P/00/008
Section 29(1)
Regulation 3.1(2)

AUSTRALIA
Patents Act 1990

Notice of Entitlement

We, ZENECA LIMITED, of 15 Stanhope Gate, London W1Y 6LN, UNITED KINGDOM being the applicant in respect of Application No. 62890/94, state the following:

1. We are the nominated person.

2. The nominated person is the assignee of the actual inventors.

3. The nominated person is the applicant of the basic application listed in the declaration under Article 8 of the PCT.

4. The basic application is the application first made in a Convention country in respect of the invention.

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Reference: IRN 420394

Dated 23 May, 1997

PHILLIPS ORMONDE & FITZPATRICK
Attorneys for:
ZENECA LIMITED

David B Fitzpatrick

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(12) PATENT ABRIDGMENT (11) Document No. AU-B-62890/94
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 692433

(54) Title
HETEROCYCLIC COMPOUNDS AS PLATELET AGGREGATION INHIBITORS

International Patent Classification(s)
(51)[5] C07D 213/74 C07D 215/44 C07K 005/06 C07K 005/08 C07K 005/10
(51)[6] C07D 213/81 C07D 215/42 C07D 239/42 C07D 401/04 C07D 401/12 A61K 031/495 A61K 031/505

(21) Application No. : 62890/94 (22) Application Date : 28.03.94

(87) PCT Publication Number : WO94/22835

(30) Priority Data

(31) Number	(32) Date	(33) Country
9306451	29.03.93	GB UNITED KINGDOM
9325610	15.12.93	GB UNITED KINGDOM

(43) Publication Date : 24.10.94

(44) Publication Date of Accepted Application : 11.06.98

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(56) Prior Art Documents
EP 100158
US 3875165

(57) Claim

1. A method for the prevention or treatment of a disease mediated by the binding of adhesion molecules to GPIIb/IIa in a warm-blooded animal requiring such treatment, which comprises administering an effective amount of a compound of formula I

$$Q\text{-}M^2\text{-}L\text{-}A \qquad I$$

wherein:

Q is 4- pyridyl optionally substituted by one or more of (1-4C)alkyl, (1-4C)alkoxy, halogeno, and (3-4C)alkylene which together with the two atoms to which it is attached forms a ring; and

M^2 is $-NR^3-$ in which R^3 is hydrogen, (1-4C)alkyl or a (2-3C)alkylene bridge attached to Q; or $-NR^4\text{-}D\text{-}TR^5-$ in which

(i) T is N; D is CH_2CO; CH_2SO_2; or (2-3C)alkylene optionally substituted by carboxy, (1-4C)alkoxycarbonyl, (1-4C)alkoxymethyl or a (2-3C)alkylene bridge attached to Q; and R^4 and R^5 together represent (2-3C)alkylene or CH_2CO, or each independently represents hydrogen or (1-4C)alkyl; or R^5 represents hydrogen or (1-4C)alkyl and R^4 represents (2-3C)alkylene attached to Q; or

. . ./2

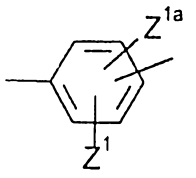
(ii) T is CH; D is CH_2CO, CH_2CH_2NH, (1-3C)alkylene optionally substituted by carboxy or (1-4C)alkoxycarbonyl, or (2-3C)alkyleneoxy; and R^4 and R^5 together represent (1-3C)alkylene; or

(iii) R^4 and -D-TR^5- together form a (5-6C)alkenylene group;

L is (4-7C)alkylene or a group of formula X^1-Y-X^2 in which

X^1 is a bond or a linking group selected from (1-4C)alkylene, (2-4C)alkenylene, (2-4C)alkynylene, (1-2C)alkylenephenylene, phenyleneoxy, phenyleneoxymethylene, phenylenecarbonyl, phenyleneCONH, (1-3C)alkylenecarbonyl, (1-2C)alkylenecarbonyl substituted by benzyl or p-hydroxybenzyl, methylidenepyrrolidin-1-ylacetyl, (1-2C)alkylenecarbonyloxy, (1-2C)alkyleneCONH, (1-2C)alkyleneCONH(1-2C)alkyleneCO, (1-2C)alkyleneCONH(1-2C)alkyleneCONH, benzyl(1-2C)alkyleneCONH, (1-4C)alkyleneoxy, (1-2C)alkyleneoxy(1-2C)alkylene, (1-2C)alkyleneoxy(1-2C)alkylenecarbonyl and (1-3C)alkyleneCH(OH), and when M^2 is -NR^4-D-TR^5-, carbonyl, carbonyl(1-3C)alkylene, CONH, (1-2C)alkyleneNHCO and CONH(1-3C)alkylene, and when T is CH, oxy, oxy(1-3C)alkylene, oxy(1-2C)alkylenecarbonyl and oxy(1-2C)alkylenephenylene;

Y is a cyclic group of formula:-



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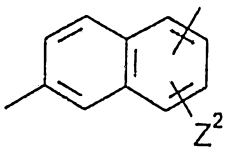

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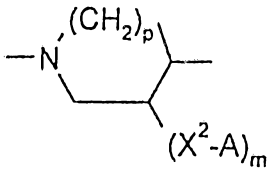

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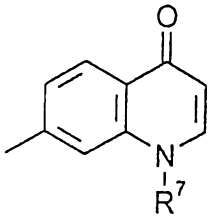

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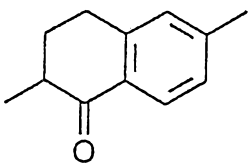

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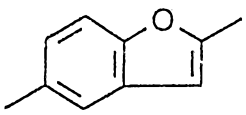

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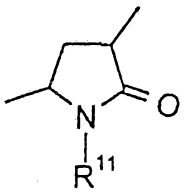

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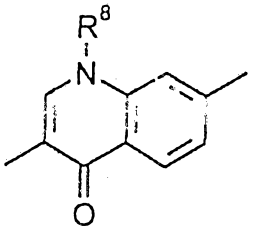

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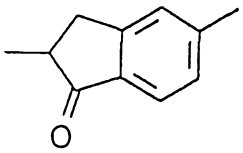

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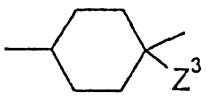

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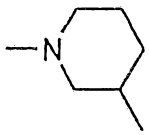

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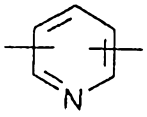

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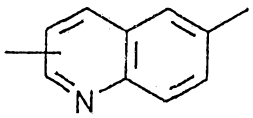

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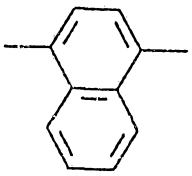

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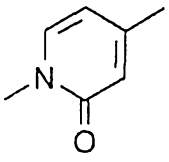

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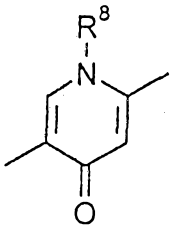

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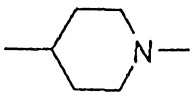

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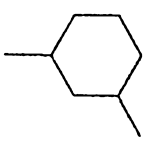

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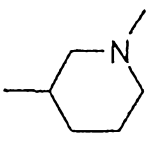

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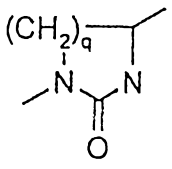
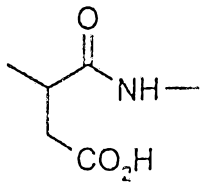


(u)

in which m is 0 or 1; p is 1 or 2; q is 0, 1, 2 or 3; Z^1, Z^{1a} and Z^2 represent hydrogen, hydroxy, halogene, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkylnyl, (1-4C)alkoxy, (1-4C)alkylthio, (2-4C)alkenyloxy, nitro, amino, (1-4C)alkylamino, (2-4C)alkanoylamino, cyano or (1-4C)alkoxycarbonyl, or have one of the meanings given for X^2-A; Z^3 represents hydrogen or hydroxy; R^7 is hydrogen, (1-4C)alkyl or phenyl(1-4C)alkyl; R^8 is as defined for R^7; E is O, S or NH; and R^{11} is hydrogen, (1-4C)alkyl, phenyl(1-4C)alkyl or a group of formula X^2-A;
or Y is an amide-containing group selected from $CONR^{22}$, $NR^{22}CO$ and a group of formula



in which R^{22} represents hydrogen, (1-4C)alkyl or phenyl(1-2C)alkyl; and
X^2 is a bond or a linking group selected from (1-4C)alkylene, (2-4C)alkenylene, oxy(1-4C)alkylene, oxy(5-6C)alkylene, oxy(2-4C)alkenylene, thio(1-3C)alkylene, SO_2(1-3C)alkylene, amino(1-3C)alkylene, SO_2NH(1-3C)alkylene, $NR^{21}CO$(1-2C)alkylene and $CONR^{21}$(1-2C)alkylene (where R^{21} represents hydrogen, (1-4C)alkyl or benzyl), in any of which the alkylene group may optionally be substituted by (2-4C)alkenyl; (2-4C)alkynyl; (1-4C)alkoxy; carboxy; (1-4C)alkoxycarbonyl; phenyl(1-2C)alkylCONH; phenyl(1-4C)alkoxycarbonyl; carboxy(1-2C)alkyl; phenyl(1-2C)alkyl; phenylsulphonyl(1-2C)alkyl; pyridyl; phenyl; amino or a group of formula $NR^{12}XR^6$ in which X is SO_2, CO or CO_2; R^{12} is hydrogen or (1-4C)alkyl and R^6 is (1-6C)alkyl, (6-10C)aryl, (6-10C)aryl(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl, morpholino(1-4C)alkyl, piperidino(1-4C)alkyl or N-(1-4C)alkylpiperidino(1-4C)alkyl; and
A is an acidic group, or an ester or amide derivative thereof, or a sulphonamide group; or a pharmaceutically acceptable salt or pro-drug thereof.

21. A compound of the general formula

$$Q\text{-}M^2\text{-}L\text{-}A \qquad I$$

wherein:

Q is 4-pyridyl optionally substituted by one or more of (1-4C)alkyl, (1-4C)alkoxy,

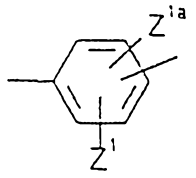
halogeno, and (3-4C)alkylene which together with the two atoms to which it is attached forms a ring;

M^2 is $-NR^3-$ in which R^3 is hydrogen, (1-4C)alkyl or a (2-3C)alkylene bridge attached to Q

L is (4-7C)alkylene or a group of formula X^1-Y-X^2 in which

X^1 is a bond or a linking group selected from (1-4C)alkylene, (2-4C)alkenylene, (2-4C)alkynylene, (1-2C)alkylenephenylene, phenyleneoxy, phenyleneoxymethylene, phenylenecarbonyl, phenyleneCONH, (1-3C)alkylenecarbonyl, (1-2C)alkylenecarbonyl substituted by benzyl or p-hydroxybenzyl, methylidenepyrrolidin-1-ylacetyl, (1-2C)alkylenecarbonyloxy, (1-2C)alkyleneCONH, (1-2C)alkyleneCONH(1-2C)alkyleneCO, (1-2C)alkyleneCONH(1-2C)alkyleneCONH, benzyl(1-2C)alkyleneCONH, (1-4C)alkyleneoxy, (1-2C)alkyleneoxy(1-2C)alkylene, (1-2C)alkyleneoxy(1-2C)alkylenecarbonyl and (1-3C)alkyleneCH(OH);

Y is a cyclic group of formula:



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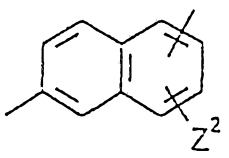

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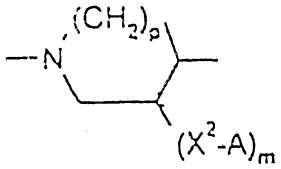

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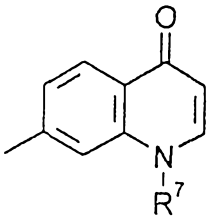

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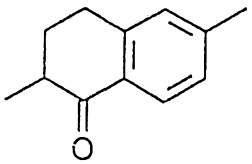

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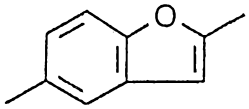

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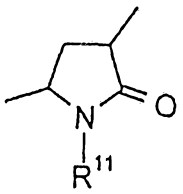
(g)



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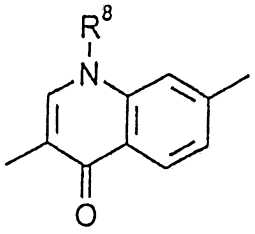

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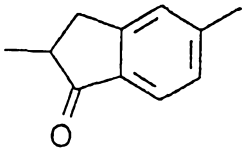

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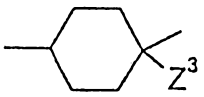

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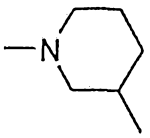

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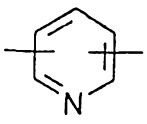

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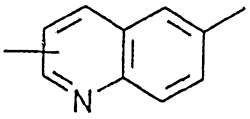

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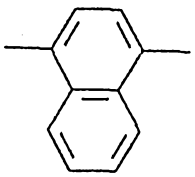

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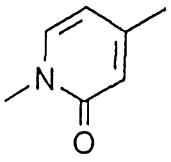

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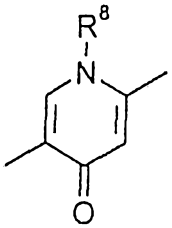

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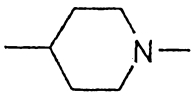

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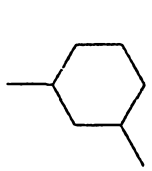

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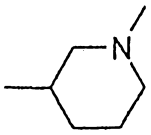

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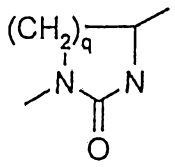
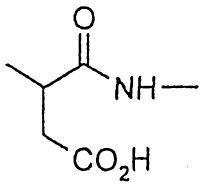


