known to those skilled in the art and as described hereinafter.

The use of protecting groups is fully described in "Protective Groups in
30 Organic Chemistry", edited by J W F McOmie, Plenum Press (1973), and

"Protective Groups in Organic Synthesis", 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).

It will also be appreciated by those skilled in the art that, "protected
5 derivatives" of compounds of formula I may be formed prior to a final
deprotection step. Although they may not possess pharmacological activity
as such, certain "protected derivatives" of compounds of formula I may be
administered parenterally or orally and thereafter metabolised in the body to
form compounds of the invention which are pharmacologically active. Such
10 derivatives may therefore be described as "prodrugs". All prodrugs of
compounds of formula I are included within the scope of the invention.

Medical and pharmaceutical use

15 The compounds of the invention are useful because they possess
pharmacological activity. They are therefore indicated as pharmaceuticals.

According to a further aspect of the invention there is thus provided the
compounds of the invention for use as pharmaceuticals.

20

In particular, the compounds of the invention are potent inhibitors of
thrombin for example as demonstrated in the tests described below.

The compounds of the invention are thus expected to be useful in those
25 conditions where inhibition of thrombin is required.

The compounds of the invention are thus indicated in the treatment or
prophylaxis of thrombosis and hypercoagulability in blood and tissues of
animals including man.

30

It is known that hypercoagulability may lead to thrombo-embolic diseases. Conditions associated with hypercoagulability and thrombo-embolic diseases which may be mentioned include activated protein C resistance, such as the factor V-mutation (factor V Leiden), and inherited or acquired deficiencies
5 in antithrombin III, protein C, protein S, heparin cofactor II. Other conditions known to be associated with hypercoagulability and thrombo-embolic disease include circulating antiphospholipid antibodies (Lupus anticoagulant), homocysteinemia, heparin induced thrombocytopenia and defects in fibrinolysis. The compounds of the invention are thus indicated
10 both in the therapeutic and/or prophylactic treatment of these conditions.

The compounds of the invention are further indicated in the treatment of conditions where there is an undesirable excess of thrombin without signs of hypercoagulability, for example in neurodegenerative diseases such as
15 Alzheimer's disease.

Particular disease states which may be mentioned include the therapeutic and/or prophylactic treatment of venous thrombosis and pulmonary embolism, arterial thrombosis (eg in myocardial infarction, unstable angina,
20 thrombosis-based stroke and peripheral arterial thrombosis) and systemic embolism usually from the atrium during arterial fibrillation or from the left ventricle after transmural myocardial infarction.

Moreover, the compounds of the invention are expected to have utility in
25 prophylaxis of re-occlusion (ie thrombosis) after thrombolysis, percutaneous trans-luminal angioplasty (PTA) and coronary bypass operations; the prevention of re-thrombosis after microsurgery and vascular surgery in general.

30 Further indications include the therapeutic and/or prophylactic treatment of

disseminated intravascular coagulation caused by bacteria, multiple trauma, intoxication or any other mechanism; anticoagulant treatment when blood is in contact with foreign surfaces in the body such as vascular grafts, vascular stents, vascular catheters, mechanical and biological prosthetic valves or any
5 other medical device; and anticoagulant treatment when blood is in contact with medical devices outside the body such as during cardiovascular surgery using a heart-lung machine or in haemodialysis.

In addition to its effects on the coagulation process, thrombin is known to
10 activate a large number of cells (such as neutrophils, fibroblasts, endothelial cells and smooth muscle cells). Therefore, the compounds of the invention may also be useful for the therapeutic and/or prophylactic treatment of idiopathic and adult respiratory distress syndrome, pulmonary fibrosis following treatment with radiation or chemotherapy, septic shock,
15 septicemia, inflammatory responses, which include, but are not limited to, edema, acute or chronic atherosclerosis such as coronary arterial disease, cerebral arterial disease, peripheral arterial disease, reperfusion damage, and restenosis after percutaneous trans-luminal angioplasty (PTA).

20 Compounds of the invention that inhibit trypsin and/or thrombin may also be useful in the treatment of pancreatitis.

According to a further aspect of the present invention, there is provided a method of treatment of a condition where inhibition of thrombin is required
25 which method comprises administration of a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, to a person suffering from, or susceptible to such a condition.

The compounds of the invention will normally be administered orally,
30 intravenously, subcutaneously, buccally, rectally, dermally, nasally,

tracheally, bronchially, by any other parenteral route or *via* inhalation, in the form of pharmaceutical preparations comprising active compound either as a free base, or a pharmaceutical acceptable non-toxic organic or inorganic acid addition salt, in a pharmaceutically acceptable dosage form. Depending
5 upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

The compounds of the invention may also be combined and/or co-administered with any antithrombotic agent with a different mechanism of
10 action, such as the antiplatelet agents acetylsalicylic acid, ticlopidine, clopidogrel, thromboxane receptor and/or synthetase inhibitors, fibrinogen receptor antagonists, prostacyclin mimetics and phosphodiesterase inhibitors and ADP-receptor (P_2T) antagonists.

15 The compounds of the invention may further be combined and/or co-administered with thrombolytics such as 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
20 thrombotic diseases, in particular myocardial infarction.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including a compound of the invention, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

25

Suitable daily doses of the compounds of the invention in therapeutical treatment of humans are about 0.001-100 mg/kg body weight at peroral administration and 0.001-50 mg/kg body weight at parenteral administration.

30 The compounds of the invention have the advantage that they may be more

efficacious, be less toxic, be longer acting, have a broader range of activity, be more potent, produce fewer side effects, be more easily absorbed than, or that they may have other useful pharmacological properties over, compounds known in the prior art.

5

Biological Tests

Test A

Determination of Thrombin clotting Time (TT)

- 10 Human thrombin (T 6769, Sigma Chem. Co) in buffer solution, pH 7.4, 100 μ l, and inhibitor solution, 100 μ l, were incubated for one minute. Pooled normal citrated human plasma, 100 μ l, was then added and the clotting time measured in an automatic device (KC 10, Amelung).
- 15 The clotting time in seconds was plotted against the inhibitor concentration, and the $IC_{50}TT$ was determined by interpolation.

$IC_{50}TT$ is the concentration of inhibitor in the test that doubles the thrombin clotting time for human plasma.

20

Test B

Determination of thrombin inhibition with a chromogenic, robotic assay.

- The thrombin 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 microtitre plates
- 25 (Costar, Cambridge, MA, USA; Cat No 3690). Stock solutions of test substance in DMSO (72 μ L), 1 mmol/L, were diluted serially 1:3 (24 + 48 μ L) with DMSO to obtain ten different concentrations, which were analysed as samples in the assay. 2 μ L of test sample was diluted with 124 μ L assay
- 30 buffer, 12 μ L of chromogenic substrate solution (S-2366, Chromogenix,

Möln dal, Sweden) in assay buffer and finally 12 μL of α -thrombin solution, (Human α -thrombin, Sigma Chemical Co.) both in assay buffer, were added, and the samples mixed. The final assay concentrations were: test substance 0.00068 - 13.3 $\mu\text{mol/L}$, S-2366 0.30 mmol/L, α -thrombin 0.020 NIHU/mL.

- 5 The linear absorbance increment during 40 minutes incubation at 37°C, was used for calculation of percentage inhibition for the test samples, as compared to blanks without inhibitor. The IC_{50} -robotic value, corresponding to the inhibitor concentration which caused 50% inhibition of the thrombin activity, was calculated from a log dose vs. % inhibition curve.

10

Test C

Determinaton of the inhibition constant K_i for human thrombin

- K_i -determinations were made using a chromogenic substrate method, performed at 37°C on a Cobas Bio centrifugal analyser (Roche, Basel, 15 Switzerland). Residual enzyme activity after incubation of human α -thrombin with various concentrations of test compound was determined at three different substrate concentrations, and was measured as the change in optical absorbance at 405 nm.

- 20 Test compound solutions (100 μL ; normally in buffer or saline containing BSA 10 g/L) were mixed with 200 μL of human α -thrombin (Sigma Chemical Co) in assay buffer (0.05 mol/L Tris-HCl pH 7.4, ionic strength 0.15 adjusted with NaCl) containing BSA (10 g/L), and analysed as samples in the Cobas Bio. A 60 μL sample, together with 20 μL of water, was 25 added to 320 μL of the substrate S-2238 (Chromogenix AB, Möln dal, Sweden) in assay buffer, and the absorbance change ($\Delta A/\text{min}$) was monitored. The final concentrations of S-2238 were 16, 24 and 50 $\mu\text{mol/L}$ and of thrombin 0.125 NIH U/ml.

- 30 The steady state reaction rate was used to construct Dixon plots, *i.e.*

diagrams of inhibitor concentration vs. $1/(\Delta A/\text{min})$. For reversible, competitive inhibitors, the data points for the different substrate concentrations typically form straight lines which intercept at $x = -K_i$.

5 Test D

Determination of Activated Partial Thromboplastin Time (APTT)

APTT was determined in pooled normal human citrated plasma with the reagent PTT Automated 5 manufactured by Stago. The inhibitors were added to the plasma (10 μL inhibitor solution to 90 μL plasma) followed by the
10 reagent and calcium chloride solution and APTT was determined in the mixture by use of the coagulation analyser KC10 (Amelung) according to the instructions of the reagent producer. The clotting time in seconds was plotted against the inhibitor concentration in plasma and the $\text{IC}_{50}\text{APTT}$ was determined by interpolation.

15

$\text{IC}_{50}\text{APTT}$ is defined as the concentration of inhibitor in human plasma that doubled the Activated Partial Thromboplastin Time.

Test E

20 Determination of thrombin time *ex vivo*

The inhibition of thrombin after oral or parenteral administration of the compounds of the invention were examined in conscious rats which, one or two days prior to the experiment, were equipped with a catheter for blood sampling from the carotid artery. On the experimental day blood samples
25 were withdrawn at fixed times after the administration of the compound into plastic tubes containing 1 part sodium citrate solution (0.13 mol per L) and 9 parts of blood. The tubes were centrifuged to obtain platelet poor plasma. The plasma was used for determination of thrombin time as described above.

30 The citrated rat plasma, 100 μL , was diluted with a saline solution, 0.9%,

100 μ L, and plasma coagulation was started by the addition of human thrombin (T 6769, Sigma Chem Co, USA) in a buffer solution, pH 7.4, 100 μ L. The clotting time was measured in an automatic device (KC 10, Amelung, Germany).

5

The invention is illustrated by way of the following examples.

Examples

10 General Experimental Procedures.

Mass spectra were recorded on a Finnigan MAT TSQ 700 triple quadrupole mass spectrometer equipped with an electrospray interface (FAB-MS) and VG Platform II mass spectrometer equipped with an electrospray interface (LC-MS). ^1H NMR and ^{13}C NMR measurements were performed on
15 BRUKER ACP 300 and Varian UNITY plus 400, 500 and 600 spectrometers, operating at ^1H frequencies of 300.13, 399.96, 499.82 and 599.94 MHz respectively, and at ^{13}C frequencies of 75.46, 100.58, 125.69 and 150.88 MHz respectively. Flash chromatography was carried out on silica gel (230-400 mesh). Preparative HPLC was performed on reverse
20 phase columns (250 mm, 20 or 50 mm; 5 to 7 μM phase Chromasil C8) with flow rates of 10 to 50 mL/min using a UV detector (270 to 280 nm).

Example 1

N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]phenyl}benzenesulfonamide
25 x HCl

(i) *t*-Butyloxycarbonylamino-3-hydroxybenzene

Amino-3-hydroxybenzene (5.46 g; 50 mmol) was dissolved in THF (50 mL) and di-*t*-butyl dicarbonate (12.0 g; 55 mmol) was added at room
30 temperature. The solution was heated for 2 hours at 60°C, the solvent was

evaporated and the residue was dissolved in EtOAc (150 mL). The EtOAc-phase was washed with 2 x 20 mL of 1M KHSO₄, 1 x 20 mL water, 1 x 20 mL brine and then dried (MgSO₄). The solvent was evaporated to give 11.74 g of a colourless oil which was crystallised from CH₂Cl₂:MeOH:light petroleum to give 9.1 g (87%) of the sub-title compound as white crystals.

¹H-NMR (400 MHz; CDCl₃): δ 7.10-7.15 (bs, 1H), 7.11 (t, 1H), 6.72 (dd, 1H), 6.53 (dd, 1H), 6.50 (bs, 1H), 5.57 (apparent bs, 1H), 1.52 (s, 9H)

¹³C-NMR (100 MHz; CDCl₃): δ 156.4, 152.8, 139.4, 129.9, 110.7, 110.2, 105.9, 80.8, 28.3

(ii) *t*-Butyloxycarbonylamino-3-[2-(4-cyanophenyl)ethoxy]benzene

To a solution of *t*-butyloxycarbonylamino-3-hydroxybenzene (418.5 mg; 2 mmol; from step (i) above), triphenylphosphine (629.5 mg; 2.4 mmol) and 2-(4-cyanophenyl)ethanol (353.2 mg; 2.4 mmol) in THF (50 mL), under an atmosphere of nitrogen, was added diethylazodicarboxylate (518 mg; 3 mmol) and the mixture was stirred for one week. Ice cold water was added and the THF was removed by evaporation. The remaining water phase was extracted three times with EtOAc. The combined organic phase was washed twice with 0.2 M NaOH, once with brine, and then dried (Na₂SO₄). Evaporation followed by flash chromatography using a stepwise gradient of toluene:EtOAc (100:0, 90:10, 80:20 and 60:40) gave 300 mg (44%) of the sub-title compound.

¹H-NMR (300 MHz; CDCl₃): δ 7.57 (d, 2H), 7.37 (d, 2H), 7.21 (bs, 1H), 7.14 (t, 1H), 6.76 (dd, 1H), 6.67 (bs, 1H, NH), 6.54 (dd, 1H), 4.16 (t, 2H), 3.10 (t, 2H), 1.50 (s, 9H)

¹³C-NMR (75 MHz; CDCl₃): δ 159.05, 152.57, 144.17, 139.65, 132.05, 129.74, 129.52, 118.84, 110.82, 110.14, 109.10, 104.52, 80.41, 67.43, 35.65, 28.20

(iii) Amino-3-[2-(4-cyanophenyl)ethoxy]benzene x HCl

t-Butyloxycarbonylamino-3-[2-(4-cyanophenyl)ethoxy]benzene (300 mg; 0.89 mmol; from step (ii) above) was dissolved in EtOAc, pre-saturated with HCl(g), at room temperature and stirred for 1 hour. The solvent and the
5 excess HCl(g) was evaporated to give 231 mg (94%) of the sub-title compound.

¹H-NMR (400 MHz; CD₃OD): δ 7.66 (d, 2H), 7.50 (d, 2H), 7.40 (t, 1H), 7.01 (bd, 1H), 6.90 (bd, 1H), 6.85 (bs, 1H), 4.28 (t, 2H), 3.18 (t, 2H)

10

(iv) N-{3-[2-(4-Cyanophenyl)ethoxy]phenyl}benzenesulfonamide

To a cold (ice:water temperature) solution of amino-3-[2-(4-cyanophenyl)ethoxy]benzene x HCl (231 mg; 0.84 mmol; from step (iii) above) in pyridine (2 mL) was added benzenesulfonyl chloride (119 μL;
15 0.93 mmol) and the mixture was allowed to reach room temperature and stirred for three days. The pyridine was removed by evaporation and the residue was partitioned between water and EtOAc. The phases was separated and the water phase was extracted twice with EtOAc and the combined organic phase was washed once with 1M KHSO₄, brine and dried
20 (Na₂SO₄). The solvent was evaporated and the residue was subjected to purification by flash chromatography using a stepwise gradient of toluene:EtOAc (100:0, 90:10, 80:20, 60:40 and 40:60) as eluent to give 277 mg (87%) of the sub-title compound.

25 LC-MS 377 (M - 1)⁺

¹H-NMR (400 MHz; CDCl₃): δ 7.82 (d, 2H), 7.75 (bs, 1H, NH), 7.56 (d, 2H), 7.47-7.53 (m, 1H), 7.40 (t, 2H), 7.35 (d, 2H), 7.07 (t, 1H), 6.75 (bt, 1H), 6.65-6.70 (m, 1H), 6.59 (dd, 1H), 4.10 (t, 2H), 3.07 (t, 2H)

(v) N-{3-[2-(4-Ethoxyiminomethylphenyl)ethoxy]phenyl} benzenesulfonamide x HCl

A gentle stream of HCl(g) was passed into a cooled (0°C) solution of N-{3-[2-(4-cyanophenyl)ethoxy]phenyl} benzenesulfonamide (257 mg; 0.68 mmol; from step (iv) above) in absolute EtOH (10 mL) until the temperature was stabilized at 0°C. The mixture was allowed to reach room temperature and stirred at this temperature for 24 hours. The solvent was evaporated to give the sub-title compound in a quantitative yield.

¹H-NMR (600 MHz; CD₃OD): δ 7.96 (d, 2H), 7.70-7.73 (m, 2H), 7.55 (d, 2H), 7.50-7.54 (m, 1H), 7.43 (t, 2H), 7.03 (t, 1H), 6.67 (t, 1H), 6.56 (dd, 2H), 4.60 (q, 2H), 4.15 (t, 2H), 3.14 (t, 2H), 1.59 (t, 3H)

(vi) N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]phenyl} benzene-sulfonamide x HCl

N-{3-[2-(4-Ethoxyiminomethylphenyl)ethoxy]phenyl} benzenesulfonamide x HCl (313 mg; 0.68 mmol; from step (v) above) was dissolved in methanol, saturated with ammonia gas and stirred at room temperature for three days. A precipitate had formed and, after addition of 0.5 mL Et₂O, the mixture was placed in a freezer overnight. The precipitate was collected by filtration and the filter-cake was washed with cool MeOH (1 mL) and Et₂O (3 mL). The crystals were dried and added to MeOH (8 mL) to form a slurry. MeOH saturated with HCl(g) was added until the solution became clear and the volume was concentrated to give 2-3 mL. Addition of Et₂O (20 mL) caused a precipitate to form which was filtered and dried under vacuum to yield 169 mg (57%) of the title compound.

FAB-MS 396 (M + 1)⁺

¹H-NMR (400 MHz; CD₃OD): δ 9.20 (bs, 1 H, NH), 8.71 (bs, 1H, NH), 7.72-7.77 (m, 4H), 7.51-7.57 (m, 3H), 7.42-7.49 (m, 2H), 7.05 (t, 1H), 6.70

(t, 1H), 6.56-6.62 (m, 2H), 4.16 (t, 2H), 3.14 (t, 2H)

¹³C-NMR (100 MHz; CDCl₃): δ 160.64, 147.36, 147.02, 141.04, 140.14, 133.89, 131.14, 130.93, 130.01, 128.99, 128.16, 114.49, 111.83, 108.52, 69.00, 36.38

5

Example 2

Benzenesulfonic acid-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methyl}-phenyl ester x HCl

10 (i) Benzenesulfonic acid-(3-hydroxy-5-methyl)phenyl ester

Benzenesulfonyl chloride (6.36 g; 36 mmol) was added to a well stirred mixture of 3,5-dihydroxytoluene x H₂O (4.26 g; 30 mmol), saturated aqueous NaHCO₃ (70 mL) and Et₂O (50 mL) and the mixture was stirred at room temperature for 19 hours. Et₂O (50 mL) was added and the organic
15 layer was separated, collected and evaporated to give 7.05 g of a powder. The crude material was recrystallized from EtOAc:heptane (30 mL:300 mL) to give 4.36 g (55%) of the sub-title compound.

