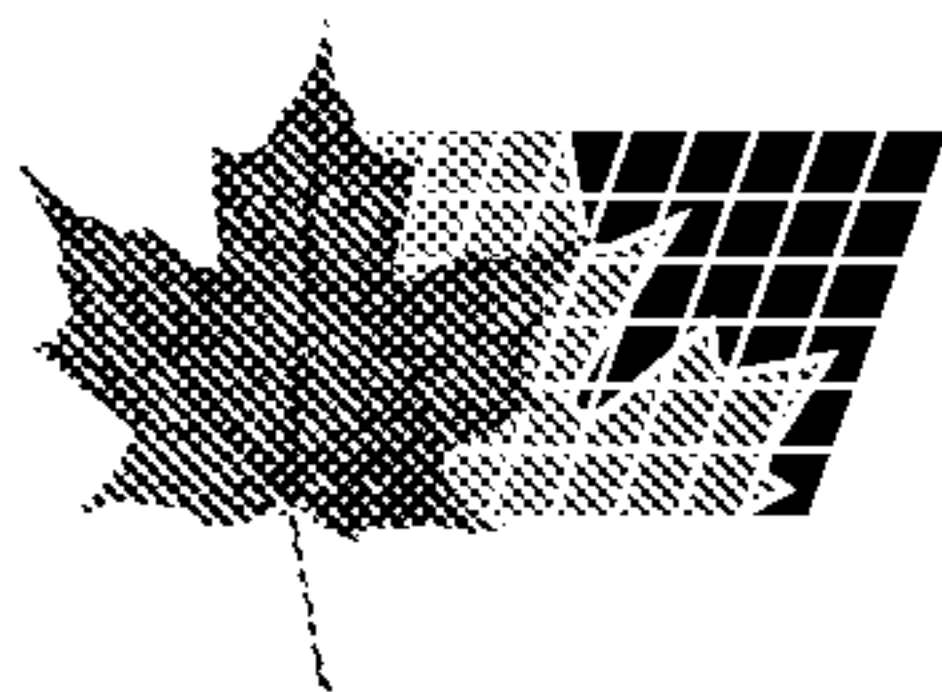




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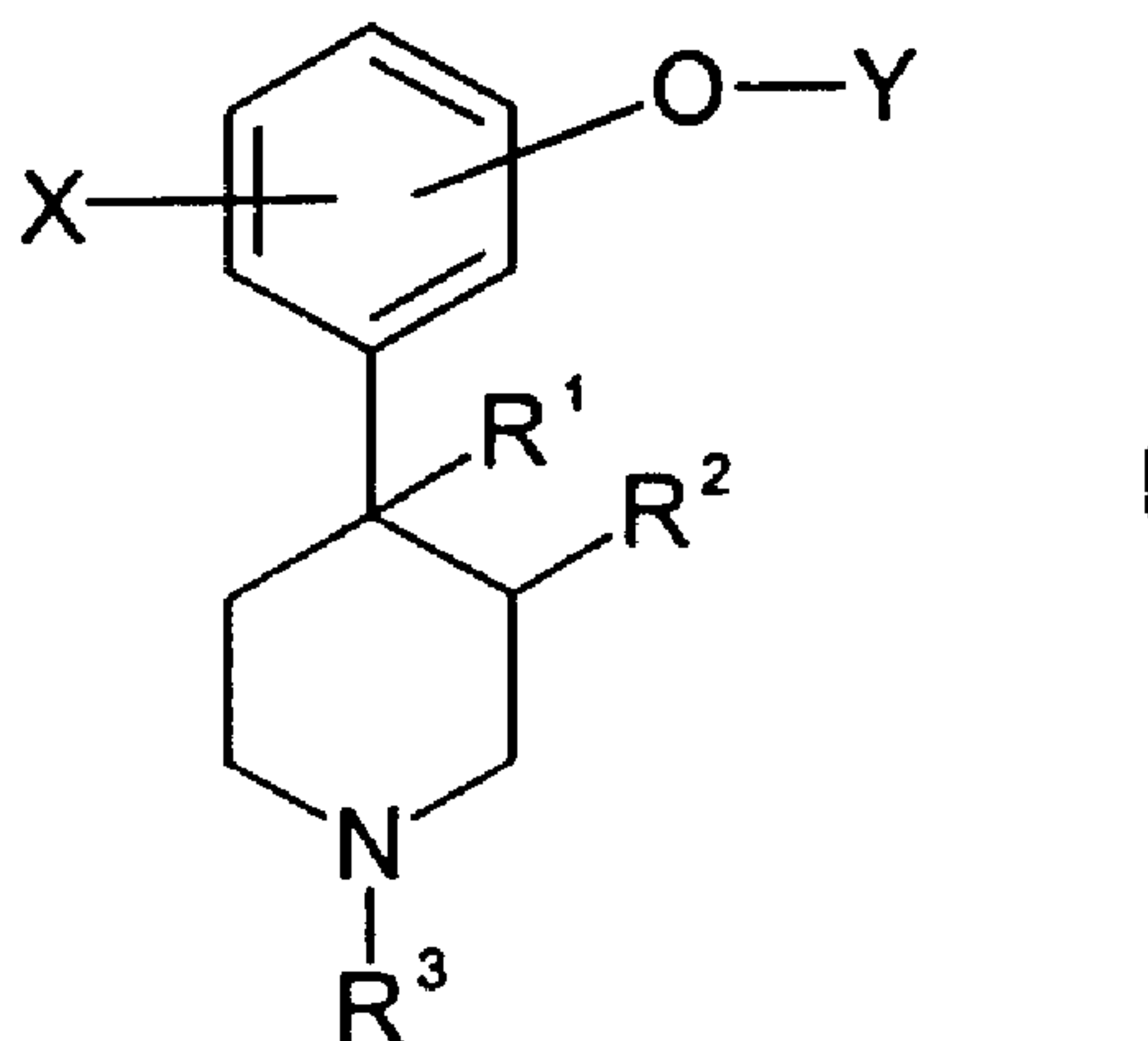
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(54) **NOUVEAUX DERIVES DE 4-ARYLPIPERIDINE POUR LE
TRAITEMENT DU PRURIT**

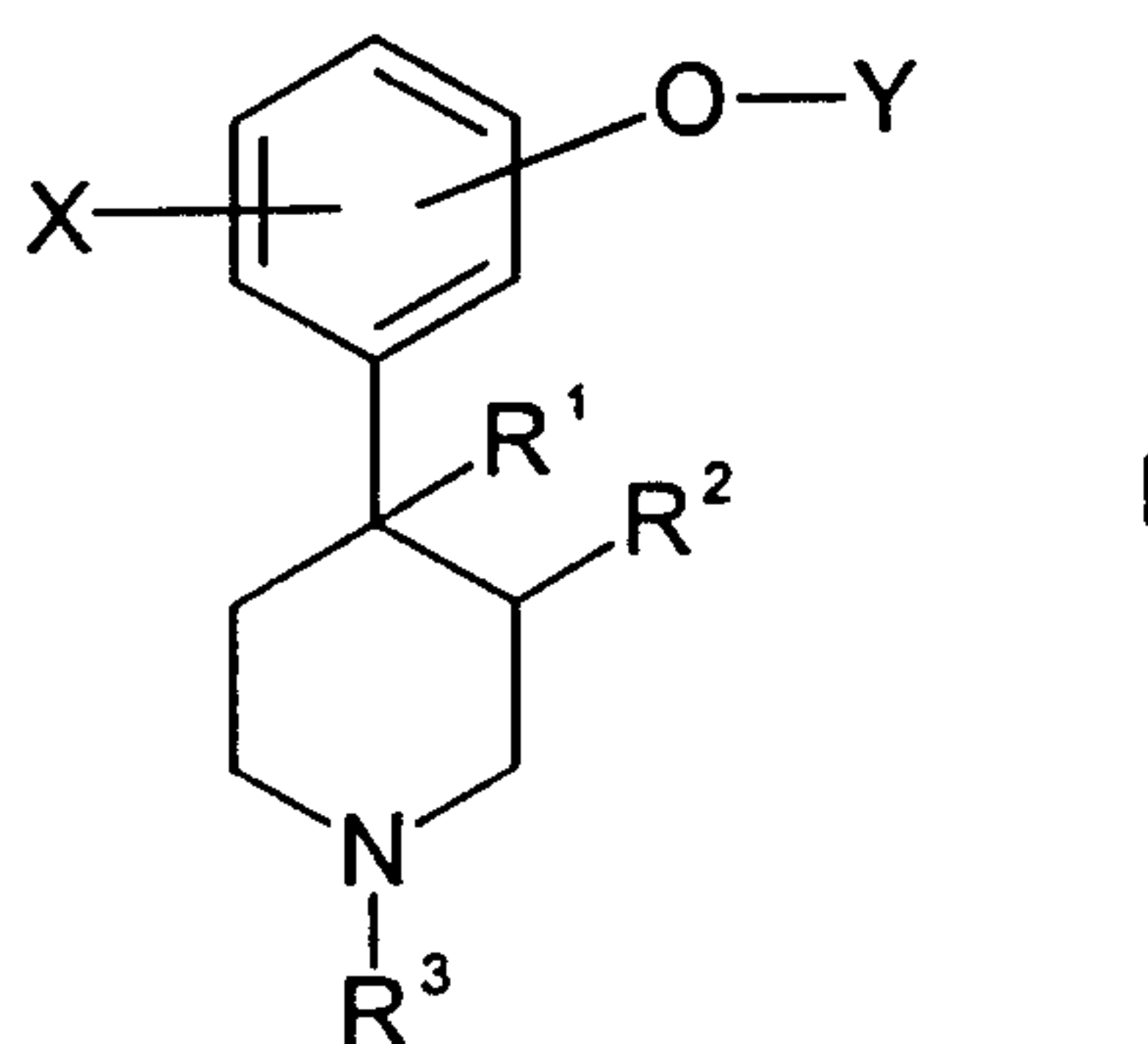
(54) **NEW 4-ARYLPIPERIDINE DERIVATIVES FOR THE
TREATMENT OF PRURITUS**



(57) There is provided a compound of formula I, (see formula I) wherein R^1 , R^2 , R^3 , X and Y have meanings given in the description, which are useful in the prophylaxis and in the treatment of pruritus.

ABSTRACT

There is provided a compound of formula I,



wherein R^1 , R^2 , R^3 , X and Y have meanings given in the description, which are useful in the prophylaxis and in the treatment of pruritus.

New 4-Arylpiperidine Derivatives for the Treatment of Pruritus

This invention relates to novel 4-phenylpiperidines having utility in the treatment of pruritic dermatoses including allergic dermatitis and atopy in
5 animals and humans, and processes for the preparation of and intermediates used in the preparation of such compounds.

Itching or pruritus is a common dermatological symptom which can give rise to considerable distress, in both humans and animals. Pruritus is
10 often associated with inflammatory skin disease which can commonly be caused by hypersensitivity reactions, such as reaction to insect bites e.g. flea bites, or to environmental allergens such as house dust mite or pollen; or by bacterial and fungal infections of the skin or ectoparasite infections. Previous treatments for pruritus include the use of corticosteroids and
15 antihistamines, however both have undesired side effects. Other therapies include the use of essential fatty acid dietary supplements which are slow to act and offer only limited efficacy against allergic dermatitis. A variety of emollients such as soft paraffin, glycerine and lanolin are also employed but with limited success and there is a continuing need for an
20 effective remedy.

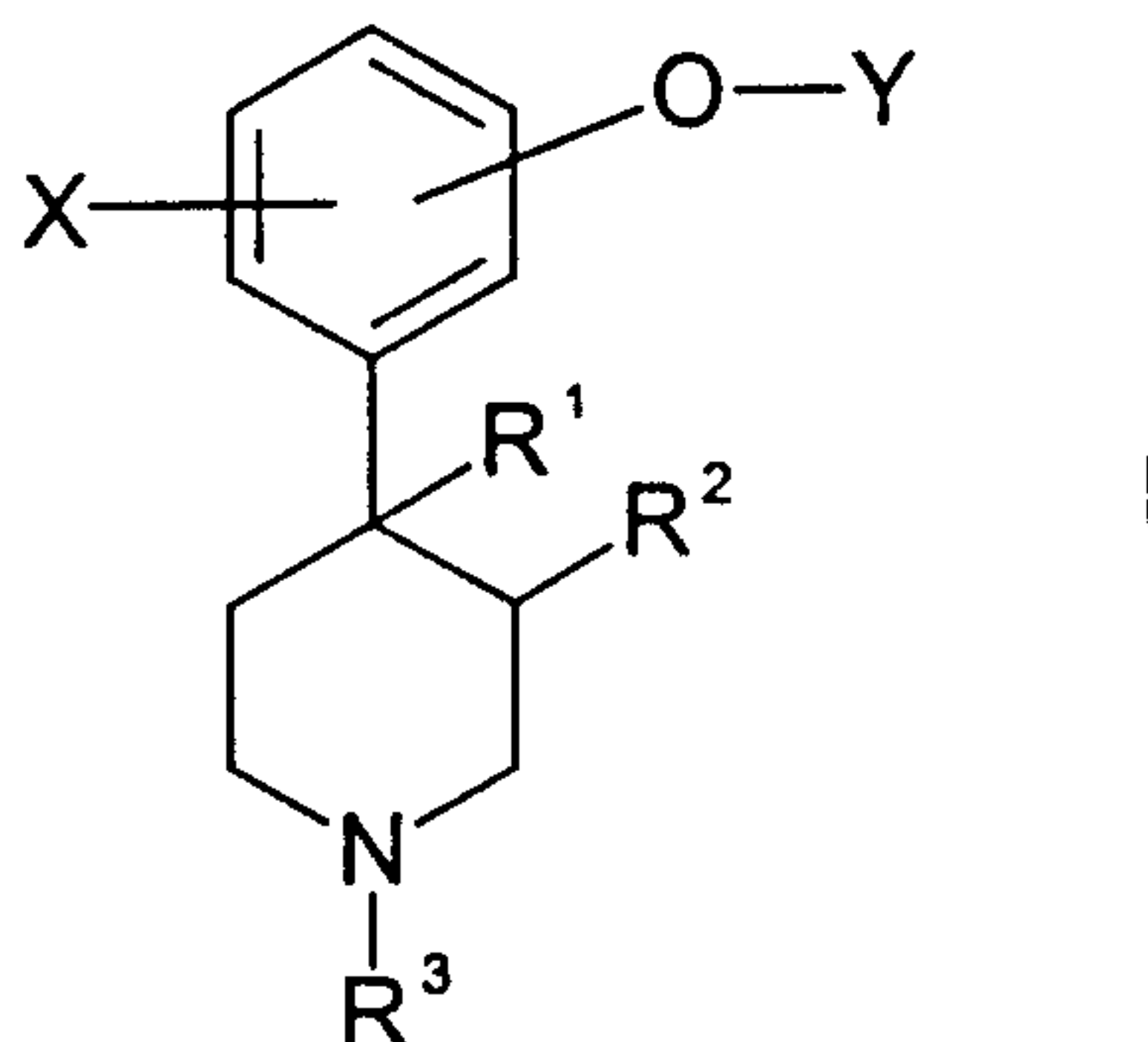
Certain 1,3,4-trisubstituted 4-aryl-piperidine derivatives are disclosed in GB-A-1525584 as potent narcotic antagonists which also display analgesic properties. These compounds are also claimed in EP-B-0287339 as opioid
25 antagonists which block the effect of agonists at the mu or kappa receptors having potential utility in treating a variety of disorders associated with these receptors such as eating disorders, opiate overdose, depression, smoking, alcoholism, sexual dysfunction, shock, stroke, spinal damage

and head trauma; utility as an appetite suppressant for weight loss has also been suggested. Further related 1-N-substituted-4-aryl piperidines are disclosed in EP-A-0506468 and EP-A-0506478. Potential utility is suggested in preventing peripherally mediated undesired opiate effects and in relieving the symptoms of idiopathic constipation and irritable bowel syndrome.

According to the present invention we provide novel 4-phenylpiperidines which are, and/or are prodrugs of, potent and effective antipruritic agents.

10

Thus, the present invention provides compounds of formula I:



15 wherein

R^1 and R^2 are each independently H or C_{1-4} alkyl;

R^3 represents aryl (optionally substituted by one or more substituents selected from OH, nitro, halo, CN, CH_2CN , $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms) and $-N(R^{4a})(R^{4b})$), C_{1-10} alkyl, C_{3-10} alkenyl or C_{3-10} alkynyl wherein said alkyl, alkenyl or alkynyl groups

20

are optionally substituted and/or terminated by one or more substituents selected from OR^{4c} , $S(O)_nR^{4d}$, CN, halo, C_{1-6} alkoxy carbonyl, C_{2-6} alkanoyl, C_{2-6} alkanoyloxy, C_{3-8} cycloalkyl, C_{4-9} cycloalkanoyl, $N(R^{5a})S(O)_2R^6$, Het¹, aryl, adamantyl (which latter two groups are
 5 optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN , $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or $-W-A^1-N(R^{5b})(R^{5c})$;

n is 0, 1 or 2;

10 W represents a single bond, C(O) or S(O)_p;

A¹ represents a single bond or C_{1-10} alkylene;

provided that when both W and A¹ represent single bonds, then the group $-N(R^{5b})(R^{5c})$ is not directly attached to an unsaturated carbon atom;

p is 0, 1 or 2;

15 R^{4a} to R^{4d} each independently represent H, C_{1-10} alkyl, C_{3-10} alkenyl, C_{3-10} alkynyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl, aryl (which latter six groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN , $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally
 20 substituted by one or more halo atoms)) or Het²;

provided that R^{4d} does not represent H when n represents 1 or 2;

R^{5a} to R^{5c} each independently represent H, C_{1-10} alkyl, C_{3-10} alkenyl, C_{3-10} alkynyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl, aryl (which latter six groups are optionally substituted by one or more substituents selected
 25 from OH, nitro, amino, halo, CN, CH_2CN , $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), Het³, or R^{5b} and R^{5c} together represent unbranched C_{2-6} alkylene which alkylene group is optionally

interrupted by O, S and/or an N(R⁷) group and is optionally substituted by one or more C₁₋₄ alkyl groups;

R⁶ represents C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₁₋₄ alkylphenyl or aryl, which four groups are optionally substituted by or one or more substituents
5 selected from C₁₋₄ alkyl, C₁₋₄ alkoxy, OH, nitro, amino or halo;

R⁷ represents H, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, A²-(C₃₋₈ cycloalkyl) or A²-aryl;

A² represents C₁₋₆ alkylene;

Het¹, Het² and Het³ independently represent 3- to 8-membered
10 heterocyclic groups, which groups contain at least one heteroatom selected from oxygen, sulfur and/or nitrogen, which groups are optionally fused to a benzene ring, and which groups are optionally substituted in the heterocyclic and/or fused benzene ring part by one or more substituents selected from OH, =O, nitro, amino, halo, CN, aryl, C₁₋₄ alkyl,
15 C₁₋₄ alkoxy and C₁₋₅ alkanoyl (which latter three groups are optionally substituted by one or more halo atoms);

Y represents -C(=E)NR⁸R⁹, C(O)R¹⁰, C(O)OR¹⁰, C(O)CH(R^{10a})N(G)G^a, R¹¹, CH(R^{12b})C(O)OR^{12a}, CH(R^{12b})OCO₂R^{12a}, C(O)C(R^{13a})=C(R^{13b})NH₂,
20 C(O)CH(R^{13a})CH(NH₂)(R^{13b}) or PO(OR¹⁴)₂;

E represents O or S;

R⁸ and R⁹ independently represents H, C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl (which latter two groups are optionally substituted by one or more aryl or C₄₋₇ cycloalkyl groups (which two groups are optionally substituted by one or more substituents selected from halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl or C₁₋₄ haloalkoxy)), aryl, C₄₋₇ cycloalkyl (optionally substituted by one or more substituents selected from halo, C₁₋₄ alkyl and C₁₋₄ alkoxy (which latter two groups are optionally substituted by one or more halo
25

atoms)), or R^8 and R^9 , together with the N-atom to which both are attached, represent Het^4 ;

Het^4 represents a 5- to 8-membered heterocyclic ring comprising at least one nitrogen atom and optionally one or more additional heteroatoms
 5 selected from oxygen and sulfur, which heterocyclic ring is optionally substituted by one or more C_{1-4} alkyl groups;

R^{10} represents H, Het^5 , C_{4-7} cycloalkyl (optionally substituted by one or more C_{1-4} alkyl groups), C_{1-11} alkyl (optionally substituted by one or more substituents selected from aryl (optionally substituted by one or more
 10 substituents selected from OH, halo, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, $N(R^8)(R^9)$, $C(O)N(R^8)(R^9)$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and C_{1-4} haloalkoxy) or C_{4-7} cycloalkyl (which latter group is optionally substituted by one or more C_{1-4} alkyl groups)) or aryl (optionally substituted by one or more substituents selected from OH, halo,
 15 C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, $N(R^8)(R^9)$, $C(O)N(R^8)(R^9)$, C_{1-4} alkyl and C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms));

R^{10a} represents H, C_{4-7} cycloalkyl, C_{1-10} alkyl (optionally substituted by one or more substituents selected from aryl or C_{4-7} cycloalkyl), aryl, or
 20 R^{10a} (optionally in conjunction with G^a) represents a naturally occurring amino acid substituent;

G and G^a independently represent H, an amino protective group, or G^a , together with R^{10a} , represents a naturally occurring amino acid substituent;

25 R^{11} represents H, C_{4-7} cycloalkyl (optionally substituted by one or more C_{1-4} alkyl groups), aryl (optionally substituted by one or more substituents selected from OH, halo, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, $N(R^8)(R^9)$, $C(O)N(R^8)(R^9)$, C_{1-4} alkyl and C_{1-4} alkoxy (which latter two groups are

optionally substituted by one or more halo atoms)), C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl, which alkyl or alkenyl group is optionally substituted by one or more substituents selected from C(O)NH₂, Het⁶, C₄₋₇ cycloalkyl (optionally substituted by one or more C₁₋₄ alkyl groups), aryl, aryloxy or
5 aryl(C₁₋₄)alkoxy (which latter three groups are optionally substituted by one or more substituents selected from OH, halo, C₁₋₄ alkanoyl, C₁₋₄ alkanoyloxy, N(R⁸)(R⁹), C(O)N(R⁸)(R⁹), C₁₋₄ alkyl and C₁₋₄ alkoxy (which latter two groups are optionally substituted by one or more halo atoms)) or R¹¹ represents Het⁷;

10 Het⁵ to Het⁷ independently represent 4- to 6-membered heterocyclic rings, which rings contain at least one heteroatom selected from oxygen, sulfur, and/or nitrogen, which rings are optionally fused to a benzene ring, and which rings are optionally substituted in the heterocyclic and/or fused benzene ring part by one or more substituents selected from OH, =O,
15 nitro, amino, halo, CN, aryl, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl and C₁₋₅ alkanoyl (which latter four groups are optionally substituted by one or more halo atoms);

R^{12a} and R^{12b} independently represent H, C₄₋₇ cycloalkyl (optionally
20 substituted by one or more C₁₋₄ alkyl groups), C₁₋₁₀ alkyl (optionally substituted by one or more substituents selected from aryl or C₄₋₇ cycloalkyl (which latter group is optionally substituted by one or more C₁₋₄ alkyl groups)) or aryl (optionally substituted by one or more substituents selected from OH, halo, C₁₋₄ alkanoyl, C₁₋₄ alkanoyloxy,
25 C₁₋₄ alkyl and C₁₋₄ alkoxy (which latter two groups are optionally substituted by one or more halo atoms));

R^{13a} and R^{13b} independently represent H, C₄₋₇ cycloalkyl (optionally substituted by one or more C₁₋₄ alkyl groups), C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl

(which alkyl and alkenyl groups are optionally substituted by one or more substituents selected from aryl or C₄₋₇ cycloalkyl (which latter group is optionally substituted by one or more C₁₋₄ alkyl groups)), or aryl (optionally substituted by one or more substituents selected from OH, halo, C₁₋₄ alkanoyl, C₁₋₄ alkanoyloxy, C₁₋₄ alkyl and C₁₋₄ alkoxy (which latter two groups are optionally substituted by one or more halo atoms));

R¹⁴ represents H, C₄₋₇ cycloalkyl (optionally substituted by one or more C₁₋₄ alkyl groups), C₁₋₁₀ alkyl (optionally substituted by one or more substituents selected from aryl or C₄₋₇ cycloalkyl (which latter group is optionally substituted by one or more C₁₋₄ alkyl groups)), or aryl (optionally substituted by one or more substituents selected from OH, halo, C₁₋₄ alkanoyl, C₁₋₄ alkanoyloxy, C₁₋₄ alkyl and C₁₋₄ alkoxy (which latter two groups are optionally substituted by one or more halo atoms));

X represents one or more substituents on the benzene ring, which substituents are independently selected from halo, CN, nitro, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl (which latter four groups are optionally substituted and/or terminated by one or more substituents selected from halo, CN, nitro, OH, C₃₋₇ cycloalkyl, C₁₋₆ alkoxy, C₃₋₇ cycloalkoxy, C₁₋₆ alkanoyl, C₄₋₈ cycloalkanoyl, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkanoyloxy or N(R^{15a})(R^{15b})), C(O)R^{16a}, C(O)OR^{16b}, OC(O)R^{16c}, S(O)_rOR^{16d}, S(O)_rR^{17a}, OR^{16e}, N(R^{18a})(R^{18b}), C(O)N(R^{18c})(R^{18d}), OC(O)N(R^{18e})(R^{18f}), N(R^{18g})C(O)R^{16f}, N(R^{18h})C(O)OR¹⁹, N(R¹⁸ⁱ)C(O)N(R^{18j})(R^{18k}), N(R^{18m})S(O)₂R^{17b} or B(OR^{15c})₂;

R^{15a} to R^{15c} independently represent H, C₁₋₆ alkyl or C₃₋₇ cycloalkyl (which latter two groups are optionally substituted by one or more halo atoms);

R^{16a} to R^{16f} independently represent H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl (which latter four groups are optionally

substituted by one or more substituents selected from halo, nitro, OH, C₁₋₄ alkyl or C₁₋₄ alkoxy) or Het⁸;

R^{17a} and R^{17b} independently represent C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl (which latter four groups are optionally substituted by one or more substituents selected from halo, nitro, OH, C₁₋₄ alkyl or C₁₋₄ alkoxy), Het⁹ or N(R^{20a})(R^{20b});

provided that R^{17a} does not represent N(R^{20a})(R^{20b}) when t is 1;

R^{18a} to R^{18m} independently represent H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl (which latter four groups are optionally substituted by one or more substituents selected from halo, nitro, OH, C₁₋₄ alkyl or C₁₋₄ alkoxy), Het¹⁰, or R^{18j} and R^{18k} together represent unbranched C₃₋₆ alkylene, which alkylene group is optionally interrupted by oxygen, sulfur or an NR^{20c} group;

R¹⁹ represents C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl (which latter four groups are optionally substituted by one or more substituents selected from halo, nitro, OH, C₁₋₄ alkyl or C₁₋₄ alkoxy) or Het¹¹;

R^{20a} to R^{20c} independently represent H, C₁₋₄ alkyl or C₃₋₇ cycloalkyl (which latter two groups are optionally substituted by one or more halo atoms);

r is 1 or 2;

t is 0, 1 or 2;

Het⁸ to Het¹¹ represent 4- to 7- membered heterocyclic rings, which rings contain at least one heteroatom selected from oxygen, sulfur and/or nitrogen, and which rings are optionally substituted by one or more substituents selected from OH, =O, nitro, amino, halo, CN, aryl, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₆ cycloalkyl and C₁₋₅ alkanoyl (which latter four groups are optionally substituted by one or more halo atoms);

or pharmaceutically, or veterinarily, acceptable derivatives thereof;
which compounds are referred to together hereinafter as "the compounds
of the invention".

5 In the definitions used herein, alkyl, alkylene, alkoxy, alkoxy carbonyl,
alkanoyl, alkanoyloxy, alkenyl, alkynyl and the alkyl parts of alkylphenyl
and aryl alkoxy groups may, when there is a sufficient number of carbon
atoms, be straight or branched-chain and/or optionally interrupted by one
or more oxygen and/or sulfur atom(s). The term halo includes fluoro,
10 chloro, bromo or iodo. The term "aryl" includes optionally substituted
phenyl, naphthyl and the like, and "aryloxy" includes optionally
substituted phenoxy and naphthyloxy and the like. Unless otherwise
specified, aryl and aryloxy groups are optionally substituted by one or
more (e.g. one to three) substituents selected from OH, nitro, amino,
15 halo, CN, CH₂CN, CONH₂, C₁₋₄ alkyl, C₁₋₄ alkoxy C₁₋₄ alkoxy carbonyl
and C₁₋₅ alkanoyl (which latter four groups are optionally substituted by
one or more halo atoms).

The heterocyclic rings that Het¹, Het², Het³, Het⁴, Het⁵, Het⁶, Het⁷, Het⁸,
20 Het⁹, Het¹⁰ and Het¹¹ represent may be fully saturated, partially
unsaturated and/or wholly or partially aromatic in character. Specific
rings that may be mentioned include: for Het⁵, pyridine or pyridine-*N*-
oxide.

25 For the avoidance of doubt, when Het (Het¹, Het², Het³, Het⁴, Het⁵, Het⁶,
Het⁷, Het⁸, Het⁹, Het¹⁰ and Het¹¹) groups are at least part-saturated,
possible points of substitution include the atom (e.g. the carbon atom) at

the point of attachment of the Het group to the rest of the molecule. Het groups may also be attached to the rest of the molecule *via* a heteroatom.

The piperidine moiety in compounds of formula I may be in N-oxidised form. Sulfur atoms that may interrupt (e.g. alkyl) substituents in compounds of formula I may be present in oxidised form (e.g. as sulfoxides or sulfones). All Het¹, Het², Het³, Het⁴, Het⁵, Het⁶, Het⁷, Het⁸, Het⁹, Het¹⁰ and Het¹¹ groups may also be in N- or S-oxidized forms.

The term "amino protective group" as used herein will be understood by the skilled person to include those mentioned in "Protective Groups in Organic Synthesis", 2nd edition, TW Greene & PGM Wutz, Wiley-Interscience (1991), in particular those indexed at pages 218 to 222 of that reference, the disclosure in which document is hereby incorporated by reference.