(u)

in which m is 0 or 1; p is 1 or 2; q is 0, 1, 2 or 3; Z^1, Z^{1a} and Z^2 represent hydrogen, hydroxy, halgeno, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkylthio, (2-4C)alkenyloxy, nitro, amino, (1-4C)alkylamino, (2-4C)alkanoylamino, cyano or (1-4C)alkoxycarbonyl, or have one of the meanings given for X^2-A; Z^3 represents hydrogen or hydroxy; R^7 is hydrogen, (1-4C)alkyl or phenyl(1-4C)alkyl; R^8 is as defined for R^7; E is O, S or NH; and R^{11} is hydrogen, (1-4C)alkyl, phenyl(1-4C)alkyl or a group of formula X^2-A;

or Y is an amide-containing group selected from $CONR^{22}$, $NR^{22}CO$ and a group of formula



in which R^{22} represents hydrogen, (1-4C)alkyl or phenyl(1-2C)alkyl; and

X^2 is a bond or a linking group selected from (1-4C)alkylene, (2-4C)alkenylene, oxy(1-4C)alkylene, oxy(5-6C)alkylene, oxy(2-4C)alkenylene, thio(1-3C)alkylene, SO_2(1-3C)alkylene, amino(1-3C)alkylene, SO_2NH(1-3C)alkylene, $NR^{21}CO$(1-2C)alkylene and $CONR^{21}$(1-2C)alkylene (where R^{21} represents hydrogen, (1-4C)alkyl or benzyl), in any of which the alkylene group may optionally be substituted by (2-4C)alkenyl; (2-4C)alkynyl; (1-4C)alkoxy; carboxy; (1-4C)alkoxycarbonyl; phenyl(1-2C)alkylCONH; phenyl(1-4C)alkoxycarbonyl; carboxy(1-2C)alkyl; phenyl(1-2C)alkyl; phenylsulphonyl(1-2C)alkyl; pyridyl; phenyl; amino or a group of formula $NR^{12}XR^6$ in which X is SO_2,CO or CO_2; R^{12} is hydrogen or (1-4C)alkyl and R^6 is (1-6C)alkyl, (6-10C)aryl, (6-10C)aryl(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl,

morpholino(1-4C)alkyl, piperidino(1-4C)alkyl or N-(1-4C)alkylpiperidino(1-4C)alkyl; and A is carboxy or an ester or amide thereof, an acyl sulphonamide group of formula $CONHSO_2R^9$, in which R^9 is (1-4C)alkyl or optionally substituted phenyl; a 1H-tetrazol-5-yl group or a sulphonamide group of formula $NHSO_2R^{10}$ in which R^{10} is (1-6C)alkyl or phenyl optionally substituted by one or two optional substituents selected from (1-4C)alkyl, (1-4C)alkoxy and halogen; or a pharmaceutically acceptable salt or pro-drug thereof, provided that Y may not represent a 1,4-phenylene group of formula (a) when A is carboxy or an amide or ester thereof, or when X^2 is a bond and A is $NHSO_2R^{10}$ in which R^{10} is (1-6C)alkyl; and provided that Y may not represent a 1,2- or 1,3-phenylene of formula (a) when X^2 is a bond or oxy(1-4C)alkylene and A is carboxy or an amide or ester thereof or A is 1H-tetrazol-5-yl.

62890/94

PCT

ANNOUNCEMENT OF THE LATER PUBLICATION OF INTERNATIONAL SEARCH REPORTS

INTERNATIONAL APPLICATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 213/74, A61K 31/44, C07D 215/44
A61K 31/47, 31/505
A3

(11) International Publication Number: WO 94/22835

(43) International Publication Date: 13 October 1994 (13.10.94)

(21) International Application Number: PCT/GB94/00648

(22) International Filing Date: 28 March 1994 (28.03.94)

(30) Priority Data:

9306451.7	29 March 1993 (29.03.93)	GB
9325610.5	15 December 1993 (15.12.93)	GB

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(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
22 December 1994 (22.12.94)

692439

(54) Title: HETEROCYCLIC COMPOUNDS AS PLATELET AGGREGATION INHIBITORS

(57) Abstract

A compound of the general formula (I): $(M^1)_n$-Q-$(M^2)_{1-n}$-L-A wherein: n is 0 or 1; M^1 is an amino group; Q is an aromatic heterocyclic group containing a basic nitrogen atom; M^2 is an imino group; L is a template group; and A is an acidic group, or an ester or amide derivative thereof, or a sulphonamide group; and pharmaceutically acceptable salts and pro-drugs thereof, for use in the treatment of a disease in which platelet aggregation mediated by the binding of adhesion molecules to GPIIb-IIIa is involved. Novel compounds are also disclosed.

HETEROCYCLIC COMPOUNDS

The present invention relates to a group of heterocyclic compounds which inhibit cell adhesion (for example, platelet aggregation), to processes for their preparation and to pharmaceutical compositions containing them.

A variety of diseases involve cell adhesion during their development. For example, platelet aggregation is involved in the formation of blood thrombi, which can lead to diseases such as thrombosis, (eg stroke and thrombotic events accompanying unstable angina and transient ischaemic attack), myocardial infarction, atherosclerosis, thromboembolism and reocclusion during and after thrombolytic therapy.

It is widely believed that the platelet membrane glycoprotein IIb/IIIa (GPIIb/IIIa) mediates platelet aggregation. Adhesion molecules such as fibrinogen and von Willebrand Factor are believed to bind to GPIIb/IIIa sites on adjacent platelets and thereby cause them to aggregate. Other adhesion molecules which are known to bind to the GPIIb/IIIa are fibronectin, vitronectin and thrombospondin.

Compounds which inhibit platelet aggregation and the binding of adhesion molecules to GPIIb/IIIa are known. Commonly these compounds are based upon the binding sites of the adhesion molecules, which are peptides. For example, the portion of fibrinogen which is believed to bind to GPIIb/IIIa is the amino acid sequence RGD. This sequence may be viewed as comprising an arginine group separated from an acidic group by a template group.

Surprisingly, as a result of random screening, the ability to inhibit platelet aggregation and to inhibit the binding of fibrinogen to GPIIb/IIIa has now been found to be possessed by certain heterocyclic compounds containing a 4-(4-pyridyl)piperazin-1-yl or related group.

It is disclosed in European Patent Application No. 0100158 that certain 3-pyridylaminoalkyl derivatives such as methyl 2-[4-(3-pyridylaminomethyl)phenoxy]acetate (Example 2 thereof) possess thromboxane A_2 synthetase inhibitory activity and that the compounds

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may be of value as anti-inflammatory agents, as inhibitors of platelet aggregration, as anti-ulcer agents, as antihypertensive agents and as inhibitors of tumour cell metastasis.

It is disclosed in Japanese Patent Application No. 57183738 (Chem. Abs., 98, 125889b) that certain pyridine derivatives such as 3-dimethylaminopropyl 4-(4-pyridinylamino)benzoate possess thrombolytic activity.

It is disclosed in European Patent Application No. 0244115 that certain piperazine derivatives such as 4-[4-(4-pyridyl)piperazin-1-yl]benzamide possess antiarrthymic activity.

It is disclosed in US Patent No. 3,875,165 that certain quinoline derivatives possess antimalarial activity and that certain of the compounds possess other activities including blood platelet aggregation inhibitory activity. One of the disclosed compounds is 3-[3-(7-chloro-4-quinolylamino)benzamido]-1-ethylpiperidine (example 18 thereof).

It is disclosed in French Patent Application No. 2298330 that certain quinoline derivatives such as 2-(7-chloro-4-quinolylamino)-N-(1-ethyl-3-piperidyl)benzamide (example 1 thereof) possess anti-inflammatory activity.

It is disclosed in International Patent Application WO 92/22533 that certain quinoline derivatives such as 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methylquinoline (example 1 thereof) possess angiotensin A2 antagonist activity.

It is disclosed in European Patent Application No. 0320032 that certain pyridazine derivatives such as ethyl 3-[3-[1-(6-chloro-3-pyridazinyl)-4-piperidinyl]propoxy]benzoate (example 99 thereof) possess anti-viral activity.

It is disclosed in European Patent Application No. 0264883 that certain pyridine derivatives such as 2-[(2-ethoxycarbonylphenyl)-ethyl]-5-methyl-4-piperidinopyridine (example 100 thereof) possess anti-ulcer activity.

It is disclosed in European Patent Application No. 0154969 that certain piperazine derivatives such as 5-[4-[4-(2-pyridyl)-1-piperazinyl]butyryl]salicylamide (compound no. 18 thereof) possess antihypertensive activity.

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According to one aspect, therefore, the present invention provides a compound of the general formula

$$(M^1)_n\text{-}Q\text{-}(M^2)_{1-n}\text{-}L\text{-}A \qquad I$$

wherein: n is 0 or 1;

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M^1 is an amino group;
Q is an aromatic heterocyclic group containing a basic nitrogen atom;
M^2 is an imino group;
L is a template group; and
A is an acidic group, or an ester or amide derivative thereof, or a sulphonamide group;
and pharmaceutically acceptable salts and pro-drugs thereof, for use in the treatment of a disease in which platelet aggregation mediated by the binding of adhesion molecules to GPIIb-IIIa is involved.

Without wishing to be bound by theory, it is believed that the basic nitrogen atom in the aromatic heterocyclic group represented by Q functions as a replacement for the strongly basic guanidine group in arginine. The function of the nitrogen atom which is attached to Q in the amino group represented by M^1 or the imino group represented by M^2 is believed to be to contribute to the ability of the nitrogen atom in Q to function as a base. For example, when $(M^1)_n$-Q-$(M^2)_{1-n}$ represents a 4-(4-pyridyl)piperazin-1-yl group, the nitrogen atom in the piperazin-1-yl group is believed to contribute to the ability of the nitrogen atom in the pyridyl group to function as a base as shown below:-



As will be described in more detail hereinafter, the group $(M^1)_n$-Q-$(M^2)_{1-n}$ has been found to be associated with ability to antagonise the binding of fibrinogen to GPIIb/IIIa when combined with an acidic or sulphonamide group and a wide variety of template groups. Ester and amide derivatives of the acids have also been found to be active, but generally with lower potency than the acids. This activity may be due to the intrinsic activity of the compounds or to their hydrolysis to the corresponding acids in the test systems used. The group $(M^1)_n$-Q-$(M^2)_{1-n}$ has also been found to be associated with a favourable effect on bioavailability. Certain of the compounds of

formula I have been found to possess particularly good activity on oral administration. Commonly, esters and amides have been found to possess superior oral activity to their parent acids.

In the compounds of formula I, M^1 is an amino group, including $-NR^1R^2$ in which R^1 and R^2 are each independently hydrogen or (1-4C)alkyl or together form (4-5C)alkylene. Examples of values for R^1 and R^2 are hydrogen and methyl. Examples of values for $-NR^1R^2$ are dimethylamino and pyrrolidin-1-yl.

Q is an aromatic heterocyclic group containing a basic nitrogen atom, including imidazolyl, pyridyl, pyrimidyl, pyrazinyl, quinolyl and purinyl, optionally substituted by one or more substituents, including (1-4C)alkyl, (1-4C)alkoxy, halogeno, and (3-4C)alkylene which, together with the two atoms to which it is attached forms a ring. Examples of values for the aromatic heterocyclic group are 2-imidazolyl, 4-imidazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 4-pyrimidyl, 2-pyrazinyl, 2-quinolinyl, 4-quinolinyl and 6-purinyl. Examples of values for optional substituents are: for (1-4C)alkyl, methyl; for (1-4C)alkoxy, methoxy; for halogeno, chloro and bromo; and for (3-4C)alkylene, butylene. Examples of values for Q are 3-pyridyl; 4-pyridyl; 2-methyl-4-pyridyl; 2,6-dimethyl-4-pyridyl; 4-pyrimidyl; 4-(5,6,7,8-tetrahydro)quinolinyl; 4-quinolinyl and 2-methyl-4-quinolinyl. Preferably, when Q is pyridyl, pyrimidyl, pyrazinyl, quinolyl or purinyl, the basic nitrogen atom contained by Q is located at the 4-position relative to M^1, when n is 1, or M^2, when n is 0. Q is preferably 4-pyridyl, optionally substituted as defined hereinabove.

M^2 is an imino group; including $-NR^3-$ in which R^3 is hydrogen, (1-4C)alkyl or a (2-3C)alkylene bridge attached to Q; and $-NR^4-D-TR^5-$ in which

(i) T is N; D is CH_2CO; CH_2SO_2; (2-3C)alkylene optionally substituted by carboxy, (1-4C)alkoxycarbonyl, (1-4C)alkoxymethyl or a (2-3C)alkylene bridge attached to Q; and R^4 and R^5 together represent (2-3C)alkylene or CH_2CO, or each independently represents hydrogen or (1-4C)alkyl or R^5 represents hydrogen or (1-4C)alkyl and R^4 represents (2-3C)alkylene attached to Q; or

(ii) T is CH; D is CH_2CO, CH_2CH_2NH, (1-3C)alkylene optionally substituted by carboxy or (1-4C)alkoxycarbonyl, or (2-3C)alkyleneoxy; and R^4 and R^5 together represent (1-3C)alkylene; or

(iii) R^4 and -D-TR^5- together form a (5-6C)alkenylene group.

Examples of values for -NR^3- when R^3 is hydrogen or (1-4C)alkyl are NH and methylimino. Examples of values for the group Q-M^2 when M^2 is a group of formula -NR^3- in which R^3 is a (2-3C)alkylene bridge attached to Q are 1,2,3,4-tetrahydro-1,6-naphthyridin-1-yl and pyrrolo[3,2-c]pyridin-1-yl.

Examples of values for -NR^4-D-TR^5- when T is N are 5-oxoimidazolidin-1,3-diyl; 2-oxopiperazin-1,4-diyl, 2,6-dioxopiperazin-1,4-diyl, 1,1-dioxo-1,2,5-thiadiazin-2,5-diyl, piperazin-1,4-diyl, 2-carboxypiperazin-1,4-diyl, 3-carboxypiperazin--1,4-diyl, 2-methoxycarbonylpiperazin-1,4-diyl, 3-methoxycarbonyl-piperazin-1,4-diyl, 2-methoxymethylpiperazin-1,4-diyl, 3-methoxymethylpiperazin-1,4-diyl and N-2-(N'-methyl)aminoethyl(N-methyl)amino.