FAB-MS 265 (M + 1)⁺

20 ¹H-NMR (400 MHz; CDCl₃): δ 7.86 (d, 2H), 7.67 (tt, 1H), 7.53 (t, 2H), 6.54 (bs, 1H), 6.38 (bs, 1H), 6.31 (t, 1H), 5.02 (s, 1H, OH), 2.21 (s, 3H)

(ii) Benzenesulfonic acid-{3-[2-(4-cyanophenyl)ethoxy]-5-methyl}phenyl ester

25 Diethylazodicarboxylate (1.74 g; 10 mmol) was added, over 5 minutes, to a stirred solution of triphenylphosphine (2.62 g; 10 mmol), 2-(4-cyanophenyl)ethanol (1.47 g; 10 mmol) and benzenesulfonic acid-(3-hydroxy-5-methyl)-phenyl ester (2.64 g; 10 mmol; from step (i) above) in THF (25 mL) at room temperature. The stirring was continued for an
30 additional 17 hours, the THF was evaporated and the residue was dissolved

in EtOAc (150 mL). The organic phase was washed with 2 x 25 mL of 1M NaOH, 1 x 25 mL of 1M KHSO₄, 1 x 10 mL of brine and dried (MgSO₄). The solvent was evaporated to give 9.09 g of an oil. Purification by flash chromatography using a stepwise gradient of toluene:EtOAc (100:0, 20:1 and
5 10:1) gave 2.79 g (71%) of the sub-title compound as a white powder.

FAB-MS 394 (M + 1)⁺

¹H-NMR (400 MHz; CDCl₃): δ 7.85 (apparent dd, 2H), 7.66 (tt, 1H), 7.60 (apparent d, 2H), 7.50-7.55 (m, 2H), 7.35 (d, 2H), 6.57 (bs, 1H), 6.35-6.38
10 (m, 2H), 4.07 (t, 2H), 3.08 (t, 2H), 2.21 (s, 3H)

(iii) Benzenesulfonic acid-{3-[2-(4-ethoxyiminomethylphenyl)ethoxy]-5-methyl}phenyl ester x HCl

EtOH (25 mL) was cooled to 5°C and a gentle stream of HCl(g) was
15 bubbled through until saturation. Benzenesulfonic acid-{3-[2-(4-cyanophenyl)ethoxy]-5-methyl}phenyl ester (590 mg; 1.5 mmol; from step (ii) above) was added to the cold solution in one portion and the mixture was allowed to reach room temperature and stirred over night. The solvent and excess HCl(g) was evaporated to give the sub-title compound in a
20 quantitative yield.

¹H-NMR (400 MHz; CD₃OD): δ 7.99 (apparent d, 2H), 7.81 (apparent d, 2H), 7.72 (dt, 1H), 7.53-7.62 (m, 4H), 6.63 (bs, 1H), 6.34 (bs, 1H), 6.30 (apparent t, 1H), 4.63 (q, 2H), 4.13 (t, 2H), 3.14 (t, 2H), 2.18 (s, 3H), 1.61
25 (t, 3H)

(iv) Benzenesulfonic acid-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methyl}phenyl ester x HCl

Benzenesulfonic acid-{3-[2-(4-ethoxyiminomethylphenyl)ethoxy]-5-methyl}phenyl ester x HCl (1.5 mmol; from step (iii) above) was dissolved
30

in MeOH pre-saturated by ammonia and the reaction was stirred at room temperature for 24 hours. The solvent and excess ammonia were evaporated and the residue was dissolved in MeOH (5 mL). 6 mL of 1.77 M HCl(g) in MeOH was added and the solution was concentrated to about 3 mL. Et₂O (60 mL) was added to precipitate the hydrochloride salt of the title compound. The volume was reduced to 45 mL and the mixture was placed in a freezer for two days. Collection of the precipitate by filtration followed by drying under vacuum gave 575 mg (86%; calculated from the nitrile above) of the pure title compound as a white powder.

FAB-MS 411 (M + 1)⁺

¹H-NMR (400 MHz; CD₃OD): δ 7.79-7.83 (m, 2H), 7.70-7.77 (m, 3H), 7.58 (apparent t, 2H), 7.52 (d, 2H), 6.63 (bs, 1H), 6.34 (bs, 1H), 6.29 (bs, 1H), 4.11 (t, 2H), 3.11 (t, 2H), 2.18 (s, 3H)

Example 3

N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]phenyl}-2-chlorobenzenesulfonamide x HOAc

(i) Nitro-3-[2-(4-cyanophenyl)ethoxy]benzene

Triphenylphosphine (11.3 g; 43.1 mmol) and diethylazodicarboxylate (7.5 g; 43 mmol) were dissolved in THF (250 mL) under nitrogen at 0°C. After 5 minutes, 3-nitrophenol (5.00 g; 35.9 mmol) and 2-(4-cyanophenyl)ethanol (6.3 g; 43 mmol) were added. The cooling bath was removed and the mixture stirred for 2 days at room temperature. A new batch was prepared as above and the two were combined before work-up. Water was added and the THF was evaporated. The mixture was extracted with EtOAc, and the organic phase was washed with aqueous 0.2M NaOH and brine, dried (Na₂SO₄) and the solvent removed *in vacuo*. Purification by flash chromatography (SiO₂; toluene) and recrystallization from CH₂Cl₂:EtOH

afforded 3.07 g (32%) of the sub-title compound.

¹H NMR (500 MHz; CDCl₃): δ 7.82 (dd, 1H), 7.61-7.71 (several peaks, 4H), 7.41 (d, 2H), 7.19 (dd, 1H), 4.27 (t, 2H), 3.19 (t, 2H)

5

(ii) Amino-3-[2-(4-cyanophenyl)ethoxy]benzene

Nitro-3-[2-(4-cyanophenyl)ethoxy]benzene (3.0 g; 11.2 mmol; from step (i) above) and NH₄Cl (2.9 g; 55 mmol) were dissolved in a mixture of EtOH (40 mL) and H₂O (10 mL) and heated to reflux. Iron powder (3.0 g; 55
10 mmol) was added and heating was continued for 1 hour. The mixture was filtered, concentrated *in vacuo* and partitioned between water and CH₂Cl₂. After separation, the aqueous phase was extracted with CH₂Cl₂. The combined organic phases were dried (MgSO₄) and the solvent was evaporated. Purification by flash chromatography (SiO₂; toluene:EtOAc
15 (9:1)) afforded 2.26 g (85%) of the sub-title compound.

LC-MS 239 (M + 1)⁺

¹H NMR (300 MHz; CDCl₃): δ 7.59 (d, 2H), 7.39 (d, 2H), 7.05 (t, 1H), 6.32 (m, 2H), 6.24 (t, 1H), 4.15 (t, 2H), 3.12 (t, 2H), 2.0 (s, 2H)

20

(iii) N-{3-[2-(4-Cyanophenyl)ethoxy]phenyl}-2-chlorobenzenesulfonamide

Pyridine (0.255 mL; 3.15 mmol) was added to a stirred solution of amino-3-[2-(4-cyanophenyl)ethoxy]benzene (0.15 g; 0.629 mmol; from step (ii) above) and 2-chlorobenzenesulfonyl chloride (0.173 mL; 0.818 mmol) in
25 CH₂Cl₂ (4 mL). After 45 minutes at room temperature the solvent was removed *in vacuo*. To remove traces of pyridine, EtOH was added and evaporated. The residue was partitioned between water and EtOAc. The organic layer was washed with 0.1M aqueous HCl and brine, dried (Na₂SO₄) and the solvent removed *in vacuo*. Purification by flash chromatography
30 (SiO₂; toluene:EtOAc (1:0 to 9:1)) afforded 0.095 g (35%) of the sub-title

compound.

¹H NMR (400 MHz; CD₃OD): δ 8.02 (dd, 1H), 7.62 (d, 2H), 7.45-7.52 (several peaks, 2H), 7.32-7.40 (several peaks, 3H), 7.09 (m, 2H), 6.75 (t, 1H), 6.65 (dd, 1H), 6.59 (dd, 1H), 4.13 (t, 2H), 3.11 (t, 2H)

(iv) N-{3-[2-(4-Ethoxyiminomethylphenyl)ethoxy]phenyl}-2-chlorobenzenesulfonamide x HCl

N-{3-[2-(4-Cyanophenyl)ethoxy]phenyl}-2-chlorobenzenesulfonamide (0.070 g; 0.163 mmol; from step (iii) above) was added to a saturated solution of HCl(g) in EtOH (100 mL) and the solution stirred for 24 hours. Evaporation of the solvent afforded the sub-title compound in a quantitative yield.

LC-MS 459 (M + 1)⁺

(v) N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]phenyl}-2-chlorobenzene-sulfonamide x HOAc

N-{3-[2-(4-Ethoxyiminomethylphenyl)ethoxy]phenyl}-2-chlorobenzene-sulfonamide x HCl (0.080 g, 0.16 mmol; from step (iv) above) was dissolved in MeOH (pre-saturated with NH₃(g)) and stirred at room temperature for 1 day. The solvent was evaporated and the residue purified by preparative HPLC (40% CH₃CN:0.1M NH₄OAc) to afford 0.020 g (25%) of the title compound.

25

LC-MS 430 (M + 1)⁺

¹H NMR (400 MHz; CD₃OD): δ 8.02 (dd, 1H), 7.73 (d, 2H), 7.50-7.55 (several peaks, 4H), 7.38 (m, 1H), 7.04 (t, 1H), 6.70 (t, 1H), 6.65 (m, 1H), 6.59 (m, 1H), 4.14 (t, 2H), 3.13 (t, 2H), 1.90 (s, 3H)

Example 4N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]phenyl}-2-cyanobenzene-sulfonamide x HCl5 (i) 3-[2-(4-Ethoxyiminomethylphenyl)ethoxy]nitrobenzene x HCl

A gentle stream of HCl(g) was passed into a cooled (NaCl:ice) suspension of nitro-3-[2-(4-cyanophenyl)ethoxy]benzene (2.80 g; 10.4 mmol; from Example 3(i) above) in EtOH (200 mL) until the temperature was stabilized at 0°C. After 3.5 hours stirring the temperature was allowed to rise to
10 ambient and the stirring was continued for 24 hours. Evaporation of the solvent *in vacuo* gave the sub-title compound in a quantitative yield.

¹H NMR (400 MHz; CD₃OD): δ 8.00 (d, 2H), 7.80 (ddd, 1H), 7.70 (t, 1H), 7.63 (d, 2H), 7.48 (t, 1H), 7.30 (ddd, 1H), 4.62 (q, 2H), 4.38 (t, 2H), 3.28
15 (t, 2H), 1.60 (t, 3H)

(ii) 3-[2-(4-Aminoiminomethylphenyl)ethoxy]nitrobenzene x HCl

3-[2-(4-Ethoxyiminomethylphenyl)ethoxy]nitrobenzene x HCl (3.6 g; 10.4 mmol; from step (i) above) was dissolved in MeOH, pre-saturated with
20 NH₃(g), and stirred at room temperature for 3 days. Addition of Et₂O (150 mL) failed to give any precipitate. Evaporation of the solvent *in vacuo* afforded the sub-title compound in a quantitative yield.

LC-MS 286 (M + 1)⁺

25

(iii) 3-[2-(4-Amino{*t*-butoxycarbonylimino}methylphenyl)ethoxy]nitrobenzene

3-[2-(4-Aminoiminomethylphenyl)ethoxy]nitrobenzene x HCl (3.49 g; 10.8 mmol; from step (ii) above) was dissolved in THF (20 mL) and water (10
30 mL). Aqueous NaOH (10 mL; 1M; 10 mmol) and di-*t*-butylcarbonate (2.24

g; 10.3 mmol) were added and the solution stirred at room temperature for 1 hour. THF was removed *in vacuo* and the aqueous residue was extracted twice with EtOAc. The combined organic phases were filtered and the solvent evaporated. Purification by flash chromatography (SiO₂; CH₂Cl₂)
5 resulted in partial decomposition of the product. The most pure fractions were combined and recrystallized from CH₂Cl₂:Et₂O to give 2.02 g (51%) of the sub-title compound.

LC-MS 386 (M + 1)⁺

10

(iv) Amino-3-[2-(4-amino{*t*-butoxycarbonylimino}methylphenyl)ethoxy]-benzene

A suspension of 3-[2-(4-amino{*t*-butoxycarbonylimino}methylphenyl)-ethoxy]nitrobenzene (1.47 g; 3.81 mmol; from step (iii) above) and Pd
15 (0.236 g; 5% on charcoal) in EtOH (75 mL) was stirred under H₂(g) (1 atm.) for 25 minutes. After filtration through Celite the solvent was evaporated. The residue was purified by preparative HPLC (60% CH₃CN/aq:0.1M NH₄OAc) to afford the sub-title compound. Yield: 1.02 g (75%).

20 FAB-MS 356 (M + 1)⁺

¹H NMR (300 MHz; CDCl₃): δ 7.80 (d, 2H), 7.35 (d, 2H), 7.05 (t, 1H), 6.25-6.35 (m, 2H), 6.20 (t, 1H), 4.15 (t, 2H), 3.65 (bs, 2H), 3.12 (t, 2H), 1.55 (s, 9H)

25 (v) N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]phenyl}-2-cyanobenzene-sulfonamide x HCl

Prepared using a Vac-Master in accordance with the following procedure.: Two solutions, one of amino-3-[2-(4-amino{*t*-butoxycarbonylimino}-methylphenyl)ethoxy]benzene (0.0804M; from step (iv) above) and 4-
30 dimethylaminopyridine (0.1046M) in CH₃CN, and one of 2-

cyanophenylsulfonyl chloride (0.124M) in CH₃CN were prepared. The solutions (0.700 mL of the first and 0.540 mL of the second) were mixed and left for 6 hours without stirring. The mixture was then filtered through a short plug of silica gel (0.50 g), that was washed with CH₃CN (2 x 1 mL).
5 The solvent was removed by a stream of nitrogen gas. The residue was treated with EtOAc, pre-saturated with HCl(g), (3 mL) overnight and the solvent was removed by a stream of nitrogen gas affording the title compound. To estimate the yield, the purity was determined by reversed phase LC (Chromasil C8, 0-100% CH₃CN/aq:0.1M NH₄OAc) with UV-
10 detection (254 nm). Yield: 48% (LC).

LC-MS 421 (M + 1)⁺, 419 (M - 1)⁻

Example 5

15 N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]phenyl}-2-fluorobenzene-sulfonamide x HCl

Prepared according to the procedure described in Example 4(v) above, using 2-fluorobenzenesulfonyl chloride instead of 2-cyanophenylsulfonyl chloride. Yield: 80% (LC).

20

LC-MS 414 (M + 1)⁺, 412 (M - 1)⁻

Example 6

N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]phenyl}-2-(trifluoromethoxy)-benzenesulfonamide x HCl
25

Prepared according to the procedure described in Example 4(v) above, using 2-(trifluoromethoxy)benzenesulfonyl chloride instead of 2-cyanophenylsulfonyl chloride. Yield: 80% (LC).

30 LC-MS 480 (M + 1)⁺, 478 (M - 1)⁻

Example 7

N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]phenyl}-4-fluorobenzene-sulfonamide x HCl

Prepared according to the procedure described in Example 4(v) above, using
5 4-fluorobenzenesulfonyl chloride instead of 2-cyanophenylsulfonyl chloride.
Yield: 83% (LC).

LC-MS 414 (M + 1)⁺, 412 (M - 1)⁻

10 Example 8

N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]phenyl}-2,5-dimethylbenzene-sulfonamide x HCl

Prepared according to the procedure described in Example 4(v) above, using
2,5-dimethylbenzenesulfonyl chloride instead of 2-cyanophenylsulfonyl
15 chloride. Yield: 88% (LC).

LC-MS 424 (M + 1)⁺, 422 (M - 1)⁻

Example 9

20 N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]phenyl}-5-chlorothiophene-2-sulfonamide x HCl

Prepared according to the procedure described in Example 4(v) above, using
5-chlorothiophene-2-sulfonyl chloride instead of 2-cyanophenylsulfonyl
chloride. Yield: 67% (LC).

25

LC-MS 436 (M + 1)⁺, 434 (M - 1)⁻

Example 10

N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]phenyl}-1-methylimidazole-4-sulfonamide x HCl

Prepared according to the procedure described in Example 4(v) above, using
5 1-methylimidazole-4-sulfonyl chloride instead of 2-cyanophenylsulfonyl chloride. Yield: 44% (LC).

LC-MS 400 (M + 1)⁺

10 Example 11

N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]phenyl}-3,5-dimethyl-isoxazole-4-sulfonamide x HCl

Prepared according to the procedure described in Example 4(v) above, using
3,5-dimethylisoxazole-4-sulfonyl chloride instead of 2-cyanophenylsulfonyl
15 chloride. Yield: 69% (LC).

LC-MS 415 (M + 1)⁺, 413 (M - 1)⁻

Example 12

20 N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]phenyl}benzylsulfonamide x HCl

Prepared according to the procedure described in Example 4(v) above, using
benzylsulfonyl chloride instead of 2-cyanophenylsulfonyl chloride. Yield:
71% (LC).

25

LC-MS 410 (M + 1)⁺, 408 (M - 1)⁻

Example 13

N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]phenyl}-2,5-dichlorothiophene-3-sulfonamide x HCl

Prepared according to the procedure described in Example 4(v) above, using
5 2,5-chlorothiophene-3-sulfonyl chloride instead of 2-cyanophenylsulfonyl chloride. Yield: 56% (LC).

LC-MS 471 (M + 1)⁺

10 Example 14

N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]-5-methylphenyl}-2-chlorobenzenesulfonamide x HOAc

The title compound was obtained as a side product from Example 22(iv) below. Yield: 0.014 g (13%).

15

LC-MS 444 (M + 1)⁺

¹H NMR (500 MHz; CD₃OD): δ 8.03 (dd, 1H), 7.75 (d, 2H), 7.50-7.55 (several peaks, 4H), 7.39 (m, 1H), 6.52 (t, 1H), 6.49 (t, 1H), 6.38 (t, 1H), 4.13 (t, 2H), 3.13 (t, 2H), 2.55 (t, 2H), 2.18 (s, 3H), 1.93 (s, 3H)

20

Example 15

N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]-2-methylphenyl}-benzenesulfonamide x CF₃COOH

25 (i) 3-*t*-Butoxycarbonylamino-2-methylphenol

3-Amino-2-methylphenol (2.0 g; 16 mmol) and di-*t*-butylcarbonate were dissolved in THF (20 mL) and refluxed overnight. Evaporation of the solvent followed by flash chromatography (SiO₂; EtOAc 5-30% in isohexane) afforded 2.48 g (69%) of the sub-title compound.

30

¹H NMR (300 MHz; CDCl₃): δ 7.35 (d, 1H), 7.02 (t, 1H), 6.52 (d, 1H), 6.25 (s, 1H), 4.86 (s, 1H), 2.13 (s, 3H), 1.52 (s, 9H)

(ii) *t*-Butoxycarbonylamino-3-[2-(4-cyanophenyl)ethoxy]-2-methylbenzene

5 Triphenylphosphine (1.31 g, 13.5 mmol) and diethylazodicarboxylate (1.7 mL) were dissolved in THF (20 mL) under nitrogen. After 15 minutes 3-*t*-butoxycarbonylamino-2-methylphenol (2.48 g; 11.1 mmol; from step (i) above) dissolved in THF (20 mL) and 2-(4-cyanophenyl)ethanol (1.9 g, 13 mmol) were added. After 5 days at room temperature water was added and
10 the stirring continued for 30 minutes. The mixture was extracted with EtOAc. The organic phase was washed with water and brine, dried (MgSO₄) and the solvent removed *in vacuo*. Purification by flash chromatography afforded 2.98 g (77%) of the sub-title compound.