Specific examples of amino protective groups thus include carbamate groups (e.g. methyl, cyclopropylmethyl, 1-methyl-1-cyclopropylmethyl, diisopropylmethyl, 9-fluorenylmethyl, 9-(2-sulfo)fluorenylmethyl, 2-furanylmethyl, 2,2,2-trichloroethyl, 2-haloethyl, 2-trimethylsilylethyl, 2-methylthioethyl, 2-methylsulfonylethyl, 2(*p*-toluenesulfonyl)ethyl, 2-phosphonioethyl, 1,1-dimethylpropynyl, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl, 1,1-dimethyl-3-(*N,N*-diethylamino)propyl, 1-methyl-1-(1-adamantyl)ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1-(4-biphenyl)ethyl, 1-methyl-1-(*p*-phenylazophenyl)ethyl, 1,1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1,1-dimethyl-2-cyanoethyl, isobutyl, *t*-butyl, *t*-amyl, cyclobutyl, 1-methylcyclobutyl, cyclopentyl, cyclohexyl, 1-methyl-

cyclohexyl, 1-adamantyl, isobornyl, vinyl, allyl, cinnamyl, phenyl, 2,4,6-tri-*t*-butylphenyl, *m*-nitrophenyl, *S*-phenyl, 8-quinolinyl, *N*-hydroxypiperidinyl, 4-(1,4-dimethylpiperidinyl), 4,5-diphenyl-3-oxazolin-2-one, benzyl, 2,4,6-trimethylbenzyl, *p*-methoxybenzyl, 3,5-dimethoxybenzyl, *p*-decyloxybenzyl, *p*-nitrobenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, *p*-bromobenzyl, chlorobenzyl, 2,4-dichlorobenzyl, *p*-cyanobenzyl, *o*-(*N,N*-dimethylcarboxamidobenzyl)benzyl, *m*-chloro-*p*-acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, *p*-(phenylazo)benzyl, *p*-(*p*'-methoxyphenylazo)benzyl, 5-benzisoxazolyl-methyl, 9-anthrylmethyl, diphenylmethyl, phenyl(*o*-nitrophenyl)methyl, di(2-pyridyl)methyl, 1-methyl-1-(4-pyridyl)ethyl, isonicotinyl or *S*-benzyl carbamate groups), amide groups (e.g. *N*-formyl, *N*-acetyl, *N*-chloroacetyl, *N*-dichloroacetyl, *N*-trichloroacetyl, *N*-trifluoroacetyl, *N*-*o*-nitrophenylacetyl, *N*-*o*-nitrophenoxyacetyl, *N*-acetoacetyl, *N*-acetylpyridinium, *N*-3-phenylpropionyl, *N*-3-(*p*-hydroxyphenyl)propionyl, *N*-3-(*o*-nitrophenyl)propionyl, *N*-2-methyl-2-(*o*-nitrophenoxy)propionyl, *N*-2-methyl-2-(*o*-phenylazophenoxy)propionyl, *N*-4-chlorobutyryl, *N*-isobutyryl, *N*-*o*-nitrocinnamoyl, *N*-picolinoyl, *N*-(*N*'-acetylmethionyl), *N*-(*N*'-benzoylphenylalanyl), *N*-benzoyl, *N*-*p*-phenylbenzoyl, *N*-*p*-methoxybenzoyl, *N*-*o*-nitrobenzoyl or *N*-*o*-(benzoyloxymethyl)benzoyl amide groups), alkyl groups (e.g. *N*-allyl, *N*-phenacyl, *N*-3-acetoxypropyl, *N*-(4-nitro-1-cyclohexyl-2-oxo-pyrrolin-3-yl), *N*-methoxymethyl, *N*-chloroethoxymethyl, *N*-benzyloxymethyl, *N*-pivaloyloxymethyl, *N*-2-tetrahydropyranyl, *N*-2,4-dinitrophenyl, *N*-benzyl, *N*-3,4-dimethoxybenzyl, *N*-*o*-nitrobenzyl, *N*-di(*p*-methoxyphenyl)methyl, *N*-triphenylmethyl, *N*-(*p*-methoxyphenyl)diphenylmethyl, *N*-diphenyl-4-pyridylmethyl, *N*-2-picolyl *N*'-oxide or *N*-dibenzosuberyl groups), phosphinyl and phosphoryl groups (e.g. *N*-diphenylphosphinyl, *N*-dimethylthiophosphinyl,

N-diphenylthiophosphinyl, *N*-diethylphosphoryl, *N*-dibenzylphosphoryl or *N*-phenylphosphoryl groups), sulfenyl groups (e.g. *N*-benzenesulfenyl, *N*-*o*-nitrobenzenesulfenyl, *N*-2,4-dinitrobenzenesulfenyl, *N*-pentachlorobenzenesulfenyl, *N*-2-nitro-4-methoxybenzenesulfenyl or *N*-triphenyl-
5 methylsulfenyl groups), sulfonyl groups (e.g. *N*-benzenesulfonyl, *N*-*p*-methoxybenzenesulfonyl, *N*-2,4,6-trimethylbenzenesulfonyl, *N*-toluenesulfonyl, *N*-benzylsulfonyl, *N*-*p*-methylbenzylsulfonyl, *N*-trifluoromethylsulfonyl or *N*-phenacylsulfonyl) or the *N*-trimethylsilyl group.

10

The term "naturally occurring amino acid" as used herein includes the amino acids glycine, alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, tyrosine, histidine, serine, threonine, methionine, cysteine, aspartic acid, glutamic acid, asparagine, glutamine, lysine, arginine and
15 proline.

The term "pharmaceutically, or veterinarily, acceptable derivatives" includes non-toxic salts. Salts which may be mentioned include: acid addition salts, for example, salts formed with sulfuric, hydrochloric,
20 hydrobromic, phosphoric, hydroiodic, sulfamic, organo-sulfonic, citric, carboxylic (e.g. acetic, benzoic, etc.), maleic, malic, succinic, tartaric, cinnamic, ascorbic and related acids; base addition salts; salts formed with bases, for example, the sodium, potassium and C₁₋₄ alkyl ammonium salts.

25 The compounds of the invention may also be in the form of quaternary ammonium salts, e.g. at the piperidine moiety, which salts may be formed by reaction with a variety of alkylating agents, such as an alkyl halide or an ester of sulfuric, or an aromatic sulfonic acid.

The compounds of the invention may exhibit tautomerism. All tautomeric forms of the compounds of formula I are included within the scope of the invention.

5 The compounds of the invention contain one or more asymmetric centres and thus they can exist as enantiomers and diastereomers. Diastereoisomers may be separated using conventional techniques e.g. by fractional crystallisation or chromatography. The various stereoisomers may be isolated by separation of a racemic or other mixture of the
10 compounds using conventional techniques e.g. fractional crystallisation or HPLC. The desired optical isomers may be prepared by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation. Alternatively, the desired optical isomers may be prepared by resolution, either by HPLC of the racemate
15 using a suitable chiral support or, where appropriate, by fractional crystallisation of the diastereoisomeric salts formed by reaction of the racemate with a suitable optically active acid or base. The invention includes the use of both the separated individual isomers as well as mixtures of isomers.

20

Also included within the scope of the invention are radiolabelled derivatives of compounds of formula I which are suitable for biological studies.

25 According to a further aspect of the invention, there is provided a compound of formula I, as hereinbefore defined, provided that when Y is H or 2-methyl-2-propionamide, OY is attached to the benzene ring at the *meta*-position relative to the piperidine ring (which ring is not in *N*-

oxidised form), and X is one or two substituents independently selected from halo, C₁₋₄ alkyl or C₁₋₄ alkoxy (which latter two groups are optionally substituted by one or more halo atoms, but are otherwise unsubstituted), then R³ represents:-

5 optionally substituted aryl;

optionally substituted C₃₋₁₀ alkenyl or C₃₋₁₀ alkynyl (which two groups are both interrupted by at least one oxygen and/or sulfur atoms);

C₂₋₁₀ alkyl, interrupted by at least two oxygen atoms and/or at least one sulfur atom;

10 C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl or C₃₋₁₀ alkynyl, which groups are all optionally interrupted by one or more oxygen and/or sulfur atoms, and are substituted and/or terminated by one or more of:

S(O)_nR^{4d}, N(R^{5a})S(O)₂R⁶, Het¹ (substituted by one or more substituents selected from nitro, amino and C₁₋₅ alkanoyl (which latter group is
15 optionally substituted by one or more halo atoms)), aryl (substituted by one or more substituents selected from nitro, amino and C₁₋₅ haloalkanoyl) or adamantyl (which latter group is substituted by one or more of the relevant substituents identified hereinbefore); or

OR^{4c}, in which R^{4c} represents C₇₋₁₀ alkyl, C₃₋₁₀ alkenyl, C₃₋₁₀ alkynyl or
20 Het² (which latter four groups are all optionally substituted by one or more of the relevant substituents identified hereinbefore), or R^{4c} represents C₁₋₁₀ alkyl, C₁₋₄ alkylphenyl, C₃₋₈ cycloalkyl or aryl (which latter four groups are all substituted by one or more of the relevant substituents identified hereinbefore);

25 -W-A¹-N(R^{5b})(R^{5c}), in which R^{5b} and/or R^{5c} independently represent C₁₋₄ alkylphenyl (which latter group is optionally substituted by one or more of the relevant substituents identified hereinbefore), C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl, C₃₋₁₀ alkynyl, C₃₋₈ cycloalkyl (which latter four groups are

all substituted by one or more of the relevant substituents identified hereinbefore), or aryl (substituted by one or more substituents selected from nitro, amino and C₁₋₅ haloalkanoyl);

which compounds may also be termed "compounds of the invention".

5

According to a further aspect of the invention, there is provided a compound of formula I, as hereinbefore defined, with the additional proviso that when OY represents O-C₁₋₄ alkyl, OY is attached to the benzene ring at the *meta*-position relative to the piperidine ring (which
10 ring is not in *N*-oxidised form), and X is one or two substituents independently selected from halo, C₁₋₄ alkyl or C₁₋₄ alkoxy (which latter two groups are optionally substituted by one or more halo atoms, but are otherwise unsubstituted), then R³ does not represent:-

straight or branched-chain C₁₋₁₀ alkyl (optionally substituted by one or
15 more substituents selected from unsubstituted aryl or unsubstituted C₃₋₈ cycloalkyl);

which compounds may also be termed "compounds of the invention".

Preferred compounds of the invention include those wherein:

20 The group OY is attached to the benzene ring in the position *meta*- relative to the piperidine group;

the substituent(s) X is/are attached to the benzene ring in position(s) that are *ortho*- and/or *para*- relative to the piperidine group;

R¹ represents C₁₋₂ alkyl;

25 R² represents H or C₁₋₂ alkyl;

R³ represents C₁₋₈ alkyl, C₃₋₈ alkenyl or C₃₋₈ alkynyl wherein said alkyl, alkenyl or alkynyl groups are optionally substituted and/or terminated by one or more substituents selected from C₃₋₈ cycloalkyl, OR^{4c}, CN, Het¹ or

aryl (which latter group is optionally substituted by one or more substituents selected from OH, C₁₋₂ alkyl, C₁₋₂ alkoxy or halo);

R^{4c} represents H, C₁₋₆ alkyl, C₄₋₆ cycloalkyl, aryl or Het²;

Het¹ and Het² independently represent 5- to 7-membered heterocyclic groups, which groups contain at least one heteroatom selected from oxygen, sulfur and/or nitrogen, and which groups are optionally substituted by one or more C₁₋₂ alkyl groups (which alkyl groups are optionally substituted by one or more halo atoms);

Y represents C(=E)NR⁸R⁹, C(O)R¹⁰ or R¹¹;

R⁸ and R⁹ independently represent H or C₁₋₄ alkyl;

R¹⁰ represents C₁₋₆ alkyl (substituted by one or more phenyl groups) or aryl (optionally substituted by one or more substituents selected from OH, halo, C₁₋₂ alkanoyloxy, NH₂, C(O)NH₂ and C₁₋₂ alkyl (which latter group is optionally substituted by one or more halo atoms));

R¹¹ represents H, C₁₋₁₀ alkyl or C₃₋₁₀ alkenyl, which latter two groups are optionally substituted by one or more substituents selected from Het⁶ and phenyl;

Het⁶ represents a 5- to 6- membered heterocyclic ring, which ring contains at least one heteroatom selected from oxygen, sulfur and/or nitrogen, which ring is optionally fused to a benzene ring, and which ring is optionally substituted in the heterocyclic and/or fused benzene ring part by one or more substituents selected from OH, =O and C₁₋₄ alkyl);

Het⁶ is in S-oxidised form;

X represents one to three substituents selected from halo, nitro, C₂₋₆ alkenyl, C₁₋₆ alkyl (which alkyl group is optionally substituted and/or terminated by a substituent selected from OH, C₁₋₄ alkoxy or N(R^{15a})(R^{15b})), C(O)R^{16a}, C(O)OR^{16b}, S(O)_tR^{17a}, N(R^{18a})(R^{18b}),

$C(O)N(R^{18c})(R^{18d})$, $N(R^{18g})C(O)R^{16f}$, $N(R^{18h})C(O)OR^{19}$,
 $N(R^{18i})C(O)N(R^{18j})(R^{18k})$ or $N(R^{18m})S(O)_2R^{17b}$;

R^{15a} and R^{15b} independently represent H or C_{1-4} alkyl;

R^{16a} to R^{16f} independently represent H or C_{1-6} alkyl (which latter group is
 5 optionally substituted by one or more halo atoms);

R^{17a} and R^{17b} independently represent C_{1-4} alkyl (optionally substituted by
 one or more halo atoms) or $N(R^{20a})(R^{20b})$;

R^{18a} to R^{18m} independently represent H, C_{1-6} alkyl, or R^{18j} and R^{18k} together
 represent unbranched C_{3-6} alkylene optionally interrupted by oxygen;

10 R^{19} represents C_{1-4} alkyl;

R^{20a} and R^{20b} independently represent H or C_{1-4} alkyl.

More preferred compounds of the invention include those wherein:

the substituent(s) X is/are attached to the benzene ring in the position(s)

15 that are *ortho*- and/or *para*- relative to the OY group;

R^1 represents methyl;

R^2 represents H or methyl;

R^3 represents linear, saturated C_{1-7} alkyl, which alkyl group is optionally
 substituted and/or terminated by one or more substituents selected from
 20 C_{4-7} cycloalkyl, OR^{4c} , CN, Het¹ or phenyl (which latter group is optionally
 substituted by one or more C_{1-2} alkyl groups);

R^{4c} represents H, C_{1-4} alkyl, C_{4-6} cycloalkyl or phenyl;

Het¹ represents a 5- or 6-membered saturated heterocyclic group, which
 groups contains one heteroatom selected from oxygen, sulfur or nitrogen;

25 R^8 and R^9 independently represent C_{1-2} alkyl;

R^{10} represents C_{1-6} alkyl;

R^{11} represents H or C_{1-5} alkyl;

X represents a substituent selected from nitro, C₂₋₄ alkenyl, C₁₋₂ alkyl (which alkyl group is optionally substituted and/or terminated by OH or N(R^{15a})(R^{15b})), C(O)R^{16a}, C(O)OR^{16b}, S(O)₂R^{17a}, N(R^{18a})(R^{18b}), C(O)N(R^{18c})(R^{18d}), N(H)C(O)R^{16f}, N(H)C(O)OR¹⁹, N(H)C(O)N(R^{18j})(R^{18k})
 5 or N(H)S(O)₂R^{17b}, or X represents one to three halo (e.g. F, Cl, and/or Br) atoms;

R^{15a} and R^{15b} independently represent H or C₁₋₃ alkyl;

R^{16a} to R^{16f} independently represent H or C₁₋₅ alkyl (which latter group is optionally substituted by one or more halo atoms);

10 R^{17a} and R^{17b} independently represent C₁₋₂ alkyl (optionally substituted by one or more halo atoms) or N(R^{20a})(R^{20b});

R^{18a} to R^{18k} independently represent H or C₁₋₅ alkyl;

R^{20a} and R^{20b} independently represent H or C₁₋₂ alkyl.

15 Particularly preferred compounds of the invention include those wherein:

R¹ and R² represent methyl groups in the mutually *trans* configuration;

Y represents H;

R³ represents linear, saturated C₁₋₆ alkyl, which alkyl group is optionally substituted and/or terminated by one or more C₄₋₇ cycloalkyl groups;

20 X represents fluoro or N(H)C(O)Et in the position *ortho*- relative to the OY group.

Preferred compounds of the invention include the compounds of the Examples described hereinafter.

25

Thus, according to a further aspect of the invention, there is provided a compound of formula I which, irrespective of any of the foregoing definitions, is:

- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-bromo-3-hydroxyphenyl)piperidine;
(±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-nitrophenyl)piperidine;
(±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(2,4-dibromo-3-hydroxyphenyl)-
piperidine;
5 (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-amino-3-hydroxyphenyl)piperidine;
(±)-*N*-hexyl-*trans*-3,4-dimethyl-4-[3-hydroxy-4-(2-methyl-butanoyl)-
phenyl]piperidine;
(±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-allyl-3-hydroxyphenyl)piperidine;
(±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-methylphenyl)piperidine;
10 (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-acetylamino-3-hydroxyphenyl)-
piperidine;
(±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-hydroxymethylphenyl)-
piperidine;
(±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-trifluoromethanesulfonyl-
15 aminophenyl)piperidine;
(±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-ethyl-3-hydroxyphenyl)piperidine;
(±)-*N*-hexyl-*trans*-3,4-dimethyl-4-[4-(2,2-dimethylpropanoylamino)-3-
hydroxyphenyl]piperidine;
(±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-methylaminomethyl-
20 phenyl)piperidine;
(±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-ethylaminomethyl-3-hydroxy-
phenyl)piperidine;
(±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-dimethylaminomethyl-3-hydroxy-
phenyl)piperidine;
25 (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-2-methylphenyl)piperidine;
(±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-methoxycarbonylphenyl)-
piperidine;

- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-ethoxycarbonyl-3-hydroxyphenyl)-piperidine;
- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-*N'*-methylaminocarbonyl-3-hydroxyphenyl)piperidine;
- 5 (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-*N',N'*-dimethylaminocarbonyl-3-hydroxyphenyl)piperidine;
- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-*N',N'*-diethylaminocarbonyl-3-hydroxyphenyl)piperidine;
- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-propionylaminophenyl)-
- 10 piperidine;
- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-*N',N'*-dimethylaminocarbonylamino-3-hydroxyphenyl)piperidine;
- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-*N'*-methylaminocarbonylaminophenyl)piperidine;
- 15 (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-methoxycarbonylamino-phenyl)piperidine;
- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-formylamino-3-aminophenyl)-piperidine;
- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-*N',N'*-dimethylaminosulfonylamino-
- 20 3-hydroxyphenyl)piperidine;
- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-pentanoylaminophenyl)-piperidine;
- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(2,4-dichloro-3-hydroxyphenyl)-piperidine;
- 25 (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-[3-hydroxy-4-(2-methylpropionylamino)phenyl]piperidine;
- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-[3-hydroxy-4-(2-methylbutanoyl)-phenyl]piperidine;

- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-butanoylaminophenyl)-piperidine;
- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-methanesulfonylamino-phenyl)piperidine;
- 5 (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-formyl-3-hydroxyphenyl)piperidine;
- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-2,4,6-trichlorophenyl)-piperidine;
- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-aminosulfonyl-3-hydroxyphenyl)-piperidine;
- 10 (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4,6-dichloro-3-hydroxyphenyl)-piperidine;
- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-*N'*-isopropylamino-carbonylphenyl)piperidine;
- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-chloro-3-hydroxyphenyl)piperidine;
- 15 (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(6-chloro-3-hydroxyphenyl)piperidine;
- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-aminocarbonyl-3-hydroxyphenyl)-piperidine;
- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-fluoro-3-hydroxyphenyl)piperidine;
- (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(2-fluoro-3-hydroxyphenyl)piperidine;
- 20 (±)-*N*-3-cyclohexylpropyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-nitro-phenyl)piperidine;
- (±)-*N*-(3-cyclohexylpropyl)-*trans*-3,4-dimethyl-4-(4-amino-3-hydroxy-phenyl)piperidine;
- (±)-*N*-(3-cyclohexylpropyl)-*trans*-3,4-dimethyl-4-(3-hydroxy-4-acetyl-
- 25 aminophenyl)piperidine;
- (±)-*N*-(3-cyclohexylpropyl)-*trans*-3,4-dimethyl-4-(3-hydroxy-4-propionylaminophenyl)piperidine;

(±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-*N'*,*N'*-dimethylamino-3-hydroxy-phenyl)piperidine;

(±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-isopropenylphenyl)-piperidine;

5 (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-allyl-3-*N'*,*N'*-diethylcarbamoyloxy-phenyl)piperidine;

(±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamoyloxy-4-methyl-phenyl)piperidine;

10 (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamoyloxy-4-ethyl-phenyl)piperidine;

(±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamoyloxy-4-*N''*-methylaminocarbonylphenyl)piperidine;

(±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylthiocarbamoyloxy-4-fluorophenyl)piperidine; or

15 (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamoyloxy-4-formyl-phenyl)piperidine,

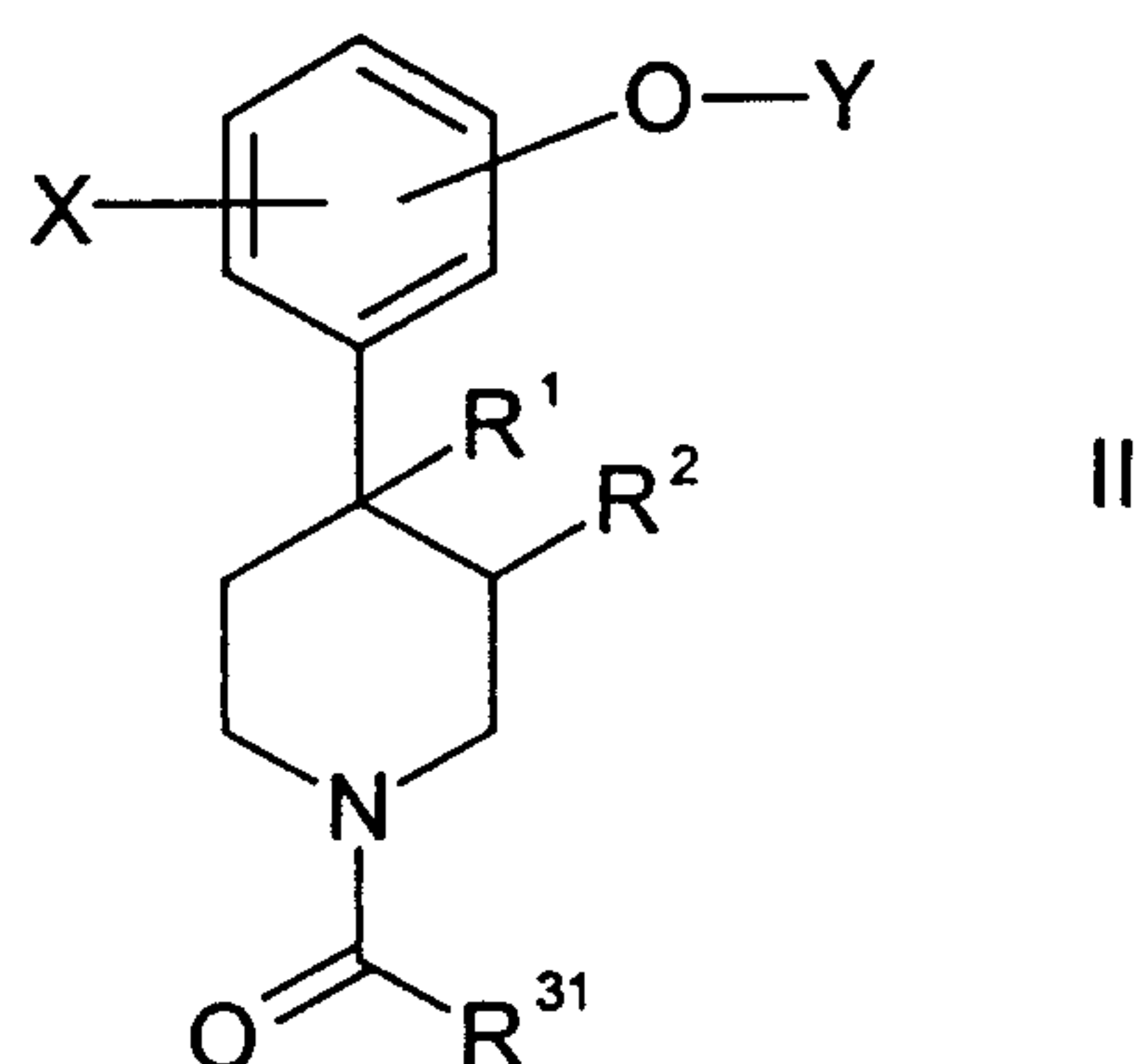
which compounds may also be termed "compounds of the invention".

20 According to a further aspect of the invention there is provided processes for the preparation of compounds of the invention, as illustrated below.

The following processes are illustrative of the general synthetic procedures which may be adopted in order to obtain the compounds of the invention.

25 1. Compounds of formula I wherein R³ represents C₁ alkyl optionally substituted by C₃₋₈ cycloalkyl, Het¹, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH₂CN, CONH₂, C₁₋₄ alkyl, C₁₋₄ alkoxy and

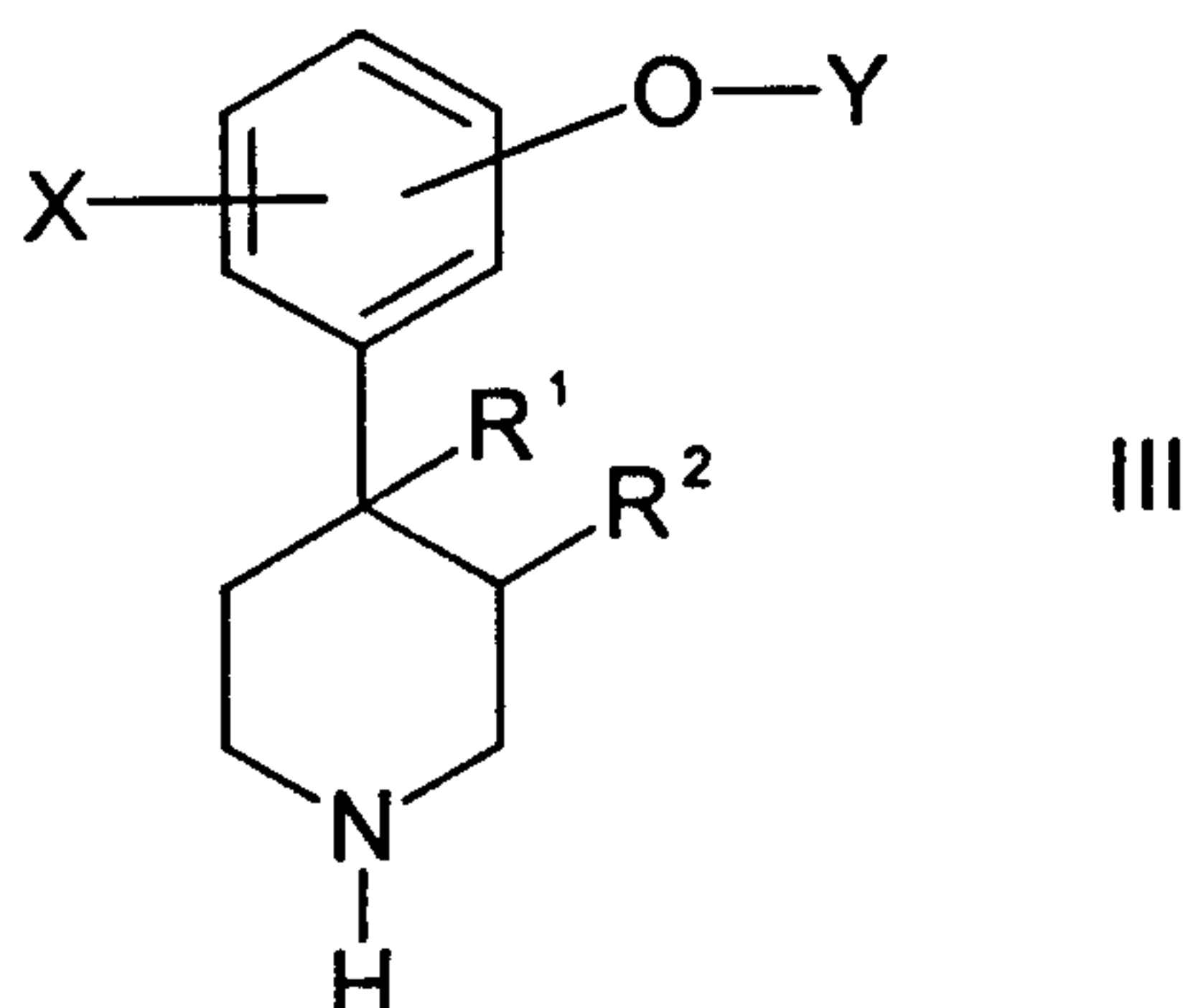
C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or R^3 represents C_{2-10} alkyl, C_{3-10} alkenyl or C_{3-10} alkynyl (which three groups are all optionally substituted by one or more of the relevant substituents identified hereinbefore in respect of R^3),
 5 which alkyl, alkenyl or alkynyl groups are attached to the piperidine nitrogen atom *via* a CH_2 group, wherein Het^1 is as hereinbefore defined, may be prepared by reduction of a corresponding compound of formula II,



wherein R^{31} represents H, C_{3-8} cycloalkyl, Het^1 , aryl, adamantyl (which
 10 latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN , $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), C_{1-9} alkyl, C_{2-9} alkenyl or C_{2-9} alkynyl, which alkyl, alkenyl or alkynyl groups are optionally
 15 substituted and/or terminated by one or more substituents selected from OR^{4c} , $S(O)_nR^{4d}$, CN, halo, C_{1-6} alkoxy carbonyl, C_{2-6} alkanoyl, C_{2-6} alkanoyloxy, C_{3-8} cycloalkyl, C_{4-9} cycloalkanoyl, $N(R^{5a})S(O)_2R^6$, Het^1 , aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN , $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three
 20 groups are optionally substituted by one or more halo atoms)), or $-W-A^1-N(R^{5b})(R^{5c})$, and R^1 , R^2 , R^{4c} , R^{4d} , R^{5a} to R^{5c} , R^6 , Het^1 , n , X , Y , W and A^1 are as hereinbefore defined, using a suitable reducing agent (e.g.

lithium aluminium hydride or a borane derivative), for example as described hereinbefore.

Compounds of formula II may be prepared by reaction of a corresponding
5 compound of formula III,



wherein R^1 , R^2 , X and Y are as hereinbefore defined with a compound of formula IV,



10 or a suitable (e.g. carboxylic acid) derivative thereof (e.g. an acid halide or anhydride), wherein R^{31} is as hereinbefore defined, using coupling conditions known to those skilled in the art.

Compounds of formula III may be prepared from appropriate precursors
15 by analogy with other methods disclosed herein that describe the production of compounds of formula I.

2. Compounds of formula I may also be prepared by reaction of a corresponding compound of formula III, as hereinbefore defined, with a
20 compound of formula V,



wherein L^1 represents a leaving group (such as halo, alkanesulfonate, perfluoroalkanesulfonate or arenesulfonate) and R^3 is as hereinbefore

defined, under conditions that are known to those skilled in the art, which include, for example, alkylation at between room temperature and reflux temperature in the presence of a reaction-inert organic solvent (e.g. *N,N*-dimethylformamide) and a suitable base (e.g. NaHCO_3), and
 5 arylation at between room temperature and reflux temperature in the presence of a suitable catalyst system (e.g. tris(dibenzylideneacetone)-palladium(0) combined with tri-*o*-tolylphosphine), an appropriate strong base (e.g. sodium *tert*-butoxide) and a reaction-inert solvent (e.g. toluene).

- 10 3. Compounds of formula I wherein R^3 represents C_1 alkyl, which, in place of being optionally substituted by the substituents as defined hereinbefore, is instead optionally substituted by R^{31} , wherein R^{31} is as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula III, as hereinbefore defined, with a compound of
 15 formula VI,



VI

wherein R^{31} is as hereinbefore defined, for example in the presence of a suitable reducing agent (e.g. sodium borohydride, sodium cyano-borohydride or sodium triacetoxyborohydride) and an appropriate solvent
 20 (e.g. methanol).

4. Compounds of formula I wherein R^3 is a C_{1-10} alkyl, C_{4-10} alkenyl or C_{4-10} alkynyl group that is fully saturated from 1- to 3-C (relative to the piperidine N-atom), and which R^3 group is substituted at 2-C (relative to
 25 the piperidine N-atom) by $\text{S}(\text{O})\text{R}^{4d}$, $\text{S}(\text{O})_2\text{R}^{4d}$, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, $-\text{C}(\text{O})-\text{A}^1-\text{N}(\text{R}^{5b})(\text{R}^{5c})$, $-\text{S}(\text{O})-\text{A}^1-\text{N}(\text{R}^{5b})(\text{R}^{5c})$, or $-\text{S}(\text{O})_2-\text{A}^1-\text{N}(\text{R}^{5b})(\text{R}^{5c})$, wherein R^{4d} , R^{5b} , R^{5c} and A^1 are as hereinbefore

defined, may be prepared by reaction of a corresponding compound of formula III, as hereinbefore defined, with a compound of formula VII,



wherein R^{3a} represents R^3 as hereinbefore defined except that it does not
 5 represent aryl, and that the R^{3a} chain contains an additional carbon-carbon double bond α, β to the Z-substituent, and Z represents $\text{S(O)}\text{R}^{4d}$, $\text{S(O)}_2\text{R}^{4d}$, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, $-\text{C(O)}-\text{A}^1-\text{N}(\text{R}^{5b})(\text{R}^{5c})$, $-\text{S(O)}-\text{A}^1-\text{N}(\text{R}^{5b})(\text{R}^{5c})$, or $-\text{S(O)}_2-\text{A}^1-\text{N}(\text{R}^{5b})(\text{R}^{5c})$, wherein R^{4d} , R^{5b} , R^{5c} and A^1 are as hereinbefore defined, for example at between room and reflux
 10 temperature in the presence of a reaction-inert solvent (e.g. THF).

5. Compounds of formula I in which Y represents $-\text{C(=E)}\text{NR}^8\text{R}^9$, wherein E, R^8 and R^9 are as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula I in which Y represents H, with a
 15 compound of formula VIII,



or a suitable (e.g. carboxylic acid) derivative thereof (e.g. an acid chloride), wherein E, R^8 and R^9 are as hereinbefore defined, or a compound of formula IX,



wherein E, R^8 and R^9 are as hereinbefore defined, for example (in both cases) at between room and reflux temperature in the presence of a suitable base (e.g. KOH, triethylamine and/or pyridine) and optionally in the presence of an appropriate solvent (e.g. THF, water, or a suitable
 25 mixture thereof).