Examples of values for Q.M^2 when T is N and D is (2-3C)alkylene optionally substituted by a (2-3C)alkylene bridge attached to Q include 1,2,3,4-tetrahydro-1,6-naphthyridin-2-yl and pyrrolo[3,2-c]pyridin-2-ylethylamino.

Examples of values for -NR^4-D-TR^5- when T is CH are pyrrolidin-3,1-diyl, 3-oxo-pyrrolidin-4,1-diyl 2-carboxypyrrolidin--4,1-diyl, 2-methoxycarbonylpyrrolidin-4,1-diyl, 2-ethoxycarbonyl-pyrrolidin-4,1-diyl, piperidin-3,1-diyl, piperidin-4,1-diyl, piperazin-2,4-diyl and morpholin-2,4-diyl.

An example of a group of formula -NR^4-D-TR^5- in which R^4 and -D-TR^5- together form a (5-6C)alkenylene group is 1,2,3,6-tetrahydro-pyridin-4,1-diyl.

Particularly preferred values for M^2 are piperazin-1,4-diyl, piperidin-4,1-diyl and 2-oxo-piperazin-1,4-diyl.

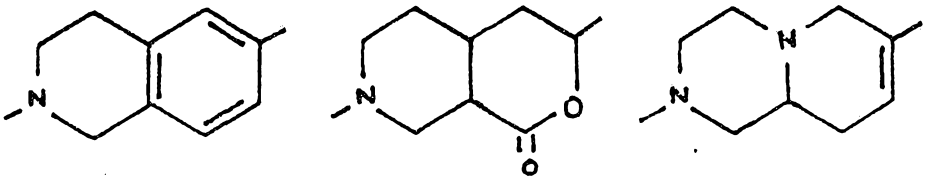
Preferably n is 0.

Accordingly, particularly preferred values for the group $(M^1)_n$-Q-$(M^2)_{1-n}$ are 4-(4-pyridyl)piperazin-1-yl, 4-(4-pyridyl)-2-oxopiperazin-1-yl and 1-(4-pyridyl)piperidin-4-yl.

L is a template group, including (4-7C)alkylene and a group of formula X^1-Y-X^2 in which

X^1 is a bond or a linking group, including (1-4C)alkylene, (2-4C)alkenylene, (2-4C)alkynylene, (1-2C)alkylenephenylene, phenyleneoxy, phenyleneoxymethylene, phenylenecarbonyl, phenyleneCONH, (1-3C)alkylenecarbonyl, (1-2C)alkylenecarbonyl substituted by benzyl or p-hydroxybenzyl, methylidenepyrrolidin-1-ylacetyl, (1-2C)-alkylenecarbonyloxy, (1-2C)alkyleneCONH, (1-2C)alkyleneCONH(1-2C)alkyleneCO, (1-2C)alkyleneCONH(1-2C)alkyleneCONH, benzyl(1-2C)alkyleneCONH, (1-4C)alkyleneoxy, (1-2C)alkyleneoxy(1-2C)alkylene, (1-2C)alkyleneoxy(1-2C)alkylenecarbonyl, (1-3C)alkyleneCH(OH), and, when M^2 is -NR^4-D-TR^5-, carbonyl, carbonyl(1-3C)alkylene, CONH, (1-2C)alkyleneNHCO and CONH(1-3C)alkylene, and when T is CH, oxy, oxy(1-3C)alkylene, oxy(1-2C)alkylenecarbonyl or oxy(1-2C)alkylenephenylene;

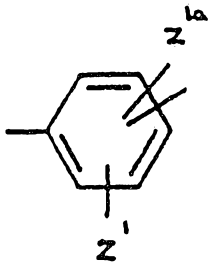
or, when n is 0, X^1 together with M^2 may form a group of formula



Examples of values for X^1 are a bond, methylene, ethylene, propylene, 1-methylethylene, ethenylene, ethynylene, methylenephenylene, phenyleneoxy, phenyleneoxymethylene, phenylenecarbonyl, phenyleneCONH, methylenecarbonyl, ethylenecarbonyl, 1-methylethylenecarbonyl, ethylidinecarbonyl, 2-propylidinecarbonyl, benzylmethylenecarbonyl, p-hydroxybenzylmethylenecarbonyl, methylidenepyrrolidin-1-ylacetyl, methylenecarbonyloxy, methyleneCONH, methyleneCONHmethyleneCONH, benzylmethyleneCONH, methyleneoxy, ethyleneoxy, propyleneoxy, butyleneoxy, methyleneoxymethylene, methyleneoxymethylenecarbonyl, methyleneCH(OH), and, when M^2 is -NR^4-D-TR^5-, carbonyl, carbonylmethylene, carbonylethylene, CONH, methyleneNHCO, CONHmethylene, and when T is CH; oxy, oxymethylene, methyleneNHCO, oxymethylenecarbonyl and oxymethylenephenylene.

Particularly preferred values for X^1 include methylenecarbonyl, ethylenecarbonyl ethylidinecarbonyl, carbonyl, carbonylethylene, methyleneoxy, ethyleneoxy and, when M^2 is $-NR^4-D-TR^5-$ and T is CH; oxy.

Y is a cyclic group, including groups of formulae:-



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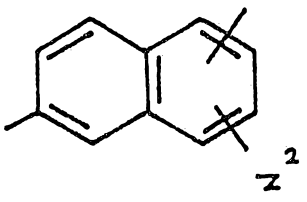

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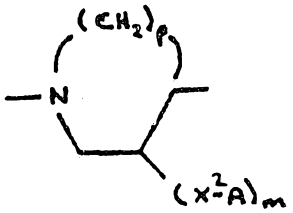

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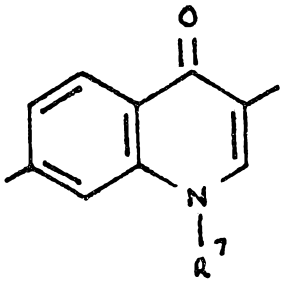

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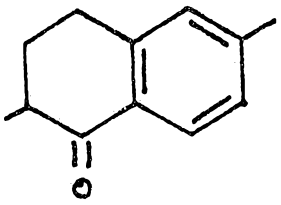

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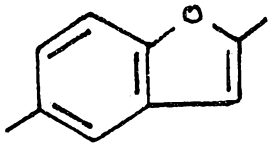

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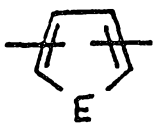

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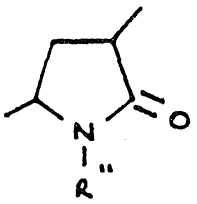

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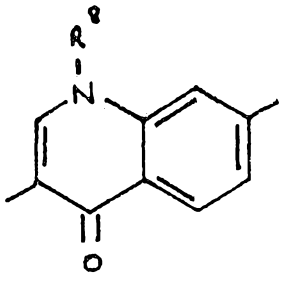

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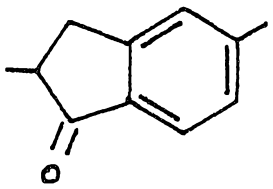

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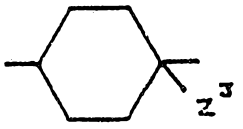

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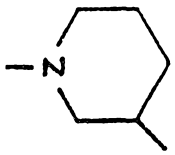

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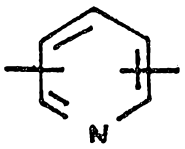

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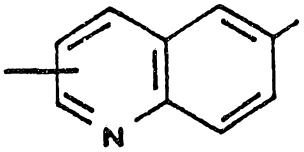

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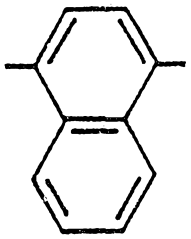

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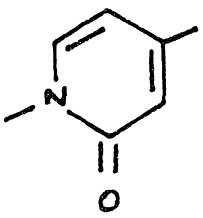

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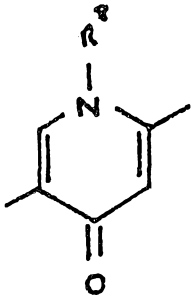
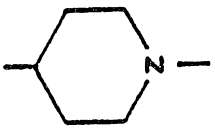


(q)



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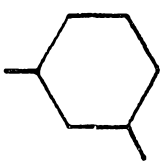

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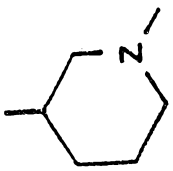
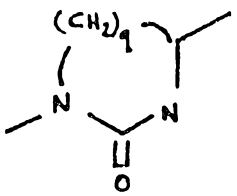
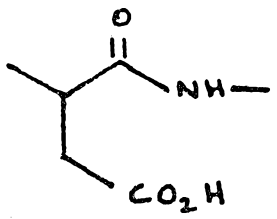


(t)



(u)

in which m is 0 or 1, p is 1 or 2, q is 0,1,2 or 3, Z^1, Z^{1a} and Z^2 represent hydrogen or optional substituents, including hydroxy, halogeno, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkylthio, (2-4C)alkenyloxy, nitro, amino, (1-4C)alkylamino, (2-4C)alkanoylamino, cyano and (1-4C)alkoxycarbonyl, or have one of the meanings given for X^2-A, Z^3 represents hydrogen or hydroxy, R^7 is hydrogen, (1-4C)alkyl or phenyl(1-4C)alkyl, R^8 is as defined for R^7, and E is O, S or NH; and R^{11} is hydrogen, (1-4C)alkyl, phenyl(1-4C)alkyl or a group of formula X^2.A.
or Y is an amide-containing group, including $CONR^{22}$, $NR^{22}CO$ and a group of formula



in which R^{22} represents hydrogen, (1-4C)alkyl or phenyl(1-2C)alkyl.

Preferred groups of formula (a) are groups in which X^1 and X^2 are attached respectively at the 1 and 3 or 1 and 4 positions. Z^1 is preferably located ortho to X^2; that is to say at the 2 or 6 position. Examples of such groups include 1,3-phenylene, 5-methoxycarbonylmethoxy-1,3,phenylene, 5-carboxymethoxy-1,3-phenylene, 1,4-phenylene, 2-methoxy-1,4-phenylene, 3-methoxy-1,4-phenylene, 2,6-dichloro-1,4-phenylene, 2,6-di-tert-butyl-1,4-phenylene, 2-carboxymethoxy-1,4-phenylene, 2-methoxycarbonylmethoxy-1,4-phenylene and 2-ethoxycarbonylmethoxy-1,4-phenylene, 3-methyl-1,4-phenylene, 2-allyl-1,4-phenylene, 2-propyl-1,4-phenylene, 2-nitro-1,4-phenylene, 2-methyl-1,4-phenylene, 3-methoxycarbonylmethoxy-1,4-phenylene, 3-ethoxycarbonylmethoxy-1,4-phenylene, 3-carboxymethoxy-1,4,phenylene, and 2-tert-butyloxycarbonylmethyloxy-1,4-phenylene.

Examples of values for Z^1, Z^{1a} and Z^2 are hydrogen, hydroxy, chloro, fluoro and bromo, methyl, ethyl, propyl, t-butyl, allyl, methoxy, methylthio, allyloxy, nitro, cyano, methoxycarbonyl, carboxymethoxy, methoxycarbonylmethoxy, ethoxycarbonylmethoxy and tert-butyloxycarbonylmethoxy.

Examples of values for R^7, R^8 and R^{11} are hydrogen, methyl and benzyl.

When Y is a group of formula (c), preferably m is 0 and p is 2.

Y is preferably a 1,2-, 1,3- or 1,4-phenylene group of formula (a); a napth-1,6-diyl group of formula (b); a piperidin-4,1-diyl group of formula (c) a 4-quinolon-3,7-diyl group of formula (d); a tetralon-6,2-diyl group of formula (e); a benzofuran-2,5-diyl group of formula (f); a 4-quinolon-7,3-diyl group of formula (i); a cyclohexa-4,1-diyl group of formula (k); a piperidin-3,1-diyl group of formula (l); a pyridin-2,5-diyl or pyridin-2,6-diyl group of formula (m); a quinolin-6,2-diyl or quinolin-6,4-diyl group of formula (n); a napth-1,4-diyl group of formula (o); a 2-pyridon-4,1-diyl group of formula (p); a 4-pyridon-2,5-diyl group of formula (q), a piperidin-1,4-diyl group of formula (r); a cyclohexa-3,1-diyl group of formula (s); a piperidin-1,3-diyl group of formula (t), CONH, NHCO or a 2-carboxyethylidinecarboxamido group.

Examples of values for Y are 1,2-phenylene; 1,3-phenylene; 5-methoxycarbonyl-1,3-phenylene; 1,4-phenylene; 2,6-dichloro-1,4-phenylene; 2-methyl-1,4-phenylene; 2-propyl-1,4-phenylene; 2-allyl-1,4-phenylene; 2,6-di-tert-butyl-1,4-phenylene; 2-methoxy-1,4-phenylene; 3-methoxy-1,4-phenylene; 2-carboxymethoxy-1,4-phenylene; 2-methoxycarbonylmethoxy-1,4-phenylene; 2-ethoxycarbonylmethoxy-1,4-phenylene; 2-tert-butyloxycarbonyl-methoxy-1,4-phenylene; 3-carboxymethoxy-1,4-phenylene; 3-methoxycarbonylmethoxy-1,4-phenylene; 2-nitro-1,4-phenylene; napth-1,6-diyl; piperidin-4,1-diyl; 3-carboxy-methoxypiperidin-4,1-diyl; 1-ethyl-4-quinolon-3,7-diyl; 1-propyl-4-quinolon-3,7-diyl; tetralon-6,2-diyl; benzofuran-2,5-diyl; 1-benzyl-4-quinolon-7,3-diyl; 1-hydroxycyclohexa-1,4-diyl; piperidin-3,1-diyl; pyridin-2,5-diyl; pyridin-2,6-diyl; quinolin-6,2-diyl; quinolin-6,4-diyl; naphth-1,4-diyl; 2-pyridon-4,1-diyl; 1-benzyl-4-pyridon-2,5-diyl; piperidin-1,4-diyl; cyclohexa-3,1-diyl; piperidin-1,3-diyl; CONH and 2-carboxyethylidenecarboxamido.