15 ¹H NMR (300 MHz; CDCl₃): δ 7.4-7.8 (m, 5H), 7.10 (m, 1H), 6.63 (dd, 1H), 6.24 (s, 1H), 4.18 (t, 2H), 3.16 (t, 2H), 2.02 (s, 3H), 1.51 (s, 9H)

(iii) Amino-3-[2-(4-cyanophenyl)ethoxy]-2-methylbenzene

t-Butoxycarbonylamino-3-[2-(4-cyanophenyl)ethoxy]-2-methylbenzene (2.69
20 g, 7.64 mmol; from step (ii) above) were dissolved in EtOAc, pre-saturated with HCl(g), (150 mL) under nitrogen and stirred at room temperature overnight. After evaporation of the solvent the residue was partitioned between 10% aqueous HCl and EtOAc. The aqueous phase was washed with EtOAc, basified with NaOH (2M, aq.) and extracted with EtOAc. The
25 combined organic phases were washed with brine, dried (MgSO₄) and the solvent evaporated to afford 0.42 g (19%) of the sub-title compound.

¹H NMR (300 MHz; CDCl₃): δ 7.59 (d, 2H), 7.40 (d, 2H), 6.94 (t, 1H), 6.31 (dd, 2H), 3.61 (s, 2H), 4.12 (t, 2H), 3.15 (t, 2H), 1.96 (s, 3H)

(iv) N-{3-[2-(4-Cyanophenyl)ethoxy]-2-methylphenyl}benzenesulfonamide

Benzenesulfonyl chloride (0.24 mL; 1.9 mmol) was added to a stirred solution of amino-3-[2-(4-cyanophenyl)ethoxy]-2-methylbenzene (0.42 g; 1.7 mmol; from step (iii) above) in dry pyridine (20 mL) under nitrogen. The reaction was left overnight at room temperature. After evaporation of the solvent the residue was partitioned between 10% aqueous HCl and EtOAc. The organic layer was washed with brine, dried (MgSO₄) and the solvent removed *in vacuo*. Purification by flash chromatography afforded 0.47 g (72%) of the sub-title compound.

¹H NMR (300 MHz; DMSO-d₆): δ 7.4 - 7.8 (m, 10 H), 7.00 (t, 1H), 6.80 (d, 1H), 6.50 (d, 1H), 4.16 (t, 2H), 3.10 (t, 2H), 1.72 (s, 3H)

(v) N-{3-[2-(4-Aminoiminomethylphenyl)-ethoxy]-2-methyl-phenyl}-benzenesulfonamide x CF₃COOH

N-{3-[2-(4-Cyanophenyl)ethoxy]-2-methylphenyl}benzenesulfonamide (0.47 g; 1.2 mmol; from step (iv) above) was added to a saturated solution of HCl(g) in EtOH (150 mL) and the solution was stirred for 2 days. The solvent was removed by rotary evaporation and the residue treated with EtOH, pre-saturated with NH₃(g), for 3 days. After removal of the solvent, the crude product was purified by preparative HPLC (5-95% MeOH:0.1% trifluoroacetic acid). Recrystallization from isopropanol afforded 0.056 g (9%) of the title compound.

LC-MS 410 (M + 1)⁺

¹H NMR (300 MHz; DMSO-d₆): δ 9.55 (bs, 1H), 9.25 (bs, 2H), 9.0 (bs, 2H), 7.75 (d, 2H), 7.50-7.70 (several peaks, 7H), 6.99 (t, 1H), 6.80 (dd, 1H), 6.45 (dd, 1H), 4.09 (t, 2H), 3.15 (t, 2H), 1.82 (s, 3H)

Analysis calculated for C₂₄H₂₄F₃N₃O₅S: C, 55.06%; H, 4.62%; N, 8.03%; S,

6.12. Found: C, 54.83; H, 4.64%; N, 7.97%; S, 6.12%

Example 16

N-{5-[2-(4-Aminoiminomethylphenyl)ethoxy]-2-methylphenyl}benzene-
5 sulfonamide x HCl

(i) [2-(4-Cyanophenyl)ethoxy]-4-methyl-3-nitrobenzene

4-Methyl-3-nitrophenol (0.765 g; 5.0 mmol), 2-(4-cyanophenyl)ethanol
(0.735 g; 5.0 mmol) and diethylazodicarboxylate (0.87 g; 5.0 mmol) were
10 dissolved in THF (20 mL). Triphenylphosphine (1.31 g; 5.0 mmol),
dissolved in THF (5 mL), was added and the solution stirred overnight.
Evaporation *in vacuo* and the addition of diethyl ether afforded a yellow
solid that was recrystallized from water:acetone (9:1), affording the sub-title
compound as yellowish crystals. Yield: 1.04 g (74%).

15

¹H NMR (400 MHz; CDCl₃): δ 7.63 (d, 2H), 7.50 (d, 1H), 7.42 (d, 2H),
7.23 (d, 1H), 7.04 (dd, 1H), 4.14 (t, 2H), 3.09 (t, 2H), 2.53 (s, 3H)

(ii) Amino-5-[2-(4-cyanophenyl)ethoxy]-2-methylbenzene

20 Sodium borohydride (0.127 g; 3.35 mmol) was added in portions to a cold
suspension (ice:water temperature) of [2-(4-cyanophenyl)ethoxy]-4-methyl-3-
nitrobenzene (0.19 g; 0.67 mmol; from step (i) above) and aqueous copper
sulfate (1.34 mL; 1 M; 1.34 mmol) in EtOH (5 mL) over five minutes. The
temperature was allowed to rise to ambient and the stirring continued for 30
25 minutes. Addition of EtOAc (50 mL) and filtration through Celite afforded
a clear solution that was washed with water, dried (K₂CO₃) and concentrated
in vacuo. Flash chromatography (SiO₂; toluene:EtOAc (10:1)) afforded 0.044
g (26%) of the sub-title compound as a white solid.

30 ¹H NMR (400 MHz; CDCl₃): δ 7.61 (d, 2H), 7.40 (d, 2H), 6.95 (d, 1H),

6.25-6.30 (m, 2H), 4.16 (t, 2H), 3.60 (bs, 2H), 3.13 (t, 2H), 2.12 (s, 3H)

(iii) N-{5-[2-(4-Cyanophenyl)ethoxy]-2-methylphenyl} benzenesulfonamide

Benzenesulfonyl chloride (22 μ L; 0.17 mmol) was added to a cold solution
5 (ice:water temperature) of amino-5-[2-(4-cyanophenyl)ethoxy]-2-methyl-
benzene (0.041 g; 0.16 mmol; from step (ii) above) in pyridine (4 mL). The
reaction flask was left overnight in a refrigerator. NaHCO_3/aq (sat.) was
added and the solution extracted twice with EtOAc. The combined organic
phases were washed with water, HCl/aq (2M) and water. Drying (MgSO_4)
10 and evaporation of the solvent *in vacuo* afforded 0.062 g (100%) of the sub-
title compound.

^1H NMR (500 MHz; CDCl_3): δ 7.78 (d, 2H), 7.66 (d, 2H), 7.59 (t, 1H),
7.43-7.50 (m, 4H), 7.02 (d, 1H), 6.99 (d, 1H), 6.65 (dd, 1H), 6.51 (bs, 1H),
15 4.18 (t, 2H), 3.17 (t, 2H), 1.91 (s, 3H)

(iv) N-{5-[2-(4-Ethoxyiminomethylphenyl)ethoxy]-2-methylphenyl}-
benzenesulfonamide x HCl

To a cooled (ice:water temperature) saturated solution of $\text{HCl}(\text{g})$ in EtOH (5
20 mL) was added N-{5-[2-(4-cyanophenyl)ethoxy]-2-methyl-phenyl} benzene-
sulfonamide (0.062 g; 0.16 mmol; from step (iii) above). After 30 minutes
the temperature was allowed to rise to ambient and the stirring was
continued for 20 hours. Evaporation of the solvent afforded the sub-title
compound in a quantitative yield. To remove traces of HCl , EtOH was
25 added and evaporated.

LC-MS 439 ($\text{M} + 1$)⁺

(v) N-{5-[2-(4-Aminoiminomethylphenyl)ethoxy]-2-methylphenyl}-benzenesulfonamide x HCl

N-{5-[2-(4-Ethoxyiminomethylphenyl)ethoxy]-2-methylphenyl}benzenesulfonamide x HCl (0.076 g; 0.16 mmol; from step (iv) above) was dissolved in MeOH, pre-saturated with NH₃(g), and stirred at room temperature for 20 hours. After evaporation of the solvent *in vacuo* the residue was redissolved in EtOH and the solvent evaporated to remove HCl(g). Trituration of the residue with methylene chloride afforded 0.045 g (62%) of the title compound.

10

LC-MS 410 (M + 1)⁺

¹H NMR (400 MHz; CD₃OD): δ 7.75 (d, 2H), 7.65 (d, 2H), 7.50-7.60 (m, 3H), 7.45 (t, 2H), 6.95 (d, 1H), 6.60-6.70 (m, 2H), 4.09 (t, 2H), 3.13 (t, 2H), 1.85 (s, 3H)

15

Example 17

N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]-5-methylphenyl}benzenesulfonamide x HCl

20 (i) *t*-Butyloxycarbonylamino-3-hydroxy-5-methylbenzene

The sub-title compound was prepared according to the method described in Example 1(i) above from amino-3-hydroxy-5-methylbenzene (8.0 g; 65 mmol). Yield: 13.2 g (91%).

25 ¹H NMR (400 MHz; CDCl₃): δ 6.83 (bs, 1H), 6.62 (s, 1H), 6.54 (bs, 1H), 6.39 (bs, 1H), 6.37 (s, 1H), 2.22 (s, 3H) 1.50 (s, 9H)

(ii) *t*-Butyloxycarbonylamino-3-[2-(4-cyanophenyl)ethoxy]-5-methylbenzene

30 The sub-title compound was prepared according to the method described in

Example 1(ii) above from *t*-butyloxycarbonylamino-3-hydroxy-5-methylbenzene (5.9 g; 26.4 mmol; from step (i) above). Yield: 6.21 g (67%).

¹H NMR (400 MHz; CDCl₃): δ 7.58 (d, 2H), 7.38 (d, 2H), 6.93 (t, 1H), 6.63 (t, 1H), 6.44 (bs, 1H), 6.37 (t, 1H), 4.16 (t, 2H), 3.11 (t, 2H), 2.25 (s, 3H), 1.50 (s, 9H)

¹³C NMR (100 MHz; CDCl₃): δ 159.2, 152.6, 144.3, 140.0, 139.4, 132.2, 129.8, 119.0, 111.8, 110.4, 110.3, 101.9, 80.5, 67.6, 35.9, 28.4, 21.6

10 (iii) Amino-3-[2-(4-cyanophenyl)ethoxy]-5-methylbenzene

t-Butyloxycarbonylamino-3-[2-(4-cyanophenyl)ethoxy]-5-methylbenzene (1.55 g; 4.4 mmol; from step (ii) above) was stirred in a mixture of trifluoroacetic acid (10 mL) and methylene chloride (10 mL) for 3 hours. The solvent was removed *in vacuo*. The residue was dissolved in EtOAc (50 mL), washed with Na₂CO₃/aq (sat.) and water, dried (Na₂CO₃) and the solvent was removed to afford a yellow oil, which crystallized upon standing. Yield: 1.19 g (100%).

¹H NMR (500 MHz; CDCl₃): δ 7.60 (d, 2H), 7.38 (d, 2H), 6.10-6.15 (m, 2H), 6.03 (t, 1H), 4.14 (t, 2H), 3.12 (t, 2H), 2.20 (s, 3H)

(iv) N-{3-[2-(4-Cyanophenyl)ethoxy]-5-methylphenyl}benzenesulfonamide

To a cold solution (ice:water temperature) of amino-[3-2-(4-cyanophenyl)ethoxy]-5-methylbenzene (0.13 g; 0.50 mmol; from step (iii) above) in pyridine (5 mL) was added benzenesulfonyl chloride (71 μL; 0.55 mmol). After 2 hours stirring, NaHCO₃/aq (sat.) was added, and the solution extracted with EtOAc. The combined organic phases were dried (MgSO₄) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (SiO₂; EtOAc:heptane (1:1)) to give 0.19 g (97%) of the sub-title compound.

¹H NMR (500 MHz; CDCl₃): δ 7.82 (d, 2H), 7.62 (d, 2H), 7.58 (t, 1H), 7.47 (t, 2H), 7.39 (d, 2H), 6.88 (bs, 1H), 6.56 (t, 1H), 6.40-6.45 (m, 2H), 4.15 (t, 2H), 3.14 (t, 2H), 2.22 (s, 3H)

5 (v) N-{3-[2-(4-Ethoxyiminomethylphenyl)ethoxy]-5-methylphenyl}-benzenesulfonamide x HCl

N-{3-[2-(4-Cyanophenyl)ethoxy]-5-methylphenyl}benzenesulfonamide (0.19 g; 0.50 mmol; from step (iv) above) was added to a cooled (ice:water temperature) saturated solution of HCl(g) in EtOH (5 mL). After 30 minutes
10 the temperature was allowed to rise to ambient temperature and the stirring was continued for 24 hours. Evaporation of the solvent afforded the sub-title compound in a quantitative yield.

¹H NMR (500 MHz; CDCl₃): δ 12.3 (bs, 1H), 11.7 (bs, 1H), 8.27 (d, 2H),
15 8.02 (bs, 1H), 7.90 (d, 2H), 7.35-7.50 (several peaks, 5H), 6.63 (t, 1H), 6.57 (t, 1H), 6.41 (t, 1H), 4.95 (q, 2H), 4.08 (t, 2H), 3.12 (t, 2H), 2.20 (s, 3H), 1.62 (t, 3H)

(vi) N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]-5-methylphenyl}-benzenesulfonamide x HCl
20

N-{3-[2-(4-Ethoxyiminomethylphenyl)ethoxy]-5-methylphenyl}benzenesulfonamide x HCl (0.22 g; 0.50 mmol; from step (v) above) was dissolved in MeOH, saturated with NH₃(g), and stirred at room temperature for 24 hours. After evaporation of the solvent *in vacuo* the residue was redissolved
25 in MeOH (5 mL) and the solution acidified to pH 1 with EtOH, saturated with HCl(g). The solvent was evaporated and the residue dissolved in MeOH (5 mL). Upon addition of dry Et₂O, white crystals precipitated, which were filtered off, affording 0.145 g (65%) of the title compound.

30 LC-MS 410 (M + 1)⁺

¹H NMR (500 MHz; CD₃OD): δ 9.25 (bs, 2H), 8.75 (bs, 2H), 7.77-7.82 (m, 4H), 7.55-7.61 (m, 3H), 7.48-7.53 (m, 2H), 6.57 (t, 1H), 6.45-6.50 (m, 2H), 4.18 (t, 2H), 4.15 (t, 2H), 2.20 (s, 3H)

5 Example 18

N-{3-[2-(4-Aminoiminomethylphenyl)ethylthio]phenyl}benzenesulfonamide
x HCl

(i) 4-Toluenesulfonic acid-2-(4-cyanophenyl)ethyl ester

10 2-(4-Cyanophenyl)ethanol (1.46 g; 9.9 mmol) and 4-toluenesulfonyl chloride (1.9 g; 10 mmol) were stirred in pyridine (20 mL) at 5°C for 3 hours. Work-up was performed by removing the solvent, addition of 2M aqueous HCl and extraction with EtOAc. The organic phase was washed with aqueous citric acid, then passed through a short plug of silica gel with Et₂O. Removal of
15 the solvent *in vacuo* afforded a colourless oil, containing ca. 30% of unreacted 2-(4-cyanophenyl)ethanol according to ¹H NMR. The oil was further subjected to the reaction conditions above for 2 hours. Work-up as above afforded 2.0 g (66%) of the sub-title compound as a yellow solid.

20 ¹H NMR (300 MHz; CDCl₃): δ 7.65 (d, 2H), 7.55 (d, 2H), 7.16 (d, 2H), 7.10 (d, 2H), 4.24 (t, 2H), 3.07 (t, 2H), 2.45 (s, 3H)

(ii) Amino-3-[2-(4-cyanophenyl)ethylthio]benzene

3-Aminothiophenol (0.87 g; 7.0 mmol), 4-toluenesulfonic acid-2-(4-cyano-
25 phenyl)ethyl ester (2.0 g; 6.6 mmol; from step (i) above) and K₂CO₃ (1 g) were stirred in a mixture of EtOH (10 mL) and CH₂Cl₂ for 4 hours. Addition of ether, washing with brine and 2M aqueous NaOH, drying (MgSO₄), evaporation of the solvent and flash chromatography (SiO₂; Et₂O:hexane (1:1)) afforded 0.82 g (49%) of the sub-title compound.

¹H NMR (300 MHz; CDCl₃): δ 7.60 (d, 2H), 7.30 (d, 2H), 7.08 (t, 1H), 6.75 (dd, 1H), 6.71 (t, 1H), 6.53 (dd, 1H), 3.7 (bs, 2H), 3.13 (t, 2H), 2.96 (t, 2H)

(iii) N-{3-[2-(4-Cyanophenyl)ethylthio]phenyl}benzenesulfonamide

- 5 Benzenesulfonyl chloride (0.62 g; 3.5 mmol) was added to a cold solution (ice:water temperature) of amino-3-[2-(4-cyanophenyl)ethylthio]benzene (0.80 g; 3.15 mmol; from step (ii) above) in a mixture of pyridine (1 mL) and CH₂Cl₂ (20 mL) over 10 minutes. After 3 hours stirring, 2M aqueous HCl was added and the solution extracted with CH₂Cl₂. The organic layer
10 was dried (MgSO₄) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (SiO₂; Et₂O:hexane (1:1)) to give 1.02 g (82%) of the sub-title compound.