6. Compounds of formula I in which Y represents $\text{C(O)}\text{R}^{10}$ or $\text{C(O)}\text{OR}^{10}$, wherein R^{10} is as hereinbefore defined, may be prepared by reaction of a

corresponding compound of formula I in which Y represents H, with a compound of formula X,



or a compound of formula XI,



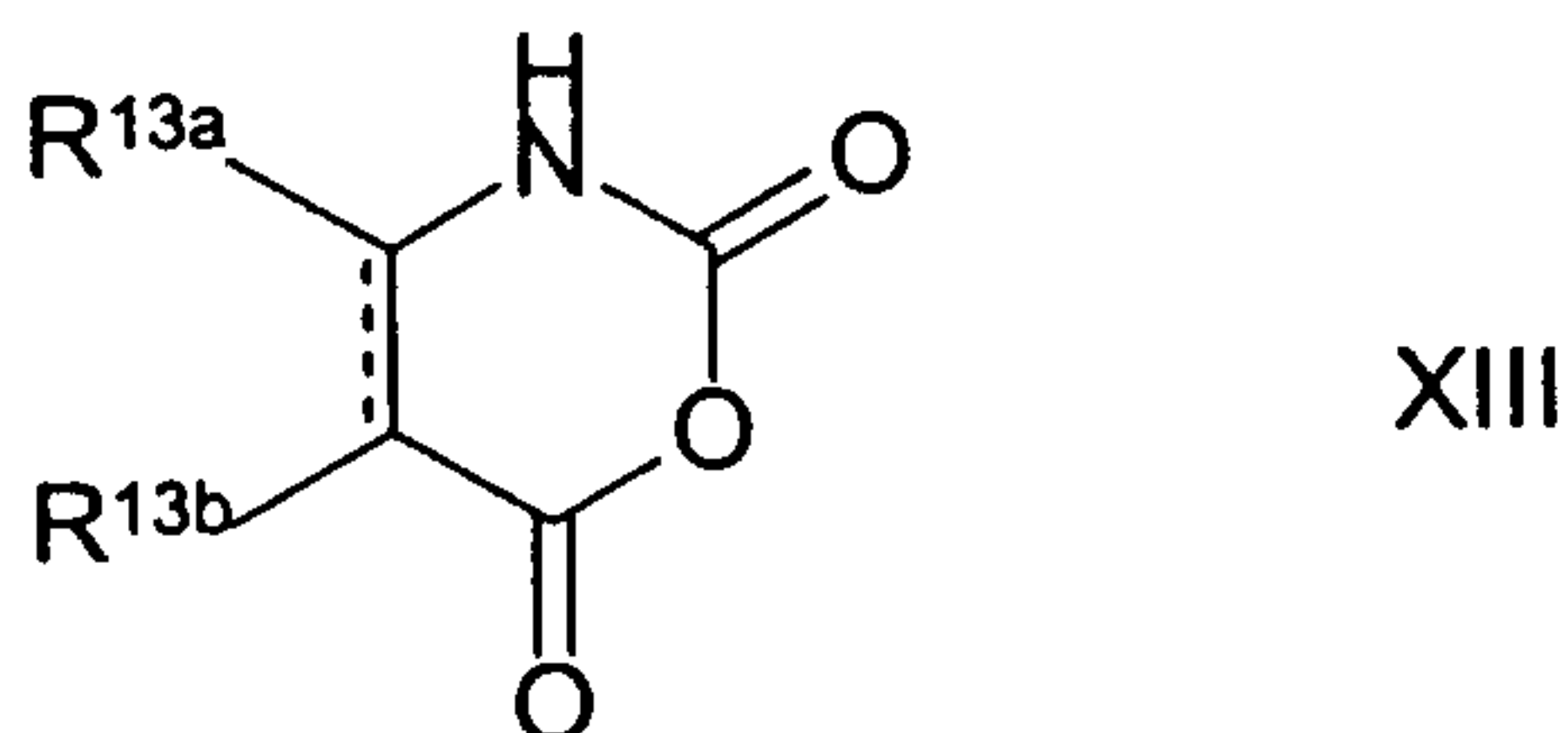
respectively, or suitable (e.g. carboxylic acid) derivatives thereof (e.g. acid halides or anhydrides), wherein R^{10} is as hereinbefore defined, under coupling conditions known to those skilled in the art.

- 10 7. Compounds of formula I in which Y represents $\text{C(O)CH(R}^{10a})\text{N(G)(G}^a)$, wherein R^{10a} , G and G^a are as hereinbefore defined may be prepared by reaction of a corresponding compound of formula I in which Y represents H, with a compound of formula XII,



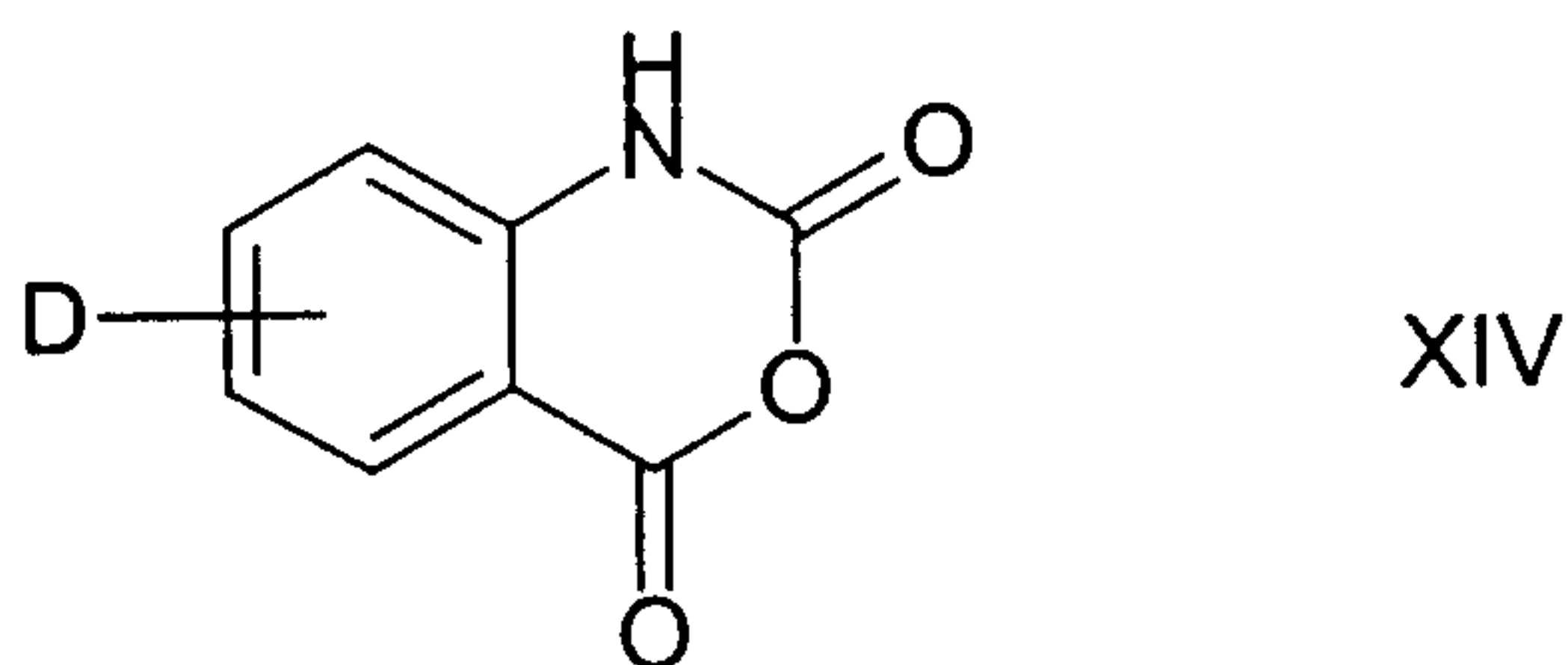
- 15 or a suitable (e.g. carboxylic acid) derivative thereof, wherein R^{10a} , G and G^a are as hereinbefore defined, under coupling conditions known to those skilled in the art.

8. Compounds of formula I in which Y represents
20 $\text{C(O)C(R}^{13a})=\text{C(R}^{13b})\text{NH}_2$ or $\text{C(O)CH(R}^{13a})\text{CH(NH}_2\text{)(R}^{13b})$, and R^{13a} and R^{13b} are as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula I in which Y represents H, with a compound of formula XIII,



wherein the dashed line represents an optional double bond, and R^{13a} and R^{13b} are as hereinbefore defined, for example at between room and reflux temperature in the presence of a suitable solvent (e.g. *N,N*-dimethylformamide) and an appropriate base (e.g. *N,N*-dimethyl-4-aminopyridine).

9. Compounds of formula I in which Y represents $C(O)R^{10}$, wherein R^{10} represents phenyl substituted in the *ortho*-position by an amino group, and optionally substituted by one or more further substituents selected from OH, halo, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, $N(R^8)(R^9)$, $C(O)N(R^8)(R^9)$, C_{1-4} alkyl and C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms), and R^8 and R^9 are as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula I in which Y represents H with a compound of formula XIV,



wherein D represents one to four optional substituents selected from OH, halo, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, $N(R^8)(R^9)$, $C(O)N(R^8)(R^9)$, C_{1-4} alkyl and C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms), and R^8 and R^9 are as hereinbefore defined, for example at between room and reflux temperature in the presence of a suitable solvent (e.g. *N,N*-dimethylformamide) and an appropriate base (e.g. *N,N*-dimethyl-4-aminopyridine).

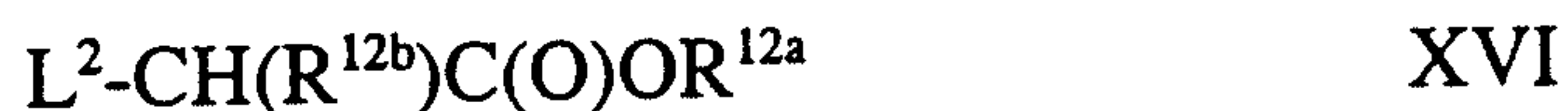
10. Compounds of formula I in which Y represents R^{11} , wherein R^{11} is as hereinbefore defined, may be prepared by reaction of a corresponding

compound of formula I in which Y represents H, with a compound of formula XV,

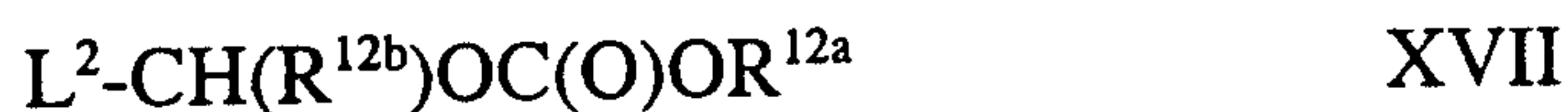


wherein L^2 represents a leaving group such as halo, arenesulfonate, alkanesulfonate, perfluoroalkanesulfonate or diazo, and R^{11} is as hereinbefore defined, for example under coupling conditions known to those skilled in the art (such as those described above in respect of process 2 above).

11. Compounds of formula I in which Y represents $\text{CH}(\text{R}^{12b})\text{C}(\text{O})\text{OR}^{12a}$ or $\text{CH}(\text{R}^{12b})\text{OC}(\text{O})\text{OR}^{12a}$, wherein R^{12a} and R^{12b} are as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula I in which Y represents H, with a compound of formula XVI,



or a compound of formula XVII,



wherein R^{12a} , R^{12b} and L^2 are as hereinbefore defined, for example under coupling conditions known to those skilled in the art (such as those described in respect of process 2 above).

20

12. Compounds of formula I in which Y represents $\text{PO}(\text{OR}^{14})_2$, wherein R^{14} is as hereinbefore defined, may be prepared by reaction of a compound of formula I in which Y represents H, with a compound of formula XVIII,

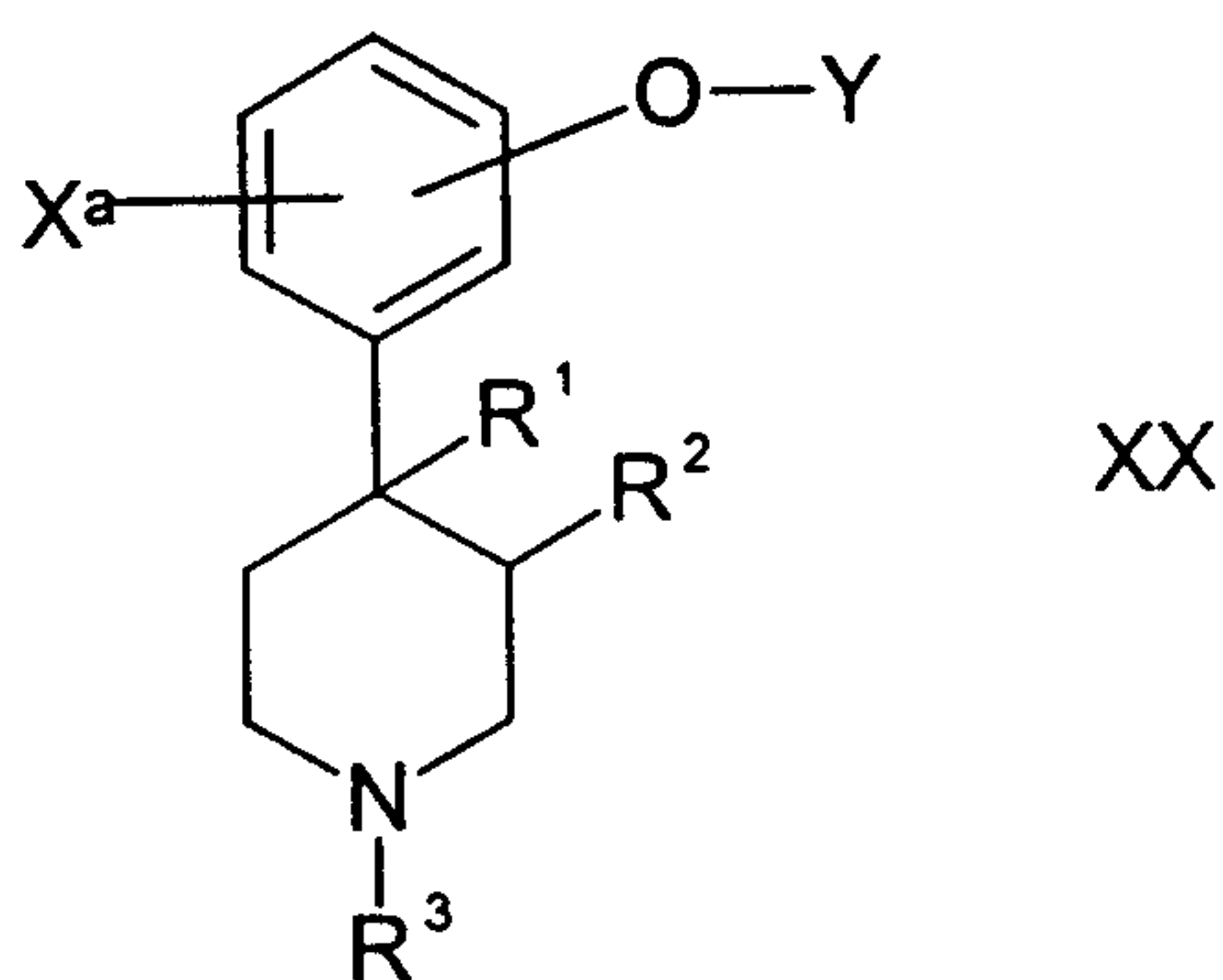


or a compound of formula XIX,



or a suitable (e.g. phosphoric acid) derivative thereof (e.g. a pyrophosphate, cyanophosphate or chlorophosphate), wherein R^{14} is as hereinbefore defined, for example at between -10°C and reflux temperature in the presence of a suitable base (e.g. NaH, triethylamine) and an appropriate organic solvent (e.g. THF, dichloromethane or carbon tetrachloride).

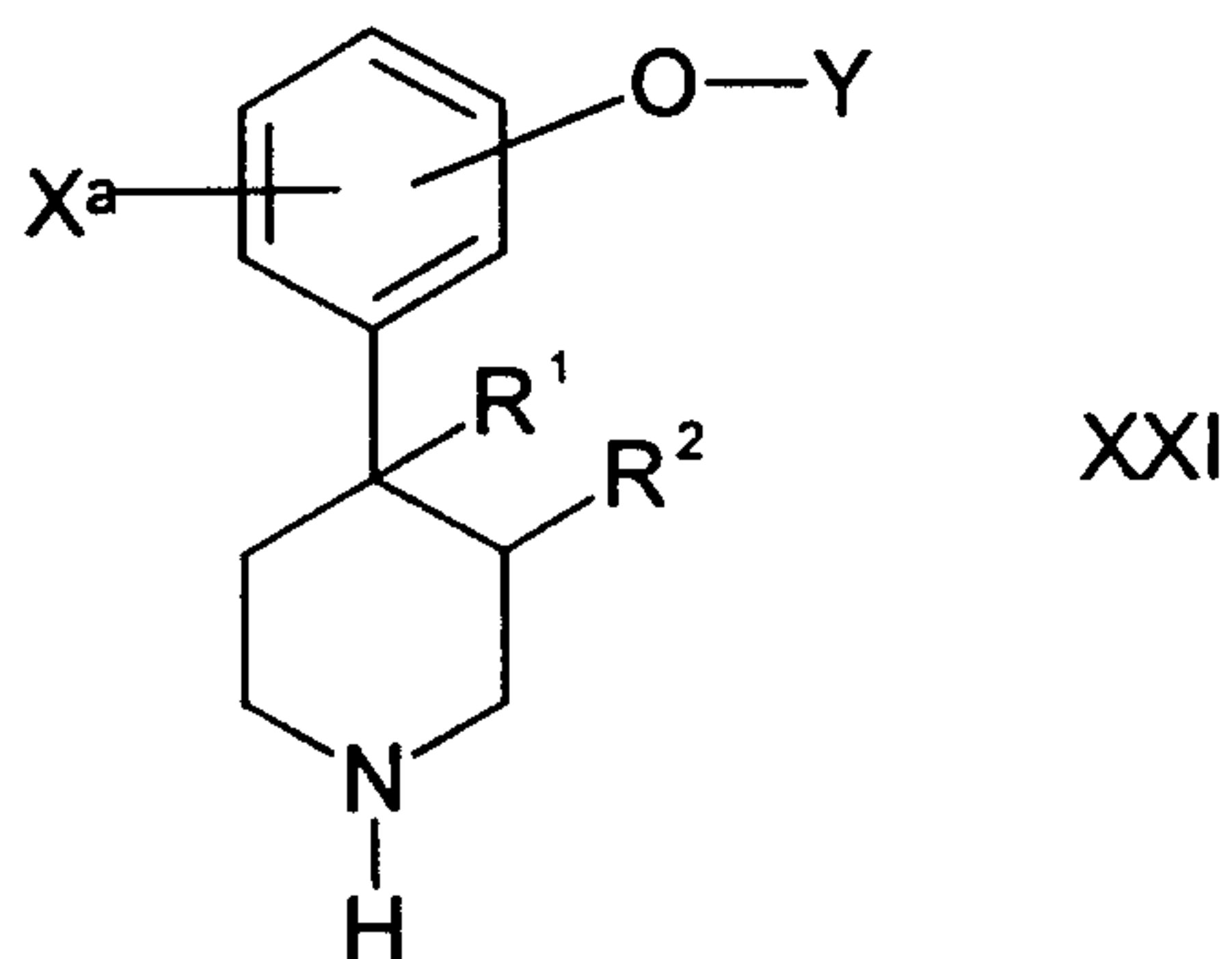
13. Compounds of formula I in which X represents halo and optionally one or more further substituents hereinbefore defined in respect of X, may be prepared by reaction of a corresponding compound of formula XX,



wherein X^a represents one H and optionally one to three of the substituents hereinbefore defined in respect of X, and R^1 , R^2 , R^3 and Y are as hereinbefore defined, with a suitable halogenating agent (e.g. a solution of the halogen in acetic acid, or a fluorinating agent such as 3,5-dichloro-1-fluoropyridinium triflate or *N*-fluorobenzenesulfonimide), for example under conditions known to those skilled in the art.

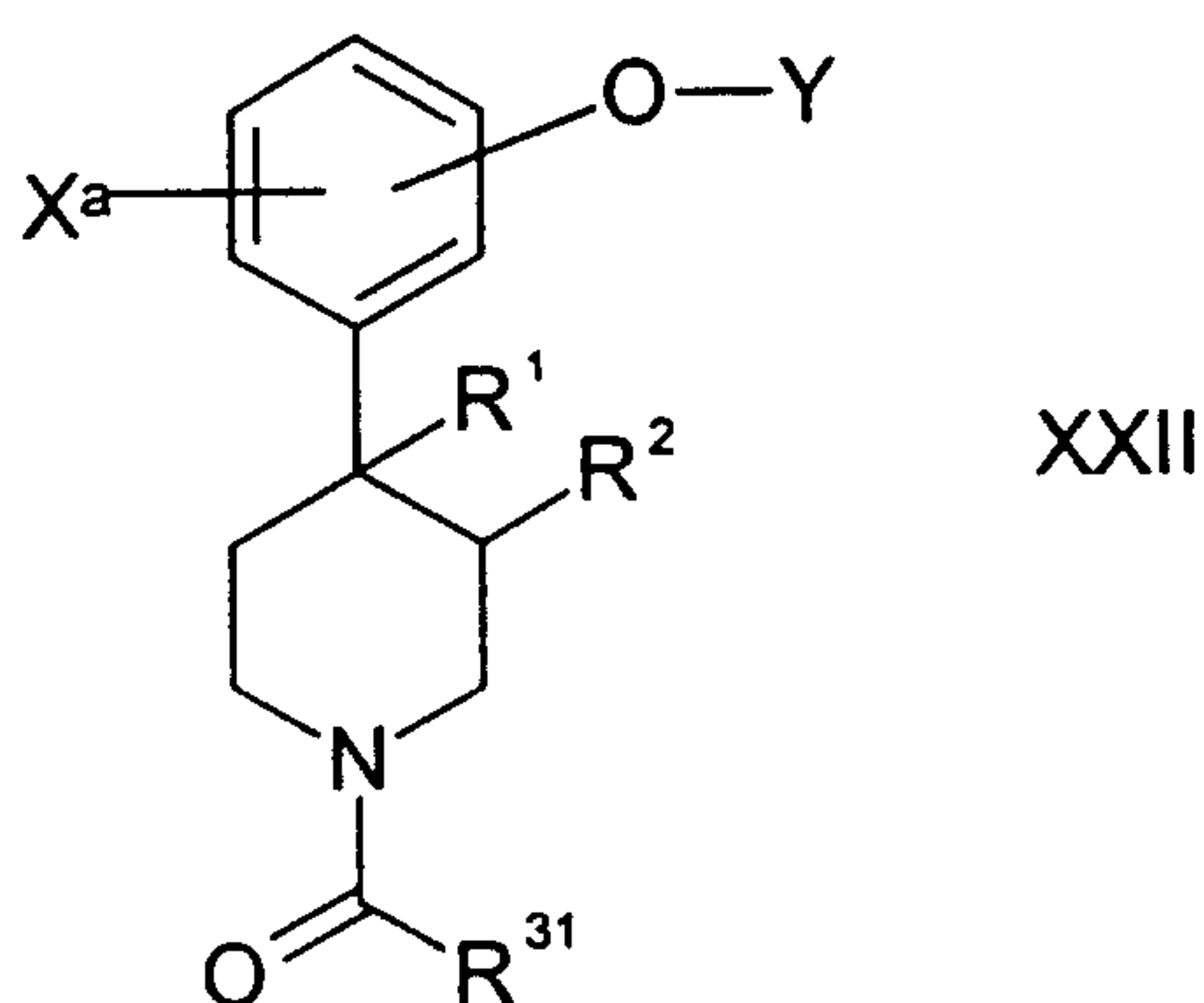
Compounds of formula XX may be prepared by N-alkylation of a corresponding compound of formula XXI,

31



wherein R^1 , R^2 , X^a and Y are as hereinbefore defined, for example under conditions hereinbefore described for the preparation of compounds of formula I (see, for example, those described in respect of processes 2 to 4
5 above).

Compounds of formula XX in which R^3 represents C_1 alkyl, which, in place of being optionally substituted by the substituents as defined hereinbefore, is instead optionally substituted by R^{31} , wherein R^{31} is as
10 hereinbefore defined, may alternatively be prepared by reduction of a corresponding compound of formula XXII,



wherein R^1 , R^2 , R^{31} , X^a and Y are as hereinbefore defined, for example under conditions hereinbefore described for the preparation of compounds
15 of formula I (see, for example, those described in respect of process 1 above).

Compounds of formula XXI and XXII may be prepared from appropriate precursors by analogy with other methods disclosed herein that describe the production of compounds of formula I.

5 14. Compounds of formula I in which X represents nitro and optionally one or more further substituents hereinbefore defined in respect of X, may be prepared by nitration of a corresponding compound of formula XX, as hereinbefore defined, under conditions known to those skilled in the art, for example by reaction with a suitable source of the nitronium ion (e.g.
10 nitronium tetrafluoroborate) at between -10°C and room temperature in the presence of a suitable solvent (e.g. acetonitrile).

15 15. Compounds of formula I in which X represents $S(O)_2OH$ and optionally one or more further substituents hereinbefore defined in respect of X, may be prepared by sulfonation of a corresponding compound of formula XX, as hereinbefore defined, under conditions known to those skilled in the art, for example by reaction with chlorosulfonic acid at between -10°C and room temperature in the presence of thionyl chloride, followed by hydrolysis of the resulting sulfonyl chloride. The reaction
20 may alternatively performed with sulfur trioxide, for example at between -10°C and reflux temperature in the presence of pyridine.

25 16. Compounds of formula I in which X represents $S(O)_tR^{17a}$, wherein t is 0, and optionally one or more further substituents hereinbefore defined in respect of X, wherein R^{17a} is as hereinbefore defined except that it does not represent $N(R^{20a})(R^{20b})$, wherein R^{20a} and R^{20b} are as hereinbefore defined, may be prepared by sulfenylation of a corresponding compound of formula XX, as hereinbefore defined, under conditions known to those

skilled in the art, for example by reaction with a compound of formula XXIII,



wherein R^{21} represents R^{17a} as hereinbefore defined except that it does not
 5 represent $\text{N}(\text{R}^{20a})(\text{R}^{20b})$, wherein R^{20a} and R^{20b} are as hereinbefore defined,
 at between -90°C and room temperature in the presence of a suitable
 strong base (e.g. an alkyllithium reagent) and an appropriate organic
 solvent (e.g. *N,N,N',N'*-tetramethylethylenediamine), or by reaction with
 a compound of formula XXIV,



wherein R^{21} is as hereinbefore defined, at between 0°C and reflux
 temperature in the presence of an appropriate organic solvent (e.g.
 dichloromethane) and optionally in the presence of a suitable catalyst (e.g.
 iron powder).

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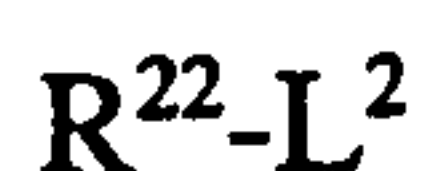
17. Compounds of formula I in which X represents $\text{C}(\text{O})\text{R}^{16a}$ and
 optionally one or more further substituents hereinbefore defined in respect
 of X, wherein R^{16a} is as hereinbefore defined except that it does not
 represent H, may be prepared by acylation of a corresponding compound
 20 of formula XX, as hereinbefore defined, under conditions known to those
 skilled in the art, for example by reaction with a compound of formula
 XXV,



wherein L^3 represents a leaving group (such as halo, OH, $\text{OS}(\text{O})_2\text{CF}_3$ or
 25 $\text{OC}(\text{O})\text{R}^{16a}$) and R^{16a} is as hereinbefore defined except that it does not
 represent H, for example under Friedel-Crafts conditions (e.g. at between
 room and reflux temperature in the presence of a suitable solvent and
 optionally in the presence of an appropriate catalyst).

18. Compounds of formula I in which X represents C(O)H and optionally one or more further substituents hereinbefore defined in respect of X, may be prepared by reaction of a corresponding compound of formula XX, as hereinbefore defined, with dimethylformamide, for example under
5 Vilsmeier-Haack conditions or at between -90°C and room temperature in the presence of a suitable strong base (e.g. an alkyl lithium reagent) and an appropriate organic solvent (e.g. *N,N,N',N'*-tetramethylethylenediamine, THF, cyclohexane or mixtures thereof).
- 10 19. Compounds of formula I in which X represents OC(O)R^{16c} and optionally one or more further substituents hereinbefore defined in respect of X, wherein R^{16c} is as hereinbefore defined, may be prepared by oxidation of a corresponding compound of formula I in which X represents C(O)R^{16a}, wherein R^{16a} is as hereinbefore defined, for example
15 under Baeyer-Villiger conditions, i.e. at between room and reflux temperature in the presence of an appropriate peroxy acid (e.g. 3-chloroperoxybenzoic acid) and a suitable organic solvent (e.g. dichloromethane).
- 20 20. Compounds of formula I in which X and/or OY represent OH may be prepared by reaction of a corresponding compound of formula I in which X represents OC(O)R^{16c}, wherein R^{16c} is as hereinbefore defined, and/or Y represents C(=E)NR⁸R⁹, wherein R⁸ and R⁹ are as hereinbefore defined, under conditions well known to those skilled in the art (e.g. hydrolysis or
25 reductive cleavage).
21. Compounds of formula I in which X represents C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl, C₃₋₁₀ alkynyl, C₃₋₇ cycloalkyl (which four groups are

optionally substituted as defined hereinbefore, and which alkenyl and alkynyl groups are fully saturated at 1-C (relative to the benzene ring)) and optionally one or more further substituents hereinbefore defined in respect of X, may be prepared by reaction of a corresponding compound
 5 of formula XX, as hereinbefore defined, with a compound of formula XXVI,

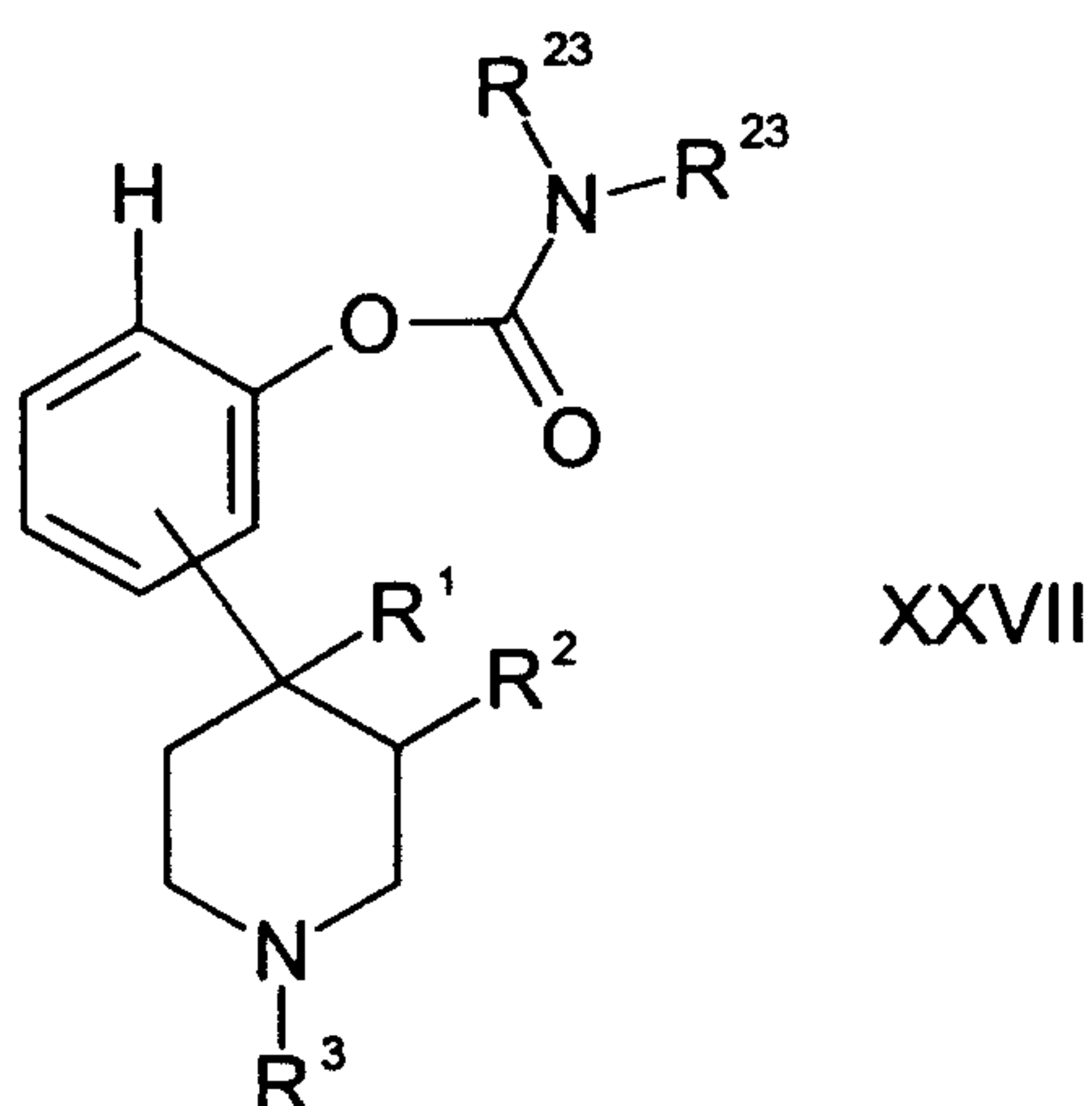


XXVI

wherein R^{22} represents C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl (which four groups are optionally substituted by one or
 10 more substituents selected from halo, CN, nitro, OH, C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{3-7} cycloalkoxy, C_{1-6} alkanoyl, C_{4-8} cycloalkanoyl, C_{2-6} alkoxycarbonyl, C_{2-6} alkanoyloxy or $N(R^{15a})(R^{15b})$, and which alkenyl and alkynyl groups are fully saturated at 1-C (relative to L^2)) and L^2 , R^{15a} and R^{15b} are as hereinbefore defined, for example either under Friedel-
 15 Crafts alkylation conditions or at between -90°C and room temperature in the presence of a suitable strong base (e.g. an alkyllithium reagent) and an appropriate organic solvent (e.g. *N,N,N',N'*-tetramethylethylenediamine, THF, cyclohexane or mixtures thereof).