X^2 is a bond or a linking group, including, (1-4C)alkylene, (2-4C)alkenylene, oxy(1-4C)alkylene, oxy(5-6C)alkylene, oxy(2-4C)alkenylene, thio(1-3C)alkylene, SO_2(1-3C)alkylene, amino(1-3C)alkylene, SO_2NH(1-3C)alkylene, $NR^{21}CO$(1-2C)alkylene, $CONR^{21}$(1-2C)alkylene (where R^{21} represents hydrogen, (1-4C)alkyl or benzyl), in any of which the alkylene group may optionally be substituted by (2-4C)alkenyl; (2-4C)alkynyl; (1-4C)alkoxy; carboxy; (1-4C)alkoxycarbonyl; phenyl(1-4C)alkoxycarbonyl; phenyl(1-2C)alkylNHCO; carboxy(1-2C)alkyl; phenyl(1-2C)alkyl; phenylsulphonyl(1-2C)alkyl; pyridyl, phenyl; amino or a group of formula $NR^{12}XR^6$ in which X is SO_2, CO or CO_2; R^{12} is hydrogen or (1-4C)alkyl and R^6 is (1-6C)alkyl, (6-10C)aryl, (6-10C)aryl(1-4C)-alkyl, di(1-4C)alkylamino(1-4C)alkyl, morpholino(1-4C)alkyl, piperidino(1-4C)alkyl or N-(1-4C)alkylpiperidino(1-4C)alkyl.

Examples of values for X^2 are a bond, methylene, ethylene, ethenylene, oxymethylene, 2-oxyethylene, 3-oxypropylene, 2-oxyprop-2-ylene, 4-oxybutylene, 5-oxypentylene, thiomethylene, aminomethylene, carboxamidomethylene, 2-carboxamidoethylene, 2-phenylethylidene, oxy(methoxycarbonyl)methylene, 1-(2-carboxyethyl)ethylene, 1-(benzyloxycarbonyl)ethylene, and groups of formula $CH_2CH(NR^{12}XR^6)$ such as 1-(butylsulphonylamino)ethylene [$CH_2CH(NHSO_2CH_2CH_2CH_2CH_3)$], 1-(methylsulphonylamino)ethylene, 1-(benzylsulphonylamino)ethylene, 1-(p-toluenesulphonylamino)ethylene, 2-(butylsulphonylamino)ethylene, 2-(p-toluenesulphonylamino)ethylene, 3-oxy(1-(butylsulphonylamino)propylene), 2-carboxamido(2-phenyl)ethylene and 2-carboxamidopropylene.

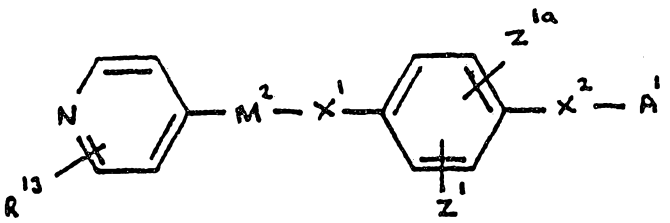
Examples of values for L when it represents (4-7C)alkylene include butylene, pentylene and hexylene.

A is an acidic group, including carboxy or an ester or amide thereof, an acyl sulphonamide group of formula $CONHSO_2R^9$, including groups in which R^9 is (1-4C)alkyl or optionally substituted phenyl; a 1H-tetrazol-5-yl group or a sulphonamide group of formula $NHSO_2R^{10}$ in which R^{10} is (1-6C)alkyl such as methyl or butyl; fluoro(1-6C)alkyl such as trifluoromethyl; or phenyl unsubstituted or substituted by one or two optional substituents selected from (1-4C)alkyl, (1-4C)alkoxy and halogen; for example p-tolyl.

A is preferably a carboxy group, a (1-4C)alkoxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, or tert-butoxycarbonyl, a (1-6C)alkylsulphonamide group such as methanesulphonylamino, butylsulphonylamino, or p-tolylsulphonylamino.

Accordingly, particularly preferred groups of formula $Y\text{-}X^2\text{-}A$ are 2-(4-phenoxy)acetic acid and 2,2'-(4-phenylene-1,2-dioxy)diacetic acid.

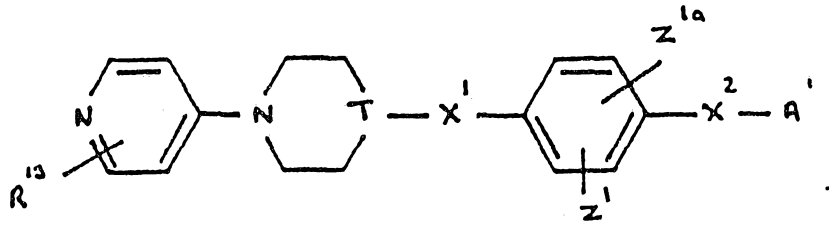
One group of compounds of particular interest is that of general formula Ia



Ia

in which M^2, X^1, Z^1, Z^{1a} and X^2 are as defined hereinabove; A^1 is a carboxyl group or an ester thereof as defined hereinabove, and R^{13} is hydrogen, (1-4C)alkyl, (1-4C)alkoxy or halogen.

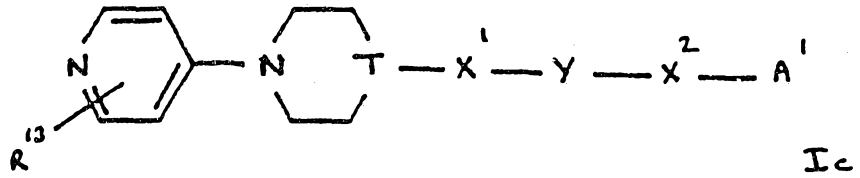
Another group of compounds of particular interest is that of general formula Ib



Ib

in which T, X^1, Z^1, Z^{1a}, X^2, R^{13} and A^1 are as defined hereinabove.

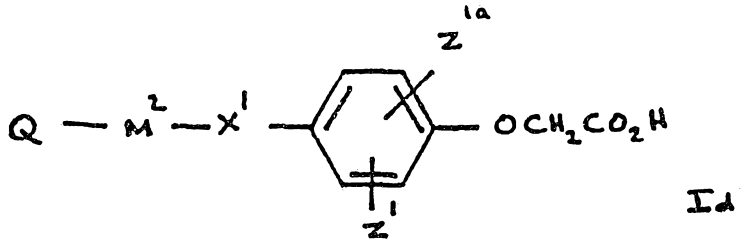
Another group of compounds of particular interest is that of general formula Ic



Ic

in which T, X^1, Y, X^2, R^{13} and A^1 are as defined hereinabove.

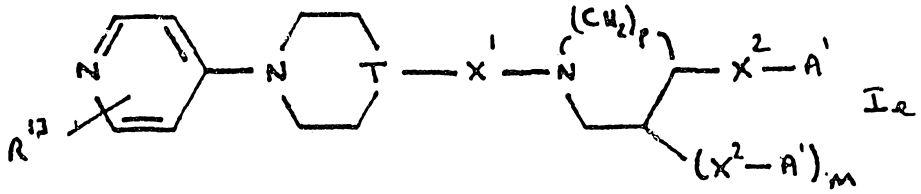
Another group of compounds of particular interest is that of general formula Id



Id

in which Q, M^2, X^1, Z^1 and Z^{1a}, are as defined hereinabove, and the ester or amide derivative thereof and pharmaceutically acceptable salts and pro-drugs thereof.

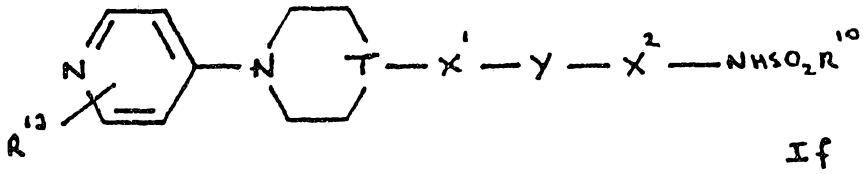
Another group of compounds of particular interest is that of general formula Ie



Ie

in which X^1, X^2, R^{13} and A^1 are as defined hereinabove.

Another group of compounds of particular interest is that of general formula If



If

in which T, X^1, Y, X^2, R^{13} and R^{10} are as defined hereinabove.

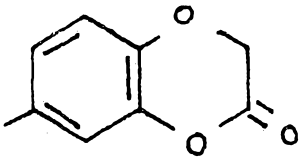
Examples of values for R^{13} are methyl, methoxy and chloro.

A particularly preferred group of compounds is that of formula Ia in which H^2 is piperazin-1,4-diyl, piperidin-4,1-diyl or 2-oxopiperazin-1,4-diyl.

Two preferred sub-groups of compounds of formula Ia may be identified. One consists of those compounds of formula Ia in which X^1 represents a bond. In this sub-group, X^2 preferably represents an oxy(2-4C)alkylene group, especially an oxypropylene group, optionally substituted on the alkylene group as defined hereinabove. The other consists of those compounds of formula Ia in which X^2 represents oxymethylene. In this sub-group, X^1 preferably represents methylenecarbonyl.

Examples of specifically preferred compounds are those of Examples 1, 2, 50, 51, 61, 62, 240, 241, 242 and 243 herein.

Examples of ester derivatives of a carboxy group are esters formed with alcohols such as (1-6C)alkanols, for example methanol, ethanol, propanol, isopropanol and tert.butanol; indanol; adamantol; (1-6C)alkanoyloxy(1-4C)alkanols such as pivaloyloxymethanol; glycolamides; (S-methyl-2-oxo-1,3-dioxol-4-yl)methyl alcohol; and (1-4C)alkoxycarbonyl(1-4C)alkanols. It will be appreciated that compounds of formula I in which Y is a group of formula (a) or (b) in which Z^1 or Z^2 is hydroxy may form internal esters. An example of such an internal ester is a compound in which X^1.Y.X^2.A represents:

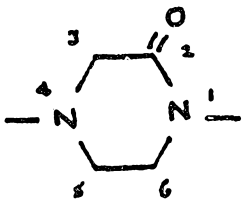


Examples of amide derivatives of a carboxy group include amides derived from ammonia or amines such as (1-4C)alkylamines, for example methylamine; di(1-4C)alkylamines); C(1-4C)alkoxy(1-4C)-alkylamines such as methoxyethylamine; phenyl(1-2C)alkylamines such as benzylamine; and amino acids such as glycine or an ester thereof.

Examples of pro-drugs of compounds of formula I include compounds possessing metabolically labile groups, in other words groups that are cleaved in vivo to afford a compound of formula I. Such groups include metabolically labile ester and amide derivatives.

It will be appreciated that certain of the compounds of general formula I are in the form of enantiomers. It will be understood that the invention includes any enantiomer which has the property of inhibiting platelet aggregation and the binding of adhesion molecules to GPIIb-IIIa, whether present in a mixture with the other enantiomer (for example in a racemic mixture), or substantially free of the other enantiomer.

As used in this specification, the terms alkyl, alkylene, alkenylene or alkynylene include branched and unbranched groups. However, where specific terms are used, for example propyl, isopropyl or propylene, these indicate whether the group is branched or not. Diradicals, for example 2-oxo-piperazin-1,4-diyl, are numbered assuming that formula I is read from right to left with the group A being at the right hand side, as depicted in formula I hereinabove. Hence, for example, 2-oxo-piperazin-1,4-diyl signifies the group:-



It will be appreciated that in this specification, the order of the two numbers immediately preceding the term "diyl" in the name of a diradical signifies the orientation of the diradical in a compound of formula I. Thus the first number signifies the position in the diradical closest to the group A. For example, the diradical

represented by formula (d) hereinbefore is named herein as a 4-oxoquinolon-3,7-diyl group whereas the diradical represented by formula (i) is named herein as a 4-oxoquinolon-7,3-diyl group.

Particular pharmaceutically acceptable salts include, for example, salts with acids affording physiologically acceptable anions, such as salts with mineral acids, for example a hydrogen halide (such as hydrogen chloride and hydrogen bromide), sulphuric acid or phosphoric acid, and salts with organic acids, for example trifluoroacetic acid. Other pharmaceutically acceptable salts include, for example salts with inorganic bases such as alkali metal and alkaline earth metal salts (for example sodium salts), ammonium salts, and salts with organic amines and quaternary bases forming physiologically acceptable cations such as salts with methylamine, dimethylamine, trimethylamine, ethylenediamine, piperidine, morpholine, pyrrolidine, piperazine, ethanolamine, triethanolamine, N-methylglucamine, tetramethylammonium hydroxide and benzyltrimethylammonium hydroxide.

Many of the compounds of formula I, and the pharmaceutically acceptable salt and pro-drugs thereof, are novel, and accordingly are provided as one aspect of the invention.

According to another aspect, the invention provides a process for preparing a compound of general formula I, or a metabolically labile ester or amide thereof, or a pharmaceutically acceptable salt thereof, which comprises

(A) For a compound of formula I in which n is 0 and M^2 is NR^3 or $-NR^4-D-NR^5-$, reacting a compound of formula

$$Q.M^2.H \qquad II$$

or an acid addition salt thereof with a compound of formula

$$U^1.L.A \qquad III$$

in which U^1 is a leaving atom or group.

Examples of values for U^1 include halogen, such as chlorine or bromine, and hydrocarbylsulphonyloxy, such as methanesulphonyloxy

and p-toluenesulphonyloxy. When the group in L to which U^1 is attached is a carbonyl group, U^1 may also represent a hydro y group or a reactive derivative thereof. Examples of reactive derivatives of a hydroxyl group include acyloxy groups such as acetyloxy, and groups formed in situ by reacting a compound of formula III in which U^1 is hydroxy with a peptide coupling reagent. Examples of peptide coupling reagents include carbodiimides such as 1,3-dicyclohexylcarbodiimide (DCC) preferably in combination with 1-hydroxybenzotriazole hydrate (HOBT).