LC-MS 395 (M + 1)⁺, 393 (M - H)⁻

- 15 ¹H NMR (300 MHz; CDCl₃): δ 7.80 (d, 2H), 7.60 (d, 2H), 7.4-7.6 (m, 3H), 7.30 (s, 1H), 7.0-7.2 (m, 3H), 6.80 (m, 2H), 3.11 (t, 2H), 2.93 (t, 2H)

(iv) N-{3-[2-(4-Aminoiminomethyl)phenyl]ethylthio]phenyl}benzenesulfonamide x HCl

- 20 Trimethyl aluminum (2.5 mL; 2M in toluene; 5.0 mmol) was added to a cold (ice:water temperature) saturated suspension of NH₄Cl (0.29 g; 5.4 mmol) in toluene. After 30 minutes stirring, N-{3-[2-(4-cyanophenyl)ethylthio]phenyl}benzenesulfonamide (1.0 g; 2.6 mmol; from step (iii) above), dissolved in toluene, was added and the mixture was refluxed for 12 hours.
25 The reaction mixture was poured into silica gel (10 g) and CHCl₃ (30 mL). The solids were removed by filtration and washed with methanol. The combined liquid phases were concentrated *in vacuo* to give a solid residue. The material was purified twice by preparative HPLC (MeOH:NH₄OAc (0.1M aq.)) to obtain the acetate, which was dissolved in MeOH, pre-
30 saturated with HCl(g), three times, and evaporated to afford the title

compound as a white solid. Yield: 0.63 g (54%).

mp 84-7°C

LC-MS 412 (M + 1)⁺

5 ¹H NMR (300 MHz; DMSO-d₆): δ 10.45 (bs, 1H), 9.33 (bs, 2H), 9.10 (bs, 2H), 7.75 (m, 4H), 7.0-7.6 (m, 9H), 3.17 (t, 2H), 2.90 (t, 2H)

Example 19

N-(2-Chlorophenyl)sulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-
10 methylphenylaminoacetic acid, ethyl ester x HOAc

(i) 3-[2-(4-Cyanophenyl)ethoxy]-5-methylphenylaminoacetic acid, ethylester
Ethyl bromoacetate (134 μL, 1.2 mmol) was added to a suspension of
amino-3-[2-(4-cyanophenyl)ethoxy]-5-methylbenzene (0.252 g; 1.00 mmol;
15 from Example 17(iii) above) and K₂CO₃ (0.165 g; 1.2 mmol) in DMF (10
mL), and the mixture was stirred for 20 hours. The solvent was removed *in vacuo* and the residue partitioned between water and Et₂O. After separation,
the aqueous phase was extracted once with Et₂O. The combined ether phases
were washed with water and brine, dried (MgSO₄) and the solvent was
20 removed *in vacuo*. The residue was purified by flash chromatography (SiO₂;
EtOAc:heptane (3:7)) to give 0.30 g (89%) of the sub-title compound, a
colourless oil which crystallized upon standing.

¹H NMR (400 MHz; CDCl₃): δ 7.60 (d, 2H), 7.40 (d, 2H), 6.15 (t, 1H), 6.08
25 (t, 1H), 5.97 (t, 1H), 4.25 (q, 2H), 4.16 (t, 2H), 3.95 (s, 2H), 3.14 (t, 2H),
2.23 (s, 3H), 1.30 (t, 3H)

(ii) N-(2-Chlorophenyl)sulfonyl-3-[2-(4-cyanophenyl)ethoxy]-5-methyl-
phenylaminoacetic acid, ethyl ester

30 2-Chlorobenzenesulfonyl chloride (0.225 g; 1.06 mmol) was added to a cold

solution (ice:water temperature) of 3-[2-(4-cyanophenyl)ethoxy]-5-methylphenylaminoacetic acid, ethyl ester (0.30 g; 0.88 mmol; from step (i) above) in pyridine (10 mL). After 2 hours stirring the temperature was allowed to rise to ambient. After 4 hours at this temperature more 2-chlorobenzenesulfonyl chloride (0.056 g; 0.26 mmol) was added and the mixture was left overnight. The mixture was then poured into aqueous saturated NaHCO₃ and extracted twice with Et₂O. The combined ether phases were washed with HCl/aq (2M), H₂O and brine, dried (MgSO₄) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (SiO₂; EtOAc:heptane (1:3)) to give 0.28 g (62%) of the sub-title compound.

¹H NMR (500 MHz; CDCl₃): δ 7.90 (dd, 1H), 7.61 (d, 2H), 7.53 (dd, 1H), 7.45 (m, 1H), 7.39 (dd, 2H), 7.25 (m, 1H), 6.73 (t, 1H), 6.62 (t, 1H), 6.58 (t, 1H), 4.62 (s, 2H), 4.19 (q, 2H), 4.08 (t, 2H), 3.08 (t, 2H), 2.19 (s, 3H), 1.27 (t, 3H)

(iii) N-(2-Chlorophenyl)sulfonyl-3-[2-(4-ethoxyiminomethylphenyl)ethoxy]-5-methylphenylaminoacetic acid, ethyl ester x HCl

N-(2-Chlorophenyl)sulfonyl-3-[2-(4-cyanophenyl)ethoxy]-5-methylphenylaminoacetic acid, ethyl ester (0.27 g; 0.53 mmol; from step (ii) above) was added to a saturated solution of HCl(g) in EtOH (100 mL) and the solution was stirred for 20 hours. Evaporation of the solvent afforded the sub-title compound in a quantitative yield.

LC-MS 559 (M + 1)⁺

(iv) N-(2-Chlorophenyl)sulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylaminoacetic acid, ethyl ester x HOAc

N-(2-Chlorophenyl)sulfonyl-3-[2-(4-ethoxyiminomethylphenyl)ethoxy]-5-methylphenylaminoacetic acid, ethyl ester x HCl (0.32 g; 0.53 mmol; from

step (iii) above) was dissolved in MeOH (pre-saturated with $\text{NH}_3(\text{g})$), and stirred at room temperature for 2 days. After evaporation of the solvent *in vacuo*, the residue was redissolved in EtOH and the solution acidified to pH 1 with EtOH (saturated with $\text{HCl}(\text{g})$). The solvent was evaporated and the
5 residue purified by preparative HPLC (30 - 60% CH_3CN :0.1M NH_4OAc) to afford 0.038 g (12%) of the title compound.

LC-MS 530 ($\text{M} + 1$)⁺

¹H NMR (400 MHz; CD_3OD): δ 7.83 (dd, 1H), 7.75 (d, 2H), 7.50-7.63
10 (several peaks, 4H), 7.36 (m, 1H), 6.71 (t, 1H), 6.60 (m, 2H), 4.62 (s, 2H), 4.17 (q, 2H), 4.12 (t, 2H), 3.12 (t, 2H), 2.16 (s, 3H), 1.90 (s, 3H), 1.22 (t, 3H)

Example 20

15 N-(2-Chlorophenyl)sulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylaminoacetamide x HOAc

The title compound was obtained as a side product in Example 19 above.

Yield: 0.036 g (12%).

20 LC-MS 501 ($\text{M} + 1$)⁺

¹H NMR (400 MHz; CD_3OD): δ 7.83 (dd, 1H), 7.75 (d, 2H), 7.50-7.63 (several peaks, 4H), 7.34 (m, 1H), 6.72 (t, 1H), 6.60 (m, 2H), 4.53 (s, 2H), 4.15 (t, 2H), 3.12 (t, 2H), 2.16 (s, 3H), 1.90 (s, 3H)

25 Example 21

N-(2-Chlorophenyl)sulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylaminoacetic acid x HOAc

N-(2-Chlorophenyl)sulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylaminoacetic acid, ethyl ester x HOAc (0.030 g; 0.050 mmol;
30 from Example 19 above) was stirred in a mixture of THF (3 mL) and 2M

LiOH/aq (3 mL) for 4 hours. THF was removed *in vacuo* and the resultant suspension was acidified to pH 3 by the addition of HCl/aq (2M). CH₃CN was added to dissolve the solid phase. Purification by preparative HPLC (30% CH₃CN:0.1M NH₄OAc) afforded 0.011 g (46%) of the title compound.

5

LC-MS 502 (M + 1)⁺, 500 (M - 1)⁻

¹H NMR (500 MHz; CD₃OD): δ 7.86 (dd, 1H), 7.75 (d, 2H), 7.58 (d, 1H), 7.52 (m, 3H), 7.34 (dt, 1H), 6.78 (t, 1H), 6.58 (t, 1H), 6.53 (t, 1H), 4.40 (s, 2H), 4.18 (t, 2H), 3.12 (t, 2H), 2.12 (s, 3H), 1.98 (s, 3H)

10

Example 22

N-(2-Chlorophenyl)sulfonyl-2-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}propanoic acid, ethyl ester x HOAc

- 15 (i) 2-{3-[2-(4-Cyanophenyl)ethoxy]-5-methylphenylamino}propanoic acid, ethyl ester

Amino-3-[2-(4-cyanophenyl)ethoxy]-5-methylbenzene (0.252 g; 1.00 mmol; from Example 17(iii) above), ethyl acrylate (130 μL; 1.2 mmol) and acetic acid (9 μL; 0.15 mmol) were refluxed together for 8 hours. After
20 evaporation *in vacuo*, the resultant black oil was purified by flash chromatography (SiO₂; EtOAc:heptane (3:7)) to give 0.102 g (29%) of the sub-title compound.

¹H NMR (500 MHz; CDCl₃): δ 7.62 (d, 2H), 7.41 (d, 2H), 6.13 (t, 1H), 6.10
25 (t, 1H), 5.99 (t, 1H), 4.15-4.20 (several peaks, 4H), 3.43 (t, 2H), 3.14 (t, 2H), 2.61 (t, 2H), 2.23 (s, 3H), 1.30 (t, 3H)

- (ii) N-(2-Chlorophenyl)sulfonyl-2-{3-[2-(4-cyanophenyl)ethoxy]-5-methylphenylamino}propanoic acid, ethyl ester

30 The sub-title compound was prepared according to the method described in

Example 19(ii) above from 2-{3-[2-(4-cyanophenyl)ethoxy]-5-methylphenyl-amino}propanoic acid, ethyl ester (0.100 g; 0.28 mmol; from step (i) above) to afford 0.120 g (81%) of a yellowish oil.

5 ¹H NMR (500 MHz; CDCl₃): δ 7.85 (dd, 1H), 7.61 (d, 2H), 7.40-7.55 (several peaks, 2H), 7.38 (d, 2H), 7.25 (m, 1H), 6.67-6.70 (m, 3H), 4.07-4.15 (several peaks, 6H), 3.10 (t, 2H), 2.58 (t, 2H), 2.20 (s, 3H), 1.22 (t, 3H)

10 (iii) N-(2-Chlorophenyl)sulfonyl-2-{3-[2-(4-ethoxyiminomethylphenyl)-ethoxy]-5-methylphenylamino}propanoic acid, ethyl ester x HCl

The sub-title compound was prepared according to the method described in Example 19(iii) above from N-(2-chlorophenyl)sulfonyl-2-{3-[2-(4-cyanophenyl)ethoxy]-5-methylphenylamino}propanoic acid, ethyl ester (0.12 g; 0.22 mmol; from step (ii) above) to afford 0.13 g (100%) as an oil.

LC-MS 572 (M + 1)⁺

(iv) N-(2-Chlorophenyl)sulfonyl-2-{3-[2-(4-aminoiminomethylphenyl)-ethoxy]-5-methylphenylamino}-propanoic acid, ethyl ester x HOAc

The title compound was prepared according to the method described in Example 19(iv) above from N-(2-chlorophenyl)sulfonyl-2-{3-[2-(4-ethoxyiminomethylphenyl)ethoxy]-5-methylphenylamino}propanoic acid, ethyl ester x HCl (0.13 g; 0.22 mmol; from step (iii) above). Yield: 0.009 g (7%).

25

LC-MS 543 (M + 1)⁺

¹H NMR (400 MHz; CD₃OD): δ 7.70-7.80 (several peaks, 3H), 7.50-7.62 (several peaks, 4H), 7.35 (m, 1H), 6.62 (t, 1H), 6.55-6.60 (m, 2H), 4.10-4.17 (several peaks, 4H), 4.03 (q, 2H), 3.13 (t, 2H), 2.50 (t, 2H), 2.18 (s, 3H), 1.90 (s, 3H), 1.19 (t, 3H)

30

Example 23

N-(2-Chlorophenyl)sulfonyl-2-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}propanamide x HOAc

The title compound was obtained as a side product in Example 22 above.

5 Yield: 0.0065 g (5%).

LC-MS 514 (M + 1)⁺

¹H NMR (400 MHz; CD₃OD): δ 7.70-7.80 (several peaks, 3H), 7.50-7.65 (several peaks, 4H), 7.35 (m, 1H), 6.62 (t, 1H), 6.59 (t, 1H), 6.55 (t, 1H),
10 4.10-4.17 (several peaks, 4H), 3.13 (t, 2H), 2.45 (t, 2H), 2.2 (bs, 2H), 2.18 (s, 3H), 1.92 (s, 3H)

Example 24

N-(2-Chlorophenyl)sulfonyl-2-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}propanoic acid x HOAc

The title compound was prepared according to the method described in Example 21 above from N-(2-chlorophenyl)sulfonyl-2-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}propanoic acid, methyl ester x HOAc (0.015 g; 0.025 mmol; from Example 25 below) to afford 0.007 g
20 (48%) of a white solid.

LC-MS 516 (M + 1)⁺

¹H NMR (500 MHz; CD₃OD): δ 7.85 (d, 1H), 7.77 (d, 2H), 7.55-7.62 (several peaks, 4H), 7.35 (m, 1H), 6.65 (t, 1H), 6.60 (t, 1H), 6.53 (t, 1H),
25 4.19 (t, 2H), 4.02 (t, 2H), 3.16 (t, 2H), 2.38 (t, 2H), 2.22 (s, 3H), 1.97 (s, 3H)

Example 25

N-(2-Chlorophenyl)sulfonyl-2-{3-[2-(4-aminoiminomethylphenyl)-ethoxy]-5-methylphenylamino}propanoic acid, methyl ester x HOAc

The title compound was obtained as a side product in Example 22(iv) above.

5 Yield: 0.024 g (19%)

LC-MS 530 (M + 1)⁺

¹H NMR (500 MHz; CD₃OD): δ 7.75-85 (several peaks, 3H), 7.50-7.65 (several peaks, 4H), 7.37 (m, 1H), 6.69 (t, 1H), 6.56-6.60 (m, 2H), 4.12-4.20 (several peaks, 4H), 3.60 (s, 3H), 3.15 (t, 2H), 2.55 (t, 2H), 2.22 (s, 3H), 1.93 (s, 3H)

Example 26

N-(2-Chlorophenyl)sulfonyl-3-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}butanoic acid, ethyl ester x HOAc

(i) 3-[2-(4-Cyanophenyl)ethoxy]-5-methylphenyl-2-chlorobenzenesulfonamide
2-Chlorophenylsulfonyl chloride (0.152 g; 0.72 mmol) was added to a cooled solution (ice:water temperature) of amino-3-[2-(4-cyanophenyl)ethoxy]-5-methylbenzene (0.16 g; 0.60 mmol; from Example 17(iii) above) in pyridine (5 mL), and the resultant orange solution was stirred for 4 hours. Addition of H₂O (30 mL), extraction with EtOAc, drying (MgSO₄), evaporation of the solvent, and purification by flash chromatography (SiO₂; 25-33% EtOAc:hexane) yielded 0.20 g (78%) of the sub-title compound.

¹H NMR (500 MHz; CDCl₃): δ 8.03 (d, 1H), 7.61 (d, 2H), 7.45-7.53 (m, 2H), 7.32-7.40 (m, 3H), 7.00 (s, 1H), 6.56 (t, 1H), 6.47 (t, 1H), 6.41 (t, 1H), 4.10 (t, 2H), 3.08 (t, 2H), 2.19 (s, 3H)

(ii) N-(2-Chlorophenyl)sulfonyl-3-{3-[2-(4-cyanophenyl)ethoxy]-5-methylphenylamino}butanoic acid, ethyl ester

Ethyl 3-bromobutanoate (87 μ L; 0.60 mmol) was added to a suspension of 3-[2-(4-cyanophenyl)ethoxy]-5-methylphenyl-2-chlorobenzenesulfonamide
5 (0.171 g; 0.40 mmol; from step (i) above) and K_2CO_3 (0.166 g; 1.2 mmol) in DMF (10 mL). The mixture was stirred overnight, then poured into water, extracted with Et_2O , dried ($MgSO_4$), and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (SiO_2 ; EtOAc:hexane (3:7)) to give 0.195 g (90%) of the sub-title compound as a colourless oil.

10

1H NMR (400 MHz; $CDCl_3$): δ 7.85 (dd, 1H), 7.61 (d, 2H), 7.40-7.52 (several peaks, 2H), 7.38 (d, 2H), 7.25 (m, 1H), 6.67-6.70 (m, 3H), 4.07-4.15 (several peaks, 4H), 3.85 (t, 2H), 3.10 (t, 2H), 2.40 (t, 2H), 2.20 (s, 3H), 1.80 (m, 2H), 1.22 (t, 3H)

15

(iii) N-(2-Chlorophenyl)sulfonyl-3-{3-[2-(4-ethoxyiminomethylphenyl)ethoxy]-5-methylphenylamino}butanoic acid, ethyl ester x HCl

The sub-title compound was prepared according to the method described in Example 19(iii) above from N-(2-chlorophenyl)sulfonyl-3-{3-[2-(4-cyano-
20 phenyl)ethoxy]-5-methylphenylamino}butanoic acid, ethyl ester (0.195 g; 0.36 mmol; from step (ii) above) to afford 0.22 g (100%) of a white foam.

1H NMR (500 MHz; $CDCl_3$): δ 12.5 (bs, 1H), 11.8 (bs, 1H), 8.35 (d, 2H), 7.82 (dd, 1H), 7.40-7.50 (several peaks, 4H), 7.23 (m, 1H), 6.58 (t, 1H),
25 6.55 (t, 1H), 6.50 (t, 1H), 4.95 (q, 2H), 4.02-4.10 (several peaks, 4H), 3.87 (t, 2H), 3.10 (t, 2H), 2.40 (t, 2H), 2.20 (s, 3H), 1.80 (m, 2H), 1.60 (t, 3H), 1.22 (t, 3H)

(iv) N-(2-Chlorophenyl)sulfonyl-3-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}butanoic acid, ethyl ester x HOAc

The title compound was prepared according to the method described in Example 19(iv) above from N-(2-chlorophenyl)sulfonyl-3-{3-[2-(4-ethoxyiminomethylphenyl)ethoxy]-5-methylphenylamino}butanoic acid, ethyl ester x HCl (0.22 g; 0.36 mmol; from step (iii) above). Yield: 0.063 g (28%).

LC-MS 557 (M + 1)⁺

¹H NMR (400 MHz; CD₃OD): δ 7.78 (dd, 1H), 7.76 (d, 2H), 7.50-7.60 (several peaks, 4H), 7.33 (m, 1H), 6.63 (t, 1H), 6.58 (t, 1H), 6.56 (t, 1H), 4.15 (t, 2H), 4.07 (q, 2H), 3.87 (t, 2H), 3.13 (t, 2H), 2.41 (t, 2H), 2.18 (s, 3H), 1.90 (s, 3H), 1.74 (m, 2H), 1.21 (t, 3H)

Example 27

15 N-(2-Chlorophenyl)sulfonyl-3-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}butanamide x HOAc

NH₃(g) was fed into cold MeOH (CO₂(s):acetone temperature) until a ca. 1:1 solution was obtained. The solution was placed in an autoclave with N-(2-chlorophenyl)sulfonyl-3-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}butanoic acid, ethyl ester x HOAc (0.027 g; 0.044 mmol) and NaCN (0.001 g). The closed system was heated to 50°C for 4 days. After cooling, the solvent was removed *in vacuo* and the residue purified by preparative HPLC (30% CH₃CN:0.1M NH₄OAc) to afford 0.021 g (81%) of the title compound.