20 22. Compounds of formula I in which X represents $C(O)N(R^{18c})(R^{18d})$, which group is in the *ortho*-position relative to OY, in which R^{18c} and R^{18d} independently represent C_{1-4} alkyl or C_{3-7} cycloalkyl, and Y represents H, may be prepared by rearrangement of a corresponding compound of formula XXVII,

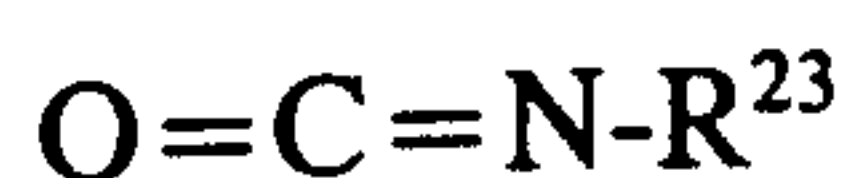
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wherein R^{23} represents C_{1-4} alkyl or C_{3-7} cycloalkyl, and R^1 , R^2 , and R^3 are as hereinbefore defined, for example at between -90°C and room temperature in the presence of a suitable strong base (e.g. an alkyllithium reagent) and an appropriate organic solvent (e.g. N,N,N',N' -tetramethylethylenediamine, THF, cyclohexane or mixtures thereof).

23. Compounds of formula I in which X represents C_{2-10} alkenyl and optionally one or more further substituents hereinbefore defined in respect of X, wherein the double bond of the alkenyl chain is α,β - to the benzene ring, may be prepared by reaction of a corresponding compound of formula XX, as hereinbefore defined, with a C_{2-10} aldehyde or a C_{2-10} ketone, for example at between -90°C and room temperature in the presence of a suitable strong base (e.g. an alkyllithium reagent) and an appropriate organic solvent (e.g. N,N,N',N' -tetramethylethylenediamine, THF, cyclohexane or mixtures thereof).

24. Compounds of formula I in which X represents $C(O)N(H)R^{18c}$ and optionally one or more further substituents hereinbefore defined in respect of X, wherein R^{18c} represents C_{1-4} alkyl or C_{3-7} cycloalkyl may be prepared by reaction of a corresponding compound of formula XX, as hereinbefore defined, with a compound of formula XXVIII,



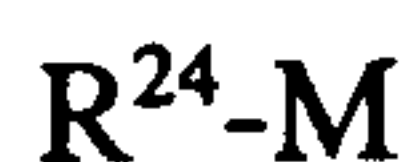
XXVIII

wherein R^{23} is as hereinbefore defined, for example at between -90°C and room temperature in the presence of a suitable strong base (e.g. an alkyl lithium reagent) and an appropriate organic solvent (e.g. N,N,N',N' -tetramethylethylenediamine, THF, cyclohexane or mixtures thereof).

25. Compounds of formula I in which X represents $\text{B}(\text{OCH}_3)_2$ and optionally one or more further substituents hereinbefore defined in respect of X, may be prepared by reaction of a corresponding compound of formula XX, as hereinbefore defined, with trimethyl borate, for example at between -90°C and room temperature in the presence of a suitable strong base (e.g. an alkyl lithium reagent) and an appropriate organic solvent (e.g. N,N,N',N' -tetramethylethylenediamine, THF, cyclohexane or mixtures thereof).

15

26. Compounds of formula I in which X represents C_{2-10} alkenyl or C_{2-10} alkynyl, which alkenyl and alkynyl groups contain a carbon-carbon multiple bond that is α,β to the benzene ring, and which alkenyl and alkynyl groups are optionally substituted as defined hereinbefore in respect of X, and optionally one or more further substituents hereinbefore defined in respect of X, may be prepared by reaction of a corresponding compound of formula I in which at least one X represents halo with a compound of formula XXIX,



XXIX

25 wherein R^{24} represents C_{2-10} terminal alkenyl or C_{2-10} terminal alkynyl, which alkenyl and alkynyl groups are optionally substituted by one or more substituents selected from halo, CN, nitro, OH, C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{3-7} cycloalkoxy, C_{1-6} alkanoyl, C_{4-8} cycloalkanoyl,

C₂₋₆ alkoxy carbonyl, C₂₋₆ alkanoyloxy or N(R^{15a})(R^{15b}), M represents (as appropriate) H, a tin-containing moiety (e.g. tributylstannyl), a boron derivative (e.g. a boronic acid), a zinc halide, a magnesium halide or an alkali metal (which latter three groups may be formed *in situ* from the corresponding halide), and R^{15a} and R^{15b} are as hereinbefore defined, for example at between room and reflux temperature in the presence of a suitable catalyst system (e.g. tetrakis(triphenylphosphine)palladium(0), bis(triphenylphosphine)palladium(II) acetate, or bis(triphenylphosphine)-palladium(II) chloride combined with copper(I) iodide) and either (as appropriate) a suitable source of halide ion (e.g. lithium chloride) or a suitable base (e.g. triethylamine).

Compounds of formulae III to XIX, XXIII to XXIX, and derivatives thereof, when not commercially available or not subsequently described, may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from readily available starting materials using appropriate reagents and reaction conditions (see, for example, "Comprehensive Organic Transformations - A Guide to Functional Group Preparations", R. C. Larrock, VCH (1989), or "Advanced Organic Chemistry - Reactions, Mechanism and Structure", 4th edition, J. March, Wiley-Interscience (1992)). For example, compounds of formula XX in which both X^a and Y represent H may be made according to or by analogy with the procedures disclosed in the publications mentioned above relating to 4-arylpiperidine-based compounds.

The skilled person will appreciate that certain groups falling within the definition of Y will serve as protective groups during the introduction

and/or interconversion of certain X groups, for the synthesis of corresponding compounds in which Y represents H. For example, the group $-C(=E)NR^8R^9$ may serve to prevent reaction at phenolic oxygen under conditions such as those described in relation to processes 16, 18,
5 19, 21 and 23 to 25 above.

Substituents on alkyl, heterocyclic and aryl groups in the above-mentioned compounds may also be introduced, removed and interconverted, using techniques which are well known to those skilled in the art (including those
10 specifically disclosed hereinbefore). For example, nitro may be reduced to amino, OH may be alkylated to give alkoxy, alkoxy and alkanoyloxy may be hydrolysed to OH, alkenes may be hydrogenated to alkanes, halo may be hydrogenated to H, etc.

15 The skilled person will also appreciate that other various standard substituent or functional group interconversions and transformations within compounds of formula I will provide other compounds of formula I. In particular, certain functional groups falling within the definitions of the group X may be converted to other such definitions. For example:
20 amino may be converted to alkylamino, dialkylamino, alkylcarbonylamino, alkylsulfonylamino, aminocarbonylamino, alkoxy-carbonylamino and aminosulfonylamino; sulfonate may be converted to aminosulfonyl; formyl may be converted to hydroxymethyl, aminomethyl, alkylaminomethyl, dialkylaminomethyl and alkoxycarbonyl; methyl may
25 be converted to ethyl; alkoxycarbonyl may be converted to aminocarbonyl, alkylaminocarbonyl and dialkylaminocarbonyl; aminocarbonyl may be converted to alkanoyl; sulfanyl may be converted to sulfinyl or sulfonyl; and dialkyl borate may be converted to

dihydroxyboryl, all of which transformations may be performed using techniques, and under reaction conditions, that are known to those skilled in the art. Also, certain groups representing Y may be converted to certain other groups representing Y.

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 course of
10 carrying out the processes described above, the functional groups of intermediate compounds may need to be protected by protecting groups.

Functional groups which it is desirable to protect include oxo, OH, amino and carboxylic acid. Suitable protective groups for oxo include acetals,
15 ketals (e.g. ethylene ketals) and dithianes. Suitable protective groups for OH include trialkylsilyl and diarylalkylsilyl groups (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl) and tetrahydropyranyl. Suitable protective groups for amino include *tert*-butyloxycarbonyl, 9-fluorenylmethoxycarbonyl or benzyloxycarbonyl.
20 Suitable protective groups for carboxylic acid include C₁₋₆ alkyl or benzyl esters. Suitable protective groups for terminal alkynes include trialkylsilyl and diarylalkylsilyl groups (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl). Suitable protective groups for arene protons include trialkylsilyl groups.

25

The protection and deprotection of functional groups may take place before or after any of the reaction steps described hereinbefore.

Protective groups may be removed in accordance with techniques which are well known to those skilled in the art.

The use of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by JWF McOmie, Plenum Press (1973), and
5 "Protective Groups in Organic Synthesis", 2nd edition, TW Greene & PGM Wutz, Wiley-Interscience (1991).

Persons skilled in the art will also appreciate that, in order to obtain
10 compounds of formula I in an alternative, and, on some occasions, more convenient, manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different
15 intermediates to those mentioned hereinbefore in conjunction with a particular reaction). This will depend *inter alia* on factors such as the nature of other functional groups present in a particular substrate, the availability of key intermediates and the protecting group strategy (if any) to be adopted. Clearly, the type of chemistry involved will influence the
20 choice of reagent that is used in the said synthetic steps, the need, and type, of protecting groups that are employed, and the sequence for accomplishing the synthesis. The procedures may be adapted as appropriate to the reactants, reagents and other reaction parameters in a manner that will be evident to the skilled person by reference to standard textbooks and to the
25 examples provided hereinafter.

Pharmaceutically acceptable acid addition salts of the compounds of formula I which contain a basic centre may be prepared in a conventional

manner. For example, a solution of the free base may be treated with the appropriate acid, either neat or in a suitable solvent, and the resulting salt may then be isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts
5 can be obtained in an analogous manner by treating a solution of a compound of formula I with the appropriate base. Both types of salt may be formed or interconverted using ion-exchange resin techniques.

The above procedures may be adapted as appropriate to the particular
10 reactants and groups involved and other variants will be evident to the skilled chemist by reference to standard textbooks and to the examples provided hereafter to enable all of the compounds of formula I to be prepared.

15 Compounds of the invention may possess pharmacological activity as such. Compounds of the invention that may possess such activity include, but are not limited to, those in which Y represents H.

Other compounds of formula I (including, but not limited to, those in
20 which Y does not represent H) may not possess such activity *per se*, but may be administered parenterally or orally, and thereafter metabolised in the body to form compounds that are pharmacologically active (including, but not limited to, corresponding compounds in which Y represents H). Such compounds (which also include compounds that may possess some
25 pharmacological activity, but that activity is appreciably lower than that of the active compounds to which they are metabolised to), may therefore be described as "prodrugs".

Further, it will be appreciated by those skilled in the art that certain protected derivatives of compounds of formula I, which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally
5 and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may also therefore be described as "prodrugs". Further, certain compounds of formula I may act as prodrugs of other compounds of formula I.

10 It will be further appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as "pro-moieties", for example as described in 'Design of Prodrugs' by H. Bundgaard, Elsevier, 1985 (the disclosure in which document is hereby incorporated by reference), may be placed on appropriate functionalities, when such functionalities are present
15 within compounds of formula I.

All protected derivatives, and prodrugs, of compounds of formula I are included within the scope of the invention.

20 The compounds of the invention are useful because they possess pharmacological activity, and/or are metabolised in the body following oral or parenteral administration to form compounds which possess pharmacological activity. The compounds of the invention are therefore indicated as pharmaceuticals and, in particular, for use as animal
25 medicaments.

According to a further aspect of the invention there is provided the compounds of the invention for use as medicaments, such as pharmaceuticals and animal medicaments.

- 5 By the term "treatment", we include both therapeutic (curative) or prophylactic treatment.

In particular, the compounds of the invention have been found to be useful in the treatment of pruritus, and conditions characterised by pruritus as a
10 symptom.

Thus, according to a further aspect of the invention there is provided the use of the compounds of the invention in the manufacture of a medicament for the treatment of pruritus or a medical condition characterised by
15 pruritus as a symptom.

The compounds of the invention are thus expected to be useful for the curative or prophylactic treatment of pruritic dermatoses including allergic dermatitis and atopy in animals and humans. Other diseases and
20 conditions which may be mentioned include contact dermatitis, psoriasis, eczema and insect bites.

Thus, the invention provides a method of treating or preventing pruritus or a medical condition characterised by pruritus as a symptom in an animal
25 (e.g. a mammal), which comprises administering a therapeutically effective amount of a compound of the invention to an animal in need of such treatment.

The compounds of the invention will normally be administered orally or by any parenteral route, in the form of pharmaceutical preparations comprising the active ingredient, optionally in the form of a non-toxic organic, or inorganic, acid, or base, addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated, as well as the route of administration, the compositions may be administered at varying doses (see below).

While it is possible to administer a compound of the invention directly without any formulation, the compounds are preferably employed in the form of a pharmaceutical, or veterinary, formulation comprising a pharmaceutically, or veterinarily, acceptable carrier, diluent or excipient and a compound of the invention. The carrier, diluent or excipient may be selected with due regard to the intended route of administration and standard pharmaceutical, and/or veterinary, practice. Pharmaceutical compositions comprising the compounds of the invention may contain from 0.1 percent by weight to 90.0 percent by weight of the active ingredient.

The methods by which the compounds may be administered for veterinary use include oral administration by capsule, bolus, tablet or drench, topical administration as an ointment, a pour-on, spot-on, dip, spray, mousse, shampoo, collar or powder formulation or, alternatively, they can be administered by injection (e.g. subcutaneously, intramuscularly or intravenously), or as an implant. Such formulations may be prepared in a conventional manner in accordance with standard veterinary practice.

The formulations will vary with regard to the weight of active compound contained therein, depending on the species of animal to be treated, the severity and type of infection and the body weight of the animal. For parenteral, topical and oral administration, typical dose ranges of the active ingredient are 0.01 to 100 mg per kg of body weight of the animal. Preferably the range is 0.1 to 10 mg per kg.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg, more usually about 5 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discreet units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

In any event, the veterinary practitioner, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which may vary with the species, age, weight and response of the particular patient. The above dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

For veterinary use, the compounds of the invention are of particular value for treating pruritus in domestic animals such as cats and dogs and in horses.

As an alternative for treating animals, the compounds may be administered with the animal feedstuff and for this purpose a concentrated feed additive or premix may be prepared for mixing with the normal animal feed.

- 5 For human use, the compounds are administered as a pharmaceutical formulation containing the active ingredient together with a pharmaceutically acceptable diluent or carrier. Such compositions include conventional tablet, capsule and ointment preparations which are formulated in accordance with standard pharmaceutical practice.

10

- Compounds of the invention may be administered either alone or in combination with one or more agents used in the treatment or prophylaxis of disease or in the reduction or suppression of symptoms. Examples of such agents (which are provided by way of illustration and should not be
- 15 construed as limiting) include antiparasitics, e.g. fipronil, lufenuron, imidacloprid, avermectins (e.g. abamectin, ivermectin, doramectin), milbemycins, organophosphates, pyrethroids; antihistamines, e.g. chlorpheniramine, trimeprazine, diphenhydramine, doxylamine; antifungals, e.g. fluconazole, ketoconazole, itraconazole, griseofulvin,
- 20 amphotericin B; antibacterials, e.g. enrofloxacin, marbofloxacin, ampicillin, amoxycillin; anti-inflammatories e.g. prednisolone, betamethasone, dexamethasone, carprofen, ketoprofen; dietary supplements, e.g. gamma-linoleic acid; and emollients. Therefore, the invention further provides a product containing a compound of the
- 25 invention and a compound from the above list as a combined preparation for simultaneous, separate or sequential use in the treatment of pruritus.

The skilled person will also appreciate that compounds of the invention may be taken as a single dose on an "as required" basis (i.e. as needed or desired).

5 Thus, according to a further aspect of the invention there is provided a pharmaceutical, or veterinary, formulation including a compound of the invention in admixture with a pharmaceutically, or veterinarily, acceptable adjuvant, diluent or carrier.

10 Compounds of the invention may also have the advantage that, in the treatment of human and/or animal patients, they may be, or may be metabolised to form compounds that may be, more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects than, be more easily absorbed than, or they
15 may have other useful pharmacological properties over, compounds known in the prior art.

The biological activity of the compounds of the present invention was determined by the following test method.

20

Biological Test

The compounds of the invention are evaluated for their activity as antipruritic agents by measuring their ability to inhibit the hind leg
25 scratching behaviour induced in rats by the administration of a known pruritogenic agent. These studies are based on the procedure described by Berendsen and Broekkamp in the European Journal of Pharmacology, 1991, 194, 201. The test is performed as follows:

Male Wistar rats (approximately 150 g body weight) are challenged with a pruritogen by subcutaneous injection of 5-methoxytryptamine hydrochloride (4 mg/3 mL/kg) dissolved in physiological saline into the scruff of the neck. At this dose a constant and quantifiable hindleg scratching response lasting up to 90 minutes is obtained.

The test compound is administered to the test animals by subcutaneous injection in an aqueous micelle formulation. The test compound is prepared in the following manner. The compound is dissolved in a vehicle (composition v/v%: glycerol formal, 24; tween 80, 17; benzyl alcohol, 1.5 and purified water to 100) then seven parts purified water is added to three parts of the above vehicle to give the aqueous micelle formulation. The compounds can be administered pre- or post-challenge or may be administered at the same time as the pruritogenic challenge.

After the pruritogen challenge has been administered, hindleg scratching is scored for each animal by recording the presence or absence of scratching during each 30 second interval as 1 or 0 scored respectively. The score for each animal is totalled after 25 minutes (maximum score 50). The efficacy of compounds is assessed by their ability to significantly reduce the score in treated groups compared to the control group.

The invention is illustrated by the following Preparations and Examples in which the following abbreviations may be used:

APCI = atmospheric pressure chemical ionisation

- br (in relation to NMR) = broad
CI = chemical ionisation
DMF = *N,N*-dimethylformamide
DMSO = dimethylsulfoxide
5 d (in relation to time) = day
d (in relation to NMR) = doublet
dd (in relation to NMR) = doublet of doublets
EtOAc = ethyl acetate
EtOH = ethanol
10 ESI = electrospray ionisation
h = hour(s)
m (in relation to NMR) = multiplet
MeOH = methanol
min = minute
15 q (in relation to NMR) = quartet
s (in relation to NMR) = singlet
t (in relation to NMR) = triplet
td (in relation to NMR) = triplet of doublets
THF = tetrahydrofuran
20 TSI = thermospray ionisation

When reverse phase HPLC is mentioned in the text the following 2 sets of conditions were employed.

- 25 Condition 1: A Phenomenex Magellen™ column, 150 x 21 mm, packed with 5m C₁₈ silica, eluting with a gradient of acetonitrile : 0.1 M aqueous ammonium acetate (30:70 to 95:5 over 10 mins, flow rate 20 mL per min).

Condition 2: A Dynamax™ column, 42 x 250 mm, packed with 8 μ C₁₈ silica, eluting with acetonitrile : 0.1 M aqueous ammonium acetate (30:70) at 45 mL per minute.

- 5 In both cases, combination and evaporation of appropriate fractions, determined by analytical HPLC, provided the desired compounds as acetate salts.

Analytical HPLC conditions used to highlight appropriate fractions were
10 Phenomenex Magellan™ column, 4.6 x 150 mm, packed with 5 μ C₁₈ silica, eluting with a gradient of acetonitrile : 0.1 M aqueous heptanesulfonic acid (10:90 to 90:10 over 30 min, followed by a further 10 min at 90:10) at 1 mL per minute. Column oven temperature was 40°C, and ultraviolet detection of components was made at 220 nM.

15

When column chromatography is referred to this usually refers to a glass column packed with silica gel (40-63 μ m). Pressure of about 165 kPa is generally applied and the ratio of crude product : silica gel required for purification is typically 50:1. Alternatively, an Isolute™ SPE (solid phase
20 extraction) column or Waters Sep-Pak™ cartridge packed with silica gel may be used under atmospheric pressure. The ratio of crude product to silica gel required for purification is typically 100:1.

Nuclear magnetic resonance (NMR) spectral data were obtained using a
25 Bruker AC3000, AM300 or AM400 spectrometer, the observed chemical shifts (δ) being consistent with the proposed structures. Mass spectral (MS) data were obtained on a Finnigan Mat. TSQ 7000 or a Fisons Instruments Trio 1000 spectrometer. The calculated and observed ions

quoted refer to the isotopic composition of lowest mass. HPLC means high performance liquid chromatography. Room temperature means 20 to 25°C.

5 Examples

Example 1: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(4-bromo-3-hydroxy-phenyl)piperidine

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-phenyl)piperidine (Preparation 7, 49 mg, 0.17 mmol) in acetic acid
10 (1 mL) at 10°C was added bromine (9 μ L, 0.17 mmol). After 5 minutes, the reaction mixture was diluted with water (10 mL), adjusted to pH 9 with 2*N* sodium hydroxide, and then extracted with dichloromethane (3 x 10 mL). The combined extracts were washed with brine (15 mL),
15 dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (10:989:1 to 20:978:2), to give the title compound as a yellow oil (53 mg).

NMR (C₆D₆, selected data from the free base): 0.82 (d, 3H), 0.86 (t, 3H),
20 1.10 (s, 3H), 1.16-1.28 (m, 6H), 1.33 (m, 1H), 1.47 (m, 2H), 1.71 (m, 1H), 2.12-2.43 (m, 6H), 2.69 (m, 1H), 6.40 (dd, 1H), 6.94 (d, 1H), 7.33 (d, 1H) and 8.16 (br s, 1H).

MS (APCI⁺): M/Z [MH⁺] 368.2; C₁₉H₃₀BrNO + H requires 368.2.

25 **Example 2: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-nitrophenyl)piperidine**

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-phenyl)piperidine (Preparation 7, 2.88 g, 9.96 mmol) in acetonitrile

(85 mL) at 0°C was added a solution of nitronium tetrafluoroborate (1.59 g, 12.0 mmol) in acetonitrile (15 mL). After 2 hours the reaction mixture was diluted with aqueous saturated sodium hydrogencarbonate (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined
5 extracts were washed with brine (100 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with methanol-dichloromethane-ammonium hydroxide (10:489:1). to give the title compound (1.07 g) as a yellow oil.

10 NMR (C₆D₆, selected data from the free base): 0.71 (d, 3H), 0.87 (t, 3H), 0.92 (s, 3 H), 1.02 (m, 1H), 1.23-1.32 (m, 6H), 1.42 (m, 2H), 1.52 (m, 1H), 1.93 (m, 2H), 2.18 (m, 3H), 2.33 (m, 1H), 2.55 (m, 1H), 6.28 (dd, 1H), 6.78 (d, 1H) and 7.62 (d, 1H).

MS (APCI⁺): M/Z [MH⁺] 335.3; C₁₉H₃₀N₂O₃ +H requires 335.2.

15

Example 3: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(2,4-dibromo-3-hydroxyphenyl)piperidine

Isolation of the slower eluting compound from Example 1 afforded the title compound (4 mg).

20 NMR (C₆D₆, selected data from the free base): 0.80 (d, 3H), 0.87 (t, 3H), 1.08-1.44 (m, 9H), 1.36 (s, 3H), 2.04 (m, 1H), 2.12-2.25 (m, 4H), 2.43 (m, 1H), 2.67 (m, 1H), 2.99 (m, 1H), 6.33 (d, 1H) and 7.05-7.11 (m, 1H).

MS (APCI⁺): M/Z [MH⁺] 446.1; C₁₉H₂₉Br₂NO +H requires 446.1.

25

Example 4: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(4-amino-3-hydroxyphenyl)piperidine

To a solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-nitrophenyl)piperidine (Example 2, 644 mg, 1.93 mmol) in tetrahydrofuran
5 (15 mL) was added platinum(IV) oxide (9 mg, 0.039 mmol) and the reaction mixture was shaken under 345 kPa of hydrogen gas for 10 hours. The reaction mixture was purged with nitrogen, filtered under nitrogen and the crude product was routinely employed directly in the subsequent reaction. The product may be purified, after concentration *in vacuo*, via
10 silica gel chromatography, eluting with methanol-dichloromethane-ammonium hydroxide (10:989:1), to give the title compound as an air-sensitive oil.

NMR (C_6D_6 , selected data from the free base): 0.86 (t, 3H), 0.97 (d, 3H), 1.24-1.32 (m, 9H), 1.45 (m, 3H), 1.81 (m, 1H), 2.16-2.41 (m, 5H), 2.53
15 (m, 1H), 2.78 (m, 1H), 6.42-6.46 (m, 2H) and 6.64 (dd, 1H).

MS (APCI⁺): M/Z [MH⁺] 305.3; $C_{19}H_{32}N_2O + H$ requires 305.3.

Example 5: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-[3-hydroxy-4-(2-methylbutanoyl)phenyl]piperidine

20 To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamoyloxyphenyl)piperidine (Preparation 4, 97 mg, 0.25 mmol) and *N,N,N',N'*-tetramethylethylenediamine (45 μ L, 0.30 mmol) in tetrahydrofuran (2 mL) at -78°C was added *s*-butyllithium (0.46 mL of 1.3 M in cyclohexane, 0.60 mmol) and the reaction mixture was allowed
25 to warm to room temperature overnight. The reaction mixture was diluted with water (25 mL) and extracted with dichloromethane (3 x 20 mL). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give the crude product, which was

purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (10:989:1 to 30:969:1), to give the title compound as a pale yellow oil (26 mg).

NMR (C_6D_6 , selected data from the free base): 0.68 (t, 3H), 0.84-0.89 (m, 6H), 0.95 (d, 3H), 1.12 (s, 3H), 1.18-1.31 (m, 8H), 1.42 (m, 2H), 1.65-1.74 (m, 2H), 2.01-2.41 (m, 6H), 2.63 (m, 1H), 2.97 (m, 1H), 6.64 (dd, 1H), 7.04 (m, 1H) and 7.36 (d, 1H).

MS (APCI⁺): M/Z [MH⁺] 374.3; $C_{24}H_{39}NO_2$ + H requires 374.3.

10 **Example 6: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(4-allyl-3-hydroxy-phenyl)piperidine**

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-allyl-3-*N*',*N*'-diethylcarbamoyloxyphenyl)piperidine (Example 50, 0.107 g, 0.25 mmol) in tetrahydrofuran (2 mL) at 0°C was added lithium aluminium hydride (0.5 mL of 1.0 M in tetrahydrofuran, 0.5 mmol) and the reaction mixture was allowed to warm to room temperature. After 4 hours, the reaction mixture was diluted sequentially with water (20 μ L), 15% aqueous sodium hydroxide (20 μ L) and water (60 μ L), and then allowed to stir for 1 hour. The reaction mixture was filtered through Celite® with the aid of tetrahydrofuran and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (10:989:1 to 30:969:1), to give the title compound as a pale yellow oil (56 mg).

25 NMR (C_6D_6 , selected data from the free base): 0.85 (t, 3H), 0.90 (d, 3H), 1.23 (s, 3H), 1.23-1.27 (m, 6H), 1.47-1.50 (m, 3H), 1.82 (m, 1H), 2.15-2.51 (m, 6H), 2.80 (m, 1H), 3.38 (d, 2H), 5.00 (m, 2H), 5.98 (m, 1H), 6.71-6.73 (m, 2H) and 7.03 (d, 1H).

MS (APCI⁺): M/Z [MH⁺] 330.3; C₂₂H₃₅NO + H requires 330.3.

Example 7: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-methyl-phenyl)piperidine

5 To a stirred solution of (±)-N-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamoyloxy-4-methylphenyl)piperidine (Example 51, 45 mg, 0.11 mmol) in tetrahydrofuran (2 mL) at 0°C was added lithium aluminium hydride (0.22 mL of 1.0 M in tetrahydrofuran, 0.22 mmol) and the reaction mixture was allowed to warm to room temperature. After
10 4 hours, the reaction mixture was diluted sequentially with water (8 µL), 15% aqueous sodium hydroxide (8 µL) and water (24 µL) and allowed to stir for 0.5 hours. The reaction mixture was filtered through Celite® with the aid of tetrahydrofuran and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a
15 gradient of methanol-dichloromethane-0.880 ammonia (10:989:1 to 30:969:1), to give the title compound as a pale yellow oil (20 mg).

NMR (C₆D₆, selected data from the free base): 0.85 (t, 3H), 0.93 (d, 3H), 1.23-1.29 (m, 6H), 1.24 (s, 3H), 1.46-1.50 (m, 3H), 1.83 (m, 1H), 2.16-2.53 (m, 6H), 2.18 (s, 3H), 2.80 (m, 1H), 6.61 (d, 1H), 6.68 (dd, 1H)
20 and 6.98 (d, 1H).

MS (APCI⁺): M/Z [MH⁺] 304.3; C₂H₃₃NO + H requires 304.3.

Example 8: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(4-acetylamino-3-hydroxyphenyl)piperidine

25 To a stirred solution of (±)-N-hexyl-*trans*-3,4-dimethyl-4-(4-amino-3-hydroxyphenyl)piperidine (Example 4, 0.100 g, 0.33 mmol) and pyridine (53 µL, 0.66 mmol) in tetrahydrofuran (3 mL) was added acetic anhydride (34 µL, 0.36 mmol). After 12 h, additional pyridine (27 µL, 0.33 mmol)

and acetic anhydride (34 μ L, 0.36 mmol) were introduced. After an additional 12 h, the reaction mixture was diluted with aqueous saturated sodium hydrogencarbonate (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined extracts were washed with brine (20 mL),
5 dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give the crude product which was dissolved in methanol and allowed to stir for 48 h. The reaction mixture was concentrated *in vacuo* and purified *via* silica gel chromatography, eluting with methanol-dichloromethane-0.880 ammonia (2:97.8 0.2), to give the title compound as a yellow oil (42 mg).

10 NMR (C_6D_6 , selected data from the free base): 0.86 (t, 3H), 0.93 (d, 3H), 1.19 (s, 3H), 1.21-1.34 (m, 6H), 1.40-1.51 (m, 3H), 1.53 (s, 3H), 1.82 (m, 1H), 2.12-2.47 (m, 6H), 2.71 (m, 1H), 6.72 (dd, 1H), 7.13 (d, 1H), 7.28 (d, 1H), 7.73 (s, 1H).

MS (APCI⁺): M/Z [MH^+] 347.3; $\text{C}_{21}\text{H}_{34}\text{N}_2\text{O}_2 + \text{H}$ requires 347.3.

15

Example 9: ($\pm$)-N-Hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-hydroxy-methylphenyl)piperidine

To a stirred solution of ($\pm$)-N-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamoyloxy-4-formylphenyl)piperidine (Example 55, 60 mg,
20 0.14 mmol) in tetrahydrofuran (2 mL) at 0°C was added lithium aluminium hydride (0.36 mL of 1.0 M in tetrahydrofuran, 0.36 mmol) and the reaction mixture was allowed to warm to room temperature. After 14 hours, the reaction mixture was diluted sequentially with water (20 μ L), 15% aqueous sodium hydroxide (20 μ L) and water (60 μ L) and
25 allowed to stir for 0.5 hours. The reaction mixture was filtered through Celite® with the aid of tetrahydrofuran and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography,

eluting with methanol-dichloromethane-0.880 ammonia (20:479:1), to give the title compound as a pale yellow oil (37 mg).

NMR (C_6D_6 , selected data from the free base): 0.84-0.89 (m, 6H), 1.20 (s, 3H), 1.23-1.31 (m, 6H), 1.38-1.44 (m, 3H), 1.80 (m, 1H), 2.10-2.43 (m, 6H), 2.65 (m, 1H), 3.29 (m, 1H), 4.47 (s, 2H), 6.69 (dd, 1H), 6.77 (d, 1H) and 6.99 (d, 1H).