Examples of acid addition salts include, for example the hydrochlorides.

The reaction may conveniently be effected at a temperature in the range of from -10 to 120 °C, preferably from 10 to 100 °C. Suitable solvents include, for example, ethers such as tetrahydrofuran, amides such as dimethylformamide, nitriles such as acetonitrile, halogenated hydrocarbons such as dichloromethane and alcohols such as ethanol or isopropanol.

In some circumstances, for example when an acid addition salt of a compound of formula II is used as starting material, or when the compound of formula II is relatively unreactive, the reaction may advantageously be performed in the presence of a base. Examples of suitable bases include tertiary amines, such as triethylamine, and alkali metal hydroxides, carbonates and bicarbonates, such as sodium or potassium hydroxide, carbonate or bicarbonate. When the compound of formula II is relatively unreactive a strong base such as an alkali metal hydride, for example potassium hydride, may conveniently be used.

(B) For a compound of formula I in which A is carboxy, decomposing an ester of formula

$$(M^1)_n\text{-}Q\text{-}(M^2)_{1-n}\text{-}L\text{-}COOR^{20} \qquad IV$$

in which R^{20} is a carboxyl protecting group.

R^{20} may be any conventional carboxyl protecting group that may be removed without interfering with other parts of the molecule. Examples of carboxyl protecting groups include (1-6C)alkyl groups

(such as methyl, ethyl, propyl or t-butyl), phenyl and benzyl, the phenyl moiety in any of which may optionally bear 1 or 2 of halogeno, (1-4C)alkyl, (1-4C)alkoxy or nitro.

The decomposition may be carried out using any one or more of the conventional reagents and conditions known in the art for converting carboxylic esters into carboxylic acids. Thus, for example, the decomposition may conveniently be performed by base catalysed hydrolysis, for example by using an alkali metal hydroxide such as lithium, potassium or sodium hydroxide or an amine such as triethylamine, in the presence of water. The base catalysed hydrolysis may conveniently be performed in the presence of a solvent such as an alcohol, for example methanol or ethanol, or an ether such as tetrahydrofuran or dioxan. Alternatively the decomposition may be carried out by acid catalysed hydrolysis, for example using aqueous acetic acid or trifluoroacetic acid. The temperature is conveniently in the range of from -10 to 100°C, for example from 10 to 50°C. When the alcohol residue is t-butyl, this may also conveniently be removed by heating, for example at a temperature in the range of from 80 to 150°C, alone or in the presence of a suitable diluent such as diphenylether or diphenylsulphone. A benzyl group may conveniently be removed by catalytic hydrogenation, for example by hydrogenation in the presence of palladium on carbon at a temperature in the range of from -10 to 100°C in the presence of a solvent such as an alcohol, for example methanol or ethanol.

(C) For a compound of formula I in which L represents $X^1.Y.X^2$ and Y is a group of formula (c), reacting a compound of formula

$$(M^1)_n\text{-}Q\text{-}(M^2)_{1-n}\text{-}X^1.U^2 \qquad V$$

in which U^2 is a leaving atom or group, or an acid addition salt thereof, with a compound of formula

$$H.Y.X^2.A \qquad VI$$

or an acid addition salt thereof, in which X^2 and A are as defined hereinabove and Y is a group of formula (c) as defined hereinabove.

Examples of values for U^2 include halogen, such as chlorine or bromine, and hydrocarbylsulphonyloxy, such as methanesulphonyloxy and p-toluenesulphonyloxy. When the group in X^1 to which U^2 is attached is a carbonyl group, U^2 may also represent a hydroxy group or a reactive derivative thereof. Examples of reactive derivatives of a hydroxyl group include acyloxy groups such as acetyloxy, and groups formed in situ by reacting a compound of formula V in which U^2 is hydroxy with a peptide coupling reagent. Examples of peptide coupling reagents include carbodiimides such as 1,3-dicyclohexylcarbodiimide (DCC), preferably in combination with 1-hydroxybenzotriazole hydrate (HOBT).

Examples of acid addition salts include, for example the hydrochlorides.

The reaction may conveniently be effected at a temperature in the range of from -10 to 120 °C, preferably from 10 to 100 °C. Suitable solvents include, for example, ethers such as tetrahydrofuran, amides such as dimethylformamide, nitriles such as acetonitrile, halogenated hydrocarbons such as dichloromethane and alcohols such as ethanol.

In some circumstances, for example when an acid addition salt of a compound of formula VI is used as starting material, the reaction may advantageously be performed in the presence of a base. Examples of suitable bases include tertiary amines, such as triethylamine, and alkali metal hydroxides, carbonates and bicarbonates, such as sodium or potassium hydroxide, carbonate or bicarbonate.

(D) For a compound of formula I in which n is 0, reacting a compound of formula

$$Q\text{-}U^3 \qquad \text{VII}$$

in which U^3 is a leaving atom or group, with a compound of formula

$HM^2.L.A$ VIII

or an acid addition salt thereof, in which L and A are as defined hereinabove.

Examples of values for U^3 include halogen, such as chlorine or bromine, and cyano.

Examples of acid addition salts include, for example the hydrochlorides.

The reaction may conveniently be effected at a temperature in the range of from -10 to 120 °C, preferably from 10 to 100 °C. Suitable solvents include, for example, ethers such as tetrahydrofuran and dioxan, amides such as dimethylformamide, nitriles such as acetonitrile, halogenated hydrocarbons such as dichloromethane, alcohols such as ethanol and water.

In some circumstances, for example when an acid addition salt of a compound of formula VIII is used as starting material, the reaction may advantageously be performed in the presence of a base. Examples of suitable bases include tertiary amines, such as triethylamine, and alkali metal hydroxides, carbonates and bicarbonates, such as sodium or potassium hydroxide, carbonate or bicarbonate.

(E) For a compound of formula I in which L is $X^1.Y.X^2$ and X^1 comprises a CONH group, reacting the appropriate carboxylic acid of formula

$$(M^1)_n\text{-}Q\text{-}(M^2)_{1-n}\text{-}X^{1a} \qquad \text{IX}$$

in which X^{1a} is a residue of a carboxylic acid group, or a reactive derivative thereof, with the appropriate amine of formula

$$X^{1b}.Y.X^2.A \qquad \text{X}$$

in which X^{1b} is a residue of an amine group.

Examples of values for X^{1a} are (1-2C)alkyleneCOOH, benzyl(1-2C)alkyleneCOOH and COOH. Examples of values for X^{1b} are H_2N and H_2N(1-3C)alkylene.

Examples of reactive derivatives of the compounds of formula IX include acyl halides such as the chlorides and bromides, and groups formed in situ by reacting a residue of a carboxylic acid with a peptide coupling reagent, such as carbodimide, for example 1,3-dicyclohexylcarbodimide, preferably in combination with 1-hydroxybenzotriazole hydrate (HOBT).

The reaction is conveniently performed at a temperature in the range of from 0 to 100°C. Suitable solvents include halogenated hydrocarbon such as methylene chloride, amide, such as dimethylformamide and tertiary amines such as triethylamine.

(F) For a compound of formula I in which L is $X^1.Y.X^2$ and X^1 is (2-4C)alkenylene, reacting a compound of formula

$$(M^1)_n\text{-}Q\text{-}(M^2)_{1-n}\text{-}X^{1c} \qquad XI$$

in which X^{1c} is an appropriate aldehyde-containing group with the appropriate Wittig reagent of formula

$$X^{1d}.Y.X^2.A \qquad XII$$

in which X^{1d} is a triarylphosphonylalkylene group such as triphenylphosphinylmethylene.

The reaction is conveniently performed at a temperature in the range of from -20 to 50°C, preferably from 0 to 25°C. Convenient solvents include ethers such as tetrahydrofuran, sulphoxides such as dimethylsulphoxide and aromatic hydrocarbons such as toluene.

(G) For a compound of formula I in which L is $X^1.Y.X^2$ and X^1 comprises an oxy (ether) link, reacting the appropriate compound of formula

$$(M^1)_n\text{-}Q\text{-}(M^2)_{1-n}\text{-}X^{1e} \qquad XIII$$

with the appropriate compound of formula

$$X^{1f}.Y.X^{2}A \qquad XIV$$

in which one of X^{1e} and X^{1f} is a residue of an alcohol group, and the other is a residue of an alcohol group or a group containing a leaving atom or group.

When X^{1e} and X^{1f} both represent residues of alcohol groups, the reaction may conveniently be effected in the presence of a dehydrating agent such as diethyl azodicarboxylate-triphenylphosphine. Suitable solvents for the reaction include ethers such as tetrahydrofuran, and amides such as dimethylformamide. The reaction is conveniently effected at a temperature in the range of from 0 to 50°C.

(H) For a compound of formula I in which X^{2} is $CH_2CH(NHXR^{6})$ reacting a compound of formula

$$(M^{1})_{n}\text{-}Q\text{-}(M^{2})_{1-n}\text{-}\ X^{1}\text{-}Y\text{-}X^{2a}\ A \qquad XV$$

in which X^{2a} is $CH_2CH(NH_2)$, or an acid addition salt thereof, with a compound of formula

$$R^{6}.X.U^{4} \qquad XVI$$

in which U^{4} is a leaving atom or group.

Examples of values for U^{4} include halogen, such as chlorine or bromine. Examples of acid addition salt include for example, the hydrochloride. The reaction may conveniently be effected at a temperature in the range of from -10 to 120°C preferably from 10 to 100°C. Suitable solvents include for example ethers such as tetrahydrofuran, amides such as dimethylformamide, nitriles such as acetonitrile, halogenated hydrocarbon such as dichloromethane and alcohols such as ethanol. The reaction is conveniently performed in the presence of a base, for example a tertiary amine such as triethylamine.

(I) For a compound of formula I in which L is $X^1.Y.X^2$ and X^2 represents oxyalkylene or oxyalkenylene, reacting a compound of formula

$$(M^1)_n\text{-}Q\text{-}(M^2)_{1-n}\text{-}X^1\text{-}Y\text{-}X^{2c} \qquad \text{XVIII}$$

with the appropriate compound of formula

$$X^{2d}\text{-}A \qquad \text{XIX}$$

in which X^{2c} is a hydroxy group, or a reactive derivative thereof (such as a halide), and X^{2d} is a hydroxyalkylene or hydroxyalkenylene group, or a reactive derivative thereof (such as a halide, for example a bromide).

The reaction is conveniently performed in the presence of a strong base, such as an alkali metal hydride, for example, sodium hydride. Suitable solvents include amides, such as dimethylformamide. The reaction is conveniently performed at a temperature in the range of from 0 to 100 ^{o}C.

(J) For a compound of formula I in which L is $X^1.Y.X^2$ and X^2 represents CONHalkylene, reacting a compound of formula

$$(M^1)_n\text{-}Q\text{-}(M^2)_{1-n}\text{-}X^1\text{-}Y\text{-}X^{2e} \qquad \text{XX}$$

with the appropriate compound of formula

$$X^{2f}\text{-}A \qquad \text{XXI}$$

in which X^{2e} represents a carboxyl group or a reactive derivative thereof (such as an acyl halide, for example an acyl chloride, or anhydride) and X^{2f} represents an aminoalkylene group, or an acid addition salt thereof (such as a hydrochloride).

Suitable solvents include tertiary amines such as triethylamine halogenated hydrocarbons such as methylene chloride and amides such as dimethylformamide. The reaction is conveniently performed at a temperature in the range of from 0 to 100°C.

(K) For a compound of formula I in which L is $X^1.Y.X^2$ and X^1 represents CONH or CONHalkylene, reacting a compound of formula

$$OCN\text{-}X^{1g}\text{-}Y\text{-}X^2\text{-}A \qquad XXII$$

in which X^{1g} is a bond or an alkylene group.

The reaction is conveniently performed at a temperature in the range of from 0 to 100 °C. Suitable solvents include halogenated hydrocarbons, such as dichloromethane.

(L) For a compound of formula I in which L is $X^1\text{-}Y\text{-}X^2$ and A is $NHSO_2R^{10}$, reacting a compound of formula

$$(M^1)_n\text{-}Q\text{-}(M^2)_{1-n}\text{-}X^1\text{-}Y\text{-}X^2\text{-}NH_2 \qquad XXIV$$

with a compound of formula

$$R^{10}SO_2U^5 \qquad XXV$$

in which U^5 is a leaving atom or group, such as a halogen atom, for example a chlorine atom.

The reaction is conveniently performed in the presence of a base such as a tertiary amine, for example triethylamine, and at a temperature in the range of from -10 to 40°C. Suitable solvents include amides such as dimethylformamide and halogenated hydrocarbons such as dichloromethane.

(M) For a compound of formula I in which L is $X^1.Y.X^2$ and X^1 is (1-2C)alkylenecarbonyloxy, reacting a compound of formula

$$(M^1)_n\text{-}Q\text{-}(M^2)_{1-n}X^{1k} \qquad XXVI$$

in which X^{1k} represents (1-2C)alkylenecarboxy or a reactive derivative thereof, with a compound of formula

$$HO\text{-}Y\text{-}X^2\text{-}A \qquad XXVII$$

The reaction is conveniently performed at a temperature in the range of from 0 to 100°C. Suitable solvents include halogenated hydrocarbons such as dichloromethane.

(N) For a compound of formula I in which L represents $X^1.Y.X^2$, X^1 represents (1-3C)alkylenecarbonyl and Y represents a phenylene group of formula (a), reacting a compound of formula

$$(M^1)_n\text{-}Q\text{-}(M^2)_{1-n}\text{-}X^{11} \qquad \text{XXVIII}$$

in which X^{11} represents a (1-3C)alkylenecarboxyl group, or a reactive derivative thereof, with a compound of formula VI in the presence of a Lewis acid.