25

LC-MS 529 (M + 1)⁺

¹H NMR (400 MHz; CD₃OD): δ 7.70-8.0 (several peaks, 3H), 7.50-7.60 (several peaks, 4H), 7.33 (m, 1H), 6.62 (t, 1H), 6.59 (t, 1H), 6.55 (t, 1H), 4.12 (t, 2H), 3.85 (t, 2H), 3.12 (t, 2H), 2.27 (t, 2H), 2.18 (s, 3H), 1.90 (s, 3H), 1.75 (m, 2H)

30

Example 28

N-(2-Chlorophenyl)sulfonyl-3-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}butanoic acid x HCl

The title compound was prepared according to the method described in
5 Example 21 above from N-(2-chlorophenyl)sulfonyl-3-{3-[2-(4-aminoimino-
methylphenyl)ethoxy]-5-methylphenylamino}butanoic acid, ethyl ester x
HOAc (0.028 g; 0.045 mmol; from Example 26 above). After purification
by preparative HPLC, the solid material was dissolved in a small volume of
MeOH. HCl/aq (2M) was added and the resultant precipitate was filtered
10 off, washed with water and dried to afford 0.016 g (63%) of a white solid.

LC-MS 530 (M + 1)⁺, 528 (M - 1)⁻

¹H NMR (400 MHz; CD₃OD): δ 7.83 (d, 2H), 7.73 (d, 1H), 7.55-7.62
(several peaks, 2H), 7.71 (d, 2H), 7.33-7.40 (m, 1H), 6.62 (t, 1H), 6.57 (t,
15 1H), 6.43 (t, 1H), 4.10 (t, 2H), 3.83 (t, 2H), 3.08 (t, 2H), 2.20 (t, 2H), 2.18
(s, 3H), 1.81 (m, 2H)

Example 29

N-(2-Chlorophenyl)sulfonyl-4-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-
20 methylphenylamino}pentanoic acid, ethyl ester x HOAc

(i) N-(2-Chlorophenyl)sulfonyl-4-{3-[2-(4-cyanophenyl)ethoxy]-5-methyl-
phenylamino}pentanoic acid, ethyl ester

The sub-title compound was prepared according to the method described in
25 Example 26(ii) above from 3-[2-(4-cyanophenyl)-ethoxy]-5-methylphenyl-2-
chlorobenzenesulfonamide (0.171 g; 0.40 mmol; from Example 26(i) above)
and ethyl 4-bromopentanoate (95 μL; 0.6 mmol). Yield: 0.189 g (85%).

¹H NMR (400 MHz; CDCl₃): δ 7.84 (dd, 1H), 7.62 (d, 2H), 7.52 (dd, 1H),
30 7.42 (m, 1H), 7.38 (d, 2H), 7.23 (m, 1H), 6.67-6.70 (m, 3H), 4.07-4.15

(several peaks, 4H), 3.91 (t, 2H), 3.10 (t, 2H), 2.31 (t, 2H), 2.21 (s, 3H), 1.69 (m, 2H), 1.53 (m, 2H), 1.22 (t, 3H)

(ii) N-(2-Chlorophenyl)sulfonyl-4-{3-[2-(4-ethoxyiminomethylphenyl)-ethoxy]-5-methylphenylamino}pentanoic acid, ethyl ester x HCl

The sub-title compound was prepared according to the method described Example 19(iii) above from N-(2-chlorophenyl)sulfonyl-4-{3-[2-(4-cyanophenyl)ethoxy]-5-methylphenylamino}pentanoic acid, ethyl ester (0.189 g, 0.34 mmol; from step (i) above) in a quantitative yield.

10

¹H NMR (500 MHz; CDCl₃): δ 12.5 (bs, 1H), 11.8 (bs, 1H), 8.35 (d, 2H), 7.82 (dd, 1H), 7.40-7.50 (several peaks, 4H), 7.23 (m, 1H), 6.58 (t, 1H), 6.55 (t, 1H), 6.50 (t, 1H), 4.95 (q, 2H), 4.02-4.10 (several peaks, 4H), 3.89 (t, 2H), 3.10 (t, 2H), 2.30 (t, 2H), 2.20 (s, 3H), 1.70 (m, 2H), 1.62 (t, 3H),
15 1.53 (m, 2H), 1.22 (t, 3H)

(iii) N-(2-Chlorophenyl)sulfonyl-4-{3-[2-(4-aminoiminomethylphenyl)-ethoxy]-5-methylphenylamino}pentanoic acid, ethyl ester x HOAc

The title compound was prepared according to the method described
20 Example 19(iv) above from N-(2-chlorophenyl)sulfonyl-4-{3-[2-(4-ethoxyiminomethylphenyl)ethoxy]-5-methylphenylamino}pentanoic acid, ethyl ester x HCl (0.22 g; 0.34 mmol; from step (ii) above). Yield: 0.070 g (33%).

LC-MS 572 (M + 1)⁺

25 ¹H NMR (400 MHz; CD₃OD): δ 7.79 (dd, 1H), 7.76 (d, 2H), 7.50-7.60 (several peaks, 4H), 7.33 (m, 1H), 6.62 (t, 1H), 6.58 (m, 2H), 4.15 (t, 2H), 4.05 (q, 2H), 3.83 (t, 2H), 3.13 (t, 2H), 2.30 (t, 2H), 2.18 (s, 3H), 1.90 (s, 3H), 1.67 (m, 2H), 1.48 (m, 2H), 1.19 (t, 3H)

Example 30

4-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]-N-(2-chlorophenyl)sulfonyl-5-methylphenylamino}pentanamide x HOAc

The title compound was prepared according to the method described in
5 Example 27 above from N-(2-chlorophenyl)sulfonyl-4-{3-[2-(4-aminoimino-
methylphenyl)ethoxy]-5-methylphenylamino}pentanoic acid, ethyl ester x
HOAc (0.022 g; 0.035 mmol; from Example 29 above). Yield: 0.009 g
(42%).

10 LC-MS 543 (M + 1)⁺

¹H NMR (400 MHz; CD₃OD): δ 7.79 (dd, 1H), 7.76 (d, 2H), 7.50-7.60
(several peaks, 4H), 7.32 (m, 1H), 6.62 (t, 1H), 6.58 (t, 1H), 6.55 (t, 1H),
4.13 (t, 2H), 3.82 (t, 2H), 3.12 (t, 2H), 2.19 (t, 2H), 2.18 (s, 3H), 1.90 (s,
3H), 1.67 (m, 2H), 1.48 (m, 2H)

15

Example 31

N-(2-Chlorophenyl)sulfonyl-4-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}pentanoic acid x HCl

The title compound was prepared according to the method described
20 Example 28 above from N-(2-chlorophenyl)sulfonyl-4-{3-[2-(4-aminoimino-
methylphenyl)ethoxy]-5-methylphenylamino}pentanoic acid, ethyl ester x
HOAc (0.026 g; 0.041 mmol; from Example 29 above). Yield: 0.016 g
(46%).

25 LC-MS 544 (M + 1)⁺

¹H NMR (400 MHz; CD₃OD): δ 7.90 (d, 2H), 7.74 (dd, 1H), 7.50-7.60
(several peaks, 4H), 7.40 (m, 1H), 6.63 (t, 1H), 6.58 (t, 1H), 6.43 (t, 1H),
4.12 (t, 2H), 3.82 (t, 2H), 3.12 (t, 2H), 2.33 (t, 2H), 2.20 (s, 3H), 1.75 (m,
2H), 1.48 (m, 2H)

Example 32

N-(2-Chlorophenyl)sulfonyl-5-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}hexanoic acid, ethyl ester x HOAc

- 5 (i) N-(2-Chlorophenyl)sulfonyl-5-{3-[2-(4-cyanophenyl)ethoxy]-5-methylphenylamino}hexanoic acid, ethyl ester

The sub-title compound was prepared according to the method described in Example 26(ii) above from 3-[2-(4-cyanophenyl)ethoxy]-5-methylphenyl-2-chlorobenzenesulfonamide (0.150 g; 0.35 mmol; from Example 26(i) above)
10 and ethyl 5-bromohexanoate (75 μ L; 0.42 mmol). Yield: 0.185 g (93%).

^1H NMR (400 MHz; CDCl_3): δ 7.83 (dd, 1H), 7.61 (d, 2H), 7.50 (dd, 1H), 7.42 (m, 1H), 7.38 (d, 2H), 7.26 (m, 1H), 6.67-6.70 (m, 3H), 4.07-4.15 (several peaks, 4H), 3.78 (t, 2H), 3.10 (t, 2H), 2.27 (t, 2H), 2.20 (s, 3H),
15 1.59 (m, 2H), 1.50 (m, 2H), 1.38 (m, 2H), 1.25 (t, 3H).

- (ii) N-(2-Chlorophenyl)sulfonyl-5-{3-[2-(4-ethoxyiminomethylphenyl)ethoxy]-5-methylphenylamino}hexanoic acid, ethyl ester x HCl

The sub-title compound was prepared according to the method described
20 Example 19(iii) above from N-(2-chlorophenyl)sulfonyl-5-{3-[2-(4-cyanophenyl)ethoxy]-5-methylphenylamino}hexanoic acid, ethyl ester (0.185 g; 0.32 mmol) from step (i) above in a quantitative yield.

^1H NMR (500 MHz; CDCl_3): δ 12.5 (bs, 1H), 11.8 (bs, 1H), 8.35 (d, 2H),
25 7.80 (dd, 1H), 7.40-7.50 (several peaks, 4H), 7.23 (m, 1H), 6.58 (t, 1H), 6.55 (t, 1H), 6.48 (t, 1H), 4.92 (q, 2H), 4.00-4.10 (several peaks, 4H), 3.79 (t, 2H), 3.10 (t, 2H), 2.22 (t, 2H), 2.19 (s, 3H), 1.70 (m, 2H), 1.52-1.60 (several peaks, 5H), 1.48 (m, 2H), 1.35 (m, 2H), 1.21 (t, 3H)

(iii) N-(2-Chlorophenyl)sulfonyl-5-{3-[2-(4-aminoiminomethylphenyl)-ethoxy]-5-methylphenylamino}hexanoic acid, ethyl ester x HOAc

The title compound was prepared according to the method described in Example 19(iv) above from N-(2-chlorophenyl)sulfonyl-5-{3-[2-(4-ethoxy-
5 iminomethylphenyl)ethoxy]-5-methylphenylamino}hexanoic acid, ethyl ester x HCl (0.21 g, 0.34 mmol; from step (ii) above). Yield: 0.11 g (74%).

LC-MS 586 (M + 1)⁺

¹H NMR (500 MHz; CD₃OD): δ 7.79 (dd, 1H), 7.76 (d, 2H), 7.50-7.60
10 (several peaks, 4H), 7.35 (m, 1H), 6.62 (t, 1H), 6.58 (m, 2H), 4.16 (t, 2H), 4.10 (q, 2H), 3.83 (t, 2H), 3.15 (t, 2H), 2.28 (t, 2H), 2.19 (s, 3H), 1.90 (s, 3H), 1.58 (m, 2H), 1.47 (m, 2H), 1.40 (m, 2H), 1.22 (t, 3H)

15 Example 33

N-(2-Chlorophenyl)sulfonyl-5-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}hexanamide x HOAc

The title compound was prepared according to the method described in Example 27 above from N-(2-chlorophenyl)sulfonyl-5-{3-[2-(4-aminoimino-
20 methylphenyl)ethoxy]-5-methylphenylamino}hexanoic acid, ethyl ester x HOAc (0.020 g; 0.031 mmol; from Example 32 above). Yield: 0.010 g (52%).

LC-MS 557 (M + 1)⁺

25 ¹H NMR (400 MHz; CD₃OD): δ 7.79 (dd, 1H), 7.76 (d, 2H), 7.50-7.60 (several peaks, 4H), 7.32 (m, 1H), 6.62 (t, 1H), 6.58 (t, 1H), 6.55 (t, 1H), 4.13 (t, 2H), 3.81 (t, 2H), 3.12 (t, 2H), 2.19 (2, 3H), 2.17 (t, 2H), 1.90 (s, 3H), 1.56 (m, 2H), 1.46 (m, 2H), 1.39 (m, 2H)

Example 34

N-(2-Chlorophenyl)sulfonyl-5-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}hexanoic acid x HOAc

The title compound was prepared according to the method described in
5 Example 21 above from N-(2-chlorophenyl)sulfonyl-5-{3-[2-(4-aminoimino-
methylphenyl)ethoxy]-5-methylphenylamino}hexanoic acid, ethyl ester x
HOAc (0.040 g; 0.062 mmol) from Example 32 above. Yield: 0.026 g
(68%).

10 ESI-MS 558 (M + 1)⁺, 556 (M - 1)⁻

¹H NMR (400 MHz; CD₃OD): δ 7.82 (dd, 1H), 7.78 (d, 2H), 7.50-7.60
(several peaks, 4H), 7.35 (m, 1H), 6.62 (t, 1H), 6.57 (t, 1H), 6.52 (t, 1H),
4.12 (t, 2H), 3.81 (t, 2H), 3.12 (t, 2H), 2.19 (s, 3H), 1.90 (s, 3H), 1.56 (m,
2H), 1.46 (m, 2H), 1.39 (m, 2H)

15

Example 35

N-Phenylsulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]phenylamino-
acetic acid, ethyl ester x HOAc

20 (i) N-Phenylsulfonyl-3-[2-(4-cyanophenyl)ethoxy]phenylaminoacetic acid,
ethyl ester

N-{3-[2-(4-Cyanophenyl)ethoxy]phenyl}benzenesulfonamide (0.179 g; 0.47
mmol; from Example 1(iv) above), K₂CO₃ (0.082 g; 0.59 mmol) and ethyl
bromoacetate (63 μL; 0.57 mmol) were stirred in DMF (10 mL) for 1 hour
25 at room temperature, then 1 hour at 60°C. The mixture was filtered and the
solvent removed *in vacuo*. The residue was dissolved in EtOAc and washed
with water. The aqueous phase was extracted with EtOAc. The combined
organic portions were dried (Na₂SO₄) and the solvent evaporated to afford
the sub-title compound in a quantitative yield.

FAB-MS 465 ($M + 1$)⁺

(ii) N-(2-Phenyl)sulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl-aminoacetic acid, ethyl ester x HOAc

- 5 Prepared according to the method described Example 1(v) and 1(vi) above from N-(2-chlorophenyl)sulfonyl-3-[2-(4-cyanophenyl)ethoxy]phenyl-aminoacetic acid, ethyl ester (0.225 g, 0.47 mmol; from step (i) above), which resulted only in a ca. 50% conversion (¹H NMR). The material was thus subjected, without further purification, to the reaction conditions as
10 described in Example 1(vi) above. Purification by preparative HPLC (50% CH₃CN:0.1M NH₄OAc/aq)) afforded the title compound. The overall yield was 0.060 g (24%).

FAB-MS 482 ($M + 1$)⁺

- 15 ¹H NMR (300 MHz; CD₃OD): δ 7.76 (d, 2H), 7.50-7.70 (several peaks, 7H), 7.15 (m, 1H), 6.80-6.90 (several peaks, 2H), 6.63 (t, 1H), 4.40 (s, 2H), 4.05-4.20 (several peaks, 4H), 3.15 (t, 2H), 1.90 (s, 3H), 1.21 (t, 3H)

Example 36

- 20 N-Phenylsulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]phenylaminoacetic acid x HCl

- Aqueous NaOH (1.6 mL; 1M, 0.16 mmol) was added to a solution of N-phenylsulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]phenylaminoacetic acid, ethyl ester x HOAc (0.041 g, 0.079 mmol; from Example 35 above)
25 in MeOH (3 mL) and the mixture was stirred overnight. Aqueous 1M HCl was added and the resultant precipitate was filtered off and dried, affording 0.016 g (41%) of the title compound.

LC-MS 454 ($M + 1$)⁺, 452 ($M - 1$)⁻; FAB-MS 454 ($M + 1$)⁺

- 30 ¹H NMR (400 MHz; CD₃OD): δ 7.73 (d, 2H), 7.55-7.65 (several peaks, 3H),

7.42-7.55 (several peaks, 4H), 7.08 (t, 1H), 6.82 (t, 1H), 6.75 (dd, 1H), 6.63 (dd, 1H), 4.20 (t, 2H), 4.17 (s, 2H), 3.15 (t, 2H)

Example 37

5 N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]phenyl}-N-(2-hydroxyethyl)-benzenesulfonamide x HOAc

(i) N-{3-[2-(4-Cyanophenyl)ethoxy]phenyl}-N-(2-hydroxyethyl)-benzenesulfonamide

- 10 N-{3-[2-(4-cyanophenyl)ethoxy]phenyl} benzenesulfonamide (0.093 g; 0.246 mmol; from Example 1(iv) above), K₂CO₃ (0.047 g, 0.34 mmol), 2-chloroethanol (0.028 g; 0.34 mmol) and NaI (0.052 g; 0.34 mmol) were stirred in DMF (4 mL) for 24 hours at 100°C. The solvent was removed *in vacuo*. The residue was dissolved in water and extracted twice with EtOAc.
- 15 The combined organic portions were washed with brine, dried (Na₂SO₄) and the solvent evaporated. Purification by flash chromatography (SiO₂; toluene:EtOAc 10:0, 9:1, 8:2, 6:4) afforded 0.047 g (45%) of the sub-title compound.

- 20 ¹H NMR (300 MHz; CDCl₃): δ 7.55-7.65 (several peaks, 4H), 7.40 (d, 2H), 7.15-7.30 (several peaks, 4H), 6.83 (dd, 1H), 6.73 (t, 1H), 6.55 (dd, 1H), 4.15 (t, 2H), 3.67 (m, 4H), 3.15 (t, 2H)

(ii) N-{3-[2-(4-Amino(hydroxyimino)methylphenyl)ethoxy]phenyl}-N-(2-hydroxyethyl)-benzenesulfonamide

- 25 N-{3-[2-(4-Cyanophenyl)ethoxy]phenyl}-N-(2-hydroxyethyl)-benzenesulfonamide (0.046 g, 0.108 mmol; from step (i) above), hydroxylamine hydrochloride (0.010 g, 0.15 mmol) and triethylamine (26 μL, 0.18 mmol) were heated to reflux for 5 hours. Evaporation *in vacuo* and flash
- 30 chromatography afforded 0.033 g (67%) of the sub-title compound.

FAB-MS 456 ($M + 1$)⁺

(iii) N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]phenyl}-N-(2-hydroxyethyl)-benzenesulfonamide x HOAc

- 5 A suspension of N-{3-[2-(4-amino(hydroxyimino)methylphenyl)ethoxy]phenyl}-N-(2-hydroxyethyl)-benzenesulfonamide (0.033 g, 0.072 mmol; from step (ii) above), Pd (0.011 g; 10% on charcoal), HOAc (21 μ L; 0.36 mmol), in EtOH (10 mL) and water (0.5 mL) was stirred under an atmosphere of H₂(g) for 6 hours. After filtration through Celite, the solvent
10 was removed *in vacuo* and the residue was purified by preparative HPLC (50% CH₃CN:0.1M NH₄OAc/aq) to afford the title compound. Yield: 0.010 g (28%).