MS (APCI⁺): M/Z [MH⁺] 320.2; $C_{21}H_{33}NO_2 + H$ requires 320.3.

Example 10: ($\pm$)-N-Hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-trifluoromethanesulfonylaminophenyl)piperidine

To a stirred solution of ($\pm$)-N-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-aminophenyl)piperidine (Example 4, 0.163 g, 0.54 mmol) and triethylamine (82 μ L, 0.59 mmol) in dichloromethane (5 mL) at 0°C was added trifluoromethanesulfonic anhydride (95 μ L, 0.56 mmol). After 2 hours, the reaction mixture was diluted with aqueous saturated sodium hydrogencarbonate (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (10:489:1 to 25:474:1), to give the title compound as a brown solid (53 mg).

NMR (CD_3OD , selected data from the free base): 0.77 (d, 3H), 0.93 (t, 3H), 1.20 (s, 3H), 1.20-1.61 (m, 9H), 1.93 (m, 1H), 2.20 (m, 1H), 2.49-2.94 (m, 6H), 6.60 (dd, 1H), 6.87 (d, 1H) and 7.51 (d, 1H).

MS (APCI⁺): M/Z [MH⁺] 437.2; $C_{20}H_{31}F_3N_2O_3S + H$ requires 437.2.

Example 11: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(4-ethyl-3-hydroxy-phenyl)piperidine

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamoyloxy-4-ethylphenyl)piperidine (Example 52, 94 mg, 0.23 mmol) in tetrahydrofuran (2.5 mL) at 0°C was added lithium aluminium hydride (0.57 mL of 1.0 M in tetrahydrofuran, 0.57 mmol) and the reaction mixture was allowed to warm to room temperature. After 14 hours, the reaction mixture was diluted sequentially with water (8 μ L), 15% aqueous sodium hydroxide (8 μ L) and water (24 μ L) and allowed to stir for 0.5 hours. The reaction mixture was filtered through Celite® with the aid of tetrahydrofuran and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (10:989:1 to 50:949:1), to give the title compound as a pale yellow oil (43 mg).

NMR (C_6D_6 , selected data from the free base): 0.85 (t, 3H), 0.92 (d, 3H), 1.18-1.25 (m, 12H), 1.46-1.51 (m, 3H), 1.84 (m, 1H), 2.16-2.53 (m, 6H), 2.66 (m, 2H), 2.82 (m, 1H), 6.61 (d, 1H), 6.73 (dd, 1H) and 7.03 (d, 1H).

MS (APCI⁺): M/Z [MH⁺] 318.3; $C_{21}H_{35}NO + H$ requires 318.3.

Example 12: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-[4-(2,2-dimethylpropanoylamino)-3-hydroxyphenyl]piperidine

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-amino-3-hydroxyphenyl)piperidine (Example 4, 0.129 g, 0.42 mmol) and triethylamine (65 μ L, 0.47 mmol) in dichloromethane (5 mL) at 0°C was added trimethylacetyl chloride (55 μ L, 0.45 mmol) in three equivalent portions. Additional trimethylacetyl chloride was introduced after 1 hour (18 μ L, 0.15 mmol) and 2.5 hour (8 μ L, 0.065 mmol). After an

additional 1 hour, the reaction mixture was diluted with aqueous saturated sodium hydrogencarbonate (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (10:489:1 to 15:484:1), to give the title compound as a pale yellow oil (77 mg, 47%). NMR (CD₃OD, selected data from the free base): 0.77 (d, 3H), 0.88 (t, 3H), 1.23-1.38 (m, 9H), 1.28 (s, 9H), 1.42-1.61 (m, 3H), 1.97 (m, 1H), 2.20-2.62 (m, 6H), 2.78 (m, 1H), 6.73 (m, 1H), 6.81 (m, 1H) and 7.69 (m, 1H).

MS (APCI⁺): M/Z [MH⁺] 389.3; C₂₄H₄₀N₂O₂ + H requires 389.3.

Example 13: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-methyl-aminomethylphenyl)piperidine

To a stirred solution of (±)-N-hexyl-*trans*-3,4-dimethyl-4-(4-formyl-3-hydroxyphenyl)piperidine (Example 34, 0.113 g, 0.36 mmol), methylamine (0.195 mL of 2.0 M in methanol, 0.39 mmol) and acetic acid (22.7 µL, 0.39 mmol) in 1,2-dichloroethane (2.5 mL) was added sodium triacetoxyborohydride (0.113 g, 0.53 mmol). After 2.5 hours, the reaction mixture was diluted with aqueous saturated sodium hydrogencarbonate (25 mL) and extracted with dichloromethane (3 x 25 mL). The combined extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (5:494:1 to 5:444:1), to give the title compound as a yellow oil (45 mg).

NMR (C_6D_6 , selected data from the free base): 0.85 (t, 3H), 1.00 (d, 3H), 1.03-1.31 (m, 6H), 1.26 (s, 3H), 1.40-1.45 (m, 3H), 1.72 (s, 3H), 1.77 (m, 1H), 2.09-2.46 (m, 6H), 2.67 (m, 1H), 3.32 (s, 2H), 6.73 (dd, 1H), 6.80 (d, 1H) and 7.12 (d, 1H).

5 MS (APCI⁺): M/Z [MH⁺] 333.3; $C_{21}H_{36}N_2O + H$ requires 333.3.

Example 14: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(4-ethylaminomethyl-3-hydroxyphenyl)piperidine

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-formyl-3-hydroxyphenyl)piperidine (Example 34, 0.139 g, 0.44 mmol), ethylamine
10 (0.241 mL of 2.0 M in methanol, 0.48 mmol) and acetic acid (28 μ L, 0.48 mmol) in 1,2-dichloroethane (3 mL) was added sodium triacetoxyborohydride (0.139 g, 0.66 mmol). After 2.5 hours, the reaction mixture was diluted with aqueous saturated sodium hydrogen-
15 carbonate (25 mL) and extracted with dichloromethane (3 x 25 mL). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (5:494:1 to 5:444:1), to give
20 the title compound as a yellow oil (64 mg).

NMR (C_6D_6 , selected data from the free base): 0.59 (t, 3H), 0.84 (t, 3H), 1.00 (d, 3H), 1.16-1.31 (m, 6H), 1.27 (s, 3H), 1.38-1.45 (m, 3H), 1.86 (m, 1H), 2.04 (q, 2H), 2.10-2.46 (m, 6H), 2.68 (m, 1H), 3.41 (s, 2H), 6.74 (dd, 1H), 6.82 (d, 1H) and 7.12 (d, 1H).

25 MS (APCI⁺): M/Z [MH⁺] 347.3; $C_{22}H_{38}N_2O + H$ requires 347.3.

Example 15: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(4-dimethylamino-methyl-3-hydroxyphenyl)piperidine

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-formyl-3-hydroxyphenyl)piperidine (Example 34, 0.101 g, 0.32 mmol),
5 dimethylamine (0.175 mL of 2.0 M in methanol, 0.35 mmol) and acetic acid (20 μ L, 0.35 mmol) in 1,2-dichloroethane (3 mL) was added sodium triacetoxyborohydride (0.101 g, 0.48 mmol). After 2.5 hours, the reaction mixture was diluted with aqueous saturated sodium hydrogen-carbonate (25 mL) and extracted with dichloromethane (3 x 25 mL). The
10 combined extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (5:494:1 to 25:474:1), to give the title compound as a yellow oil (54 mg).

15 NMR (C₆D₆, selected data from the free base): 0.85 (t, 3H), 1.00 (d, 3H), 1.23-1.29 (m, 6H), 1.26 (s, 3H), 1.38-1.44 (m, 3H), 1.71 (s, 6H), 1.86 (m, 1H), 2.12-2.43 (m, 6H), 2.66 (m, 1H), 3.15 (s, 2H), 6.74 (dd, 1H), 6.79 (d, 1H) and 7.15 (d, 1H).

MS (APCI⁺): M/Z [MH⁺] 347.3; C₂₂H₃₈N₂O + H requires 347.3.

20

Example 16: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-2-methyl-phenyl)piperidine

A mixture of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-2-methyl-4-trimethylsilylphenyl)piperidine (Preparation 2, 51 mg, 0.11 mmol) and
25 20% aqueous hydrochloric acid (2.5 mL) was allowed to stir at room temperature for 1 hour. The reaction mixture was diluted with water (10 mL) adjusted to pH 9 with 5*N* sodium hydroxide and extracted with dichloromethane (3 x 20 mL). The combined extracts were concentrated

in vacuo to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (5:494:1 to 15:484:1), to give the title compound as a yellow oil (27 mg).

5 NMR (C_6D_6 , selected data from the free base): 0.85 (t, 3H), 0.92 (d, 3H), 1.21 (s, 3H), 1.21-1.29 (m, 6H), 1.37-1.44 (m, 3H), 1.83 (m, 1H), 2.09-2.45 (m, 6H), 2.66 (m, 1H), 3.33 (s, 3H), 6.59 (dd, 1H), 6.82 (d, 1H), 6.95 (s, 1H) and 7.10-7.14 (m, 1H).

MS (APCI⁺): M/Z [MH⁺] 304.4; $C_{20}H_{33}NO$ + H requires 304.3.

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Example 17: ($\pm$)-N-Hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-methoxy-carbonylphenyl)piperidine

To a stirred solution of ($\pm$)-N-hexyl-*trans*-3,4-dimethyl-4-(4-formyl-3-hydroxyphenyl)piperidine (Example 34, 93 mg, 0.29 mmol) and acetic acid (10 μ L, 0.18 mmol) in methanol (10 mL) was added sodium cyanide
15 (26 mg, 0.53 mmol) and manganese(IV) oxide (0.291 g, 3.51 mmol). After 36 hours, the reaction mixture was filtered through Celite[®] with the aid of methanol and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient
20 of methanol-dichloromethane-0.880 ammonia (5:494:1 to 15:484:1), to give the title compound as a yellow oil (42 mg).

NMR (C_6D_6 , selected data from the free base): 0.84-0.88 (m, 6H), 1.09 (s, 3H), 1.21-1.31 (m, 6H), 1.37-1.42 (m, 3H), 1.70 (m, 1H), 1.99-2.39 (m, 6H), 2.60 (m, 1H), 3.28 (s, 3H), 6.63 (dd, 1H), 7.03 (d, 1H) and
25 7.72 (d, 1H).

MS (APCI⁺): M/Z [MH⁺] 348.3; $C_{22}H_{33}NO_3$ + H requires 348.3.

Example 18: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(4-ethoxycarbonyl-3-hydroxyphenyl)piperidine

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-formyl-3-hydroxyphenyl)piperidine (Example 34, 93 mg, 0.29 mmol) and acetic acid (10 μ L, 0.18 mmol) in ethanol (10 mL) was added sodium cyanide (26 mg, 0.53 mmol) and manganese(IV) oxide (0.291 g, 3.51 mmol). After 36 hours, the reaction mixture was filtered through Celite® with the aid of methanol and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (5:494:1 to 15:484:1), to give the title compound as a yellow oil (48 mg).

NMR (C_6D_6 , selected data from the free base): 0.84-0.89 (m, 9H), 1.10 (s, 3H), 1.22-1.31 (m, 6H), 1.37-1.44 (m, 3H), 1.70 (m, 1H), 1.99-2.39 (m, 6H), 2.60 (m, 1H), 3.92 (q, 2H), 6.65 (dd, 1H), 7.04 (d, 1H) and 7.77 (d, 1H).

MS (APCI⁺): M/Z [MH^+] 362.3; $C_{22}H_{35}NO_3 + H$ requires 362.3.

Example 19: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(4-*N'*-methylamino-carbonyl-3-hydroxyphenyl)piperidine

A stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethyl-carbamoyloxy-4-*N''*-methylaminocarbonylphenyl)piperidine (Example 53, 0.163 g, 0.37 mmol) in methanol (2.5 mL) was treated with methylamine (5.5 mL of 2.0 M in methanol, 11 mmol). After 24 hours, the reaction mixture was concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (5:494:1 to 15:484:1), to give the title compound as a pale yellow oil (28 mg).

NMR (C_6D_6 , selected data from the free base): 0.86 (t, 3H), 0.91 (d, 3H), 1.15 (s, 3H), 1.25-1.32 (m, 6H), 1.39-1.44 (m, 3H), 1.76 (m, 1H), 2.04-2.40 (m, 9H), 2.64 (m, 1H), 5.31 (br s, 1H), 6.61 (dd, 1H), 6.69 (d, 1H) and 7.07 (d, 1H).

5 MS (APCI⁺): M/Z [MH⁺] 347.3; $C_{21}H_{34}N_2O_2$ + H requires 347.3.

Example 20: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(4-*N'*,*N'*-dimethyl-aminocarbonyl-3-hydroxyphenyl)piperidine

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-
 10 dimethylcarbamoyloxyphenyl)piperidine (Preparation 5, 0.285 g, 0.71 mmol) and *N,N,N',N'*-tetramethylethylenediamine (0.118 mL, 0.78 mmol) in tetrahydrofuran (5 mL) at -78°C was added *s*-butyllithium (0.6 mL of 1.3 M in cyclohexane, 0.78 mmol) and the reaction mixture was allowed to warm to room temperature overnight. The reaction
 15 mixture was diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (10:989:1 to
 20 30:969:1), to give the title compound as a yellow oil (65 mg).

NMR (C_6D_6 , selected data from the free base): 0.86 (t, 3H), 0.92 (d, 3H), 1.17 (s, 3H), 1.21-1.34 (m, 7H), 1.42 (m, 2H), 1.78 (m, 1H), 2.05-2.33 (m, 6H), 2.43 (s, 6H), 2.64 (m, 1H), 6.61 (dd, 1H), 6.96 (m, 1H) and 7.13 (m, 1H).

25 MS (APCI⁺): M/Z [MH⁺] 361.3; $C_{24}H_{36}N_2O_2$ + H requires 361.3.

Example 21: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(4-*N'*,*N'*-diethylamino-carbonyl-3-hydroxyphenyl)piperidine

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamyloxyphenyl)piperidine (Preparation 4, 0.109 g, 0.28 mmol) and *N,N,N',N'*-tetramethylethylenediamine (47 μ L, 0.31 mmol) in tetrahydrofuran (5 mL) at -78°C was added *s*-butyllithium (0.238 mL of 1.3 M in cyclohexane, 0.31 mmol) and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). The combined extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (10:989:1 to 30:969:1), to give the title compound as a yellow oil (38 mg).

NMR (C₆D₆, selected data from the free base): 0.80 (t, 6H), 0.86 (t, 3H), 0.93 (d, 3H), 1.18 (s, 3H), 1.24-1.34 (m, 7H), 1.41 (m, 2H), 1.77 (m, 1H), 2.05-2.43 (m, 6H), 2.65 (m, 1H), 3.00 (q, 4H), 6.62 (dd, 1H), 7.06 (d, 1H) and 7.16 (d, 1H).

MS (APCI⁺): M/Z [MH⁺] 389.3; C₂₄H₄₀N₂O₂ + H requires 389.3.

Example 22: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-propionylaminophenyl)piperidine

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-aminophenyl)piperidine (Example 4, 0.185 g, 0.61 mmol) and pyridine (0.108 mL, 1.28 mmol) in tetrahydrofuran (8 mL) at 0°C was added propionyl chloride (0.109 mL, 1.25 mmol) and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was then cooled again to 0°C and additional pyridine (54 μ L, 0.64 mmol)

and propionyl chloride (25 μ L, 0.31 mmol) were introduced. After an additional 4 hours, the reaction mixture was diluted with aqueous saturated sodium hydrogencarbonate (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined extracts were washed with brine (20 mL),
5 dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (10:989:1 to 30:967:3), to give the title compound as a pale yellow oil (38 mg).

NMR (C₆D₆, selected data from the free base): 0.84-0.90 (m, 6H), 0.93
10 (d, 3H), 1.22 (s, 3H), 1.22-1.29 (m, 6H), 1.39-1.46 (m, 3H), 1.75 (q, 2H), 1.81 (m, 1H), 2.11-2.47 (m, 6H), 2.69 (m, 1H), 6.72 (dd, 1H), 7.12-7.17 (m, 2H) and 7.38 (m, 1H).

MS (APCI⁺): M/Z [MH⁺] 361.4; C₂₂H₃₆N₂O₂ + H requires 361.3.

15 **Example 23: ($\pm$)-N-Hexyl-*trans*-3,4-dimethyl-4-(4-*N'*,*N'*-dimethyl-aminocarbonylamino-3-hydroxyphenyl)piperidine**

To a stirred solution of ($\pm$)-N-hexyl-*trans*-3,4-dimethyl-4-(4-amino-3-hydroxyphenyl)piperidine (Example 4, 0.189 g, 0.62 mmol) in pyridine (5 mL) at 0°C was added dimethylcarbamyl chloride (0.12 mL, 1.3 mmol)
20 and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was diluted with aqueous saturated sodium hydrogencarbonate (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude
25 product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (10:989:1 to 40:969:1), to give the title compound as a pale yellow oil (52 mg).

NMR (C_6D_6 , selected data from the free base): 0.85 (t, 3H), 0.97 (d, 3H), 1.22 (s, 3H), 1.22-1.25 (m, 6H), 1.38-1.41 (m, 3H), 1.80 (m, 1H), 2.11-2.43 (m, 6H), 2.48 (s, 3H), 2.54 (s, 3H), 2.65 (m, 1H), 3.18 (s, 1H), 6.46 (m, 1H), 6.86 (m, 1H) and 7.15 (m, 1H).

5 MS (APCI⁺): M/Z [MH⁺] 376.3; $C_{22}H_{37}N_3O_2$ + H requires 376.3.

Example 24: ($\pm$)-N-Hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-*N'*-methylaminocarbonylaminophenyl)piperidine

To a stirred solution of ($\pm$)-N-hexyl-*trans*-3,4-dimethyl-4-(4-amino-3-
10 hydroxyphenyl)piperidine (Example 4, 0.283 g, 0.93 mmol) and pyridine (0.23 mL, 2.9 mmol) in tetrahydrofuran (8 mL) at 0°C was added methyl isocyanate (58 μ L, 0.98 mmol) and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was diluted with aqueous saturated sodium hydrogencarbonate (10 mL) and extracted
15 with dichloromethane (3 x 10 mL). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of ethyl acetate-dichloromethane (10:90 to 60:40), to give the title compound as a pale yellow oil (28 mg).

20 NMR (C_6D_6 , selected data from the free base): 0.87 (t, 3H), 0.93 (d, 3H), 1.24 (s, 3H), 1.24-1.31 (m, 6H), 1.42-1.51 (m, 3H), 1.87 (m, 1H), 2.24-2.51 (m, 6H), 2.46 (s, 3H), 2.74 (m, 1H), 5.69 (br s, 1H), 6.70 (m, 1H), 7.10-7.12 (m, 1H), 7.32 (m, 1H) and 7.74 (br s, 1H).

MS (APCI⁺): M/Z [MH⁺] 362.3; $C_{21}H_{35}N_3O_2$ + H requires 362.3.

Example 25: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-methoxy-carbonylaminophenyl)piperidine

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-amino-3-hydroxyphenyl)piperidine (Example 4, 0.183 g, 0.60 mmol) in tetrahydrofuran (10 mL) was added methyl chloroformate (50 μ L, 0.66 mmol). After 6 hours, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of ethyl acetate-dichloromethane-0.880 ammonia (150:349:1 to 200:299:1), to give the title compound as a pale yellow oil (44 mg).

NMR (C₆D₆, selected data from the free base): 0.83-0.86 (m, 6H), 1.17 (s, 3H), 1.21-1.34 (m, 6H), 1.37-1.45 (m, 3H), 1.74 (m, 1H), 2.08-2.43 (m, 6H), 2.70 (m, 1H), 3.25 (s, 3H), 6.66 (m, 1H), 6.77 (br s, 1H), 6.93 (s, 1H) and 7.45 (m, 1H).

MS (APCI⁺): M/Z [MH⁺] 363.4; C₂₁H₃₄N₂O₃ + H requires 363.3.

Example 26: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(4-formylamino-3-aminophenyl)piperidine

To a stirred solution of formic acid (26 μ L, 0.69 mmol) and acetyl chloride (49 μ L, 0.69 mmol) in tetrahydrofuran (5 mL) at 0°C was added pyridine (55 μ L, 0.69 mmol). After 0.5 hours, a solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(4-amino-3-hydroxyphenyl)piperidine (Example 4, 0.200 g, 0.66 mmol) and pyridine (55 μ L, 0.69 mmol) in tetrahydrofuran (5 mL) was added to the reaction vessel. After a further 4 hours, the reaction mixture was diluted with aqueous saturated sodium hydrogen-carbonate (20 mL) and extracted with dichloromethane (3 x 20 mL). The

combined extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with ethyl acetate-dichloromethane-0.880 ammonia (150:349:12), to give the title compound
5 as a pale yellow oil (22 mg).

NMR (C₆D₆, selected data from the free base): 0.82-0.88 (m, 6H), 1.16 (s, 3H), 1.21-1.33 (m, 6H), 1.36-1.42 (m, 3H), 1.76 (m, 1H), 2.10-2.45 (m, 6H), 2.68 (m, 1H), 6.65 (m, 1H), 7.06-7.10 (m, 1H), 7.21 (m, 1H), 7.55 (s, 1H) and 8.46 (br s, 1H).

10 MS (APCI⁺): M/Z [MH⁺] 333.4; C₂₀H₃₂N₂O₂ + H requires 333.3.

Example 27: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(4-*N'*,*N'*-dimethyl-aminosulfonylamino-3-hydroxyphenyl)piperidine

To a stirred solution of (±)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-aminophenyl)piperidine (Example 4, 0.194 g, 0.64 mmol) and pyridine
15 (0.108 mL, 1.34 mmol) in tetrahydrofuran (10 mL) was added dimethylsulfonyl chloride (0.144 mL, 1.34 mmol). The reaction was then heated to reflux overnight. Upon cooling, the reaction mixture was diluted with aqueous saturated sodium hydrogencarbonate (20 mL) and
20 extracted with dichloromethane (3 x 20 mL). The combined extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of ethyl acetate-dichloromethane-0.880 ammonia (150:349:1 to 200:299:1), to give the title compound as a
25 pale yellow oil (77 mg).

NMR (C₆D₆, selected data from the free base): 0.81 (d, 3H), 0.87 (t, 3H), 1.18 (s, 3H), 1.23-1.27 (m, 6H), 1.38-1.49 (m, 3H), 1.80 (m, 1H), 2.18-

2.44 (m, 6H), 2.51 (s, 6H), 2.83 (m, 1H), 6.62 (m, 1H), 6.97 (s, 1H), 7.56 (d, 1H) and 7.82 (br s, 1H).

MS (APCI⁺): M/Z [MH⁺] 412.2; C₂₁H₃₇N₃O₃S + H requires 412.3.

5 **Example 28: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-pentanoylamino-phenyl)piperidine**

To a stirred solution of (±)-N-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-aminophenyl)piperidine (Example 4, 0.155 g, 0.51 mmol) and pyridine (43 µL, 0.53 mmol) in tetrahydrofuran (5 mL) at 0°C was added valeryl chloride (63 µL, 0.53 mmol). After 2 hours, the reaction mixture was
10 diluted with aqueous saturated sodium hydrogencarbonate (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel
15 chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (10:989:1 to 30:967:3), to give the title compound as a pale yellow oil (96 mg).

NMR (C₆D₆, selected data from the free base): 0.72 (t, 3H), 0.85 (t, 3H), 0.93 (d, 3H), 1.07-1.16 (m, 2H), 1.22 (s, 3H), 1.22-1.25 (m, 6H), 1.42-
20 1.50 (m, 5H), 1.83 (m, 1H), 1.90-1.94 (m, 2H), 2.14-2.48 (m, 6H), 2.71 (m, 1H), 6.73 (dd, 1H), 7.10-7.12 (m, 1H), 7.46 (d, 1H) and 7.98 (s, 1H).

MS (APCI⁺): M/Z [MH⁺] 389.3; C₂₄H₄₀N₂O₂ + H requires 389.3.

25 **Example 29: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(2,4-dichloro-3-hydroxyphenyl)piperidine**

To a solution of (±)-N-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine (Preparation 7, 662 mg, 2.28 mmol) in acetic acid (20 mL) was

added dropwise a solution of chlorine (324 mg, 4.56 mmol) in acetic acid (6 mL). The reaction was monitored by mass spectrometry for the formation of the title compound, as well as for the loss of starting material and monochlorinated product. The acetic acid was then removed *in vacuo* and the residue washed with saturated sodium hydrogencarbonate solution then extracted with dichloromethane. The solvent was removed *in vacuo* and the residue purified by preparative silica thin layer chromatography eluting with hexane-ethyl acetate (2:1) to give the title compound (150 mg) from the faster running band.

10 NMR (CDCl₃, selected data from the free base): 0.77 (d, 3H), 0.88 (t, 3H), 1.28 (s, 3H), 6.83 (d, 1H) and 7.20 (d, 1H).

MS (APCI⁺): M/Z [MH⁺] 358.4; C₁₉H₂₉Cl₂NO + H requires 358.2.

Example 30: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-[3-hydroxy-4-(2-methylpropionylamino)phenyl]piperidine

To a stirred solution of (±)-N-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-aminophenyl)piperidine (Example 4, 0.188 g, 0.62 mmol) and pyridine (52 µL, 0.65 mmol) in tetrahydrofuran (10 mL) at 0°C was added isobutyryl chloride (68 µL, 0.65 mmol). After 1.5 hours, the reaction mixture was diluted with aqueous saturated sodium hydrogencarbonate (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (10:989:1 to 30:967:3), to give the title compound as a pale yellow oil (0.112 g).

25 NMR (C₆D₆, selected data from the free base): 0.85 (t, 3H), 0.91 (d, 3H), 0.95 (d, 6H), 1.21 (s, 3H), 1.21-1.27 (m, 6H), 1.40-1.45 (m, 3H), 1.81

(m, 1H), 2.02 (m, 1H), 2.12-2.46 (m, 6H), 2.70 (m, 1H), 6.70 (dd, 1H), 7.09-7.10 (m, 1H), 7.43 (d, 1H) and 7.81 (s, 1H).

MS (APCI⁺): M/Z [MH⁺] 375.3; C₂₃H₃₈N₂O₂ + H requires 375.3.

5 **Example 31: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-[3-hydroxy-4-(2-methylbutanoyl)phenyl]piperidine**

To a stirred solution of (±)-N-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-aminophenyl)piperidine (Example 4, 0.183 g, 0.60 mmol) and pyridine (51 µL, 0.63 mmol) in tetrahydrofuran (5 mL) at 0°C was added
10 isovaleryl chloride (77 µL, 0.63 mmol). After 2.5 hours, the reaction mixture was diluted with aqueous saturated sodium hydrogencarbonate (10 mL) and extracted with dichloromethane (3 x 15 mL). The combined extracts were washed with aqueous saturated sodium hydrogencarbonate (10 mL) and brine (15 mL), dried over Na₂SO₄, filtered and concentrated
15 *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with methanol-dichloromethane-0.880 ammonia (10:489:1), to give the title compound as a pale yellow oil (0.100 g).

NMR (C₆D₆, selected data from the free base): 0.76 (d, 6H), 0.85 (t, 3H), 0.92 (d, 3H), 1.22 (s, 3H), 1.22-1.28 (m, 6H), 1.40-1.46 (m, 3H), 1.79-
20 1.83 (m, 3H), 2.02-2.09 (m, 1H), 2.13-2.47 (m, 6H), 2.70 (m, 1H), 6.72 (dd, 1H), 7.09-7.11 (m, 1H), 7.46 (d, 1H) and 7.94 (s, 1H).

MS (APCI⁺): M/Z [MH⁺] 389.4; C₂₄H₄₀N₂O₂ + H requires 389.3.

25 **Example 32: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-butanoyl-aminophenyl)piperidine**

To a stirred solution of (±)-N-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-aminophenyl)piperidine (Example 4, 0.188 g, 0.62 mmol) and pyridine (52 µL, 0.65 mmol) in tetrahydrofuran (10 mL) at 0°C was added butyryl

chloride (67 μ L, 0.65 mmol). After 2.5 hours, the reaction mixture was diluted with aqueous saturated sodium hydrogencarbonate (10 mL) and extracted with dichloromethane (3 x 15 mL). The combined extracts were washed with aqueous saturated sodium hydrogencarbonate (10 mL) and brine (15 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (10:489:1 to 15:484:1), to give the title compound as a pale yellow oil (0.104 g).

10 NMR (C₆D₆, selected data from the free base): 0.68 (t, 3H), 0.85 (t, 3H), 0.93 (d, 3H), 1.21 (s, 3H), 1.23-1.30 (m, 6H), 1.37-1.47 (m, 5H), 1.68-1.72 (m, 2H), 1.80 (m, 1H), 2.10-2.46 (m, 6H), 2.68 (m, 1H), 6.72 (dd, 1H), 7.04 (d, 1H) and 7.09-7.20 (m, 2H).

MS (APCI⁺): M/Z [MH⁺] 375.3; C₂₃H₃₈N₂O₂ + H requires 375.3.

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Example 33: ($\pm$)-N-Hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-methanesulfonylaminophenyl)piperidine

To a stirred solution of ($\pm$)-N-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-aminophenyl)piperidine (Example 4, 0.129 g, 0.42 mmol) and pyridine (38 μ L, 0.47 mmol) in dichloromethane (5 mL) at 0°C was added methanesulfonyl chloride (34 μ L, 0.45 mmol). Additional methanesulfonyl chloride was introduced at 0.5 hours (12 μ L, 0.16 mmol), 1 hour (12 μ L, 0.16 mmol), 3 hours (10 μ L, 0.13 mmol) and 4 hours (6 μ L, 8 μ mol) and the reaction was allowed to warm to room temperature while stirring overnight. The reaction mixture was diluted with aqueous saturated sodium hydrogencarbonate (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to

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give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (10:489:1 to 15:484:1), to give the title compound as a brown solid (11 mg).

5 NMR (C_6D_6 , selected data from the free base): 0.82 (d, 3H), 0.87 (t, 3H), 1.23 (s, 3H), 1.26-1.28 (m, 6H), 1.44-1.49 (m, 3H), 1.78 (m, 1H), 2.15-2.52 (m, 6H), 2.44 (s, 3H), 2.81 (m, 1H), 6.38 (br s, 2H), 6.63 (m, 1H), 6.98 (m, 1H) and 7.39 (m, 1H).

MS (APCI⁺): M/Z [MH⁺] 383.2; $C_{20}H_{34}N_2O_3S$ + H requires 383.2.

10

Example 34: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(4-formyl-3-hydroxy-phenyl)piperidine

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamoyloxyphenyl)piperidine (Preparation 4, 0.495 g, 1.27 mmol) and *N,N,N',N'*-tetramethylethylenediamine (0.231 mL, 1.53 mmol) in tetrahydrofuran (5 mL) at -78°C was added *s*-butyllithium (1.18 mL of 1.3 M in cyclohexane, 1.53 mmol). After 1 hour, DMF (0.493 mL, 6.37 mmol) was added and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was diluted with aqueous saturated sodium hydrogencarbonate (25 mL) and extracted with dichloromethane (3 x 30 mL). The combined extracts were washed with brine (15 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (2:197:1 to 4:195:1), to give the title compound as a pale yellow oil (0.308 g).

20

NMR (C_6D_6 , selected data from the free base): 0.79 (d, 3H), 0.86 (t, 3H), 1.04 (s, 3H), 1.16-1.33 (m, 6H), 1.38-1.42 (m, 3H), 1.66 (m, 1H), 1.99-

25

2.39 (m, 6H), 2.59 (m, 1H), 6.57 (dd, 1H), 6.78 (d, 1H), 6.88 (d, 1H) and 9.25 (s, 1H).

MS (APCI⁺): M/Z [MH⁺] 318.2; C₂₀H₃₁NO₂ + H requires 318.2.

5 **Example 35: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-2,4,6-trichlorophenyl)piperidine**

To a solution of (±)-N-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine (Preparation 7, 100 mg, 0.345 mmol) in acetic acid (2 mL) was added dropwise a solution of chlorine (98 mg, 1.38 mmol) in acetic acid
10 (1 mL). The reaction was monitored by mass spectrometry for the formation of the title compound. The acetic acid was then removed *in vacuo* and the residue washed with saturated sodium hydrogencarbonate solution, which solution was then extracted with dichloromethane. The dichloromethane was removed *in vacuo* and the residue was
15 chromatographed on Merck 230-400 mesh silica gel, eluting with ethyl acetate-hexane (1:25), to give the title compound (18 mg).

NMR (CDCl₃, selected data from the free base): 0.80 (d, 3H), 0.88 (t, 3H), 1.29 (s, 3H) and 7.15 (s, 1H).