Example of suitable Lewis acids include aluminium trichloride. Examples of reactive derivatives of compounds of formula XXVIII include the halides, such as the chlorides.

The reaction is conveniently performed at a temperature in the range of from -10 to 50°C. Suitable solvents include halogenated hydrocarbons, such as dichloromethane.

(O) For a compound of formula I in which L represents $X^1.Y.X^2$ and X^2 represents $NR^{21}CO$(1-2C)alkylene, reacting a compound of formula

$$(M^1)_n\text{-}Q\text{-}(M^2)_{1-n}\text{-}X^1\text{-}Y\text{-}NHR^{21} \qquad \text{XXX}$$

with a compound of formula

$$X^{2h}\text{-}A \qquad \text{XXX}$$

in which X^{2h} represents a carboxy(1-2C)alkyl group, or a reactive derivative thereof.

Examples of reactive derivatives of compounds of formula XXX include halides, such as chlorides, and anhydrides.

The reaction is conveniently performed at a temperature in the range of from 0 to 100°C. Suitable solvents include amides such as dimethylformamide.

Certain compounds of formula I may be converted into other compounds of formula I using conventional methods. For example, a compound of formula I in which L represents $X^1.Y.X^2.A$ in which X^1 is a (2-4C)alkylene group may be prepared by hydrogenating a corresponding compound of formula I in which X^1 represents a (2-4C)alkenylene group. The hydrogenation may be effected, for example, in the presence of palladium on charcoal and in a suitable solvent such as an alcohol, for example ethanol. A compound of formula I in which L represents $X^1.Y.X^2.A$ in which X^1 is (1-3C)alkyleneCH(OH) may be prepared by reducing a corresponding compound of formula I in which X^1 is (1-3C)alkylenecarbonyl. The reduction may be effected, for example, using an alkali metal borohydride such as sodium borohydride.

The intermediates used in the aforementioned processes are known or may be prepared by methods analogous to those known for the preparation of known compounds.

Thus, the compounds of formula IV may be prepared by methods analogous to processes (A) and (C) to (H) herein, but starting from the appropriately protected starting materials. It will be appreciated that some compounds of formula IV are compounds according to the invention.

The compounds of formula II in which n is 0 and M^2 is a 2-oxopiperazin-1,4-diyl group may be prepared by reacting piperazinone with a compound of formula VII.

The compounds of formula XV may be prepared by deprotecting a corresponding compound of formula:-

$$(M^1)_n\text{-}Q\text{-}(M^2)_{1-n}\ X^1\text{-}Y\text{-}X^{2b}.A \qquad \text{XVII}$$

wherein X^{2b} is $CH_2CH(NHR^{11})$ and R^{11} is an amine protecting group.

Examples of amine protecting groups include oxycarbonyl groups such as benzyloxycarbonyl. A benzyloxycarbonyl group may conveniently be removed, for example, by hydrogenation in the presence of a catalyst such as palladium on charcoal.

The compounds of formula XVII may be prepared by a method analogous to the preparation of a compound of formula I, but starting from the appropriate starting material. For example, if a compound of

formula XVII in which X^1 is methyleneoxy and Y is phenylene, is desired this may be prepared by a method analogous to process (G) herein, starting with a compound of formula XIII and the appropriate N-protected derivative of tyrosine.

The compounds of formula XVIII may be prepared by reacting a compound of formula VII with a compound of formula

$$H\text{-}X^1\text{-}Y\text{-}X^{2g} \qquad \text{XXIII}$$

in which X^{2g} is a hydroxy group or a protected derivative thereof (for example a methoxy group), followed if necessary by the removal of any protecting group, (for example by treatment with hydrobromic acid) and, if desired, conversion of the hydroxy group into a reactive derivative thereof by a known method.

Many of the intermediates, for example compounds of formulae XV and XVII, and the compounds of formula II and VIII in which M^2 is 2-oxopiperazin-1,4-diyl are novel and form further aspects of this invention.

The compounds of formula I may be converted into pharmaceutically acceptable salts and/or metabolically labile esters or amides thereof by methods well known in the art. For example, a pharmaceutically acceptable salt may be formed by reacting a compound of formula I with an acid capable of affording a physiologically acceptable anion, or a base capable of affording a physiologically acceptable cation. A pharmaceutically acceptable metabolically labile ester or amide may be formed respectively by esterifying a compound of formula I using a conventional technique, or reacting an acid, or a reactive derivative thereof with the appropriate amine.

The ability of the compounds of formula I to inhibit platelet aggregation may be demonstrated using a standard test (a) based on that described by Born (Nature, 1962, 194, 927-929) and involving:

(i) aggregating human, citrated, platelet-rich plasma by addition of adenosine diphosphate so as to generate a dose-response curve;

(ii) generating a dose-response curve for ADP stimulated platelet aggregation in the presence of increasing amounts of a test compound

(generally in the range 10^{-5}M to 10^{-10}M); and

(iii) calculating a pA_2 value indicating potency of platelet aggregation inhibition for the test compound, averaged over several concentrations, from the calculated 50% response value for ADP aggregation in the presence and absence of the test compound.

Test (a) may be modified so as to assess the effects of a test compound ex vivo on the aggregation of human blood platelets after administration of the test compound to a laboratory animal, such as a rat, rabbit, guinea pig, mouse or dog. For example, groups of four male, fasted Alderley Park Wistar rats are orally dosed with a test compound or appropriate vehicle, and at suitable time intervals (1,3,5 and 8 hours after dosing) animals are anaesthetised with fluothane and bled by heart puncture. Blood is collected into 3.2% citrate (1 part to 9 parts whole blood) and platelet poor plasma (ppp) prepared by centrifugation (4500 x g for 10 min).

Human blood is collected into 3.2% trisodium citrate (1 part to 9 parts whole blood) and centrifugated (200 x g for 15 min) to produce platelet rich plasma (prp).

Equal volumes (125µl) of rat ppp and human prp are mixed together, ADP added, and the whole incubated (37°C) and stirred (900 rpm) in a BioData platelet aggregometer. Aggregation is induced with ADP and agonist EC_{50} values calculated for human prp/rat ppp mixtures from animals dosed with test compound or vehicle. A mean concentration ratio (concentration of ADP required to cause a 50% aggregation response in human prp/rat ppp mixtures from animals dosed with antagonist, divided by the concentration of ADP to cause 50% aggregation in human prp/rat ppp mixtures from animals dosed with vehicle) is calculated at each time point.

The ability of the compounds of formula I to inhibit binding of fibrinogen to GPIIb-IIIa may be demonstrated using the following standard test (b) involving:

(i) Preparation of human platelet lysates.

Platelet rich plasma (PRP) is harvested by centrifugation (1000 rpm, 15 mins) of whole blood anticoagulated with acid citrate dextrose (trisodium citrate 85mM, citric acid 70mM, d-glucose 110mM) 1 part to

6 parts blood. Prostacyclin (PGI_2, 1μM) is added to the PRP before centrifugation (2400rpm, 15mins) and the resulting pellet is resuspended in modified Tyrodes' solution (NaCl 130mM, KCl 26mM, $NaHCO_3$ 12mM, NaH_2PO_4 0.5mM, $MgCl_2$ 1mM, $CaCl_2$ 20mM, Glucose 12mM, HEPES 5mM) containing bovine serum albumin 3.5g/L, PGI2 1μM and hirudin 0.5U/ml. The platelet suspension is centrifuged (2400rpm, 15mins) and the resultant pellet resuspended in 500μl of lysis buffer (octyl glucoside 50mM, HEPES 10mM, NaCl 150mM, $CaCl_2$ 1mM, $MgCl_2$ 1mM, PMSF 1mM, NEM 10mM, leupeptin 0.1mM), agitated at 4°C for 15 minutes then centrifuged at 24000rpm, 15 mins. The supernatant is stored at 4°C and the pellet re-suspended in 500μl of lysis buffer. The centrifugation process is repeated a further 3 times, the pooled supernatants being stored at -70°C.

(ii) Receptor purification.

Glycoprotein IIb/IIIa is isolated from human platelet lysates using a 2ml peptide (KYGRGDS) coupled CNBr activated Sepharose affinity column. A 1.5ml volume of platelet lysate is placed on the column and allowed to stand overnight at 4°C. Buffer (30mls, octyl glucoside 25mM, HEPES 10mM, NaCl 150mM, CaCl2 1mM, MgCl2 1mM, PMSF 1mM, NEM 10mM, leupeptin 0.1mM) is passed through the column and 2ml fractions are collected throughout. GPIIb/IIIa is eluted with 12mls of buffer containing HHLGGAKQAGDV (2mg/ml, pH 7.5), the column is washed using 4mls buffer and the remaining GPIIb/IIIa eluted using 12mls buffer containing GRGDSPG (1mg/ml pH 7.5). The column is finally washed using 20mls of buffer and can be used for up to three such preparations. Fractions containing GPIIb/IIIa are identified using gel electrophoresis and immunoblotting, pooled and stored at -70°C.

(iii) GPIIb/IIIa ELISA

96 well microtitre plates are coated with 100μl purified human platelet fibrinogen receptor (GPIIb/IIIa) diluted in coating buffer (Tris-HCl 20mM, NaCl 150mM, $CaCl_2$ 1mM, pH 7.4) and left overnight at 4°C. The plates are washed using washing buffer (Tris-HCl 50mM, NaCl

100mM, $CaCl_2$ 2mM, pH 7.4) and non-specific binding blocked by the addition of 200µl 2% BSA (2 hours, 30°C). The plates are washed prior to incubation (2 hours, 30°C) with 100µl biotinylated fibrinogen (10nm) containing either vehicle or test compound. The plates are washed, incubated with streptavidin (5µg/ml, 1 hour, ambient temperature), then washed again before the addition of 100µl biotinylated horse radish peroxidase (0.1µg/ml, 1 hour, ambient temperature). The plates are then washed and equal volumes of peroxidase substrate (3, 5, tetramethyl benzidine 0.4g/l) and H_2O_2 (0.02%) are mixed together immediately before addition of 150µl to each well. Colour is allowed to develop for 10-15 mins before optical densities are read at 650nM.

Abbreviations

PMSF	Phenylmethylsulphonyl fluoride
HEPES	(N-[2-Hydroxyethyl]piperazine-N-[2-ethanesulphonic acid]
NEM	N-ethyl maleimide

The concentration of compound required to cause 50% inhibition of biotinylated fibrinogen binding is calculated and expressed as a pIC_{50} ($-\log(IC_{50})$).

In general, test compounds showing activity in this test show a pIC_{50} of greater than about 4.0.

The effects of each of the compounds of formula I exemplified herein in the above tests are given in the table below. Where a range of values is given, the compound has been tested more than once. A dash (-) signifies that a compound has not been tested.

Throughout the description and claims of the specification the word "comprise" and variations of the word, such as "comprising" and "comprises" is not intended to exclude other additives, components, integers or steps.

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TABLE OF BIOLOGICAL TEST RESULTS

Example	Test (a)	Test (b)	Example	Test (a)	Test (b)
1	6.5-6.8	5.8-6.4	34	8.7	8.7
2	7.1-7.3	7.6	35	6.4	7.2
3	6.3	6.6	36	8.7	9.0
4	8.9	9.1	37	5.6	6.7
5	6.0	6.0	38	7.5	8.7
6	7.2	7.6	39	4.6	6.6
7	6.3	5.2-5.4	40	7.1	7.7
8	6.5	7.1	41	<4	<4
9	4.9	4.3	42	4.3	5.2
10	5.7	6.0	43	4.4	5.5
11	5.7	4.4	44	5	7
12	6.3	7.2	45	5.4	6.1
13	5.3	4.4-4.8	46	6	7.6
14	5.1	<4	47	5.2	4.4
15	5.6	5.9	48	5.0	6.6
16	6.8	6.7	49	7.1	8.2
17	7.4	7.7	50	6.0-6.1	<4
18	6.3	6.5	51	7-7.9	7.6 8.4
19	5.6	5.7	52	5	<4
20	5.3	4.8	53	5.8	5.9
21	6.8-7.2	6.3-6.8	54	4.8	<4
22	6.7-6.9	5.4	55	4.5	4.8
23	6.0	4.5-5.2	56	5.5	4.8
24	5.7	4.5	57	7.6	7.6
25	5.1	4.8	58	5.5	4.4
26	5.8	6.2	59	7.2	7.5
27	5.1	5.6	60	5	4.8
28	4.7	5.7	61	7.5	6.7
29	-	-	62	7.9-8.6	8.1
30	5.3	5.9	63	6.9	6.5
31	-	-	64	7.5	7.7
32	6.7	7.3	65	5.2	5.6
33	6.4	6.9	66	5.7	6.6

Example	Test (a)	Test (b)	Example	Test (a)	Test (b)
67	8.6	8.5	101	6.3	7.5
68	6.5	7.9	102	5.7	5.8
69	4.9	5.4	103	4.5	5.1
70	7.1	7.8	104	<4	4.7
71	4.9	4.4	105	6.6	6.6
72	6.3	4.4	106	4.8	4.4
73	6.3	7.2	107	4.5	<4
74	5	5.7	108	6.3	5.9
75	4.5	5.4	109	6.5	6.2
76	4.5	5.9	110	5.2	<4
77	5.1	6.3	111	5.3	5.2
78	6.8	6.6	112	5.2	5.5
79	7.9	8.5	113	<4	4.6
80	6.6	6.4	114	<4	5.6
81	4.8	6.7	115	5.4	<4
82	6.3	7.9	116	5.7	5.6
83	4.4	5.7	117	4.9	5.4
84	7.2	7.7	118	6.7	6.4
85	5.8	6.6	119	4.5	<4
86	5.4	6.7	120	5.4	4.3
87	5.6	7.2	121	5.9	5.4
88	9	8.6	122	6.2	5.4
89	7.4	8.7	123	6.0	7.0
90	8	8.5	124	6.1	6.6
91	6.8	6.7	125	6.8	7.8
92	5.7	7.1	126	4.8	5.5
93	7.9	8.5	127	5.8	6.7
94	6.5	8.6	128	6.8	6.3
95	5	5.1	129	7.9	6.5
96	7.1	8.4	130	<4	5.4
97	5.4	7.5	131	4.6	4.5
98	7.6	8.5	132	4.2	4.5
99	5.4	6.6	133	5.7	4.5
100	4.4	5.4	134	4.8	4.6