LC-MS 440 ($M + 1$)⁺

- 15 ¹H NMR (300 MHz; D₂O): δ 7.45-7.80 (several peaks, 9H), 7.30 (t, 1H), 6.97 (dd, 1H), 6.80 (dd, 1H), 6.55 (t, 1H), 4.22 (t, 2H), 3.72 (t, 2H), 3.55 (t, 2H), 3.13 (t, 2H), 1.98 (s, 3H)

¹³C NMR (75 MHz; D₂O): δ 167.2, 159.1, 146.2, 139.8, 136.8, 134.5, 130.9, 130.5, 130.0, 128.5, 128.1, 126.6, 122.9, 116.7, 116.0, 69.2, 59.2, 53.5, 35.2

20

Example 38

N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]phenyl}-N-(dimethyloxophosphinylmethyl)-benzenesulfonamide x HOAc

- 25 (i) N-{3-[2-(4-Cyanophenyl)ethoxy]phenyl}-N-(dimethyloxophosphinylmethyl)-benzenesulfonamide

N-{3-[2-(4-Cyanophenyl)ethoxy]phenyl}benzenesulfonamide (0.224 g; 0.59 mmol; from Example 1(iv) above), K₂CO₃ (0.111 g; 0.803 mmol) and chloromethyl dimethylphosphin oxide (0.090 g; 0.711 mmol) were stirred in
30 DMF (10 mL) at 60°C for 8 hours, 3 days at room temperature, and then 24

hours at 60°C. NaI (0.11 g; 0.73 mmol) was subsequently added and the mixture was heated to 100°C for 1 day. The solvent was removed *in vacuo* and the residue dissolved in water. Extraction with EtOAc, drying (Na₂SO₄), evaporation *in vacuo* and purification by flash chromatography (SiO₂; 5 toluene:EtOAc) afforded 0.125 g (45%) of the sub-title compound.

FAB-MS 469 (M + 1)⁺

¹H NMR (400 MHz; CDCl₃): δ 7.58-7.63 (several peaks, 3H), 7.52 (d, 2H), 7.45 (t, 2H), 7.38 (d, 2H), 7.18 (t, 1H), 6.82 (dd, 1H), 6.68 (t, 1H), 6.55 10 (dd, 1H), 4.11 (t, 2H), 3.96 (d, 2H), 3.12 (t, 2H), 1.46 (d, 6H)

(ii) N-{3-[2-(4-Amino(hydroxyimino)methylphenyl)ethoxy]phenyl}-N-(dimethyloxophosphinylmethyl)-benzenesulfonamide

Hydroxylamine hydrochloride (0.018 g; 0.26 mmol) and triethylamine (45 15 μL, 0.33 mmol) were added to a solution of N-{3-[2-(4-cyanophenyl)-ethoxy]phenyl}-N-(dimethyloxophosphinylmethyl)-benzenesulfonamide (0.090 g; 0.192 mmol; from step (i) above) in EtOH (6 mL). The mixture was heated at reflux for 3 hours, stirred at room temperature overnight and then refluxed for 1 hour. Evaporation of the solvent *in vacuo* and flash 20 chromatography (SiO₂; EtOAc:MeOH (9:1)) afforded 0.054 g (56%) of the sub-title compound.

¹H NMR (400 MHz; CDCl₃): δ 7.58-7.64 (several peaks, 3H), 7.53 (dd, 2H), 7.46 (t, 2H), 7.27 (d, 2H), 7.19 (t, 1H), 6.84 (ddd, 1H), 6.56-6.61 (m, 2H), 25 4.9 (bs, 2H), 4.10 (t, 2H), 3.95 (d, 2H), 3.08 (t, 2H), 1.45 (d, 6H)

(iii) N-{3-[2-(4-Aminoiminomethylphenyl)ethoxy]phenyl}-N-(dimethyl-oxophosphinylmethyl)-benzenesulfonamide x HOAc

The title compound was prepared according to the method described in 30 Example 37(iii) above from N-{3-[2-(4-amino(hydroxyimino)methylphenyl)-

ethoxy]phenyl}-N-(dimethyloxophosphinylmethyl)-benzenesulfonamide
(0.012 g; 0.024 mmol; from step (ii) above). Yield: 0.009 g (69%).

¹H NMR (300 MHz; D₂O): δ 7.70-7.80 (several peaks, 3H), 7.47-7.62
5 (several peaks, 6H), 7.30 (t, 1H), 6.97 (dd, 1H), 6.83 (dd, 2H), 6.65 (t, 1H),
4.1-4.3 (several peaks, 4H), 3.13 (t, 2H), 1.90 (s, 3H), 1.52 (d, 6H)
¹³C NMR (100 MHz; D₂O): δ 177.8, 166.5, 158.6, 145.7, 139.9, 134.9,
134.4, 130.6, 130.0, 129.5, 127.9, 127.8, 125.9, 121.8, 116.4, 115.1, 68.6,
50.2 (d), 34.7, 21.2, 13.7 (d)

10

Example 39

2-Chlorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-
methylphenyl ester x HOAc

15 (i) 3-[2-(4-Cyanophenyl)ethoxy]-5-methylphenol

Triphenylphosphine (7.86 g; 30 mmol), 3,5-dihydroxytoluene (2.5 g; 20
mmol) and 2-(4-cyanophenyl)ethanol (4.41 g; 30 mmol) were dissolved in
THF (50 mL). Diethylazodicarboxylate (5.22 g; 30 mmol; dissolved in THF
(10 mL)), was added and the solution was stirred at room temperature
20 overnight. The solvent was removed *in vacuo* and the white solid residue
extracted with Et₂O. Purification by flash chromatography (SiO₂;
toluene:EtOAc (10:1)) afforded 1.85 g (37%) of the sub-title compound as
a white solid.

25 LC-MS 252 (M - 1)⁺

¹H NMR (500 MHz; CDCl₃): δ 7.60 (d, 2H), 7.39 (d, 2H), 6.28 (t, 1H), 6.26
(t, 1H), 6.20 (t, 1H), 4.95 (bs, 1H), 4.17 (t, 2H), 3.13 (t, 2H), 2.25 (s, 3H)

(ii) 3-[2-(4-Amino(hydroxyimino)methylphenyl)ethoxy]-5-methylphenol x HCl

3-[2-(4-Cyanophenyl)ethoxy]-5-methylphenol (0.39 g; 1.54 mmol; from step (i) above), hydroxylamine hydrochloride (0.128 g; 1.85 mmol) and
5 triethylamine (281 μ L; 2.00 mmol) were dissolved in EtOH (4 mL) and stirred at 80°C for 20 minutes, then at room temperature overnight. The solvent was removed by evaporation and the residue was partitioned between dilute HCl/aq (pH 3) and CH₂Cl₂. The aqueous phase was washed with CH₂Cl₂ and stored in a refrigerator for 3 days. The precipitate which was
10 obtained was filtered off and washed with Et₂O, yielding 0.33 g (75%) of the sub-title compound.

LC-MS 287 (M + 1)⁺

¹H NMR (400 MHz; CD₃OD): δ 7.63 (d, 2H), 7.55 (d, 2H), 6.19 (m, 2H),
15 6.10 (t, 1H), 4.16 (t, 2H), 3.14 (t, 2H), 2.18 (s, 3H)

(iii) 3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenol x HOAc

The sub-title compound was prepared using the method described in Example 37(iii) above from 3-[2-(4-amino(hydroxyimino)methylphenyl)-
20 ethoxy]-5-methylphenol x HCl (0.27 g; 0.94 mmol; from step (ii) above). Yield: 0.265 g (85%).

LC-MS 271 (M + 1)⁺

¹H NMR (400 MHz; CD₃OD): δ 7.78 (d, 2H), 7.53 (d, 2H), 6.21 (t, 1H),
25 6.18 (t, 1H), 6.13 (t, 1H), 4.13 (t, 2H), 3.11 (t, 2H), 2.18 (s, 3H), 2.0 (bs, 3H)

(iv) 3-[2-(4-amino(*t*-butoxycarbonylimino)methylphenyl)ethoxy]-5-methylphenol

30 Di-*t*-butylcarbonate (1.38 g; 6.3 mmol) was added to a suspension of 3-[2-

(4-aminoiminomethylphenyl)ethoxy]-5-methylphenol x HCl (1.9 g; 6.0 mmol; from step (iii) above) and NaHCO₃ (1.51 g; 18 mmol) in THF (50 mL) and water (20 mL). After stirring overnight at room temperature, more di-*t*-butylcarbonate (0.263 g; 1.2 mmol) was added and the stirring continued
5 for 6 hours. THF was removed *in vacuo* and the aqueous residue was extracted with MeOH:CH₂Cl₂ (1:4). The combined organic phases were washed with brine, dried (MgSO₄) and the solvent was evaporated. Purification by flash chromatography (SiO₂; EtOAc:hexane (1:2, 1:1)) afforded 1.8 g (81%) of the sub-title compound.

10

LC-MS 371 (M + 1)⁺, 369 (M - 1)⁻

¹H NMR (500 MHz; CD₃OD): δ 7.76 (d, 2H), 7.41 (d, 2H), 6.21 (m, 2H), 6.14 (t, 1H), 4.14 (t, 2H), 3.10 (t, 2H), 2.20 (s, 3H), 1.52 (s, 9H)

15 (v) 2-Chlorobenzenesulfonic acid, 3-[2-(4-amino{*t*-butoxycarbonylimino}-methylphenyl)ethoxy]-5-methylphenyl ester

To a solution of 3-[2-(4-amino{*t*-butoxycarbonylimino}methylphenyl)-ethoxy]-5-methylphenol (0.025 g; 67.5 mmol; from step (iv) above) and 4-dimethylaminopyridine (0.011 g; 88 mmol) in CH₃CN (5 mL) was added 2-
20 chlorobenzenesulfonyl chloride (0.023 g; 81 mmol). The mixture was stirred at room temperature for one day, then filtered through a short plug of silica gel. After removal of the solvent *in vacuo* the residue was purified by flash chromatography (SiO₂; CH₂Cl₂:MeOH (1:0, 98:2)) yielding 0.018 g (49%) of the sub-title compound.

25

¹H NMR (500 MHz; CD₃OD): δ 7.89 (dd, 1H), 7.75 (d, 2H), 7.70 (m, 1H), 7.66 (tt, 1H), 7.44 (dt, 1H), 7.35 (d, 2H), 6.62 (t, 1H), 6.46 (t, 1H), 6.38 (t, 1H), 4.07 (t, 2H), 3.04 (t, 2H), 2.19 (s, 3H), 1.51 (s, 9H)

30

(vi) 2-Chlorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenyl ester x HOAc

2-Chlorobenzenesulfonic acid, 3-[2-(4-amino{*t*-butoxycarbonylimino}-methylphenyl)ethoxy]-5-methylphenyl ester (0.015 g; 0.028 mmol; from step 5 (v) above) was added to EtOAc, presaturated with HCl(g), (3 mL) and the mixture was stirred at room temperature overnight. Evaporation of the solvent and purification by preparative HPLC (50% CH₃CH:0.1M NH₄OAc/aq) afforded the title compound: Yield: 0.010 g (80%).

10 LC-MS 444 (M + 1)⁺

¹H NMR (500 MHz; CD₃OD): δ 7.90 (dd, 1H), 7.66-7.76 (several peaks, 4H), 7.52 (d, 2H), 7.45 (dt, 1H), 6.63 (t, 1H), 6.46 (t, 1H), 6.42 (t, 1H), 4.13 (t, 2H), 3.13 (t, 2H), 2.19 (s, 3H), 1.90 (s, 3H)

15 Example 40

Benzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl ester x HOAc

(i) Benzenesulfonic acid, 3-hydroxyphenyl ester

20 The sub-title compound was prepared according to the method described in Example 2(i) above from 1,3-dihydroxybenzene (4.50 g; 40.9 mmol). Yield: 5.1 g (50%).

LC-MS 249 (M - 1)⁺

25

(ii) Benzenesulfonic acid, 3-[2-(4-cyanophenyl)ethoxy]phenyl ester

The sub-title compound was prepared according to the method described in Example 2(ii) above from benzenesulfonic acid, 3-hydroxyphenyl ester (3.57 g; 14.3 mmol; from step (i) above). Yield: 3.7 g (69%).

30

¹H NMR (400 MHz; CDCl₃): δ 7.85 (dd, 2H), 7.66 (tt, 1H), 7.61 (d, 2H), 7.52 (t, 2H), 7.36 (d, 2H), 7.13 (t, 1H), 6.75 (dd, 1H), 6.60 (t, 1H), 6.50 (dd, 1H), 4.11 (t, 2H), 3.11 (t, 2H)

5 (iii) Benzenesulfonic acid, 3-[2-(4-amino{hydroxyimino}methylphenyl)-ethoxy]phenyl ester

The sub-title compound was prepared using the method described in Example 38(ii) above from benzenesulfonic acid, 3-[2-(4-cyanophenyl)-ethoxy]phenyl ester (0.100 g; 0.264 mmol; from step (ii) above). Yield:
10 0.095 g (88%).

LC-MS 413 (M + 1)⁺

(iv) Benzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl
15 ester x HOAc

The title compound was prepared according to the method described in Example 37 (iii) from benzenesulfonic acid, 3-[2-(4-amino{hydroxyimino}-methylphenyl)ethoxy]phenyl ester (0.085 g; 0.21 mmol; from step (iii) above). Yield: 0.021 g (25%).

20

LC-MS 397 (M + 1)⁺

¹H NMR (400 MHz; CDCl₃): δ 7.81 (m, 2H), 7.75 (d, 2H), 7.73 (tt, 1H), 7.58 (m, 2H), 7.53 (d, 2H), 7.16 (t, 1H), 6.80 (ddd, 1H), 6.53 (t, 1H), 6.50 (ddd, 1H), 4.15 (t, 2H), 3.14 (t, 2H), 1.89 (s, 3H)

25

Example 41

2-Chloro-4-fluorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)-ethoxy]-5-chlorophenyl ester x HOAc

5 (i) Chloro-3,5-dihydroxybenzene

BBr₃ (26 mL; 0.275 mmol) was added to a solution of chloro-3,5-dimethoxybenzene (10 g; 30 mmol) in CH₂Cl₂ (100 mL) at -70°C. The cooling bath was removed and the solution was stirred at room temperature for 4 days. After re-cooling to -70°C, MeOH was added (150 mL). After
10 evaporation of the solvent, toluene was added and removed *in vacuo*. Purification by kugelrohr distillation afforded 9 g (100%) of the sub-title compound.

¹H NMR (300 MHz; CD₃OD): δ 6.30 (d, 2H), 6.18 (t, 1H), 4.9 (bs, 1H)

15

(ii) 3-Chloro-5-[2-(4-cyanophenyl)ethoxy]phenol

Triphenylphosphine (32 g; 122 mmol) and diethylazodicarboxylate (19.2 mL; 122 mmol) were dissolved in CH₂Cl₂ (150 mL). Chloro-3,5-dihydroxybenzene (9.1 g; 63 mmol; from step (i) above) and 2-(4-
20 cyanophenyl)ethanol (9.04 g; 61 mmol) were added and the solution was stirred at room temperature overnight. The mixture was diluted with Et₂O and filtered through Celite. The solvent was removed *in vacuo*. Purification, first by flash chromatography (SiO₂; CH₂Cl₂:MeOH), then by preparative HPLC (60% CH₃CN:0.1 M NH₄OAc/aq), afforded 3.55 g (21%) of the sub-
25 title compound.

¹H NMR (300 MHz; CDCl₃): δ 7.60 (d, 2H), 7.40 (d, 2H), 6.45-50 (m, 2H), 6.27 (t, 1H), 5.5 (bs, 1H), 4.15 (t, 2H), 3.12 (t, 2H)

(iii) 2-Chloro-4-fluorobenzenesulfonic acid, 3-[2-(4-cyanophenyl)ethoxy]-5-chlorophenyl ester

2-Chloro-4-fluorobenzenesulfonyl chloride (1.16 g; 5.0 mmol) was added to a cold solution (ice:water temperature) of 3-chloro-5-[2-(4-cyanophenyl)ethoxy]phenol (0.689 g; 2.5 mmol; from step (ii) above) in pyridine (8 mL). The temperature was allowed to rise (slowly) to ambient overnight. The mixture was re-cooled (ice:water temperature) and ice was added to the reaction flask. After stirring for 4 hours, the pyridine was removed *in vacuo*. CH₂Cl₂ was then added and the organic layer was washed with aqueous KHSO₄ and water. Drying (MgSO₄), evaporation of the solvent and purification by flash chromatography (SiO₂; CH₂Cl₂) afforded 0.84 g (72%) of the sub-title compound.

¹H NMR (300 MHz; CDCl₃): δ 7.97 (m, 1H), 7.60 (d, 2H), 7.30-7.40 (several peaks, 3H), 7.12 (m, 1H), 6.80 (t, 1H), 6.72 (t, 1H), 6.63 (t, 1H), 4.14 (t, 2H), 3.12 (t, 2H)

(iv) 2-Chloro-4-fluorobenzenesulfonic acid, 3-[2-(4-ethoxyiminomethylphenyl)ethoxy]-5-chlorophenyl ester x HCl

The sub-title compound was prepared according to the method described Example 19(iii) above from 2-chloro-4-fluorobenzenesulfonic acid, 3-[2-(4-cyanophenyl)ethoxy]-5-chlorophenyl ester (0.576 g; 1.2 mmol; from step (iii) above) in a quantitative yield.

¹H NMR (400 MHz; CD₃OD): δ 7.97-8.03 (several peaks, 3H), 7.63 (dd, 1H), 7.57 (d, 2H), 7.28 (m, 1H), 6.89 (t, 1H), 6.70 (t, 1H), 6.60 (t, 1H), 4.62 (q, 2H), 4.22 (t, 2H), 3.18 (t, 2H), 1.61 (t, 3H)

(v) 2-Chloro-4-fluorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-chlorophenyl ester x HOAc

The title compound was prepared according to the method described in Example 19(iv) above from 2-chloro-4-fluorobenzenesulfonic acid, 3-[2-(4-ethoxyiminomethylphenyl)ethoxy]-5-chlorophenyl ester x HCl (0.718 g; 1.3 mmol; from step (iv) above). Yield: 0.097 g (15%).

LC-MS 483 (M + 1)⁺

¹H NMR (400 MHz; CD₃OD): δ 8.01 (m, 1H), 7.74 (d, 2H), 7.63 (dd, 1H), 7.53 (d, 2H), 7.28 (m, 1H), 6.89 (t, 1H), 6.70 (t, 1H), 6.61 (t, 1H), 4.20 (t, 2H), 3.16 (t, 2H), 1.88 (s, 3H)

Example 42

2-Chlorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methoxyphenyl ester x HCl

(i) 2-Chlorobenzenesulfonic acid, 3-hydroxy-5-methoxyphenyl ester

Triethylamine (1.4 g; 14 mmol) was added to a solution of 3,5-dihydroxymethoxybenzene (2.0 g; 14 mmol) and 2-chlorobenzenesulfonyl chloride (3.3 g; 15.7 mmol) in pyridine (50 mL), and the mixture was stirred at room temperature overnight. Filtration through silica and purification by preparative HPLC afforded 0.998 g (22%) of the sub-title compound.

¹H NMR (500 MHz; CDCl₃): δ 7.97 (dd, 1H), 7.55-7.62 (m, 2H), 7.38 (dt, 1H), 6.27 (m, 3H), 5.4 (bs, 1H), 3.68 (s, 3H)

(ii) 2-Chlorobenzenesulfonic acid, 3-[2-(4-cyanophenyl)ethoxy]-5-methoxyphenyl ester

The sub-title compound was prepared using the method described in Example 1(ii) above from 2-chlorobenzenesulfonic acid, 3-hydroxy-5-

methoxyphenyl ester (0.80 g; 2.5 mmol; from step (i) above). Purification by preparative HPLC afforded 0.50 g (45%) of the sub-title compound.