MS (APCI⁺): M/Z [MH⁺] 392.1; C₁₉H₂₈Cl₃NO + H requires 392.1.

20

Example 36: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(3-aminosulfonyl-3-hydroxyphenyl)piperidine

A solution of (±)-N-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamyl-oxyphenyl)piperidine (Preparation 4, 200 mg, 0.51 mmol) in
25 chlorosulfonic acid (0.5 mL) was cooled to 0°C before thionyl chloride (0.2 mL) was added and the reaction mixture stirred at room temperature overnight. To the reaction mixture was added a mixture of ice and water (50:50, 10 mL), and the resulting cream precipitate was filtered off and

dried under vacuum. This crude intermediate (0.10 g, 0.20 mmol) was dissolved in methylamine (5 mL of 2 M in tetrahydrofuran, excess) and the reaction mixture was stirred overnight. The solvents were removed *in vacuo* and the residue was chromatographed on silica gel, eluting with
5 methanol and dichloromethane (5:95), to give the product as a white powder (25 mg).

NMR (DMSO, selected data from the free base) : 0.7 (d, 3H), 0.85 (t, 3H), 1.2-1.4 (m, 10H), 2.45 (s, 3H), 6.6 (s, 1H), 6.75 (d, 1H), 7.4 (d, 1H) and 10.5 (s, 1H).

10 MS (ES⁺): M/Z [MH⁺] 383.3; C₂₀H₃₄N₂O₃S + H requires 383.2.

Example 37: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(4,6-dichloro-3-hydroxyphenyl)piperidine

Isolation of the slowest running compound from Example 29 followed by
15 preparative silica thin layer chromatography, eluting with hexane-ethyl acetate (2:1), gave the title compound (56 mg).

NMR (CDCl₃, selected data from the free base): 0.75 (d, 3H), 0.91 (t, 3H), 1.32 (s, 3H), 6.95 (s, 1H) and 7.28 (s, 1H).

MS (APCI⁺): M/Z [MH⁺] 358.3; C₁₉H₂₉Cl₂NO + H requires 358.2.

20

Example 38: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-*N'*-isopropylaminocarbonylphenyl)piperidine

A solution of (±)-N-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-methoxy-carbonylphenyl)piperidine (Example 17, 20 mg, 0.055 mmol) in
25 isopropylamine (5 mL) was heated at 100°C overnight in a Wheaton vial. The solution was then cooled and evaporated to dryness *in vacuo* to yield the desired product (20 mg) as a colourless oil.

NMR (CDCl₃, selected data from the free base): 0.95 (d, 3H), 1.30 (d, 6H), 1.33 (s, 3H), 4.28 (m, 1H), 6.22 (br s, 1H), 6.75 (d, 1H), 6.85 (s, 1H) and 7.35 (d, 1H).

MS (CI⁺): M/Z [MH⁺] 375.3; C₂₃H₃₈N₂O₂ + H requires 375.6.

5

Example 39: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(4-chloro-3-hydroxy-phenyl)piperidine

Isolation of a slower running compound from Example 29 followed by preparative HPLC, eluting with 0.05 M aqueous ammonium acetate-methanol (3:7), gave the title compound (10 mg) as its acetate salt.

NMR (CDCl₃, selected data from the free base): 0.88 (d, 3H), 0.92 (t, 3H), 1.31 (s, 3H), 6.77 (d, 1H), 6.97 (s, 1H) and 7.23 (d, 1H).

MS (APCI⁺): M/Z [MH⁺] 324.0; C₁₉H₃₀ClNO + H requires 324.2.

15 **Example 40: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(6-chloro-3-hydroxy-phenyl)piperidine**

To a solution of (±)-N-hexyl-*trans*-3,4-dimethyl-4-(3-triisopropylsilyloxyphenyl)piperidine (Preparation 3, 151.8 mg, 0.340 mmol) in acetic acid (2 mL) was added dropwise a solution of chlorine (36 mg, 0.510 mmol) in acetic acid (0.5 mL). The reaction was monitored by mass spectrometry for the loss of starting material, the acetic acid was then removed *in vacuo* and the residue washed with saturated sodium hydrogencarbonate solution then extracted with dichloromethane. The dichloromethane was removed *in vacuo*, the residue dissolved in tetrahydrofuran (3 mL) and stirred overnight with tetrabutylammonium fluoride solution (0.66 mL of 1 M in tetrahydrofuran, 0.66 mmol). The reaction mixture was washed with saturated sodium hydrogencarbonate solution, the solvents removed *in vacuo*, and the solid mixture of

25

monochlorophenols purified by preparative HPLC on a Beckmann Ultrasphere™ column, 250 mm x 10 mm; Flow 20 mL min⁻¹; employing UV detection at 220 nm; eluant methanol-0.05 M aqueous ammonium acetate (30:70) to give the title compound (6 mg) as its acetate salt.

5 NMR (CDCl₃, selected data from the free base): 0.84 (d, 3H), 0.91 (t, 3H), 1.28 (s, 3H), 6.67 (d, 1H), 6.90 (s, 1H) and 7.13 (d, 1H).

MS (APCI⁺): M/Z [MH⁺] 323.9; C₁₉H₃₀ClNO + H requires 324.2.

Example 41: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(4-aminocarbonyl-3-hydroxyphenyl)piperidine

A solution of (±)-N-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-methoxycarbonylphenyl)piperidine (Example 17, 40 mg, 0.11 mmol) in ammoniacal 1,4-dioxan (4 mL of 0.5 M NH₃, 2.0 mmol). The solution was heated at 100°C overnight in a Wheaton vial. The solution was then cooled, evaporated to dryness *in vacuo* and the crude residue was chromatographed on Merck 230-400 mesh silica gel (10 g), using hexane-ethyl acetate (1:1) as eluant, to yield an oil (30 mg). This oil was dissolved in dichloromethane (5 mL) and extracted into 2N hydrochloric acid (5 mL). The aqueous phase was then evaporated to dryness *in vacuo* to yield the desired product (10 mg) as an oil.

NMR (CD₃OD, selected data from the free base): 0.85 (d, 3H), 1.33 (s, 3H), 6.82 (d, 1H), 6.85 (s, 1H) and 7.75 (d, 1H).

MS (CI⁺): M/Z [MH⁺] 333.5; C₂₀H₃₂N₂O₂ + H requires 333.5.

Example 42: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(4-fluoro-3-hydroxy-phenyl)piperidine

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylthiocarbamyloxy-4-fluorophenyl)piperidine (Example 54, 35 mg, 0.08 mmol) in tetrahydrofuran (2.5 mL) at 0°C was added lithium triethylborohydride (0.82 mL of 1.0 M in tetrahydrofuran, 0.82 mmol) and the reaction mixture was allowed to warm to room temperature. After 72, 96 and 120 hours, additional lithium triethylborohydride (1.6 mL of 1.0 M in tetrahydrofuran, 1.6 mmol) was introduced and stirring was continued at reflux. After an additional 24 hours, the reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined extracts were dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (10:989:1 to 50:949:1), to give the title compound as a pale yellow oil (13 mg).

NMR (C₆D₆, selected data from the free base): 0.83-0.86 (m, 6H), 1.10 (s, 3H), 1.18-1.24 (m, 6H), 1.42-1.46 (m, 3H), 1.70 (m, 1H), 2.07-2.44 (m, 6H), 2.67 (m, 1H), 6.44 (m, 1H), 6.80 (m, 1H) and 6.93 (m, 1H).

MS (APCI⁺): M/Z [MH⁺] 308.3; C₁₉H₃₀FNO + H requires 308.2.

Example 43: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(2-fluoro-3-hydroxy-phenyl)piperidine

To a solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine (Preparation 7, 100 mg, 0.26 mmol) in dichloromethane (5 mL) at room temperature was added 3,5-dichloro-1-fluoropyridinium triflate (481 mg, 1.54 mmol). The mixture was heated at reflux for 3 hours and then cooled to room temperature. The solution was poured onto water

(5 mL) and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 5 mL) and the combined organics were dried over MgSO_4 , filtered and concentrated *in vacuo* to give the crude product. This was chromatographed on Merck 230-400 mesh silica gel, eluting with hexane-ethyl acetate (4:1), to give the title compound (10 mg) as a colourless oil.

$^1\text{H-NMR}$ (CDCl_3) (selected data from free base): 0.90 (m, 3H), 0.96 (d, 3H), 1.20-1.36 (m, 7H), 1.38 (s, 3H), 1.40-1.50 (m, 2H), 2.10-2.53 (m, 7H), 2.70 (m, 1H), 6.54 (td, 1H), 6.67 (td, 1H) and 6.77 (td, 1H).

MS (TSI^+) : M/Z [MH^+] 308.0; $\text{C}_{19}\text{H}_{30}\text{FNO} + \text{H}$ requires 308.2.

Example 44: ($\pm$)-*N*-3-Cyclohexylpropyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-nitrophenyl)piperidine

To a stirred solution of ($\pm$)-*N*-(3-cyclohexylpropyl)-*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (Preparation 8, 0.997 g, 3.02 mmol) in acetonitrile (9 mL) and dichloromethane (1 mL) at 0°C was added nitronium tetrafluoroborate (0.341 g, 3.02 mmol) and the reaction mixture was allowed to warm to room temperature. After 2 hours, the reaction mixture was diluted with aqueous saturated sodium hydrogencarbonate (30 mL) and extracted with dichloromethane (3 x 30 mL). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with ethyl acetate-dichloromethane-0.880 ammonia (300:699:1), to give the title compound as a yellow oil (0.213 g).

NMR (C_6D_6 , selected data from the free base): 0.78 (d, 3H), 0.78-0.87 (m, 2H), 1.07-1.23 (m, 6H), 1.28 (s, 3H), 1.41-1.47 (m, 2H), 1.59-1.67

(m, 6H), 2.01 (m, 1H), 2.23-2.39 (m, 4H), 2.48-2.61 (m, 2H), 2.83 (m, 1H), 6.92 (dd, 1H), 7.01 (d, 1H) and 8.00 (d, 1H).

MS (APCI⁺): M/Z [MH⁺] 375.3; C₂₂H₃₄N₂O₃ + H requires 375.3.

5 **Example 45: (±)-N-(3-Cyclohexylpropyl)-*trans*-3,4-dimethyl-4-(4-amino-3-hydroxyphenyl)piperidine**

To a solution of (±)-N-(3-cyclohexylpropyl)-*trans*-3,4-dimethyl-4-(3-hydroxy-4-nitrophenyl)piperidine (Example 44, 0.213 g, 0.57 mmol) in tetrahydrofuran (4 mL) was added platinum(IV) oxide (2 mg, 0.57 mmol)
10 and the reaction mixture was shaken under 345 kPa of hydrogen gas for 14 hours. The reaction mixture was purged with nitrogen, filtered under nitrogen and the air-sensitive product was employed without further purification.

MS (APCI⁺): M/Z [MH⁺] 345.2; C₂₂H₃₆N₂O + H requires 345.3.

15

Example 46: (±)-N-(3-Cyclohexylpropyl)-*trans*-3,4-dimethyl-4-(3-hydroxy-4-acetylamino-phenyl)piperidine

To a stirred solution of (±)-N-(3-cyclohexylpropyl)-*trans*-3,4-dimethyl-4-(4-amino-3-hydroxyphenyl)piperidine (Example 45, 0.106 g, 0.30 mmol)
20 and pyridine (27 µL, 0.33 mmol) in tetrahydrofuran (7 mL) at 0°C was added acetyl chloride (45 µL, 0.63 mmol). After 1.5 hours, the reaction mixture was diluted with aqueous saturated sodium hydrogencarbonate (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered and
25 concentrated *in vacuo* to give a residue which was dissolved in methanol (10 mL) and allowed to stir for 18 hours. The reaction mixture was concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-

dichloromethane-0.880 ammonia (10:989:1 to 30:967:3), to give the title compound as a pale yellow oil (33 mg).

NMR (C_6D_6 , selected data from the free base): 0.82-0.88 (m, 2H), 0.94 (d, 3H), 1.10-1.22 (m, 6H), 1.22 (s, 3H), 1.39-1.49 (m, 3H), 1.42 (s, 3H), 1.58-1.69 (m, 5H), 1.82 (m, 1H), 2.15-2.48 (m, 6H), 2.71 (m, 1H), 6.72 (dd, 1H), 7.00 (d, 1H), 7.14 (d, 1H) and 7.16 (br s, 1H).

MS (APCI⁺): M/Z [MH⁺] 387.3; $C_{24}H_{38}N_2O_2$ + H requires 387.3.

Example 47: ($\pm$)-*N*-(3-Cyclohexylpropyl)-*trans*-3,4-dimethyl-4-(3-hydroxy-4-propionylaminophenyl)piperidine

To a stirred solution of ($\pm$)-*N*-(3-cyclohexylpropyl)-*trans*-3,4-dimethyl-4-(4-amino-3-hydroxyphenyl)piperidine (Example 45, 0.106 g, 0.30 mmol) and pyridine (27 μ L, 0.33 mmol) in tetrahydrofuran (7 mL) at 0°C was added propionyl chloride (28 μ L, 0.33 mmol). After 1.5 hours, the reaction mixture was diluted with aqueous saturated sodium hydrogen-carbonate (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give a residue which was dissolved in methanol (10 mL) and allowed to stir for 18 hours. The reaction mixture was concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (10:989:1 to 30:967:3), to give the title compound as a pale yellow oil (33 mg).

NMR (C_6D_6 , selected data from the free base): 0.82-0.88 (m, 2H), 0.84 (t, 3H), 0.94 (d, 3H), 1.07-1.21 (m, 6H), 1.21 (s, 3H), 1.39-1.51 (m, 3H), 1.58-1.69 (m, 7H), 1.81 (m, 1H), 2.12-2.48 (m, 6H), 2.70 (m, 1H), 6.71 (dd, 1H), 6.84 (s, 1H), 6.86 (d, 1H) and 7.15 (d, 1H).

MS (APCI⁺): M/Z [MH⁺] 401.4; $C_{25}H_{40}N_2O_2$ + H requires 401.3.

Example 48: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(4-*N'*,*N'*-dimethyl-amino-3-hydroxyphenyl)-piperidine

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-aminophenyl)piperidine (Example 4, 0.100 g, 0.33 mmol) and formic acid (41 μ L, 1.09 mmol) in chloroform (3 mL) was added formaldehyde (82 μ L of 37% aqueous w/w solution, 1.09 mmol) and the reaction mixture was heated to reflux. Additional formaldehyde (82 μ L of 37% aqueous w/w solution) and formic acid (41 μ L, 1.09 mmol) was introduced after 12 and 36 hours and the reaction was stirred at reflux for an additional 4 hours. Upon cooling, the reaction mixture was diluted with water (10 mL), adjusted to pH 11 with 5*N* sodium hydroxide and extracted with 3:1 *n*-butanol-toluene (3 x 10 mL). The combined extracts were dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with methanol-dichloromethane-0.880 ammonia (10:489:1), to give the title compound as a pale yellow oil (5 mg).

NMR (C₆D₆, selected data from the free base): 0.85 (t, 3H), 0.95 (d, 3H), 1.21 (s, 3H), 1.21-1.27 (m, 6H), 1.40-1.44 (m, 3H), 1.81 (m, 1H), 2.06-2.41 (m, 6H), 2.18 (s, 6H), 2.66 (m, 1H), 6.74 (m, 1H), 6.88 (m, 1H) and 7.13 (m, 1H).

MS (APCI⁺): M/Z [MH⁺] 333.4; C₂₁H₃₆N₂O + H requires 333.3.

Example 49: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-4-isopropenylphenyl)piperidine

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamoyloxyphenyl)piperidine (Preparation 4, 0.103 g, 0.27 mmol) and *N,N,N',N'*-tetramethylethylenediamine (48 μ L, 0.32 mmol) in tetrahydrofuran (1 mL) at -78°C was added *s*-butyllithium (0.25 mL of

1.3 M in cyclohexane, 0.32 mmol). After 1 hour, acetone (98 μ L, 1.33 mmol) was added and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was diluted with aqueous saturated sodium hydrogencarbonate (25 mL) and extracted with dichloromethane (3 x 30 mL). The combined extracts were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (2:197:1 to 4:195:1), to give the title compound as a pale yellow oil (64 mg).

NMR (C₆D₆, selected data from the free base): 0.85 (t, 3H), 0.94 (d, 3H), 1.19-1.28 (m, 6H), 1.21 (s, 3H), 1.38-1.46 (m, 3H), 1.81 (m, 1H), 1.89 (s, 3H), 2.10-2.46 (m, 6H), 2.69 (m, 1H), 5.01 (m, 2H), 6.73 (dd, 1H), 6.91 (d, 1H) and 7.04 (d, 1H).

MS (APCI⁺): M/Z [MH⁺] 330.3; C₂₂H₃₅NO + H requires 330.3.

Example 50: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(4-allyl-3-*N'*,*N'*-diethylcarbamoyloxyphenyl)piperidine

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamoyloxyphenyl)piperidine (Preparation 4, 0.104 g, 0.27 mmol) and *N,N,N',N'*-tetramethylethylenediamine (48 μ L, 0.32 mmol) in tetrahydrofuran (1 mL) at -78°C was added *s*-butyllithium (0.246 mL of 1.3 M in cyclohexane, 0.32 mmol). After 1 hour, allyl bromide (0.115 mL, 1.33 mmol) was added and stirring was continued for an additional 1 hour. The reaction mixture was diluted with water (25 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered and

concentrated *in vacuo* to give the crude product, which was employed without further purification (0.107 g).

NMR (C₆D₆, selected data from the free base): 0.84-0.95 (m, 12H), 1.17 (s, 3H), 1.19-1.24 (m, 6H), 1.32-1.41 (m, 3H), 1.76 (m, 1H), 2.05-2.40 (m, 6H), 2.63 (m, 1H), 3.08 (m, 4H), 3.33 (d, 2H), 4.98 (m, 2H), 5.93 (m, 1H), 6.96 (dd, 1H), 7.07-7.10 (d, 1H) and 7.23 (d, 1H).

MS (APCI⁺): M/Z [MH⁺] 429.3; C₂₇H₄₄N₂O₂ + H requires 429.3.

Example 51: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(3-*N*',*N*'-diethyl-carbamyloxy-4-methylphenyl)piperidine

To a stirred solution of (±)-N-hexyl-*trans*-3,4-dimethyl-4-(3-*N*',*N*'-diethylcarbamyloxyphenyl)piperidine (Preparation 4, 0.215 g, 0.55 mmol) and *N,N,N',N'*-tetramethylethylenediamine (0.100 mL, 0.67 mmol) in tetrahydrofuran (1 mL) at -78°C was added *s*-butyllithium (0.511 mL of 1.3 M in cyclohexane, 0.67 mmol). After 1 hour, methyl iodide (0.173 mL, 2.77 mmol) was added and stirring was continued for an additional 1 hour. The reaction mixture was diluted with water (25 mL) and extracted with dichloromethane (3 x 20 mL). The combined extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product, which was employed without further purification (0.213 g).

NMR (C₆D₆, selected data from the free base): 0.80-1.04 (m, 12H), 1.17 (s, 3H), 1.20-1.24 (m, 6H), 1.32-1.41 (m, 3H), 1.76 (m, 1H), 2.05-2.40 (m, 6H), 2.11 (s, 3H), 2.63 (m, 1H), 3.08 (m, 4H), 6.90 (m, 1H), 6.99 (m, 1H) and 7.10-7.15 (m, 1H).

MS (APCI⁺): M/Z [MH⁺] 403.4; C₂₅H₄₂N₂O₂ + H requires 403.3.

Example 52: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamoyloxy-4-ethylphenyl)piperidine

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamoyloxy-4-methylphenyl)piperidine (Example 51, 0.260 g, 0.65 mmol) and *N,N,N',N'*-tetramethylethylenediamine (0.117 mL, 0.78 mmol) in tetrahydrofuran (2 mL) at -78°C was added *s*-butyllithium (0.597 mL of 1.3 M in cyclohexane, 0.78 mmol). After 1 hour, methyl iodide (0.201 mL, 3.23 mmol) was added and stirring was continued for an additional 1 hour. The reaction mixture was diluted with water (25 mL) and extracted with dichloromethane (3 x 20 mL). The combined extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (5:494:1 to 10:489:1), to give the title compound as a pale yellow oil (90 mg).

NMR (C₆D₆, selected data from the free base): 0.86 (t, 3H), 0.90-0.96 (m, 12H), 1.08 (s, 3H), 1.10-1.26 (m, 6H), 1.43-1.58 (m, 3H), 1.71 (m, 1H), 2.08-2.62 (m, 6H), 2.29 (q, 2H), 2.71 (m, 1H), 3.09 (m, 4H), 6.86 (dd, 1H), 7.04 (d, 1H) and 7.10-7.13 (d, 1H).

MS (APCI⁺): M/Z [MH⁺] 417.3; C₂₆H₄₄N₂O₂ + H requires 417.3.

Example 53: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamoyloxy-4-*N''*-methylaminocarbonylphenyl)piperidine

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamoyloxyphenyl)piperidine (Preparation 4, 0.111 g, 0.29 mmol) and *N,N,N',N'*-tetramethylethylenediamine (52 μ L, 0.34 mmol) in tetrahydrofuran (1 mL) at -78°C was added *s*-butyllithium (0.263 mL of 1.3 M in cyclohexane, 0.34 mmol). After 1 hour, methyl isocyanate

(84 μ L, 1.43 mmol) was added and stirring was continued for an additional 1 hour. The reaction mixture was diluted with water (25 mL) and extracted with dichloromethane (3 x 20 mL). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give the crude product, which was employed without further purification (0.113 g).

MS (APCI⁺): M/Z [MH^+] 446.3; $\text{C}_{26}\text{H}_{43}\text{N}_3\text{O}_3 + \text{H}$ requires 446.3.

Example 54: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(3-*N*',*N*'-diethylthiocarbamyloxy-4-fluorophenyl)piperidine

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-*N*',*N*'-diethylthiocarbamyloxyphenyl)piperidine (Preparation 6, 0.104 g, 0.26 mmol) and *N,N,N',N'*-tetramethylethylenediamine (78 μ L, 0.51 mmol) in tetrahydrofuran (2 mL) at -78°C was added *s*-butyllithium (0.395 mL of 1.3 M in cyclohexane, 0.51 mmol). After 1 hour, a solution of *N*-fluorobenzenesulfonimide (0.405 g, 1.28 mmol) in tetrahydrofuran (1 mL) was added and stirring was continued for an additional 3 hours. The reaction mixture was diluted with saturated aqueous sodium hydrogencarbonate (25 mL) and extracted with dichloromethane (3 x 20 mL). The combined extracts were dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of ethyl acetate-dichloromethane (30:70 to 50:50), to give the title compound as a yellow oil (40 mg).

NMR (C_6D_6 , selected data from the free base): 0.83-0.97 (m, 12H), 1.12 (s, 3H), 1.18-1.27 (m, 6H), 1.37-1.42 (m, 3H), 1.68 (m, 1H), 2.07-2.39 (m, 6H), 2.62 (m, 1H), 3.12 (m, 2H), 3.50 (m, 2H), 6.73 (m, 1H), 6.83 (m, 1H) and 7.14 (m, 1H).

MS (APCI⁺): M/Z [MH⁺] 423.3; C₂₄H₃₉FN₂OS + H requires 423.3.

Example 55: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamoyloxy-4-formylphenyl)piperidine

5 To a stirred solution of (±)-N-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamoyloxyphenyl)piperidine (Preparation 4, 0.515 g, 1.32 mmol) and *N,N,N',N'*-tetramethylethylenediamine (0.240 mL, 1.59 mmol) in tetrahydrofuran (5 mL) at -78°C was added *s*-butyllithium (1.22 mL of 1.3 M in cyclohexane, 1.59 mmol). After 1 hour, *N,N*-dimethyl-
10 formamide (0.513 mL, 6.62 mmol) was added and stirring was continued for an additional 1 hour. The reaction mixture was diluted with saturated aqueous sodium hydrogencarbonate (25 mL) and extracted with dichloromethane (3 x 20 mL). The combined extracts were dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product
15 which was used without further purification (0.456 g).

NMR (C₆D₆, selected data from the free base): 0.77 (d, 3H), 0.82-0.94 (m, 9H), 1.04 (s, 3H), 1.18-1.34 (m, 6H), 1.37-1.40 (m, 3H), 1.66 (m, 1H), 1.99-2.38 (m, 6H), 2.58 (m, 1H), 3.07 (q, 4H), 6.57 (dd, 1H), 6.86-6.89 (m, 2H) and 9.32 (s, 1H).

20 MS (APCI⁺): M/Z [MH⁺] 417.3; C₂₅H₄₀N₂O₃ + H requires 417.3.

Example 56

Compounds according to the present invention, for example the compound of Example 8, were found to display anti-pruritic activity when tested in
25 accordance with the above procedure.

Preparation of Starting Materials

Preparation 1: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamoyloxy-4-trimethylsilylphenyl)piperidine

5 To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylcarbamoyloxyphenyl)piperidine (Preparation 4, 0.206 g, 0.53 mmol) and *N,N,N',N'*-tetramethylethylenediamine (96 μ L, 0.66 mmol) in tetrahydrofuran (2 mL) at -78°C was added *s*-butyllithium (0.489 mL of 1.3 M in cyclohexane, 0.66 mmol). After 1 hour, chlorotrimethylsilane
10 (0.336 mL, 2.65 mmol) was added and stirring was continued for an additional 10 minutes. The reaction mixture was diluted with saturated aqueous sodium hydrogencarbonate (25 mL) and extracted with dichloromethane (3 x 20 mL). The combined extracts were dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product,
15 which was used without further purification (0.241 g).

NMR (C₆D₆, selected data from the free base): 0.28 (s, 9H), 0.83 (t, 3H), 0.91-0.96 (m, 9H), 1.18 (s, 3H), 1.21-1.27 (m, 6H), 1.35-1.38 (m, 3H), 1.79 (m, 1H), 2.06-2.40 (m, 6H), 2.62 (m, 1H), 3.14 (m, 4H), 7.03 (dd, 1H), 7.18 (d, 1H) and 7.39 (d, 1H).

20 MS (APCI⁺): M/Z [MH⁺] 461.3; C₂₇H₄₈N₂O₂Si + H requires 461.3.

Preparation 2: ($\pm$)-*N*-Hexyl-*trans*-3,4-dimethyl-4-(3-hydroxy-2-methyl-4-trimethylsilylphenyl)piperidine

To a stirred solution of ($\pm$)-*N*-hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-
25 diethylcarbamoyloxy-4-trimethylsilylphenyl)piperidine (Preparation 1, 0.251 g, 0.51 mmol) and *N,N,N',N'*-tetramethylethylenediamine (99 μ L, 0.65 mmol) in tetrahydrofuran (2 mL) at -78°C was added *s*-butyllithium (0.503 mL of 1.3 M in cyclohexane, 0.65 mmol). After 1 hour, methyl

iodide (0.170 mL, 2.72 mmol) was added and stirring was continued for an additional 2 hours. The reaction mixture was diluted with saturated aqueous sodium hydrogencarbonate (25 mL) and extracted with dichloromethane (3 x 20 mL). The combined extracts were dried over
5 Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product, which was purified *via* silica gel chromatography, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (5:494:1 to 20:479:1), to give the title compound as a yellow oil (71 mg).

NMR (C₆D₆, selected data from the free base): 0.36 (s, 9H), 0.87 (t, 3H),
10 1.02 (d, 3H), 1.21 (s, 3H), 1.21-1.32 (m, 6H), 1.46-1.79 (m, 3H), 2.03 (m, 1H), 2.44-2.82 (m, 6H), 3.03 (m, 1H), 3.39 (s, 3H), 6.60 (s, 1H), 6.73 (d, 1H) and 7.36 (d, 1H).

MS (APCI⁺): M/Z [MH⁺] 376.3; C₂₃H₄₁NOSi + H requires 376.3.

15 **Preparation 3: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(3-triisopropylsilyloxyphenyl)piperidine**

To a solution of (±)-N-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine (Preparation 7, 100 mg, 0.345 mmol) in *N,N*-dimethylformamide (1 mL) was added imidazole (47 mg, 0.690 mmol) and
20 chlorotriisopropylsilane (106 mg, 0.552 mmol). The reaction was stirred under nitrogen for 60 hours then washed with saturated sodium hydrogencarbonate solution and extracted with dichloromethane. The solvents were removed *in vacuo* and the residue was dissolved in hexane, filtered and the hexane removed *in vacuo* to give the title compound as an
25 oil (152 mg).

NMR (CDCl₃, selected data from the free base): 0.77 (3H, d), 0.87 (3H, t), 1.09 (21H, m), 1.31 (3H, s), 6.67 (1H, d), 6.80 (1H, s), 6.87 (1H, d) and 7.13 (1H, t).

MS (APCI⁺): M/Z [MH⁺] 446.1; C₂₈H₅₁NOSi + H requires 446.4.

Preparation 4: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethyl-carbamyloxyphenyl)piperidine

5 To a solution of (±)-N-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine (Preparation 7, 8.0 g, 28 mmol) in pyridine (32 mL) was added 1-[(chlorocarbonyl)(ethyl)amino]ethane (3.8 mL, 30.0 mmol), and the reaction mixture was stirred overnight. Water (200 mL) was added to the reaction mixture and the product was extracted with dichloromethane
10 (3 x 200 mL). The organics were dried (Na₂SO₄) and then concentrated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with ethyl acetate-hexane (20:80), to give the product as a colourless oil (4.0 g).

NMR (CDCl₃, selected data from the free base): 0.8 (d, 3H), 0.9 (t, 3H),
15 1.2-1.4 (m, 14H), 3.3-3.5 (m, 4H), 6.9 (d, 1H), 7.0 (s, 1H), 7.1 (d, 1H) and 7.3 (t, 1H).

MS (ESI⁺): M/Z [MH⁺] 389.2; C₂₄H₄₀N₂O₂ + H requires 389.3.

Preparation 5: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-dimethyl-carbamyloxyphenyl)piperidine

20 To a stirred solution of (±)-N-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (Preparation 7, 0.289 g, 1.00 mmol) and dimethylcarbamyl chloride (0.101 mL, 1.1 mmol) in tetrahydrofuran (2 mL) and pyridine (2 mL) was added triethylamine (0.279 mL, 2 mmol). After 24 hours, the reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined
25 extracts were washed with brine (30 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give the crude product, which was

chromatographed on silica gel, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (10:989:1 to 30:967:3), to give the title compound as a yellow oil (0.329 g).

NMR (C_6D_6 , selected data from the free base) : 0.85 (t, 3H), 0.90 (d, 3H), 1.17 (s, 3H), 1.19-1.29 (m, 6H), 1.33-1.43 (m, 3H), 1.78 (m, 1H), 2.05-2.40 (m, 6H), 2.51 (s, 3H), 2.55 (s, 3H), 2.63 (m, 1H), 6.93 (m, 1H), 7.04-7.12 (m, 2H) and 7.24 (m, 1H).

MS (APCI⁺): M/Z [MH^+] 361.3; $C_{22}H_{36}N_2O_2 + H$ requires 361.3.

10 **Preparation 6: ($\pm$)-N-Hexyl-*trans*-3,4-dimethyl-4-(3-*N'*,*N'*-diethylthiocarbamyloxyphenyl)piperidine**

To a stirred solution ($\pm$)-N-hexyl-*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (Preparation 7, 0.710 g, 2.45 mmol) and potassium hydroxide (0.137 g, 2.45 mmol) in water (5 mL) and tetrahydrofuran (5 mL) was added diethylthiocarbamyl chloride (0.485 g, 3.2 mmol). After 24 hours, additional potassium hydroxide (0.137 g, 2.45 mmol) and diethylthiocarbamyl chloride (0.485 g, 3.2 mmol) was introduced. After an additional 24 hours, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 x 25 mL). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give the crude product, which was chromatographed on silica gel, eluting with a gradient of methanol-dichloromethane-0.880 ammonia (10:989:1 to 30:967:3), to give the title compound as a yellow oil (0.627 g).

25 NMR (C_6D_6 , selected data from the free base) : 0.83-0.88 (m, 6H), 0.95-1.01 (m, 6H), 1.20 (s, 3H), 1.23-1.42 (m, 9H), 1.77 (m, 1H), 2.05-2.42 (m, 6H), 2.64 (m, 1H), 3.10 (q, 2H), 3.55 (q, 2H), 6.91 (m, 1H), 6.98 (m, 1H), 7.05-7.13 (m, 1H) and 7.19 (m, 1H).

MS (APCI⁺): M/Z [MH⁺] 405.3; C₂₄H₄₀N₂OS + H requires 405.3.