Example	Test (a)	Test (b)	Example	Test (a)	Test (b)
135	4.5	<4	170	4.8	<4
136	6.9	5.6	171	5.2	<4
137	7.2	5.5	172	5.2	4.3
138	5	4.9	173	5.9	6.7
139	6.6	5.4	174	6.4-6.8	8.0-8.3
140	5.8	6.3	175	5.9	6.2
141	4.5	4.5	176	6.7	8.0
142	5.3	5.3	177	5.8	4.1
143	5.0	4.5	178	5.5	6.0
144	5.3	5.3	179	4.8	5.4
145	5.5	5.3	180	5.5	-
146	5.1	5.2	181	6.5	-
147	6.4	6.2	182	5.1	4.7
148	7.3	7.5	183	4.5	<4
149	4.7	4.7	184	5.3	<4
150	6.5	6.5	185	5.4	4.8
151	6.2	5.4	186	5.3	5.9
152	7.0	7.0	187	4.8	-
153	4.8	4.3	188	6.0	-
154	5.0	5.6	189	5.9	6.5
155	5.5	<4	190	4.2	4.7
156	4.7	5.8	191	<4	5.4
157	6.5	7.1	192	<4	6.6
158	6.2	7.0	193	4.4	6.6
159	6.3	5.7	194	5.4	6.9
160	6.1	7.8	195	5.6	6.8
161	4.9	4.3	196	4.0	5.2
162	4.7	6.2	197	4.2	4.8
163	6.4	6.6	198	6.1	7.7
164	8.1	7.2-7.4	199	6.3	-
165	5.9	4.7	200	7.9	8.4
166	5.8	6.5	201	4.3	<4
167	6.6	6.7	202	-	-
168	6.1	6.4	203	7.2	8
169	4.4	5.0	204	7.1	8.9

Example	Test (a)	Test (b)	Example	Test (a)	Test (b)
205	6.6	-	239	5.6	-
206	6.6	8.0	240	7.6	-
207	6.5	6	241	8.2	-
208	6.5	-	242	6.5	-
209	6.7	-	243	8.0	-
210	6.5	-			
211	5.8	6.8			
212	7.1	-			
213	6.7	6.3			
214	-	-			
215	6.9	-			
216	5.7	-			
217	6.5	-			
218	6.0	-			
219	7.5	-			
220	5.5	-			
221	6.8	-			
222	6.5	5.6			
223	6.0	5.8			
224	4.5	6.3			
225	6.8	-			
226	4.7	5.5			
227	5.6	7.0			
228	5.0	<4			
229	5.4	7.1			
230	5.0	5.3			
231	6.7	7.5			
232	4.5	-			
233	5.2	6.3			
234	6.2	6.7			
235	5.2	6.7			
236	6.1	-			
237	6.1	7.5			
238	5.9	-			

In general, it has been found that compounds of formula I in which A is carboxy show a higher level of activity in test (a), and test (b) than those in which A is an ester group. However, the compounds in which A is an ester group have often been found to show a higher level of activity than those where A is carboxy in test (a) when the test is modified to assess the activity of test compounds on oral administration. For example, the compound described in Example 1 hereinafter has been found to give a pA_2 of 6.5-6.8 in test (a) and a pIC_{50} of 5.8-6.4 in test (b), whereas the compound of Example 2 has been found to give a pA_2 of 7.1-7.3 in test (a) and a pIC_{50} of 7.6 in test (b). However, the compound of Example 1 has been found to be active for up to 12 hours when dosed orally to dogs at 5mg/kg. Without wishing to be bound by theory it is accordingly believed that the compounds of formula I in which A represents an ester group function as pro-drugs for compounds of formula I in which A is a carboxyl group.

As stated previously, the compounds of formula I may be used in the therapy or prevention of diseases in which cell adhesion (especially platelet aggregation) is involved, for example thrombosis (e.g. stroke and thrombotic events accompanying unstable angina and transient ischaemic attack), myocardial infarction, atherosclerosis, thromboembolism and reocclusion during and after thrombolytic therapy. The compounds may also be useful for the prevention of reocclusion and restenosis following percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft. It will also be appreciated that the compounds may be useful in the treatment of other diseases mediated by binding of adhesion molecules to GPIIb/IIIa, for example cancer.

According to another aspect, therefore, the invention provides a method of inhibiting platelet aggregation in a warm-blooded mammal requiring such treatment, which comprises administering an effective amount of a compound of formula I, or a pharmaceutically acceptable salt or pro-drug thereof.

According to yet another aspect, the invention provides a method of inhibiting binding of fibrinogen to GPIIb/IIIa in a warm-blooded animal requiring such treatment, which comprises

administering an effective amount of a compound of formula I, or a pharmaceutically acceptable salt or pro-drug thereof.

According to a further aspect, the invention provides the use of a compound of formula I or a pharmaceutically acceptable salt or pro-drug thereof for the manufacture of a medicament for the prevention or treatment of a disease involving platelet aggregation.

According to yet another aspect, the invention provides the use of a compound of formula I or a pharmaceutically acceptable salt or pro-drug thereof, for the manufacture of a medicament for the prevention or treatment of a disease involving binding of fibrinogen to GPIIb/IIIa.

In general, a compound of formula I will be administered for this purpose by an oral, rectal, topical, intravenous, subcutaneous, intramuscular or inhalation route, so that a dose in the range of from 0.01 to 50 mg/kg body weight will be given, depending upon the route of administration, the age and sex of the patient, and the severity of the condition to be treated.

The compounds of formula I will generally be used in the form of a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof as defined hereinabove, together with a pharmaceutically acceptable diluent or carrier. Such a composition is provided as a further feature of the invention and may be in a variety of dosage forms. For example, it may be in the form of tablets, capsules, solutions or suspensions for oral administration; in the form of cream or ointments or a transdermal (skin) patch for topical administration; in the form of a suppository for rectal administration; in the form of a sterile solution or suspension for administration by intravenous or intramuscular injection; in the form of an aerosol or a nebuliser solution or suspension, for administration by inhalation; and in the form of a powder, together with pharmaceutically acceptable inert solid diluents such as lactose, for administration by insufflation. Depending upon the route of administration, the composition may comprise, for example, from 0.1 to 99.9% by weight of a compound of formula I.

The pharmaceutical compositions may be obtained by conventional procedures using pharmaceutically acceptable diluents and carriers well known in the art. Tablets and capsules for oral administration may conveniently be formed with an enteric coating, for example comprising cellulose acetate phthalate, to minimise contact of the active ingredient of formula I with stomach acids.

The compounds according to the invention may be co-adminstrated or co-formulated with one or more agents known to be of value in diseases or conditions intended to be treated; for example a known platelet aggregation inhibitor (e.g. aspirin, a thromboxane antagonist or a thromboxane synthase inhibitor), hypolipidemic agent, anti-hypertensive agent, thrombolytic agent (such as streptokinase, urokinase, prourokinase, tissue plasminogen activator and derivatives thereof), beta-adrenergic blocker or a vasodilator may usefully also be present in a pharmaceutical composition of the invention for use in treating a heart or vascular disease or condition.

In addition to their use in therapeutic medicine, the compounds of formula I are also useful as pharmacological tools in the development and standardisation of test systems for the evaluation of the effects of adhesion molecules in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents. The compounds of formula I may also be used because of their platelet aggregation inhibitory properties in helping to store blood and to maintain the viability of blood and blood vessels in warm-blooded animals (or parts thereof) under-going artificial extracorporeal circulation, for example during limb or organ transplants. When used for this purpose a compound of formula I, or a physiologically acceptable salt thereof, will generally be administered so that a steady state concentration in the range, for example, 0.1 to 10 mg. per litre is achieved in the blood.

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

(i) concentrations and evaporations were carried out by rotary evaporation in vacuo;

(ii) operations were carried out at ambient temperature, that is in the range 18-26°C;

(iii) column chromatography was carried out on silica (Merck Art. 9385) available from E Merck and Co., Darmstadt, Germany; and on neutral alumina (ICN Alumina N, Akt. I, III or IV) available from ICN Biomedicals GmbH, D-3440 Eschwege, Germany;

(iv) yields are given for illustration only and are not necessarily the maximum attainable by diligent process development;

(v) proton NMR spectra were normally determined at 200 MHz or 250 MHz in dimethylsulphoxide-d_6 using tetramethylsilane (TMS) as an internal standard, and are expressed as chemical shifts (delta values) in parts per million relative to TMS using conventional abbreviations for designation of major peaks: s, singlet; m, multiplet; t, triplet; br, broad; d,doublet; and

(vi) ether refers to diethyl ether, THF to tetrahydrofuran, DMF to N,N-dimethylformamide, DMSO to dimethylsulphoxide, TFA to trifluoroacetic acid; HOBT to 1-hydroxybenzotriazole; and NBA to m-nitrobenzylalcohol.

(vii) drying with PS paper refers to the use of Whatmans PS phase separating paper.

EXAMPLE 1: Methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-phenoxyacetate.

A solution of methyl 4-bromoacetylphenoxyacetate (4.3g) in acetonitrile (50ml) was added dropwise over 40 minutes to a stirred solution of 1-(4-pyridyl)piperazine (4.9g) in acetonitrile (100ml). Stirring was continued for a further 1.5 hours, then the solution was filtered and the filtrate evaporated *in vacuo*. The solid residue was triturated with water (50ml), then dried and suspended in methylene chloride (50ml). The suspension was then filtered and the filtrate concentrated to a small volume. Purification by flash chromatography on neutral alumina eluting first with dichloromethane, then 0.5% v/v methanol/dichloromethane and finally 1% v/v methanol/dichloromethane gave the title compound, 1.93g, as a solid: m.p. 150 - 152°C; NMR(d_6DMSO) δ 8.14(2H,d), 7.98(2H,d), 7.03(2H,d), 6.78(2H,d), 4.90(2H,s), 3.83(2H,s), 3.72(3H,s), 3.34(4H,bt), 2.65(4H,bt); m/e 370

$(M+H)^+$; calculated for $C_{20}H_{23}N_3O_4$: C, 65.0; H, 6.3; N, 11.4. found: C, 65.2; H, 6.4; N, 11.3%.

EXAMPLE 2: 4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]phenoxyacetic acid

A stirred solution of the product of Example 1 (550mg) in methanol (10ml) was treated with a M sodium hydroxide solution (1.65ml) and stirring continued for a further 2 hours. The mixture was diluted with water (10ml) and the resulting solution concentrated in vacuo. Water (20ml) was added and then a M hydrochloric acid solution (1.65ml). On cooling to 4°C, a solid precipitated. This mixture was concentrated in vacuo, the solid collected and washed with ice-water, then dried to give the title compound, 320mg, as a solid: m.p. 294-296°C; NMR (d_6DMSO+TFA) δ 8.34(2H,d), 7.95(2H,d), 7.26(2H,d), 7.10(2H,d), 5.06(2H,s), 4.82(2H,s), 4.06(4H,bs), 3.52(4H,bs); m/e 356$(M+H)^+$; calculated for $C_{19}H_{21}N_3O_4$: C, 64.2; H, 6.0; N, 11.8. found: C, 64.1; H, 6.1; N, 11.6%.

EXAMPLE 3: Dimethyl 2,2'-[4-[2-[4-(4-pyridyl)piperazin-1-yl)]-acetyl]phenylene-1,2-dioxy]diacetate.

A solution of dimethyl 2,2'-[(4-bromoacetyl)phenylene--1,2-dioxy]diacetate (3.0g) in acetonitrile (15ml) was added dropwise over 30 minutes to a stirred solution of 1-(4-pyridyl)piperazine (2.6g) in acetonitrile (75ml) and the mixture stirred overnight. The mixture was then filtered and the filtrate evaporated to give an oil. Purification by flash chromatography on silica eluting first with 2.5% v/v methanol/dichloromethane then 5% v/v methanol/dichloromethane gave a solid. Trituration with ether gave the title compound, 0.95g, as a solid: m.p. 81 - 83°C; NMR (d_6DMSO) δ 8.14(2H,d), 7.67(1H,dd), 7.52(1H,d), 7.03(1H,d), 6.80(2H,d), 4.94(2H,s), 4.88(2H,s), 3.81(2H,s), 3.69(6H,s), 3.29(4H,t), 2.60(4H,t); m/e 458 $(M+H)^+$; calculated for $C_{23}H_{27}O_7N_3$. $0.25H_2O$: C, 59.8; H, 6.0; N, 9.1. found C, 59.7; H, 6.2; N, 8.8%.

The starting material was prepared as follows:-

(i) Methyl bromoacetate (19.1ml) was added dropwise to a stirred mixture of 3,4-dihydroxyacetophenone (12.6g) and anhydrous potassium carbonate (27.5g) in acetone (250ml). Stirring was continued for 16 hours when the mixture was filtered and the solvent removed in vacuo. The residue after trituration with ether gave dimethyl 2,2'-[(4-acetyl)phenylene-1,2-dioxy)]diacetate, 13.1g, as an off-white solid: m.p. 101-102°C; NMR (d_6DMSO) δ 7.60(1H,dd), 7.41(1H,d), 7.02(1H,d), 4.94(2H,s), 4.89(2H,s), 3.71(6H,s), 2.50(3H,s); m/e 297$(M+H)^+$; calculated for $C_{14}H_{16}O_7$: C, 56.8; H, 5.4. found: C, 56.4; H, 5.5%.

(ii) A solution of bromine (2.27ml) in chloroform (10ml) was added dropwise over 15 minutes to a stirred solution of the product of step (i) (12.9g) in chloroform (40ml) at 30°C. The mixture was then stirred for 2 hours at ambient temperature when the solvent was removed in vacuo. The resulting waxy solid, on trituration with ethanol, gave dimethyl 2,2'-([4-bromoacetyl]phenylene-1,2-dioxy)diacetate, 11.5g, as a cream solid: m.p. 76-78°C; NMR(d_6DMSO) δ 7.66(1H,dd), 7.47(1H,d), 7.06(1H,d), 4.96(2H,s), 4.90(2H,s), 4.62(2H,s), 3.71(6H,s); m/e 375/377 $(M+h)^+$, 1 Br pattern.