¹H NMR (400 MHz; CDCl₃): δ 7.97 (dd, 1H), 7.55-7.62 (several peaks, 4H),
5 7.38 (dt, 1H), 7.35 (d, 2H), 6.32 (t, 1H), 6.28 (t, 1H), 6.25 (t, 1H), 4.08 (t, 2H), 3.68 (s, 3H), 3.08 (t, 2H)

(iii) 2-Chlorobenzenesulfonic acid, 3-[2-(4-ethoxyiminomethylphenyl)-ethoxy]-5-methoxyphenyl ester x HCl

10 The sub-title compound was prepared using the method described in Example 3(iv) above from 2-chlorobenzenesulfonic acid and 3-[2-(4-cyanophenyl)ethoxy]-5-methoxyphenyl ester (0.50 g; 1.1 mmol; from step (ii) above) yielding 0.48 g (87%) of the sub-title compound.

15 LC-MS 490 (M + 1)⁺

(iv) 2-Chlorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methoxyphenyl ester x HCl

The title compound was prepared using the method described in Example
20 3(v) above from 2-chlorobenzenesulfonic acid, 3-[2-(4-ethoxyiminophenyl)-ethoxy]-5-methoxyphenyl ester x HCl (0.48 g; 0.98 mmol; from step (iii) above). Freeze-drying with 1 molar equivalent of HCl afforded 0.39 g (80%) of the title compound.

25 LC-MS 461 (M + 1)⁺

¹H NMR (500 MHz; CD₃OD): δ 7.92 (dd, 1H), 7.63-7.76 (several peaks, 4H), 7.52 (d, 2H), 7.47 (m, 1H), 6.34 (t, 1H), 6.24 (t, 1H), 6.19 (t, 1H), 4.14 (t, 2H), 3.69 (s, 3H), 3.13 (t, 2H)

Example 432-Chlorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-ethylphenyl ester x HOAc5 (i) Ethyl-3,5-dimethoxybenzene

The sub-title compound was prepared according to the procedure described in J. Chem. Soc. 859 (1949) from 3,5-dimethoxyacetophenone (5.0 g; 28 mmol). Yield 3.41 g (74%).

10 ¹H NMR (400 MHz; CD₃OD): δ 7.23 (m, 2H), 7.18 (t, 1H), 3.72 (s, 3H), 2.50 (q, 2H), 1.18 (t, 3H)

(ii) Ethyl-3,5-dihydroxybenzene

The sub-title compound was prepared according to the procedure described
15 in J. Chem. Soc. 859 (1949) from ethyl-3,5-dimethoxybenzene (3.5 g; 21 mmol; from step (i) above). Yield 2.85 g (98%).

LC-MS 139 (M - 1)⁻

¹H NMR (400 MHz; CD₃OD): δ 7.14 (m, 2H), 7.08 (t, 1H), 2.46 (q, 2H),
20 1.17 (t, 3H)

(iii) 3-[2-(4-Cyanophenyl)ethoxy]-5-ethylphenol

The sub-title compound was prepared using the method described in Example 39(i) above from ethyl-3,5-dihydroxybenzene (1.2 g; 8.69 mmol;
25 from step (ii) above). Yield: 0.182 g (7.8%).

LC-MS 266 (M - 1)⁻

¹H NMR (400 MHz; CDCl₃): δ 7.62 (d, 2H), 7.41 (d, 2H), 6.33 (t, 1H), 6.30 (t, 1H), 6.20 (t, 1H), 4.75 (bs, 1H), 4.17 (t, 2H), 3.15 (t, 2H), 2.57 (q, 2H),
30 1.22 (t, 3H)

(iv) 2-Chlorobenzenesulfonic acid, 3-[2-(4-ethoxyiminomethylphenyl)-ethoxy]-5-ethylphenyl ester x HCl

3-[2-(4-Cyanophenyl)ethoxy]-5-ethylphenol (0.040 g; 0.15 mmol; from step (iii) above) and triethylamine (0.018 g; 0.18 mmol) were dissolved in CH₂Cl₂ and 2-chlorobenzenesulfonyl chloride (0.050 g; 0.18 mmol) was added. After stirring for 2 hours, the mixture was washed with saturated K₂CO₃/aq and NaCl/aq. Filtration through a short plug of silica gel and evaporation of the solvent afforded 0.064 g of a solid. The solid material was stirred in EtOH (presaturated with HCl) overnight. Removal of excess HCl and the solvent *in vacuo* afforded 0.076 g (97%) of the sub-title compound.

LC-MS 488 (M + 1)⁺

(v) 2-Chlorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-ethylphenyl ester x HOAc

2-Chlorobenzenesulfonic acid, 3-[2-(4-ethoxyiminomethylphenyl)ethoxy]-5-ethylphenyl ester x HCl (0.076 g; 0.15 mmol; from step (iv) above) was stirred in MeOH, presaturated with NH₃(s), (20 mL) for 1 day at room temperature. After evaporation *in vacuo*, the residue was purified by ion exchange chromatography to obtain the free amidine, which was freeze-dried from aqueous HOAc yielding 0.015 g (22%) of the title compound.

LC-MS 459 (M + 1)⁺

Example 44

N-{2-[2-(4-Aminoiminomethylphenyl)ethylthio]phenyl}-benzenesulfonamide
x HCl

5 (i) Amino-2-[2-(4-cyanophenyl)ethylthio]benzene

4-Toluenesulfonic acid, 2-(4-cyanophenyl)ethyl ester (1.9 g; 6.3 mmol; from Example 18(i) above) and K_2CO_3 (2.0 g) were added to a solution of 2-aminothiophenol (0.875 g; 7.0 mmol) in EtOH (20 mL). The mixture was heated to reflux for 48 hours, cooled, filtered and concentrated *in vacuo* to
10 an oil which was dissolved in EtOAc (50 mL) and washed with water (25 mL). The organic portion was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (SiO_2 ; Et_2O :hexane (1:1)) to obtain 1.32 g (78%) of the sub-title product as a viscous oil.

15 1H NMR (300 MHz; $CDCl_3$): δ 7.57 (dd, 2H), 7.36 (dd, 2H), 7.26 (d, 2H), 7.14 (dt, 1H), 6.67-6.75 (m, 2H), 4.30 (bs, 2H), 3.05-3.10 (m, 2H), 2.95-3.05 (m, 2H)

20 (ii) N-{2-[2-(4-Aminoiminomethylphenyl)ethylthio]phenyl}-benzene-sulfonamide x HCl

Benzenesulfonyl chloride (1.0 g; 5.7 mmol) was added dropwise over 10 minutes to a solution of amino-2-[2-(4-cyanophenyl)ethylthio]benzene (1.30 g; 5.11 mmol; from step (i) above) in a mixture of pyridine (2 mL) and CH_2Cl_2 (10 mL). After 2 hours stirring at room temperature the solution
25 was diluted with CH_2Cl_2 (25 mL) and washed with aqueous 2M citric acid (25 mL). The organic portion was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was filtered through a short column of silica with diethylether to afford a colourless oil (1.41 g). This oil was dissolved in a saturated solution of HCl in EtOH (30 mL) and maintained at room
30 temperature for 48 hours. The solvent was removed *in vacuo* and the brown

residue was dissolved in 7M methanolic ammonia. After a further 24 hours the solvent was evaporated and the product was purified by preparative HPLC (MeOH:CF₃COOH/aq (0.1M)) to obtain the trifluoroacetate, which was dissolved three times in MeOH, presaturated with HCl(g), and
5 evaporated, to afford the title compound as a white solid. Yield: 0.63 g (28%).

mp 78-83°C

LC-MS 412 (M + 1)⁺

10 ¹H NMR (300 MHz; CDCl₃): δ 9.60 (bs, 1H), 9.38 (s, 2H), 9.16 (s, 2H), 7.70-7.80 (m, 4H), 7.60-7.70 (m, 3H), 7.52 (d, 2H), 7.40 (dd, 2H), 7.22 (dt, 2H), 7.18 (dt, 1H), 6.94 (dd, 1H), 3.08 (t, 2H), 2.85 (t, 2H)

Example 45

15 N-{2-[2-(4-Aminoiminomethylphenyl)ethylthio]phenyl}-2,4,5-trichlorobenzenesulfonamide x CF₃COOH

(i) Amino-2-[2-(4-aminoiminomethylphenyl)ethylthio]benzene

Amino-2-[2-(4-cyanophenyl)ethylthio]benzene (0.670 g; 2.63 mmol) from
20 Example 44(i) above was dissolved in EtOH (presaturated with HCl; 2.5 mL), and stirred for 2 days. The solvent was evaporated, the residue was dissolved in toluene (50 mL) and concentrated *in vacuo*. The residue was dissolved in 7M methanolic ammonia at 0°C and stirred overnight. The solvent was evaporated and crude product purified by preparative HPLC to
25 afford the sub-title compound. Yield: 0.47 g (66%).

mp 228-30°C

LC-MS 272 (M + H)⁺

¹H NMR (300 MHz; DMSO-d₆): δ 9.42 (s, 2H), 7.80 (d, 2H), 7.4-7.5 (m,
30 3H), 7.2-7.3 (m, 2H), 7.12 (t, 1H), 3.23 (t, 2H), 2.95 (t, 2H)

(ii) N-{2-[2-(4-Aminoiminomethylphenyl)ethylthio]phenyl}-2,4,5-trichloro-benzenesulfonamide x CF₃COOH

Amino-2-[2-(4-aminoiminomethylphenyl)ethylthio]benzene (from step (i) above) was attached to a Wang resin (0.7 mmol functional groups (benzyl alcohol)/g) that had been modified with 4-nitrophenyl chloroformate as follows: Wang resin (0.100 g; 0.7 mmol/g; 0.07 mmol) was added to a solution of amino-2-[2-(4-aminoiminomethylphenyl)ethylthio]benzene (0.054 g; 0.20 mmol) in *N*-methylpyrrolidone (2 mL). Triethylamine (0.100 mL) was added and the mixture was gently stirred overnight at room temperature. The Wang resin was filtered off and washed five times with CH₂Cl₂.

The resin was then sulfonated and deprotected as follows: The resin (0.004 g; 0.7 mmol/g; 0.0028 mmol) was swelled with CH₂Cl₂ (0.100 mL) and a solution of 2,6-lutidine in CH₂Cl₂ (0.040 mL; 1.0 mol/L; 0.040 mmol) was added. A solution of 2,4,5-trichlorobenzenesulfonyl chloride (0.020 mL; 0.25 mol/L; 0.0050 mmol) was then added and the resultant mixture was shaken at room temperature overnight. More 2,4,5-trichlorobenzenesulfonyl chloride (0.040 mL; 0.25 mol/L; 0.010 mmol) was added and the reaction continued for 3 days. The resin was filtered off and washed five times with CH₂Cl₂. The title compound was cleaved off using a 20% solution of trifluoroacetic acid in CH₂Cl₂ (2 x 5 mL) and the solvents were removed in a vacuum desiccator. To estimate the yield, the purity was determined by LC-MS to 89%.

LC-MS: 516 (M + H)⁺, 514 (M - 1)⁻

Example 46

N-{2-[2-(4-Aminoiminomethylphenyl)ethylthio]phenyl}-2-chloro-5-methoxybenzenesulfonamide x CF₃COOH

The title compound was prepared according to the procedure described in
5 Example 45 above, using 2-chloro-5-methoxyphenylsulfonyl chloride instead of 2,4,5-trichlorobenzenesulfonyl chloride. Yield: 87% (LC).

LC-MS: 476 (M + H)⁺, 474 (M - 1)⁻

10 Example 47

N-{2-[2-(4-Aminoiminomethylphenyl)ethylthio]phenyl}-2,5-dibromobenzenesulfonamide x CF₃COOH

The title compound was prepared according to the procedure described in
Example 45 above, using 2,5-dibromophenylsulfonyl chloride instead of
15 2,4,5-trichlorobenzenesulfonyl chloride. Yield: 81% (LC).

LC-MS: 570 (M + 1)⁺, 568 (M - 1)⁻

Example 48

20 N-{2-[2-(4-Aminoiminomethylphenyl)ethylthio]phenyl}-2,5-dichlorobenzenesulfonamide x CF₃COOH

The title compound was prepared according to the procedure described in
Example 45 above, using 2,5-dichlorophenylsulfonyl chloride instead of
2,4,5-trichlorobenzenesulfonyl chloride. Yield: 69% (LC).

25

LC-MS: 480 (M + H)⁺, 478 (M - 1)⁻

Example 49

N-{2-[2-(4-Aminoiminomethylphenyl)-ethylthio]-phenyl}-2-methoxy-5-methylbenzenesulfonamide x CF₃COOH

The title compound was prepared according to the procedure described in
5 Example 45 above, using 2-methoxy-5-methylphenylsulfonyl chloride instead of 2,4,5-trichlorobenzenesulfonyl chloride. Yield: 84% (LC).

LC-MS: 456 (M + H)⁺

10 Example 50

N-{2-[2-(4-Aminoiminomethylphenyl)ethylthio]phenyl}-2,3,5,6-tetramethylbenzenesulfonamide x CF₃COOH

The title compound was prepared according to the procedure described in
Example 45 above, using 2,3,5,6-tetramethylphenylsulfonyl chloride instead
15 of 2,4,5-trichlorobenzenesulfonyl chloride. Yield: 84% (LC).

LC-MS: 468 (M + H)⁺, 466 (M - 1)⁻

Example 51

20 N-{2-[2-(4-Aminoiminomethylphenyl)ethylthio]phenyl}-3,4-dimethoxybenzenesulfonamide x CF₃COOH

The title compound was prepared according to the procedure described in
Example 45 above, using 3,4-dimethoxyphenylsulfonyl chloride instead of
2,4,5-trichlorobenzenesulfonyl chloride. Yield: 88% (LC).

25

LC-MS: 472 (M + H)⁺, 470 (M - 1)⁻

Example 52

N-{2-[2-(4-Aminoiminomethylphenyl)ethylthio]phenyl}-3-bromo-benzenesulfonamide x CF₃COOH

The title compound was prepared according to the procedure described in
5 Example 45 above, using 3-bromophenylsulfonyl chloride instead of 2,4,5-trichlorobenzenesulfonyl chloride. Yield: 80% (LC).

LC-MS: 490 (M + H)⁺, 488 (M - 1)⁻

10 Example 53

N-{2-[2-(4-Aminoiminomethylphenyl)ethylthio]phenyl}-3,4-dibromobenzene-sulfonamide x CF₃COOH

The title compound was prepared according to the procedure described in
Example 45 above, using 3,4-dibromophenylsulfonyl chloride instead of
15 2,4,5-trichlorobenzenesulfonyl chloride. Yield: 75% (LC).

LC-MS: 570 (M + H)⁺, 568 (M - 1)⁻

Example 54

20 N-{2-[2-(4-Aminoiminomethylphenyl)ethylthio]phenyl}-2-chloro-4-fluorobenzenesulfonamide x CF₃COOH

The title compound was prepared according to the procedure described in
Example 45 above, using 2-chloro-4-fluorophenylsulfonyl chloride instead
of 2,4,5-trichlorobenzenesulfonyl chloride. Yield: 100% (LC).

25

LC-MS: 465 (M + H)⁺, 463 (M - 1)⁻

Example 55

N-{2-[2-(4-Aminoiminomethylphenyl)ethylthio]phenyl}-5-bromo-2-methoxybenzenesulfonamide x CF₃COOH

The title compound was prepared according to the procedure described in
5 Example 45 above, using 5-bromo-2-methoxyphenylsulfonyl chloride instead of 2,4,5-trichlorobenzenesulfonyl chloride. Yield: 85% (LC).

LC-MS: 520 (M + H)⁺

10 Example 56

The title compounds of Examples 1 to 55 were tested in Test A and/or B and/or Test C above and were found to exhibit an IC₅₀ value and/or a K_i value (as appropriate) of less than 0.3 μM.

15 **Abbreviations**

Ac =	acyl
DCC =	dicyclohexylcarbodiimide
DMF =	dimethylformamide
20 EDC =	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et =	ethyl
Et ₂ O =	diethyl ether
EtOAc =	ethyl acetate
EtOH =	ethanol
25 h =	hours
HCl(g) =	hydrogen chloride gas
HPLC =	high performance liquid chromatography
HOAc =	acetic acid
HOBt =	N-hydroxybenzotriazole
30 LC =	liquid chromatography

Me = methyl

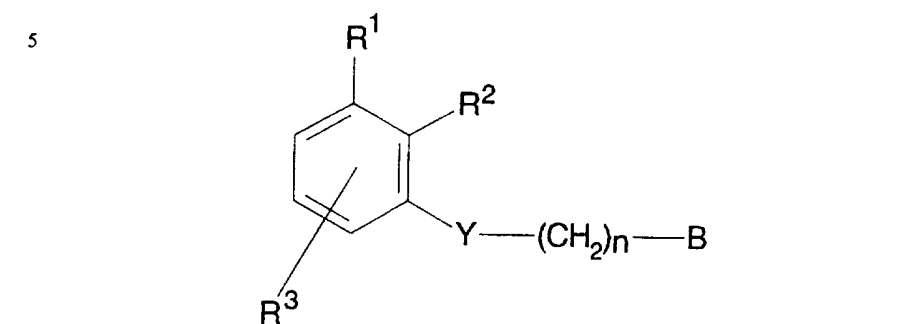
MeOH = methanol

THF = tetrahydrofuran

- 5 Prefixes *n*, *s*, *i* and *t* have their usual meanings: normal, iso, secondary and tertiary.