Preparation 7: (±)-N-Hexyl-*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine

5 To a stirred solution of (±)-*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine (J. A. Werner *et al.*, *J. Org. Chem.*, 1996, 61, 587: 2.0 g, 9.8 mmol) in *N,N*-dimethylformamide (50 mL) was added sodium hydrogencarbonate (1.76 g, 20.95 mmol) and bromohexane (1.64 g, 9.9 mmol). The reaction mixture was heated under reflux for 3 hours and
10 then cooled to room temperature. The reaction mixture was diluted with water (100 mL) and extracted with dichloromethane (4 x 50 mL). The combined extracts were washed with brine (100 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give the crude product. The crude product was chromatographed on silica gel (50 g), eluting with ethyl
15 acetate-hexane-0.880 ammonia (30:69:1), to give the title compound as a light brown oil (2.68 g).

NMR (CDCl₃, selected data from the free base): 0.75 (d, 3H), 0.85 (t, 3H), 1.15-1.25 (m, 6H), 1.3 (s, 3H), 2.0 (m, 1H), 2.35 (m, 4H), 2.6 (m, 2H) and 6.55-7.2 (m, 4H).

20 MS (TSI⁺): M/Z [MH⁺] 290.2; C₁₉H₃₁NO + H requires 290.3.

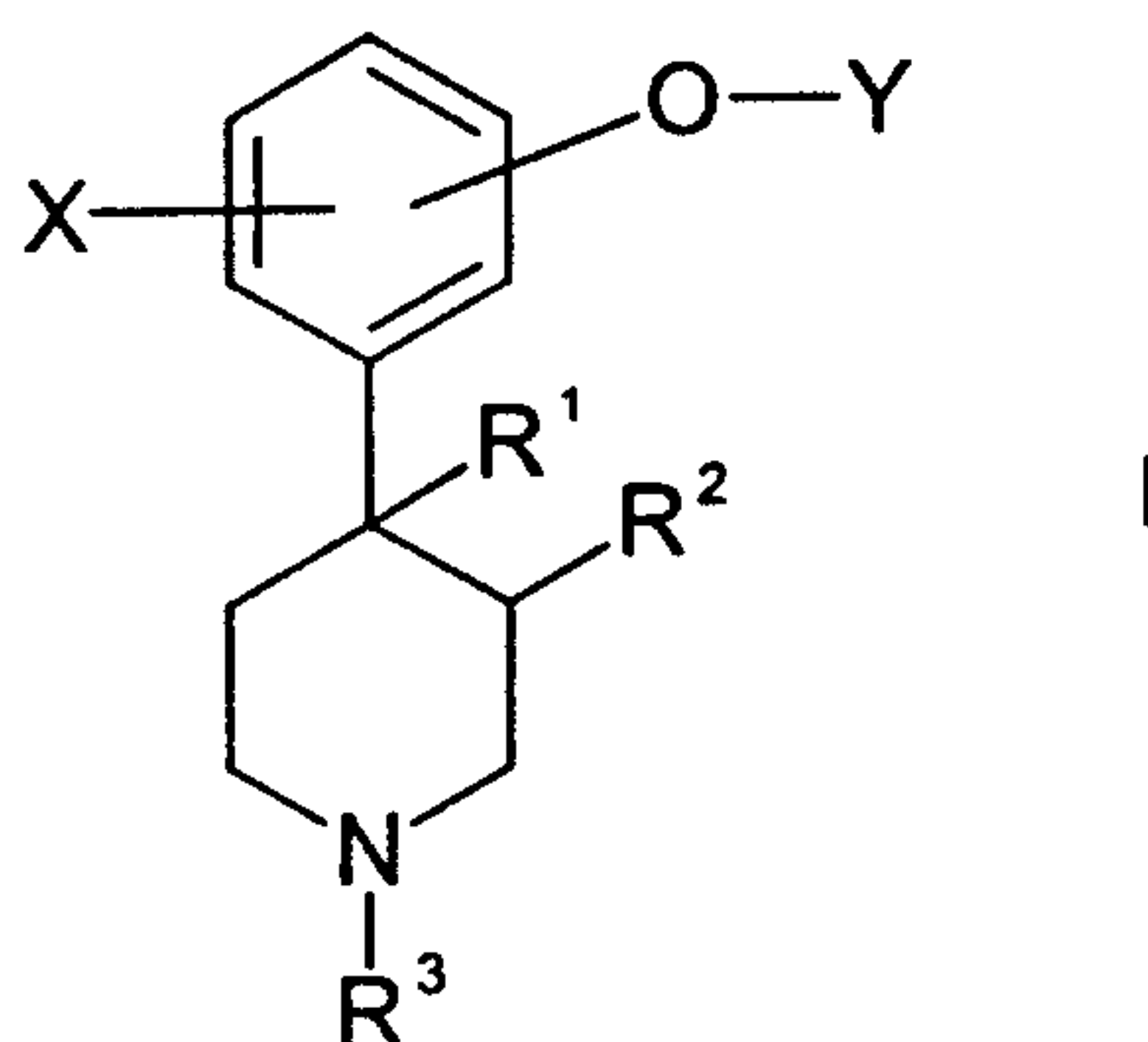
Preparation 8: (±)-N-(3-Cyclohexylpropyl)-*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine

A mixture of (±)-*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (J. A.
25 Werner *et al.*, *J. Org. Chem.*, 1996, 61, 587: 82 mg, 0.4 mmol), 3-(cyclohexyl)chloropropane (71 mg, 0.4 mmol), sodium hydrogen-carbonate (37 mg, 0.44 mmol), sodium iodide (3 mg, 0.02 mmol) and dimethylformamide (5 mL) was heated at 70°C for 8 hours, then it was

- cooled to room temperature and quenched with water (30 mL). The resultant mixture was extracted with dichloromethane (30 mL), and the organic layer retained. The aqueous layer was re-extracted with dichloromethane (2 x 20 mL), and the organic portions were combined, washed with brine (40 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*, to afford the crude material. This was chromatographed on silica gel, eluting with a gradient system of methanol-dichloromethane-0.880 ammonia (10:989:1 to 20:978:2), to give the title compound as a colourless viscous oil (56 mg).
- 10 NMR (C_6D_6 , selected data from the free base): 0.90 (d, 3H), 1.20 (s, 3H), 1.80 (m, 1H), 2.80 (m, 1H) and 6.60-7.10 (m, 4H).
- MS (APCI⁺): M/Z [MH^+] 330.3; $\text{C}_{22}\text{H}_{35}\text{NO}$ + H requires 330.5.

Claims

1. A compound of formula I,



5

wherein

R^1 and R^2 are each independently H or C_{1-4} alkyl;

10

R^3 represents aryl (optionally substituted by one or more substituents selected from OH, nitro, halo, CN, CH_2CN , $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms) and $-N(R^{4a})(R^{4b})$), C_{1-10} alkyl, 15 C_{3-10} alkenyl or C_{3-10} alkynyl wherein said alkyl, alkenyl or alkynyl groups are optionally substituted and/or terminated by one or more substituents selected from OR^{4c} , $S(O)_nR^{4d}$, CN, halo, C_{1-6} alkoxy carbonyl, C_{2-6} alkanoyl, C_{2-6} alkanoyloxy, C_{3-8} cycloalkyl, C_{4-9} cycloalkanoyl, $N(R^{5a})S(O)_2R^6$, Het¹, aryl, adamantyl (which latter two groups are 20 optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN , $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or $-W-A^1-N(R^{5b})(R^{5c})$;

n is 0, 1 or 2;

W represents a single bond, C(O) or S(O)_p;

A¹ represents a single bond or C₁₋₁₀ alkylene;

provided that when both W and A¹ represent single bonds, then the group
5 -N(R^{5b})(R^{5c}) is not directly attached to an unsaturated carbon atom;

p is 0, 1 or 2;

R^{4a} to R^{4d} each independently represent H, C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl,
C₃₋₁₀ alkynyl, C₃₋₈ cycloalkyl, C₁₋₄ alkylphenyl, aryl (which latter six
groups are optionally substituted by or one or more substituents selected
10 from OH, nitro, amino, halo, CN, CH₂CN, CONH₂, C₁₋₄ alkyl,
C₁₋₄ alkoxy and C₁₋₅ alkanoyl (which latter three groups are optionally
substituted by one or more halo atoms)) or Het²;

provided that R^{4d} does not represent H when n represents 1 or 2;

R^{5a} to R^{5c} each independently represent H, C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl,
15 C₃₋₁₀ alkynyl, C₃₋₈ cycloalkyl, C₁₋₄ alkylphenyl, aryl (which latter six
groups are optionally substituted by or one or more substituents selected
from OH, nitro, amino, halo, CN, CH₂CN, CONH₂, C₁₋₄ alkyl,
C₁₋₄ alkoxy and C₁₋₅ alkanoyl (which latter three groups are optionally
substituted by one or more halo atoms)), Het³, or R^{5b} and R^{5c} together
20 represent unbranched C₂₋₆ alkylene which alkylene group is optionally
interrupted by O, S and/or an N(R⁷) group and is optionally substituted by
one or more C₁₋₄ alkyl groups;

R⁶ represents C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₁₋₄ alkylphenyl or aryl, which
four groups are optionally substituted by or one or more substituents
25 selected from C₁₋₄ alkyl, C₁₋₄ alkoxy, OH, nitro, amino or halo;

R⁷ represents H, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, A²-(C₃₋₈ cycloalkyl) or
A²-aryl;

A² represents C₁₋₆ alkylene;

Het¹, Het² and Het³ independently represent 3- to 8-membered heterocyclic groups, which groups contain at least one heteroatom selected from oxygen, sulfur and/or nitrogen, which groups are optionally fused to a benzene ring, and which groups are optionally substituted in the
 5 heterocyclic and/or fused benzene ring part by one or more substituents selected from OH, =O, nitro, amino, halo, CN, aryl, C₁₋₄ alkyl, C₁₋₄ alkoxy and C₁₋₅ alkanoyl (which latter three groups are optionally substituted by one or more halo atoms);

10 Y represents -C(=E)NR⁸R⁹, C(O)R¹⁰, C(O)OR¹⁰, C(O)CH(R^{10a})N(G)G^a, R¹¹, CH(R^{12b})C(O)OR^{12a}, CH(R^{12b})OCO₂R^{12a}, C(O)C(R^{13a})=C(R^{13b})NH₂, C(O)CH(R^{13a})CH(NH₂)(R^{13b}) or PO(OR¹⁴)₂;

E represents O or S;

R⁸ and R⁹ independently represents H, C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl (which
 15 latter two groups are optionally substituted by one or more aryl or C₄₋₇ cycloalkyl groups (which two groups are optionally substituted by one or more substituents selected from halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl or C₁₋₄ haloalkoxy)), aryl, C₄₋₇ cycloalkyl (optionally substituted by one or more substituents selected from halo, C₁₋₄ alkyl and C₁₋₄ alkoxy
 20 (which latter two groups are optionally substituted by one or more halo atoms)), or R⁸ and R⁹, together with the N-atom to which both are attached, represent Het⁴;

Het⁴ represents a 5- to 8-membered heterocyclic ring comprising at least one nitrogen atom and optionally one or more additional heteroatoms
 25 selected from oxygen and sulfur, which heterocyclic ring is optionally substituted by one or more C₁₋₄ alkyl groups;

R¹⁰ represents H, Het⁵, C₄₋₇ cycloalkyl (optionally substituted by one or more C₁₋₄ alkyl groups), C₁₋₁₁ alkyl (optionally substituted by one or more

substituents selected from aryl (optionally substituted by one or more substituents selected from OH, halo, C₁₋₄ alkanoyl, C₁₋₄ alkanoyloxy, N(R⁸)(R⁹), C(O)N(R⁸)(R⁹), C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl and C₁₋₄ haloalkoxy) or C₄₋₇ cycloalkyl (which latter group is optionally substituted by one or more C₁₋₄ alkyl groups)) or aryl (optionally substituted by one or more substituents selected from OH, halo, C₁₋₄ alkanoyl, C₁₋₄ alkanoyloxy, N(R⁸)(R⁹), C(O)N(R⁸)(R⁹), C₁₋₄ alkyl and C₁₋₄ alkoxy (which latter two groups are optionally substituted by one or more halo atoms));

10 R^{10a} represents H, C₄₋₇ cycloalkyl, C₁₋₁₀ alkyl (optionally substituted by one or more substituents selected from aryl or C₄₋₇ cycloalkyl), aryl, or R^{10a} (optionally in conjunction with G^a) represents a naturally occurring amino acid substituent;

G and G^a independently represent H, an amino protective group, or G^a,
15 together with R^{10a}, represents a naturally occurring amino acid substituent;

R¹¹ represents H, C₄₋₇ cycloalkyl (optionally substituted by one or more C₁₋₄ alkyl groups), aryl (optionally substituted by one or more substituents selected from OH, halo, C₁₋₄ alkanoyl, C₁₋₄ alkanoyloxy, N(R⁸)(R⁹),
20 C(O)N(R⁸)(R⁹), C₁₋₄ alkyl and C₁₋₄ alkoxy (which latter two groups are optionally substituted by one or more halo atoms)), C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl, which alkyl or alkenyl group is optionally substituted by one or more substituents selected from C(O)NH₂, Het⁶, C₄₋₇ cycloalkyl (optionally substituted by one or more C₁₋₄ alkyl groups), aryl, aryloxy or
25 aryl(C₁₋₄)alkoxy (which latter three groups are optionally substituted by one or more substituents selected from OH, halo, C₁₋₄ alkanoyl, C₁₋₄ alkanoyloxy, N(R⁸)(R⁹), C(O)N(R⁸)(R⁹), C₁₋₄ alkyl and C₁₋₄ alkoxy

(which latter two groups are optionally substituted by one or more halo atoms)) or R¹¹ represents Het⁷;

Het⁵ to Het⁷ independently represent 4- to 6-membered heterocyclic rings, which rings contain at least one heteroatom selected from oxygen, sulfur, and/or nitrogen, which rings are optionally fused to a benzene ring, and which rings are optionally substituted in the heterocyclic and/or fused benzene ring part by one or more substituents selected from OH, =O, nitro, amino, halo, CN, aryl, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl and C₁₋₅ alkanoyl (which latter four groups are optionally substituted by one or more halo atoms);

R^{12a} and R^{12b} independently represent H, C₄₋₇ cycloalkyl (optionally substituted by one or more C₁₋₄ alkyl groups), C₁₋₁₀ alkyl (optionally substituted by one or more substituents selected from aryl or C₄₋₇ cycloalkyl (which latter group is optionally substituted by one or more C₁₋₄ alkyl groups)) or aryl (optionally substituted by one or more substituents selected from OH, halo, C₁₋₄ alkanoyl, C₁₋₄ alkanoyloxy, C₁₋₄ alkyl and C₁₋₄ alkoxy (which latter two groups are optionally substituted by one or more halo atoms));

R^{13a} and R^{13b} independently represent H, C₄₋₇ cycloalkyl (optionally substituted by one or more C₁₋₄ alkyl groups), C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl (which alkyl and alkenyl groups are optionally substituted by one or more substituents selected from aryl or C₄₋₇ cycloalkyl (which latter group is optionally substituted by one or more C₁₋₄ alkyl groups)), or aryl (optionally substituted by one or more substituents selected from OH, halo, C₁₋₄ alkanoyl, C₁₋₄ alkanoyloxy, C₁₋₄ alkyl and C₁₋₄ alkoxy (which latter two groups are optionally substituted by one or more halo atoms));

R^{14} represents H, C_{4-7} cycloalkyl (optionally substituted by one or more C_{1-4} alkyl groups), C_{1-10} alkyl (optionally substituted by one or more substituents selected from aryl or C_{4-7} cycloalkyl (which latter group is optionally substituted by one or more C_{1-4} alkyl groups)), or aryl
 5 (optionally substituted by one or more substituents selected from OH, halo, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, C_{1-4} alkyl and C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms));

X represents one or more substituents on the benzene ring, which
 10 substituents are independently selected from halo, CN, nitro, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl (which latter four groups are optionally substituted and/or terminated by one or more substituents selected from halo, CN, nitro, OH, C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{3-7} cycloalkoxy, C_{1-6} alkanoyl, C_{4-8} cycloalkanoyl, C_{2-6} alkoxycarbonyl,
 15 C_{2-6} alkanoyloxy or $N(R^{15a})(R^{15b})$), $C(O)R^{16a}$, $C(O)OR^{16b}$, $OC(O)R^{16c}$, $S(O)_rOR^{16d}$, $S(O)_tR^{17a}$, OR^{16e} , $N(R^{18a})(R^{18b})$, $C(O)N(R^{18c})(R^{18d})$, $OC(O)N(R^{18e})(R^{18f})$, $N(R^{18g})C(O)R^{16f}$, $N(R^{18h})C(O)OR^{19}$, $N(R^{18i})C(O)N(R^{18j})(R^{18k})$, $N(R^{18m})S(O)_2R^{17b}$ or $B(OR^{15c})_2$;

R^{15a} to R^{15c} independently represent H, C_{1-6} alkyl or C_{3-7} cycloalkyl (which
 20 latter two groups are optionally substituted by one or more halo atoms);

R^{16a} to R^{16f} independently represent H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl (which latter four groups are optionally substituted by one or more substituents selected from halo, nitro, OH, C_{1-4} alkyl or C_{1-4} alkoxy) or Het⁸;

25 R^{17a} and R^{17b} independently represent C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl (which latter four groups are optionally substituted by one or more substituents selected from halo, nitro, OH, C_{1-4} alkyl or C_{1-4} alkoxy), Het⁹ or $N(R^{20a})(R^{20b})$;

provided that R^{17a} does not represent $N(R^{20a})(R^{20b})$ when t is 1;

R^{18a} to R^{18m} independently represent H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl (which latter four groups are optionally substituted by one or more substituents selected from halo, nitro, OH, C_{1-4} alkyl or C_{1-4} alkoxy), Het^{10} , or R^{18j} and R^{18k} together represent
 5 unbranched C_{3-6} alkylene, which alkylene group is optionally interrupted by oxygen, sulfur or an NR^{20c} group;

R^{19} represents C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl (which latter four groups are optionally substituted by one or more
 10 substituents selected from halo, nitro, OH, C_{1-4} alkyl or C_{1-4} alkoxy) or Het^{11} ;

R^{20a} to R^{20c} independently represent H, C_{1-4} alkyl or C_{3-7} cycloalkyl (which latter two groups are optionally substituted by one or more halo atoms);

r is 1 or 2;

15 t is 0, 1 or 2;

Het^8 to Het^{11} represent 4- to 7- membered heterocyclic rings, which rings contain at least one heteroatom selected from oxygen, sulfur and/or nitrogen, and which rings are optionally substituted by one or more substituents selected from OH, =O, nitro, amino, halo, CN, aryl,
 20 C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-6} cycloalkyl and C_{1-5} alkanoyl (which latter four groups are optionally substituted by one or more halo atoms);

or pharmaceutically, or veterinarily, acceptable derivatives thereof.

25 2. A compound as claimed in Claim 1, wherein the group OY is attached to the benzene ring in the position *meta*- relative to the piperidine group.

3. A compound as claimed in Claim 1 or Claim 2, wherein the substituent(s) X is/are attached to the benzene ring in position(s) that are *ortho*- and/or *para*- relative to the piperidine group.
- 5 4. A compound as claimed in any one of Claims 1 to 3, wherein R¹ represents C₁₋₂ alkyl.
5. A compound as claimed in any one of Claims 1 to 4, wherein R² represents H or C₁₋₂ alkyl.
- 10 6. A compound as claimed in any one of Claims 1 to 5, wherein R³ represents C₁₋₈ alkyl, C₃₋₈ alkenyl or C₃₋₈ alkynyl wherein said alkyl, alkenyl or alkynyl groups are optionally substituted and/or terminated by one or more substituents selected from C₃₋₈ cycloalkyl, OR^{4c}, CN, Het¹ or
- 15 aryl (which latter group is optionally substituted by one or more substituents selected from OH, C₁₋₂ alkyl, C₁₋₂ alkoxy or halo).
7. A compound as claimed in any one of Claims 1 to 6, wherein R^{4c} represents H, C₁₋₆ alkyl, C₄₋₆ cycloalkyl, aryl or Het².
- 20 8. A compound as claimed in any one of Claims 1 to 7, wherein Het¹ and Het² independently represent 5- to 7-membered heterocyclic groups, which groups contain at least one heteroatom selected from oxygen, sulfur and/or nitrogen, and which groups are optionally substituted by one or more
- 25 C₁₋₂ alkyl groups (which alkyl groups are optionally substituted by one or more halo atoms).

9. A compound as claimed in any one of Claims 1 to 8, wherein Y represents $C(=E)NR^8R^9$, $C(O)R^{10}$ or R^{11} .

10. A compound as claimed in any one of Claims 1 to 9, wherein R^8 and R^9 independently represent H or C_{1-4} alkyl; R^{10} represents C_{1-6} alkyl (substituted by one or more phenyl groups) or aryl (optionally substituted by one or more substituents selected from OH, halo, C_{1-2} alkanoyloxy, NH_2 , $C(O)NH_2$ and C_{1-2} alkyl (which latter group is optionally substituted by one or more halo atoms)); R^{11} represents H, C_{1-10} alkyl or C_{3-10} alkenyl, which latter two groups are optionally substituted by one or more substituents selected from Het⁶ and phenyl; Het⁶ represents a 5- to 6-membered heterocyclic ring, which ring contains at least one heteroatom selected from oxygen, sulfur and/or nitrogen, which ring is optionally fused to a benzene ring, and which ring is optionally substituted in the heterocyclic and/or fused benzene ring part by one or more substituents selected from OH, =O and C_{1-4} alkyl); and/or Het⁶ is in S-oxidised form.

11. A compound as claimed in any one of Claims 1 to 10, wherein X represents one to three substituents selected from halo, nitro, C_{2-6} alkenyl, C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by a substituent selected from OH, C_{1-4} alkoxy or $N(R^{15a})(R^{15b})$), $C(O)R^{16a}$, $C(O)OR^{16b}$, $S(O)_tR^{17a}$, $N(R^{18a})(R^{18b})$, $C(O)N(R^{18c})(R^{18d})$, $N(R^{18g})C(O)R^{16f}$, $N(R^{18h})C(O)OR^{19}$, $N(R^{18i})C(O)N(R^{18j})(R^{18k})$ or $N(R^{18m})S(O)_2R^{17b}$.

12. A compound as claimed in any one of Claims 1 to 11, wherein R^{15a} and R^{15b} independently represent H or C_{1-4} alkyl; R^{16a} to R^{16f} independently represent H or C_{1-6} alkyl (which latter group is optionally substituted by

one or more halo atoms); R^{17a} and R^{17b} independently represent C₁₋₄ alkyl (optionally substituted by one or more halo atoms) or N(R^{20a})(R^{20b}); R^{18a} to R^{18m} independently represent H, C₁₋₆ alkyl, or R^{18j} and R^{18k} together represent unbranched C₃₋₆ alkylene optionally interrupted by oxygen; R¹⁹ represents C₁₋₄ alkyl; and/or R^{20a} and R^{20b} independently represent H or C₁₋₄ alkyl.

13. A compound as claimed in any one of Claims 1 to 12, wherein the substituent(s) X is/are attached to the benzene ring in the position(s) that are *ortho*- and/or *para*- relative to the OY group.

14. A compound as defined in any one of Claims 1 to 13, for use as a medicament.

15. A compound as defined in any one of Claims 1 to 13, for use as an animal medicament.

16. A formulation comprising a compound as defined in any one of Claims 1 to 13, in admixture with a pharmaceutically, or a veterinarily, acceptable adjuvant, diluent or carrier.

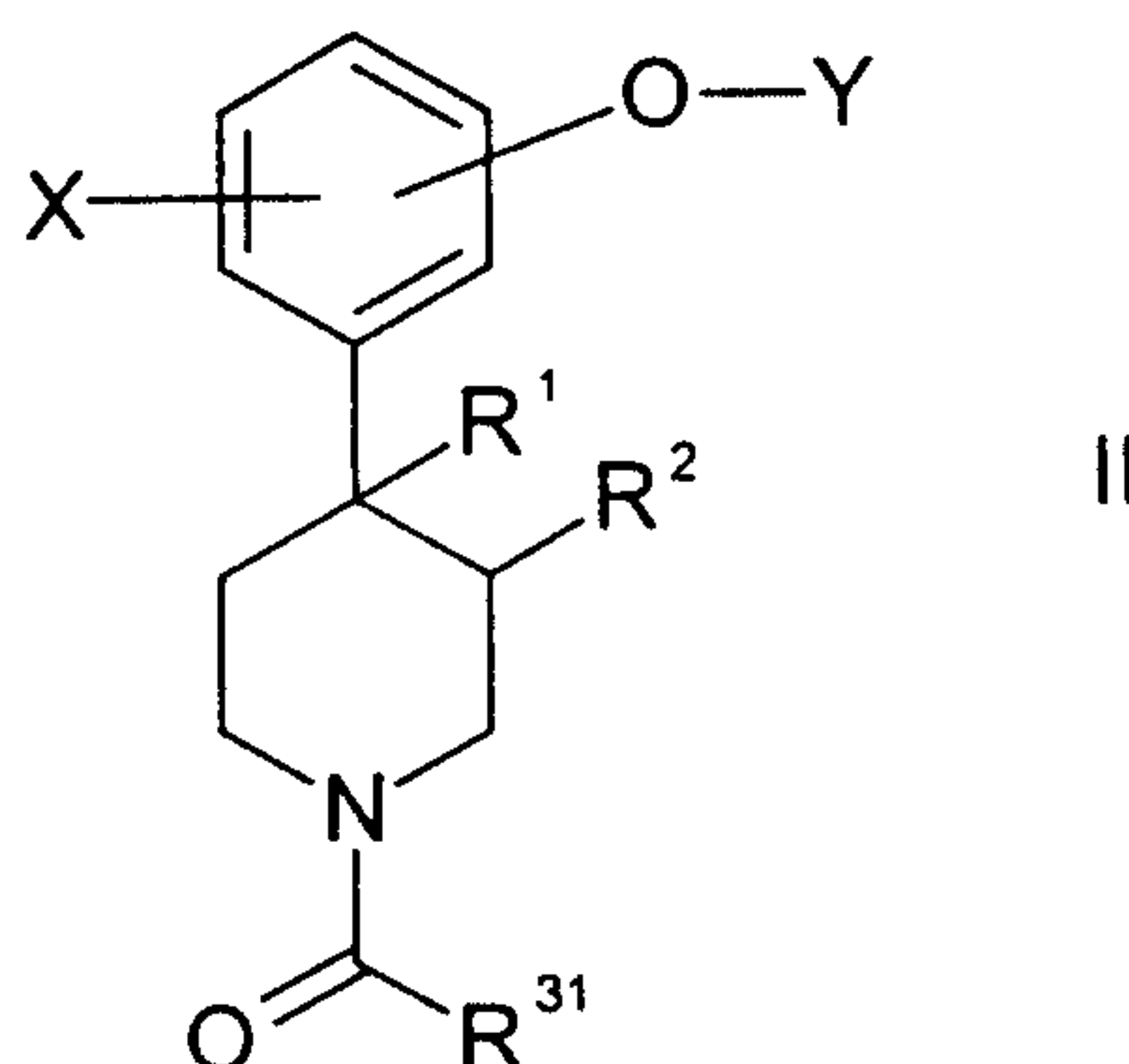
17. A formulation as claimed in Claim 16, which is a veterinary formulation.

18. The use of a compound as defined in any one of Claims 1 to 13, in the manufacture of a medicament for the curative or prophylactic treatment of pruritus.

19. A method of treating or preventing pruritus, which comprises administering a therapeutically effective amount of a compound as defined in any one of Claims 1 to 13, to a patient in need of such treatment.

5 20. A process for the preparation of a compound as defined in Claim 1, which comprises:

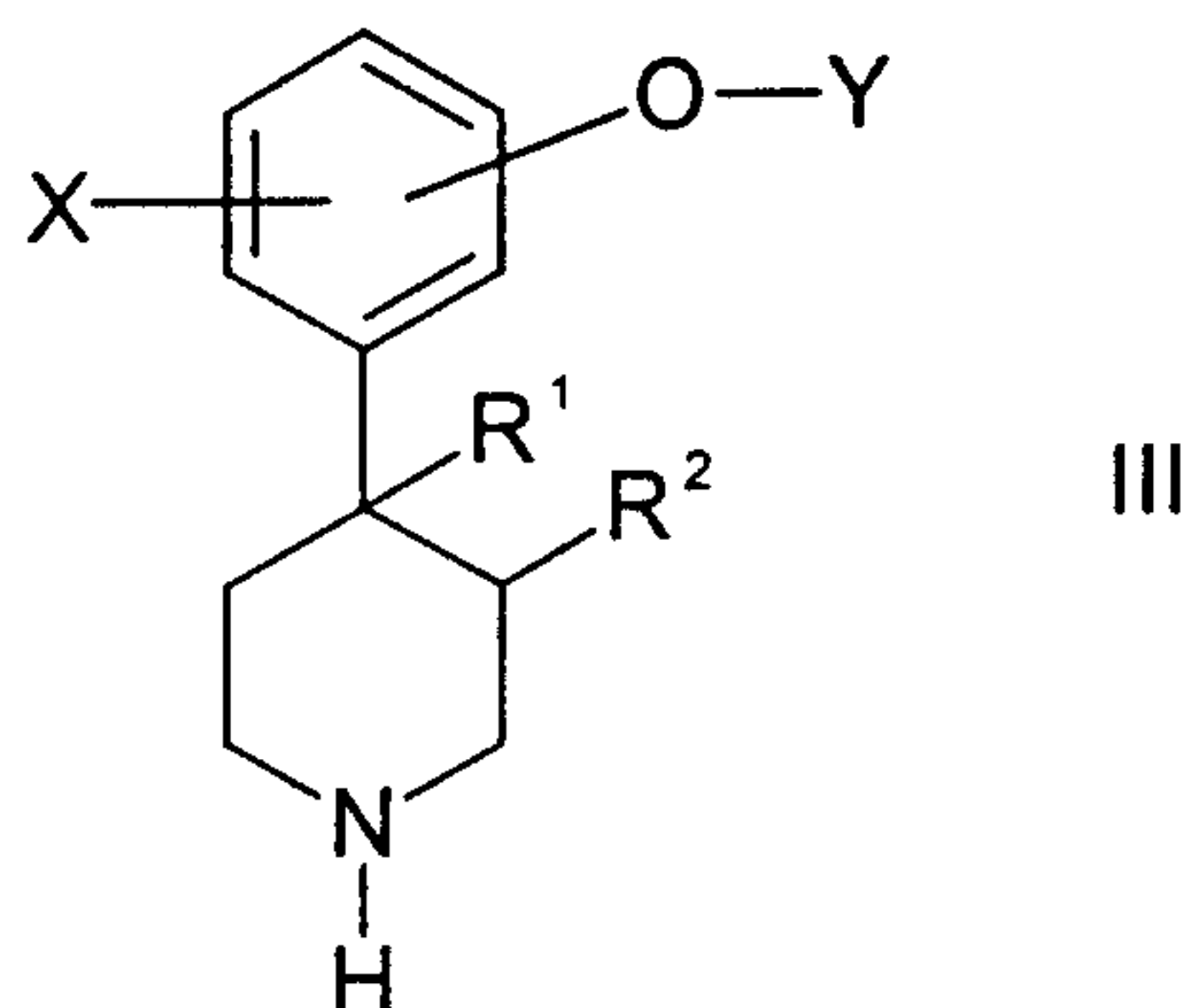
a) for compounds of formula I wherein R^3 represents C_1 alkyl optionally substituted by C_{3-8} cycloalkyl, Het^1 , aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from
 10 OH, nitro, amino, halo, CN, CH_2CN , $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or R^3 represents C_{2-10} alkyl, C_{3-10} alkenyl or C_{3-10} alkynyl (which three groups are all optionally substituted by one or more of the relevant substituents identified in Claim 1 in respect of R^3),
 15 which alkyl, alkenyl or alkynyl groups are attached to the piperidine nitrogen atom *via* a CH_2 group, wherein Het^1 is as defined in Claim 1, reduction of a corresponding compound of formula II,



wherein R^{31} represents H, C_{3-8} cycloalkyl, Het^1 , aryl, adamantyl (which
 20 latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN , $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), C_{1-9} alkyl, C_{2-9} alkenyl or