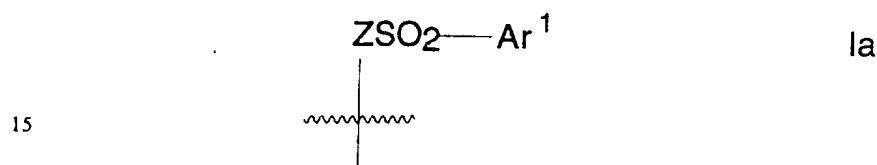
Claims

1. A compound of formula I,



wherein

one of R¹ and R² represents a structural fragment of formula Ia



and the other represents R⁴;

Z represents O or N(R⁵);

R³ represents one or more optional substituents selected from OH, halo, cyano, nitro, C(O)OR⁶, C₁-₆ alkoxy or C₁-₆ alkyl (which two latter groups are optionally substituted and/or terminated by one or more halo or hydroxy group) or N(R⁷)R⁸;

R⁴ represents H, OH, halo, cyano, nitro, C(O)OR⁶, C₁-₆ alkoxy or C₁-₆ alkyl (which two latter groups are optionally substituted and/or terminated by one or more halo or hydroxy group) or N(R⁷)R⁸;

Ar¹ represents phenyl, C₁-₃ alkylphenyl, C₁-₃ alkylidiphenyl, C₃-₇ cycloalkyl, C₁-₃-alkyl-C₃-₇-cycloalkyl, C₁-₃-alkyl-di-C₃-₇-cycloalkyl, naphthyl, C₁-₃ alkylnaphthyl, thienyl, imidazolyl or isoxazolyl, all of which may be substituted by one or more substituent selected from OH, halo, cyano, nitro, C(O)OR⁶, C₁-₆ alkoxy or C₁-₆ alkyl (which two latter groups are optionally

substituted and/or terminated by one or more halo or hydroxy group) or $N(R^7)R^8$;

R^5 represents H, C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl (which three latter groups are optionally substituted and/or terminated by one or more
 5 substituent selected from OH, halo, cyano, nitro, $C(O)OR^9$, $C(O)N(R^{10})R^{11}$, $P(O)(R^{12})R^{13}$, $P(O)(OR^{14})OR^{15}$, $S(O)_2(R^{16})R^{17}$, $S(O)_2N(R^{18})R^{19}$, C_{1-6} alkoxy or C_{1-6} alkyl (which two latter groups are optionally substituted and/or terminated by one or more halo or hydroxy group) or $N(R^{20})R^{21}$);

Y represents O, S, $S(O)$, $S(O)_2$ or $N(R^{22})$;

10 R^{10} and R^{11} independently represent H, OR^{23} , $C(O)R^{24}$, $OC(O)R^{25}$, $C(O)OR^{26}$, C_{1-4} alkyl, (which latter group is optionally substituted and/or terminated by one or more substituent selected from C_{1-4} alkyl, OR^{27} , $N(R^{28})R^{29}$, $C(O)OR^{30}$, $C(O)N(R^{31})R^{32}$, $P(O)(R^{33})R^{34}$, $P(O)(OR^{35})OR^{36}$ and $S(O)_2N(R^{37})R^{38}$),
 $-(CH_2CH_2O)_pR^{39}$ or, together with the nitrogen atom to which they are
 15 attached, form a C_{4-7} nitrogen-containing, aromatic or non-aromatic, ring which ring may contain a further heteroatom or group (as appropriate) selected from O, S and $N(R^{40})$ and may further be substituted by one or more substituent selected from $C(O)R^{41}$, $C(O)OR^{42}$ or $C(O)N(R^{43})R^{44}$;

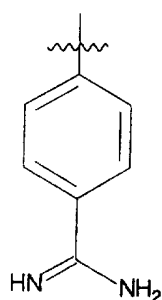
R^{28} , R^{29} , R^{30} , R^{31} , R^{32} and R^{40} independently represent H or C_{1-6} alkyl, which
 20 latter group is optionally substituted and/or terminated by one or more substituent selected from $C(O)R^{45}$, $C(O)OR^{46}$ or $C(O)N(R^{47})R^{48}$;

at each occurrence, R^6 , R^7 and R^8 independently represent H or C_{1-4} alkyl;
 R^9 , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} ,
 R^{33} , R^{34} , R^{35} , R^{36} , R^{37} , R^{38} , R^{39} , R^{41} , R^{42} , R^{43} , R^{44} , R^{45} , R^{46} , R^{47} and R^{48}
 25 independently represent H or C_{1-4} alkyl;

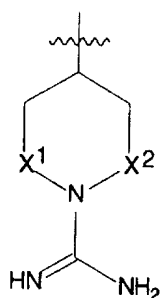
n represents 0, 1, 2, 3 or 4;

p represents 1, 2, 3, 4, 5 or 6; and

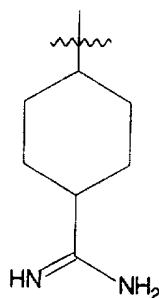
B represents a structural fragment of formula Ib, Ic, Id or Ie



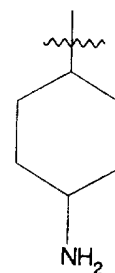
Ib



Ic



Id



Ie

wherein

X^1 and X^2 independently represent a single bond or CH_2 ;
or a pharmaceutically acceptable salt thereof.

- 5 2. A compound of formula I, as defined in Claim 1, wherein, when B represents a structural fragment of formula Ib, Id, Ie or Ic in which latter fragment X^1 and X^2 both represent CH_2 , then n represents 2.
3. A compound of formula I, as defined in one Claim 1, wherein n
10 represents 2.
4. A compound of formula I, as defined in any one of the preceding claims, wherein R^2 represents a structural fragment of formula Ia and R^1 represents R^4 .
- 15 5. A compound of formula I, as defined in any one of the preceding claims, wherein Z represents O or $N(R^5)$, in which latter case R^5 represents C_{1-6} alkyl terminated by $C(O)N(R^{10})R^{11}$.
- 20 6. A compound of formula I, as defined in any one of the preceding claims, wherein R^3 is not present, or represents methyl, chloro or methoxy.

7. A compound of formula I, as defined in any one of the preceding claims, wherein Ar¹ represents substituted phenyl.
8. A compound of formula I, as defined in any one of the preceding claims
5 wherein Y represents O.
9. A compound of formula I, as defined in any one of the preceding claims wherein B represents a structural fragment of formula Ib.
- 10 10. A compound as claimed in Claim 1 which is:
- N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}benzenesulfonamide;
benzenesulfonic acid-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-
methyl}phenyl ester;
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-2-
15 chlorobenzenesulfonamide;
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-2-cyanobenzene-
sulfonamide;
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-2-fluorobenzene-
sulfonamide;
20 N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-2-(trifluoromethoxy)-
benzenesulfonamide;
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-4-fluorobenzene-
sulfonamide;
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-2,5-dimethylbenzene-
25 sulfonamide;
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-5-chlorothiophene-2-
sulfonamide;
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-1-methylimidazole-3-
sulfonamide;
30 N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-3,5-dimethylisoxazole-

- 4-sulfonamide;
- N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}benzylsulfonamide;
- N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-2,5-dichlorothiophene-3-sulfonamide;
- 5 N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenyl}-2-chlorobenzenesulfonamide;
- N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-2-methylphenyl}-benzenesulfonamide;
- N-{5-[2-(4-aminoiminomethylphenyl)ethoxy]-2-methylphenyl}benzene-
- 10 sulfonamide;
- N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenyl}benzenesulfonamide;
- N-{3-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}benzenesulfonamide;
- N-(2-chlorophenyl)sulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-
- 15 methylphenylaminoacetic acid, ethyl ester;
- N-(2-chlorophenyl)sulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylaminoacetamide;
- N-(2-chlorophenyl)sulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylaminoacetic acid;
- 20 N-(2-chlorophenyl)sulfonyl-2-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}propanoic acid, ethyl ester;
- 2-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-N-(2-chlorophenyl)sulfonyl-5-methylphenylamino}propanamide;
- N-(2-chlorophenyl)sulfonyl-2-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-
- 25 methylphenylamino}propanoic acid;
- N-(2-chlorophenyl)sulfonyl-2-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}propanoic acid, methyl ester;
- N-(2-chlorophenyl)sulfonyl-3-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}butanoic acid, ethyl ester;
- 30 3-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-N-(2-chlorophenyl)sulfonyl-5-

- methylphenylamino} butanamide;
- N-(2-chlorophenyl)sulfonyl-3-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino} butanoic acid;
- N-(2-chlorophenyl)sulfonyl-4-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino} pentanoic acid, ethyl ester;
- 4-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-N-(2-chlorophenyl)sulfonyl-5-methylphenylamino} pentanamide;
- N-(2-chlorophenyl)sulfonyl-4-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino} pentanoic acid;
- 10 N-(2-chlorophenyl)sulfonyl-5-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino} hexanoic acid, ethyl ester;
- 5-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-N-(2-chlorophenyl)sulfonyl-5-methylphenylamino} pentanamide;
- N-(2-chlorophenyl)sulfonyl-5-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino} hexanoic acid;
- 15 N-phenylsulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]phenylaminoacetic acid, ethyl ester;
- N-phenylsulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]phenylaminoacetic acid;
- 20 N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-N-(2-hydroxyethyl)-benzenesulfonamide;
- N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-N-(dimethyloxophosphinylmethyl)-benzenesulfonamide;
- 2-chlorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenyl ester;
- 25 benzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl ester;
- 2-chloro-4-fluorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-chlorophenyl ester;
- 2-chlorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methoxyphenyl ester;
- 30

- 2-chlorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-ethylphenyl ester;
- N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl} benzenesulfonamide;
- N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-2,4,5-trichloro-
5 benzenesulfonamide;
- N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-2-chloro-5-methoxybenzenesulfonamide;
- N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-2,5-dibromobenzenesulfonamide;
- 10 N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-2,5-dichlorobenzenesulfonamide;
- N-{2-[2-(4-aminoiminomethylphenyl)-ethylthio]-phenyl}-2-methoxy-5-methylbenzenesulfonamide;
- N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-2,3,5,6-
15 tetramethylbenzenesulfonamide;
- N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-3,4-dimethoxybenzenesulfonamide;
- N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-3-bromobenzenesulfonamide;
- 20 N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-3,4-dibromobenzenesulfonamide;
- N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-2-chloro-4-fluorobenzenesulfonamide; or
- N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-5-bromo-2-
25 methoxybenzenesulfonamide.

11. A compound of formula I, as defined in Claim 1, provided that R¹ represents a structural fragment of formula Ia and R² represents R⁴.

30 12. A compound of formula I, as defined in Claim 1, provided that Ar¹

represents optionally substituted phenyl.

13. A compound of formula I, as defined in Claim 1, provided that R^5 is not substituted by $P(O)(OR^{14})OR^{15}$, $S(O)_2(R^{16})R^{17}$ or $S(O)_2N(R^{18})R^{19}$.

5

14. A compound of formula I, as defined in Claim 1, provided that R^{10} and/or R^{11} represent H or unsubstituted C_{1-4} alkyl.

15. A compound of formula I, as defined in Claim 1, provided that Y
10 represents O, S or $N(R^5)$.

16. A compound of formula I, as defined in Claim 1, provided that B represents a structural fragment of formula Ib, Ic or Id.

15 17. A compound of formula I, as defined in Claim 1, provided that R^2 represents a structural fragment of formula Ia and R^1 represents R^4 .

18. A compound of formula I, as defined in Claim 1, provided that Ar^1 does not represent optionally substituted phenyl.

20

19. A compound of formula I, as defined in Claim 1, provided that R^5 is substituted by $P(O)(OR^{14})OR^{15}$, $S(O)_2(R^{16})R^{17}$ or $S(O)_2N(R^{18})R^{19}$.

20. A compound of formula I, as defined in Claim 1, provided that R^{10}
25 and/or R^{11} do not represent H or unsubstituted C_{1-4} alkyl.

21. A compound of formula I, as defined in Claim 1, provided that Y represents $S(O)$ or $S(O)_2$.

30 22. A compound of formula I, as defined in Claim 1, provided that B

represents a structural fragment of formula Ie.

23. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, in
5 admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

24. A compound as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

10 25. A compound as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition where inhibition of thrombin is required.

26. A compound as defined in any one of Claims 1 to 22, or a
15 pharmaceutically acceptable salt thereof, for use in the treatment of thrombosis.

27. A compound of formula I as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, for use as an anticoagulant.

20

28. The use of a compound I as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof as active ingredient in the manufacture of a medicament for the treatment of a condition where inhibition of thrombin is required.

25

29. The use as claimed in Claim 28, wherein the condition is thrombosis.

30. The use of a compound defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, as active ingredient in the
30 manufacture of an anticoagulant.

31. A method of treatment of a condition where inhibition of thrombin is required which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, to a person suffering from, or
 5 susceptible to, such a condition.

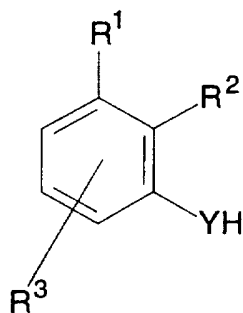
32. A method as claimed in Claim 31, wherein the condition is thrombosis.

33. A method as claimed in Claim 31, wherein the condition is
 10 hypercoagulability in blood and tissues.

34. A process for the preparation of compounds of formula I which comprises:

(a) reaction of a compound of formula II,

15



II

20

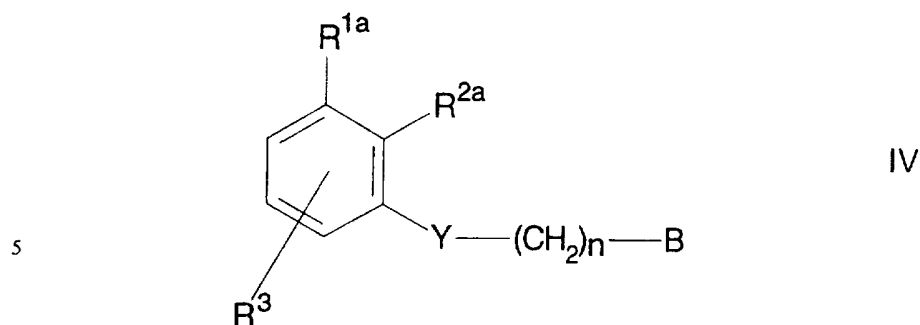
wherein R¹, R², R³ and Y are as defined in Claim 1 with a compound of formula III,



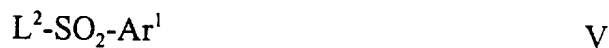
wherein L¹ represents a suitable leaving group and n and B are as defined
 25 in Claim 1;

(b) reaction of a compound of formula IV,

100



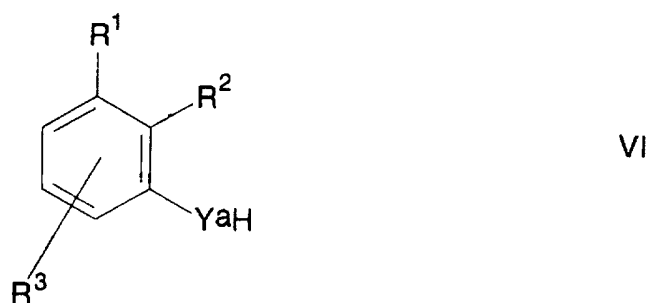
wherein one of R^{1a} and R^{2a} represents ZH and the other represents R^4 , and
 Z, R^3 , R^4 , Y, n and B are as defined in Claim 1 with a compound of formula
 10 V,



wherein L^2 is a suitable leaving group and Ar^1 is as defined in Claim 1;

(c) for compounds of formula I in which Y represents O or S, reaction of
 a compound of formula VI,

15



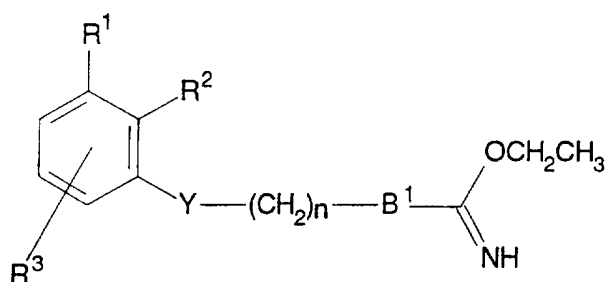
20

wherein Y^a represents O or S and R^1 , R^2 and R^3 are as defined in Claim 1
 with a compound of formula VII,



25 wherein n and B are as defined in Claim 1;

(d) for compounds of formula I wherein B represents a structural fragment
 of formula Ib or Id, reaction of a compound of formula VIII,

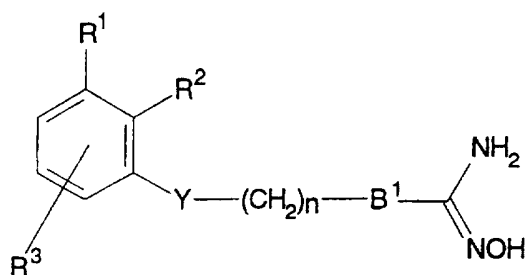


VIII

wherein B¹ represents 1,4-phenylene or 1,4-cyclohexylene and R¹, R², R³, Y and n are as defined in Claim 1 with ammonia gas;

(e) for compounds of formula I wherein B represents a structural fragment of formula Ib or Id, reduction of a compound of formula IX,

5



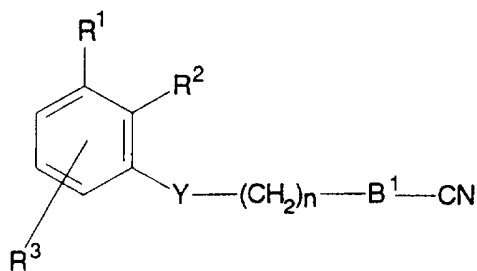
IX

10

wherein R¹, R², R³, Y and n are as defined in Claim 1 and B¹ is as defined above;

(f) for compounds of formula I wherein B represents a structural fragment of formula Ib or Id, reaction of a compound of formula X,

15



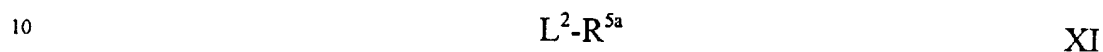
X

20

wherein R^1 , R^2 , R^3 , Y and n are as defined in Claim 1 and B^1 is as defined above;

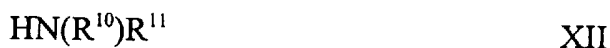
(g) for compounds of formula I wherein Y represents $S(O)$ or $S(O)_2$, oxidation of a corresponding compound of formula I wherein Y represents
 5 S;

(h) for compounds of formula I wherein Z represents $N(R^5)$ and R^5 represents optionally substituted C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl, reaction of a corresponding compound of formula I wherein Z represents NH with a compound of formula XI,



wherein R^{5a} represents optionally substituted C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl and L^2 is as defined above;

(i) for compounds of formula I wherein Z represents $N(R^5)$ and R^5 represents C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl, all of which are substituted and/or
 15 terminated by $C(O)N(R^{10})R^{11}$, reaction of a corresponding compound of formula I wherein R^5 represents C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl, all of which are substituted and/or terminated, by $C(O)OR^9$, and R^9 is as defined in Claim 1, with a compound of formula XII,

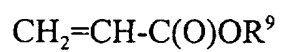


20 wherein R^{10} and R^{11} are as defined in Claim 1;

(j) for compounds of formula I wherein Z represents $N(R^5)$ and R^5 represents C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl, all of which are substituted and/or terminated by $C(O)OH$, hydrolysis of a corresponding compound of formula I wherein R^5 represents C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl, all of which
 25 are substituted and/or terminated by $C(O)OR^9$ and R^9 represents C_{1-4} alkyl;
 or

(k) for compounds of formula I wherein Z represents $N(R^5)$ and R^5 represents $(CH_2)_2C(O)OR^9$ and R^9 is as defined in Claim 1, reaction of a corresponding compound of formula I wherein R^5 represents H with a
 30 compound of formula XIII,

103



XIII

wherein R⁹ is as defined in Claim 1.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/01150

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07C 311/21, C07C 311/14, C07C 309/72, C07C 309/71, C07D 333/34,
C07D 261/10, C07D 233/56, A61K 31/18, A61K 31/255, A61K 31/33

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)

IPC6: C07C, C07D, A61K

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)

CA, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9616940 A1 (YAMANOUCHI PHARMACEUTICAL CO., LTD.), 6 June 1996 (06.06.96), page 136, no. 53; page 137, numbers 65-68; page 138, number 74; the claims	1-30, 34
	--	
A	WO 9420467 A1 (BOEHRINGER MANNHEIM GMBH), 15 Sept 1994 (15.09.94)	1-30, 34
	--	
A	WO 9316038 A1 (G. D. SEARLE & CO.), 19 August 1993 (19.08.93)	1-30, 34
	--	
P, A	WO 9637482 A1 (THE DU PONT MERCK PHARMACEUTICAL COMPANY), 28 November 1996 (28.11.96)	1-30, 34
	--	

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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

"E" earlier document 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

9 October 1997

Date of mailing of the international search report

16-10-1997

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/01150

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 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.: 31-33
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1 (iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
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 II Observations where unity of invention is lacking (Continuation of Item 2 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

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☐

- The additional search fees were accompanied by the applicant's protest.
No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/09/97

International application No.

PCT/SE 97/01150

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