C₂₋₉ alkynyl, which alkyl, alkenyl or alkynyl groups are optionally substituted and/or terminated by one or more substituents selected from OR^{4c}, S(O)_nR^{4d}, CN, halo, C₁₋₆ alkoxy carbonyl, C₂₋₆ alkanoyl, C₂₋₆ alkanoyloxy, C₃₋₈ cycloalkyl, C₄₋₉ cycloalkanoyl, N(R^{5a})S(O)₂R⁶, Het¹, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH₂CN, CONH₂, C₁₋₄ alkyl, C₁₋₄ alkoxy and C₁₋₅ alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or -W-A¹-N(R^{5b})(R^{5c}), and R¹, R², R^{4c}, R^{4d}, R^{5a} to R^{5c}, R⁶, Het¹, n, X, Y, W and A¹ are as defined in Claim 1;

b) reaction of a corresponding compound of formula III,



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



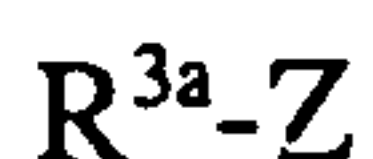
wherein L¹ represents a leaving group and R³ is as defined in Claim 1;

c) for compounds of formula I wherein R³ represents C₁ alkyl, which, in place of being optionally substituted by the substituents as defined in Claim 1, is instead optionally substituted by R³¹, wherein R³¹ is as defined
20 above, reaction of a corresponding compound of formula III, as defined above, with a compound of formula VI,



wherein R³¹ is as defined above, in the presence of a reducing agent;

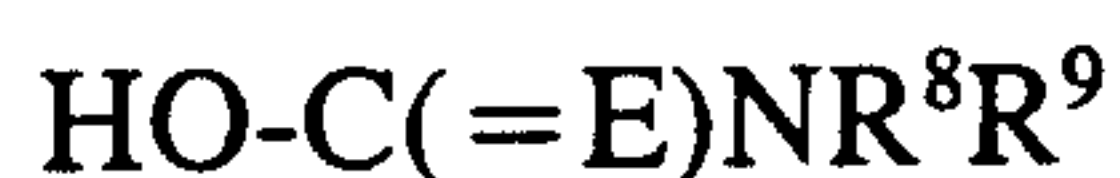
d) for compounds of formula I wherein R^3 is a C_{1-10} alkyl, C_{4-10} alkenyl or C_{4-10} alkynyl group that is fully saturated from 1- to 3-C (relative to the piperidine N-atom), and which R^3 group is substituted at 2-C (relative to the piperidine N-atom) by $S(O)R^{4d}$, $S(O)_2R^{4d}$, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, $-C(O)-A^1-N(R^{5b})(R^{5c})$, $-S(O)-A^1-N(R^{5b})(R^{5c})$, or $-S(O)_2-A^1-N(R^{5b})(R^{5c})$, wherein R^{4d} , R^{5b} , R^{5c} and A^1 are as defined in Claim 1, reaction of a corresponding compound of formula III, as defined above, with a compound of formula VII,



VII

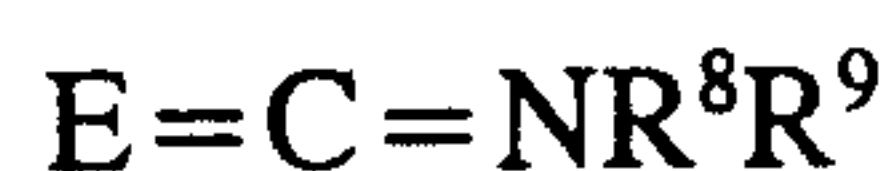
wherein R^{3a} represents R^3 as defined in Claim 1 except that it does not represent aryl, and that the R^{3a} chain contains an additional carbon-carbon double bond α,β to the Z-substituent, and Z represents $S(O)R^{4d}$, $S(O)_2R^{4d}$, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, $-C(O)-A^1-N(R^{5b})(R^{5c})$, $-S(O)-A^1-N(R^{5b})(R^{5c})$, or $-S(O)_2-A^1-N(R^{5b})(R^{5c})$, wherein R^{4d} , R^{5b} , R^{5c} and A^1 are as defined in Claim 1;

e) for compounds of formula I in which Y represents $-C(=E)NR^8R^9$, wherein E, R^8 and R^9 are as defined in Claim 1, reaction of a corresponding compound of formula I in which Y represents H, with a compound of formula VIII,



VIII,

or a suitable derivative thereof, wherein E, R^8 and R^9 are as defined in Claim 1, or a compound of formula IX,



IX

wherein E, R^8 and R^9 are as defined in Claim 1;

f) for compounds of formula I in which Y represents $C(O)R^{10}$ or $C(O)OR^{10}$, wherein R^{10} is as defined in Claim 1, reaction of a corresponding compound of formula I in which Y represents H, with a compound of formula X,



or a compound of formula XI,



respectively, or suitable derivatives thereof, wherein R^{10} is as defined in

5 Claim 1;

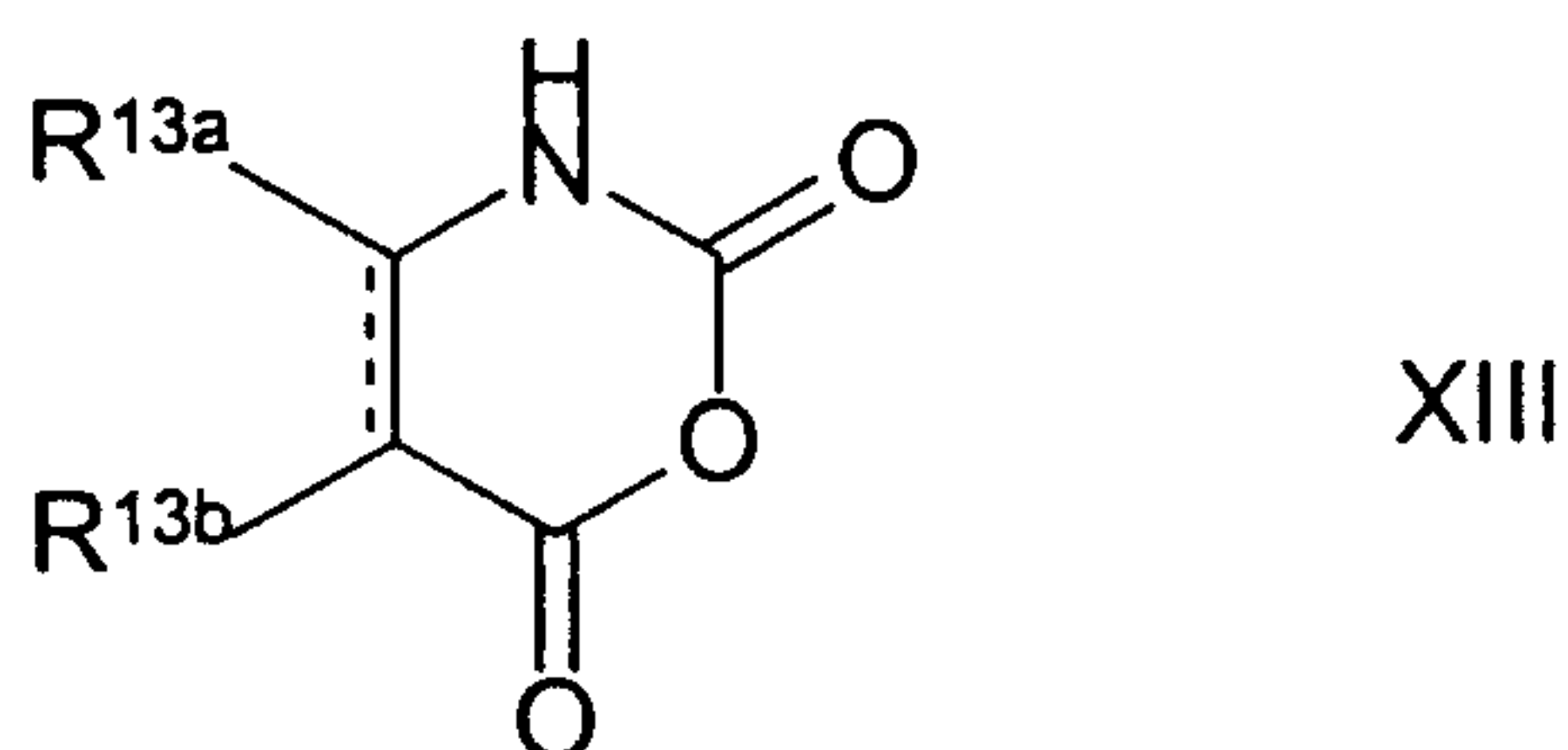
g) for compounds of formula I in which Y represents $\text{C(O)CH(R}^{10a})\text{N(G)(G}^a\text{)}$, wherein R^{10a} , G and G^a are as defined in Claim 1, reaction of a corresponding compound of formula I in which Y represents H, with a compound of formula XII,



or a suitable derivative thereof, wherein R^{10a} , G and G^a are as defined in Claim 1;

h) for compounds of formula I in which Y represents $\text{C(O)C(R}^{13a})=\text{C(R}^{13b})\text{NH}_2$ or $\text{C(O)CH(R}^{13a})\text{CH(NH}_2\text{)(R}^{13b})$, and R^{13a} and R^{13b} are as defined in Claim 1, reaction of a corresponding compound of

15 formula I in which Y represents H, with a compound of formula XIII,

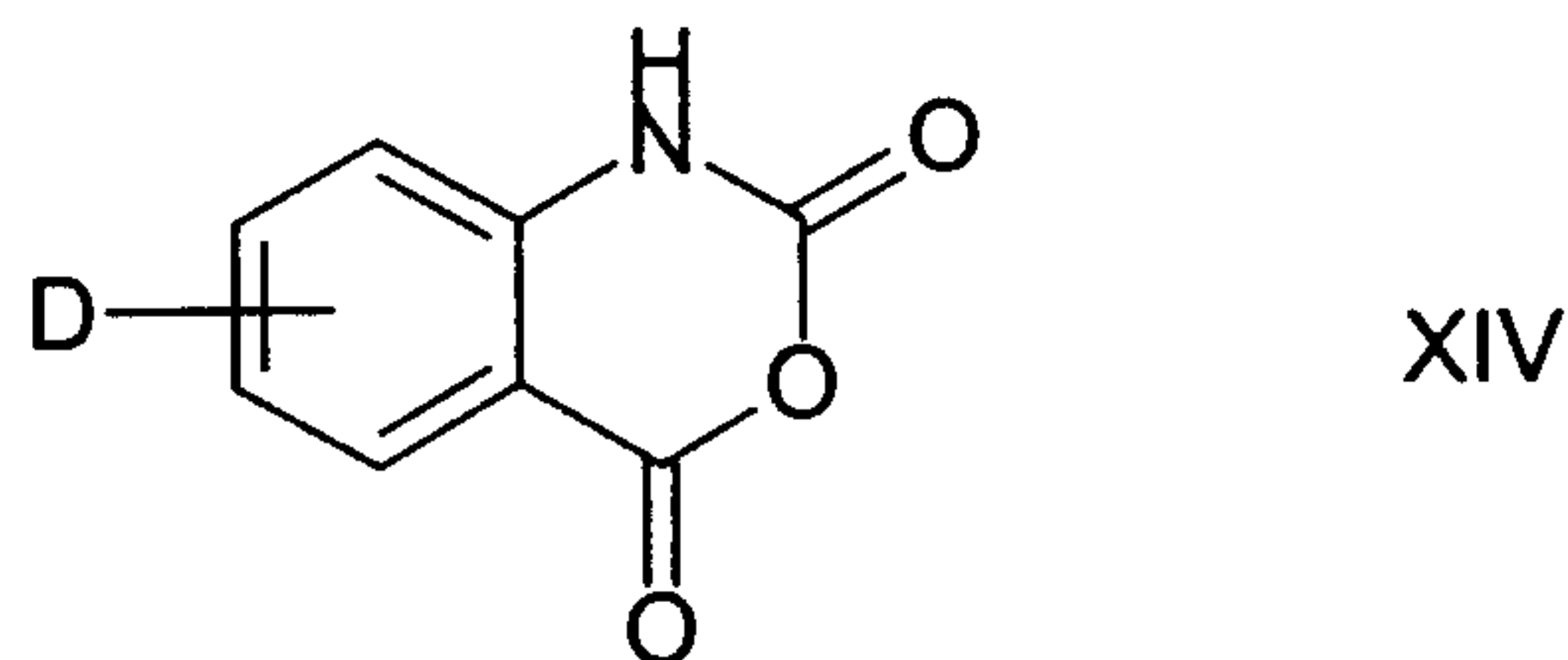


wherein the dashed line represents an optional double bond, and R^{13a} and R^{13b} are as defined in Claim 1;

20 i) for compounds of formula I in which Y represents C(O)R^{10} , wherein R^{10} represents phenyl substituted in the *ortho*-position by an amino group, and optionally substituted by one or more further substituents selected from OH, halo, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, $\text{N(R}^8\text{)(R}^9\text{)}$, $\text{C(O)N(R}^8\text{)(R}^9\text{)}$, C_{1-4} alkyl and C_{1-4} alkoxy (which latter two groups are optionally

25 substituted by one or more halo atoms), and R^8 and R^9 are as defined in

Claim 1, reaction of a corresponding compound of formula I in which Y represents H with a compound of formula XIV,



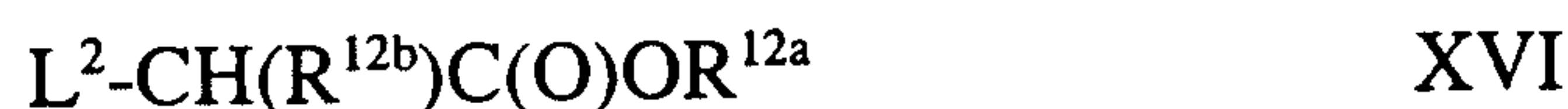
wherein D represents one to four optional substituents selected from OH,
 5 halo, C₁₋₄ alkanoyl, C₁₋₄ alkanoyloxy, N(R⁸)(R⁹), C(O)N(R⁸)(R⁹),
 C₁₋₄ alkyl and C₁₋₄ alkoxy (which latter two groups are optionally
 substituted by one or more halo atoms), and R⁸ and R⁹ are as defined in
 Claim 1;

j) for compounds of formula I in which Y represents R¹¹, wherein R¹¹ is as
 10 defined in Claim 1, reaction of a corresponding compound of formula I in
 which Y represents H, with a compound of formula XV,



wherein L² represents a leaving group and R¹¹ is as defined in Claim 1;

k) for compounds of formula I in which Y represents CH(R^{12b})C(O)OR^{12a}
 15 or CH(R^{12b})OC(O)OR^{12a}, wherein R^{12a} and R^{12b} are as defined in Claim 1,
 reaction of a corresponding compound of formula I in which Y represents
 H, with a compound of formula XVI,

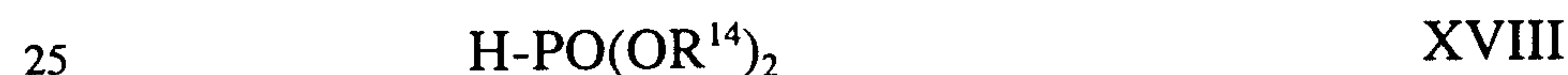


or a compound of formula XVII,



wherein R^{12a}, R^{12b} are as defined in Claim 1 and L² is as defined above;

l) for compounds of formula I in which Y represents PO(OR¹⁴)₂, wherein
 R¹⁴ is as defined in Claim 1, reaction of a compound of formula I in which
 Y represents H, with a compound of formula XVIII,



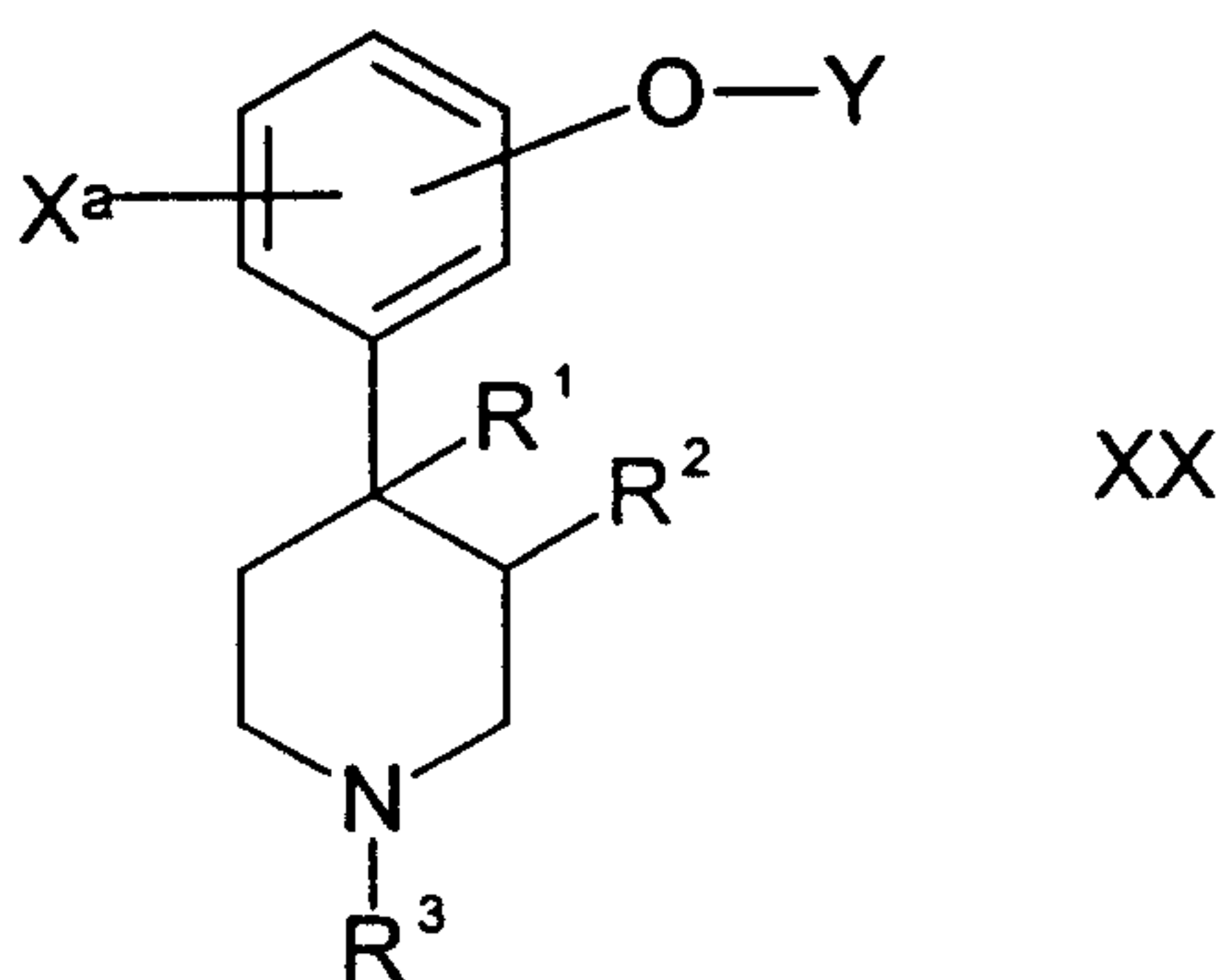
or a compound of formula XIX,



XIX

or a suitable derivative thereof, wherein R^{14} is as defined in Claim 1;

- m) for compounds of formula I in which X represents halo and optionally
 5 one or more further substituents defined in Claim 1 in respect of X,
 reaction of a corresponding compound of formula XX,



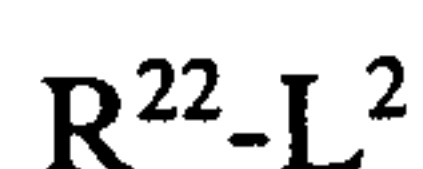
- wherein X^a represents one H and optionally one to three of the substituents
 defined in Claim 1 in respect of X, and R^1 , R^2 , R^3 and Y are as defined in
 10 Claim 1, with a halogenating agent;

- n) for compounds of formula I in which X represents nitro and optionally
 one or more further substituents defined in Claim 1 in respect of X,
 nitration of a corresponding compound of formula XX, as defined above;

- o) for compounds of formula I in which X represents $\text{S(O)}_2\text{OH}$ and
 15 optionally one or more further substituents defined in Claim 1 in respect
 of X, sulfonation of a corresponding compound of formula XX, as defined
 above;

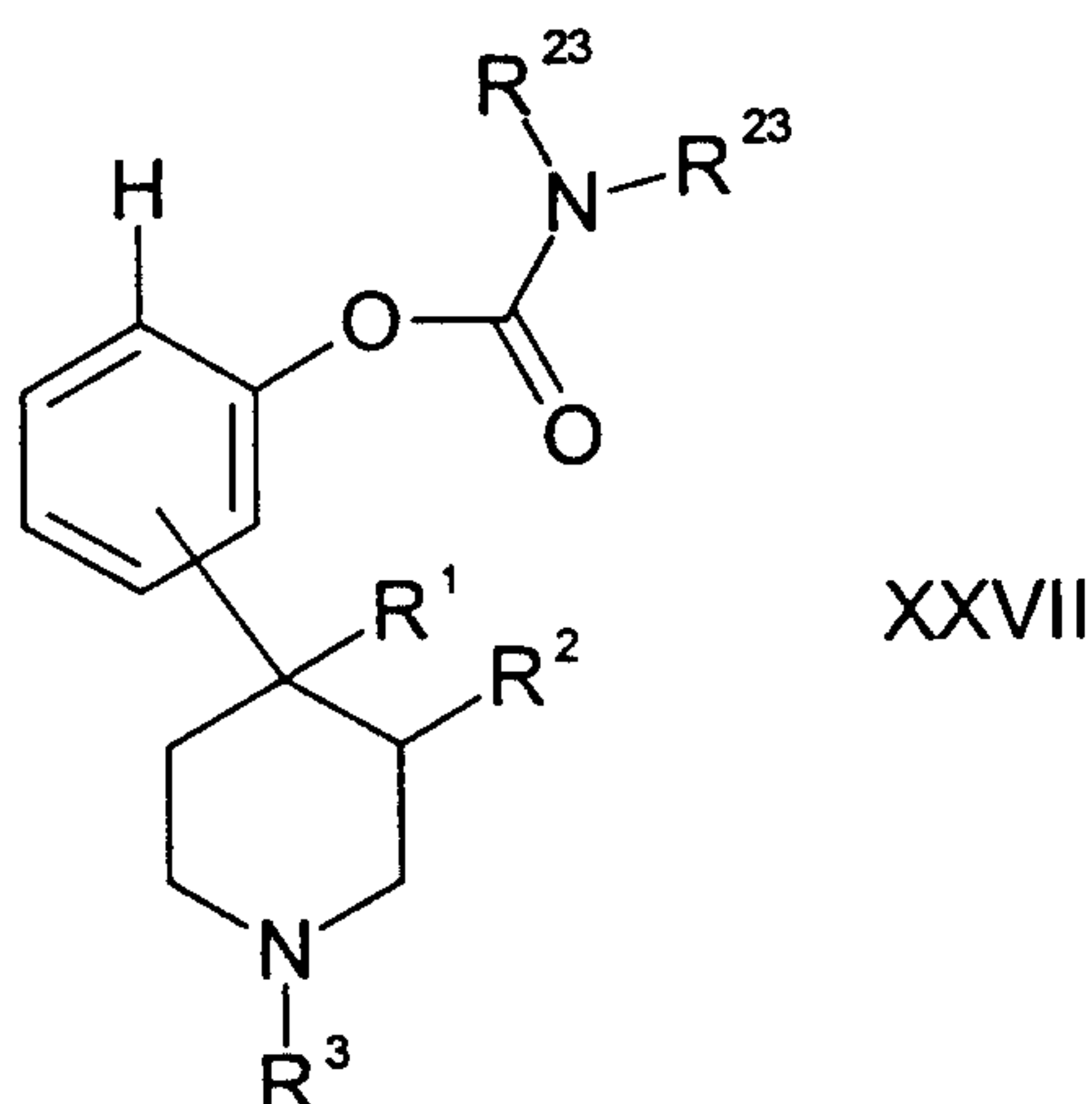
- p) for compounds of formula I in which X represents $\text{S(O)}_t\text{R}^{17a}$, wherein t
 is 0, and optionally one or more further substituents defined in Claim 1 in
 20 respect of X, wherein R^{17a} is as defined in Claim 1 except that it does not
 represent $\text{N(R}^{20a}\text{)(R}^{20b}\text{)}$, wherein R^{20a} and R^{20b} are as defined in Claim 1,
 sulfenylation of a corresponding compound of formula XX, as defined
 above;

- q) for compounds of formula I in which X represents $C(O)R^{16a}$ and optionally one or more further substituents defined in Claim 1 in respect of X, wherein R^{16a} is as defined in Claim 1 except that it does not represent H, acylation of a corresponding compound of formula XX, as
5 defined above;
- r) for compounds of formula I in which X represents $C(O)H$ and optionally one or more further substituents defined in Claim 1 in respect of X, reaction of a corresponding compound of formula XX, as defined above, with dimethylformamide;
- 10 s) for compounds of formula I in which X represents $OC(O)R^{16c}$ and optionally one or more further substituents defined in Claim 1 in respect of X, wherein R^{16c} is as defined in Claim 1, oxidation of a corresponding compound of formula I in which X represents $C(O)R^{16a}$, wherein R^{16a} is as defined in Claim 1;
- 15 t) for compounds of formula I in which X and/or OY represent OH, hydrolysis and/or reductive cleavage of a corresponding compound of formula I in which X represents $OC(O)R^{16c}$, wherein R^{16c} is as defined in Claim 1, and/or Y represents $C(=E)NR^8R^9$, wherein R^8 and R^9 are as defined in Claim 1;
- 20 u) for compounds of formula I in which X represents C_{1-10} alkyl, C_{3-10} alkenyl, C_{3-10} alkynyl, C_{3-7} cycloalkyl (which four groups are optionally substituted as defined in Claim 1, and which alkenyl and alkynyl groups are fully saturated at 1-C (relative to the benzene ring)) and optionally one or more further substituents defined in Claim 1 in
25 respect of X, reaction of a corresponding compound of formula XX, as defined above, with a compound of formula XXVI,



wherein R^{22} represents C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl (which four groups are optionally substituted by one or more substituents selected from halo, CN, nitro, OH, C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{3-7} cycloalkoxy, C_{1-6} alkanoyl, C_{4-8} cycloalkanoyl, C_{2-6} alkoxycarbonyl, C_{2-6} alkanoyloxy or $N(R^{15a})(R^{15b})$, and which alkenyl and alkynyl groups are fully saturated at 1-C (relative to L^2)) and L^2 , R^{15a} and R^{15b} are as defined in Claim 1;

v) for compounds of formula I in which X represents $C(O)N(R^{18c})(R^{18d})$, which group is in the *ortho*-position relative to OY, in which R^{18c} and R^{18d} independently represent C_{1-4} alkyl or C_{3-7} cycloalkyl, and Y represents H, rearrangement of a corresponding compound of formula XXVII,



wherein R^{23} represents C_{1-4} alkyl or C_{3-7} cycloalkyl, and R^1 , R^2 , and R^3 are as defined in Claim 1;

w) for compounds of formula I in which X represents C_{2-10} alkenyl and optionally one or more further substituents defined in Claim 1 in respect of X, wherein the double bond of the alkenyl chain is α,β - to the benzene ring, reaction of a corresponding compound of formula XX, as defined above, with a C_{2-10} aldehyde or a C_{2-10} ketone;

x) for compounds of formula I in which X represents $C(O)N(H)R^{18c}$ and optionally one or more further substituents defined in Claim 1 in respect of X, wherein R^{18c} represents C_{1-4} alkyl or C_{3-7} cycloalkyl, reaction of a

corresponding compound of formula XX, as defined above, with a compound of formula XXVIII,



wherein R^{23} is as defined above;

5 y) for compounds of formula I in which X represents $\text{B}(\text{OCH}_3)_2$ and optionally one or more further substituents defined in Claim 1 in respect of X, reaction of a corresponding compound of formula XX, as defined above, with trimethyl borate;

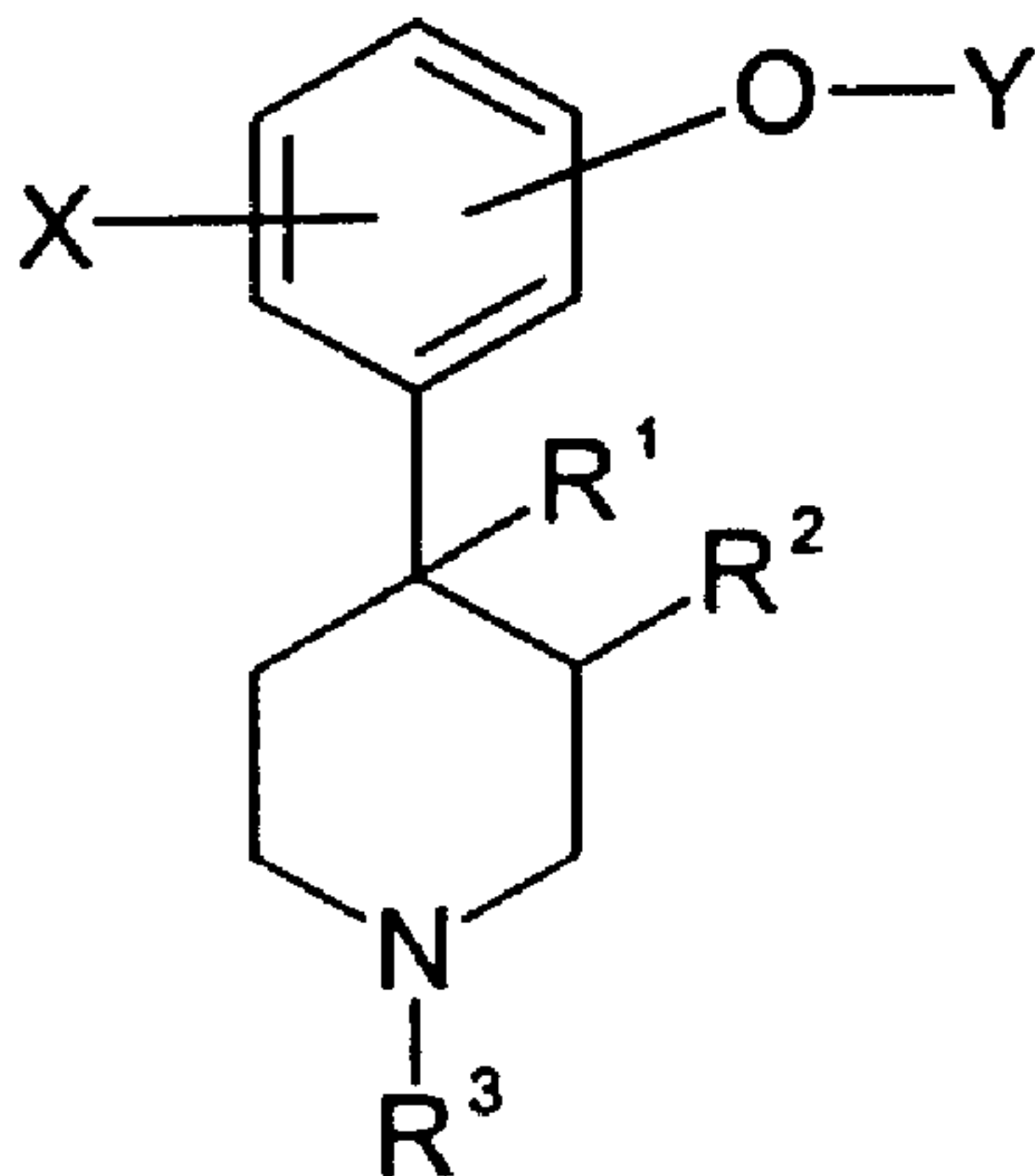
z) for compounds of formula I in which X represents C_{2-10} alkenyl or
10 C_{2-10} alkynyl, which alkenyl and alkynyl groups contain a carbon-carbon multiple bond that is α, β to the benzene ring, and which alkenyl and alkynyl groups are optionally substituted as defined in Claim 1 in respect of X, and optionally one or more further substituents defined in Claim 1 in respect of X, reaction of a corresponding compound of formula I in which
15 at least one X represents halo with a compound of formula XXIX,



wherein R^{24} represents C_{2-10} terminal alkenyl or C_{2-10} terminal alkynyl, which alkenyl and alkynyl groups are optionally substituted by one or more substituents selected from halo, CN, nitro, OH, C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{3-7} cycloalkoxy, C_{1-6} alkanoyl, C_{4-8} cycloalkanoyl, C_{2-6} alkoxycarbonyl, C_{2-6} alkanoyloxy or $\text{N}(\text{R}^{15a})(\text{R}^{15b})$, M represents (as
20 appropriate) H, a tin-containing moiety, a boron derivative, a zinc halide, a magnesium halide or an alkali metal (which latter three groups may be formed *in situ* from the corresponding halide), and R^{15a} and R^{15b} are as
25 defined in Claim 1;

aa) conversion of one functional group on an alkyl, heterocyclic or aryl group in a compound of formula I to another.

21. A compound of formula II, as defined in Claim 20.
22. A compound of formula III, as defined in Claim 20.
- 5 23. A compound of formula XX, as defined in Claim 20.
24. A Compound of formula XXVII, as defined in Claim 20.



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