EXAMPLE 4: 2,2'-[4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenylene-1,2-dioxy]diacetic acid.

A stirred solution of the product of Example 3 (300mg) in methanol (4ml) was treated with a M sodium hydroxide solution (1.31ml) and the mixture stirred for 1 hour. The mixture was diluted with water (10ml) and the resulting solution concentrated to about 7ml when a M hydrochloric acid solution (1.31ml) was added. On cooling to 4°C the solid formed was collected, then washed with ice-water and dried to give the title compound, 120mg, as a white solid: m.p. 180-184°C (dec); NMR(d_6DMSO) δ 8.16(2H,d), 7.61(2H,t), 6.93(1H,d), 6.87(2H,d), 4.73(2H,s), 4.68(2H,s), 3.77(2H,s), 3.44(4H,bt), 2.58(4H,bt); m/e 430 $(M+H)^+$; calculated for $C_{21}H_{23}O_7N_3$. $0.75H_2O$: C, 56.9; H, 5.5; N, 9.5. found C, 57.0; H, 5.6; N, 9.3%.

EXAMPLE 5: Methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-2-methoxyphenoxyacetate

A solution of methyl 4-bromoacetyl 2-methoxyphenoxyacetate (1.27g) in acetonitrile (10ml) was added dropwise over 15 minutes to a stirred solution of 1-(4-pyridyl)piperazine (1.30g) in acetonitrile (30ml). After stirring overnight the liquors were decanted from the solid residue, then concentrated in vacuo. Purification by flash chromatography on silica, eluting with dichloromethane then 5% v/v methanol/dichloromethane gave a solid. Trituration with ether gave the title compound, 420mg: m.p. 110 - 112°C; NMR (d_6DMSO) δ 8.14(2H,d), 7.65(1H,dd), 7.55(1H,d), 6.97(1H,d), 6.80(2H,d), 4.90(2H,s), 3.87(5H,s), 3.72(3H,s), 3.33(4H,t), 2.62(4H,t); m/e 400$(M+H)^+$; calculated for $C_{21}H_{25}N_3O_5$: C, 63.1; H, 6.3; N, 10.5. found: C, 62.9; H, 6.3; N, 10.4%.

EXAMPLE 6: 4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]-2-methoxyphenoxyacetic acid

In a similar manner to Example 2, but starting from the product of Example 5, the title compound was prepared in 47% yield: m.p. 218 - 224°C; NMR(d_6DMSO) δ 8.16(2H,d), 7.65(1H,dd), 7.53(1H,d), 6.92(1H,d), 6.85(2H,d), 4.73(2H,s), 3.86(2H,s), 3.82(3H,s), 3.36(4H,t), 2.63(4H,t); m/e 386$(M+H)^+$; calculated for $C_{20}H_{23}N_3O_5 \cdot H_2O$: C, 59.5; H, 6.2; N, 10.4. found: C, 59.5; H, 5.9; N, 10.1%.

EXAMPLE 7: Methyl 4-[3-[4-(4-pyridyl)piperazin-1-yl]propanoyl]-phenoxyacetate

In a similar manner to Example 3, but starting from methyl 4-[3-chloropropanoyl]phenoxyacetate was prepared the title compound in 65% yield: m.p. 93 - 95°C; NMR (d_6DMSO) δ 8.14(2H,d), 7.96(2H,d), 7.04(2H,d), 6.81(2H,d), 4.92(2H,s), 3.71(3H,s), 3.29(4H,t), 3.17(2H,t), 2.72(2H,t), 2.51(4H,t); m/e 384 $(M+H)^+$; calculated for $C_{21}H_{25}N_3O_4$ C, 65.8; H, 6.6; N, 11.0. found C, 65.6; H, 6.8; N, 10.8%.

The necessary starting material was prepared as follows:-

Aluminium chloride (33.35g) was added portionwise to a stirred cooled (<0°C) solution of methyl phenoxyacetate (14.46ml) and 3-chloropropionyl chloride (9.55ml) in dichloromethane (500ml). After the addition the ice-bath was removed and the mixture stirred for 1 hour when it was poured into ice-water (500ml). The organic phase was separated and the aqueous portion extracted two times with dichloromethane. The combined dichloromethane extracts were washed with water, then brine and dried ($MgSO_4$). The residue, after removal of the solvent in vacuo and trituration with ether gave methyl 4-[3-chloropropanoyl]phenoxyacetate, 22.3g, as a solid: m.p. 89 - 90°C; NMR (d_6DMSO) δ 7.95(2H,d), 7.05(2H,d), 4.92(2H,s), 3.91(2H,t), 3.71(3H,s), 3.49(2H,t); m/e 257$(M+H)^+$; calculated for $C_{12}H_{13}ClO_4$: C, 56.1; H, 5.0. found: C, 55.8; H, 5.1%.

EXAMPLE 8: 4-[3-[4-(4-Pyridyl)piperazin-1-yl]propanoyl]phenoxyacetic acid

In a similar manner to Example 2, but starting from the product of Example 7, the title compound was prepared in 60% yield: m.p. 238 - 239°C; NMR (d_6DMSO + d^4 acetic acid) δ 8.21(2H,d), 7.97(2H,d), 7.15(2H,d), 7.02(2H,d), 4.77(2H,s), 3.64(4H,t), 3.21(2H,t), 2.82(2H,t), 2.62(4H,t); m/e 370$(M+H)^+$; calculated for $C_{20}H_{23}N_3O_4$: C, 65.0; H, 6.3; N, 11.4. found C, 64.6; H, 6.4; N, 11.1%.

EXAMPLE 9: Methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-phenylthioacetate

In a similar manner to Example 3, but starting from methyl 4-bromoacetylphenylthioacetate, the title compound was prepared in 27% yield: m.p. 109-110°C; NMR (d_6DMSO) δ 8.15(2H,d), 7.93(2H,d), 7.40(2H,d), 6.80(2H,d), 4.07(2H,s), 3.86(2H,s), 3.66(3H,s), 3.30(4H,t), 2.61(4H,t); m/e 386 $(M+H)^+$; calculated for $C_{20}H_{23}N_3O_3S$. 0.25 H_2O: C, 61.4; H, 6.0; H, 10.7. found C, 61.8; H, 6.0; H, 10.6%.

The necessary starting material was prepared as follows:-

Aluminium chloride (18.03g) was added portionwise to a stirred cooled (<5°C) solution of methyl phenylthioacetate (9.84g) and bromoacetyl chloride (4.46ml) in dichloromethane (250ml) keeping the temperature below 5°C. The mixture was then stirred for one hour at ambient temperature then poured onto ice. After a filtration, the organic phase was separated and the aqueous portion extracted two times with dichloromethane. The combined dichloromethane extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated to give 4-bromoacetylphenylthioacetate; 11.52g, as a solid: m.p. 48 - 50°C; NMR ($CDCl_3$) δ 7.91(2H,d), 7.40(2H,d), 4.39(2H,s), 3.76(5H,s); m/e 302/304 $(M+H)^+$, 1 Br pattern.

EXAMPLE 10: 4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]phenylthioacetic acid

In a similar manner to Example 2, but starting from the product of Example 9, the title compound was prepared in 83% yield: m.p. 240-244°C; NMR(d_6DMSO) δ 8.16(2H,d), 7.93(2H,d), 7.39(2H,d), 6.66(2H,d), 3.92(2H,s), 3.86(2H,s), 3.38(4H,t), 2.64(4H,t); m/e 372$(M+H)^+$; calculated for $C_{19}H_{21}N_3O_3S$. $0.25H_2O$: C, 60.6; H, 5.7; N, 11.2. found C, 60.5; H, 5.6; N, 10.8%.

EXAMPLE 11: Methyl 3-[2-[4-[4-(4-pyridyl)piperazin-1-yl]acetyl]-phenyl]propionate

A solution of methyl 3-(4-bromoacetylphenyl)propionate (380mg) in acetonitrile (4ml) was added dropwise over 15 minutes to a stirred solution of 1-(4-pyridyl)piperazine (450mg) in acetonitrile (10ml) and the mixture stirred overnight. The mixture was then filtered and the filtrate concentrated in vacuo to give an oil. Purification by flash chromatography on silica eluting first with dichloromethane then 5% v/v methanol/dichloromethane gave a solid. Trituration with ether gave the title compound, 172mg, as a solid: m.p. 141-143°C; NMR(d_6DMSO) δ 8.15(2H,d), 7.92(2H,d), 7.37(2H,d), 6.83(2H,d), 3.89(2H,s), 3.59(3H,s), 3.37(4H,t), 2.93(2H,t),

2.69(2H,t), 2.65(4H,t); m/e 368$(M+H)^+$; calculated for $C_{21}H_{25}N_3O_3 \cdot 0.25H_2O$: C, 67.8; H, 6.9; N, 11.3. found: C, 67.8; H, 6.9; N,11.1%.

EXAMPLE 12: 3-[2-[4-[4-(4-Pyridyl)piperazin-1-yl]acetyl]phenyl]-propionic acid

A stirred solution of the product of Example 11 (70mg) in methanol (0.5ml) was treated with a M sodium hydroxide solution (0.19ml) and stirring continued for 3 hours. The methanol was removed in vacuo and the residue diluted with water (1ml), then a M hydrochloric acid solution (0.19ml) added. On cooling to 4°C a solid precipitated which was collected, washed with ice-water, then dried to give the title compound, 36.5mg: m.p. 245-247°C; NMR (d_6DMSO) δ 8.05(2H,d), 7.91(2H,d), 7.36(2H,d), 6.86(2H,d), 3.89(2H,s), 3.34(4H,t), 2.87(2H,t), 2.62(4H,t), 2.58(2H,t); m/e 354 $(M+H)^+$: calculated for $C_{20}H_{23}N_3O_3.0.2\ H_2O$: C, 67.2; H, 6.6; N, 11.8. found: C, 67.6; H, 6.6; N, 11.4%.

EXAMPLE 13: Methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-phenylacetate

A solution of methyl 4-chloroacetylphenylacetate (260mg) in acetonitrile (4ml) was added dropwise over 15 minutes to a stirred solution of 1-(4-pyridyl)piperazine (375mg) in acetonitrile (10ml) and the mixture stirred overnight. The supernatent was decanted from the solid formed, concentrated in vacuo and purified by flash chromatography on neutral alumina, eluting with dichloromethane then 0.25% v/v methanol/dichloromethane and finally 0.5% v/v methanol dichloromethane. Concentration of the fractions in vacuo gave the title compound, 96mg, as a white crystalline solid: m.p. 127 - 129°C; NMR (d_6DMSO) δ 8.15(2H,d), 7.98(2H,d), 7.41(2H,d), 6.81(2H,d), 3.91(2H,s), 3.78(2H,s), 3.53(3H,s), 3.33(4H,t), 2.64(4H,t); m/e 354$(M+H)^+$; calculated for $C_{20}H_{23}N_3O_3$: C, 68.0; H, 6.6; N, 11.9. found: C, 68.2; H, 6.6; N, 11.9%.

EXAMPLE 14: Ethyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-phenylacetate

Using a method similar to that of Example 13, but starting from ethyl 4-chloroacetylphenylacetate and purification by flash chromatography on silica, eluting with dichloromethane then 5% v/v methanol/dichloromethane, the title compound was prepared in 13% yield as solid: m.p. 122 - 124°C; NMR(d_6DMSO) δ 8.01(2H,d), 7.29(2H,d), 7.25(2H,d), 6.67(2H,d), 3.93(2H,q), 3.75(2H,s), 3.60(2H,s), 3.18(4H,t), 2.47(4H,t), 1.03(3H,t); m/e 368 $(M+H)^+$; calculated for $C_{21}H_{25}N_3O_3$: C, 68.6; H, 6.9: N, 11.4. found: C, 68.2; H, 6.8; N, 11.3%.

EXAMPLE 15: 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenylacetic acid, trifluoroacetate salt

A stirred solution of the product of Example 13 (142mg) in methanol (1ml) was treated with M sodium hydroxide solution (0.46ml) and stirring continued for 2 hours. The methanol was removed in vacuo, the residue diluted with water (1ml), then a M hydrochloric acid solution (0.46ml) was added. This solution was transferred to a 1 inch preparative reverse phase hplc column (VYDAC^R 218TP1022) and eluted with water/acetonitrile/trifluoroacetic acid in a gradient from 98:2:0.1 v/v/v to 75:25:0.1 v/v/v. The pure fractions, on freeze-drying gave, the title compound 96mg, as a foam: NMR (d_6DMSO) δ 8.34(2H,d), 7.95(2H,d), 7.48(2H,d), 7.25(2H,d), 4.67(2H,b), 3.93(4H,b), 3.72(2H,s), 3.20(4H,b); m/e 340 $(M+H)^+$; calculated for $C_{19}H_{21}N_3O_3 \cdot 2.25\ CF_3COOH$: C, 47.4; H, 3.9; N, 7.1. found: C, 47.8; H, 3.8; N, 7.0%.

EXAMPLE 16: (RS) Methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]-2-methyl-acetyl]phenoxyacetate

A solution of RS methyl 4-(2-methylbromoacetyl)phenoxy-acetate (1.2g) in acetonitrile (10ml) was added dropwise over 30 minutes to a stirred solution of 1-(4-pyridyl)piperazine (1.3g) in

acetonitrile (30ml) and the mixture stirred overnight. The mixture was then filtered and the filtrate evaporated to give an oil. Purification by flash chromatography, eluting first with dichloromethane then successively 2.5%, 3%, 4%, 5% and 10% v/v methanol/dichloromethane gave the title compound, 220mg as a solid: m.p. 81 - 83°C; NMR (d_6DMSO) δ 8.13(2H,d), 8.06(2H,d), 7.02(2H,d), 6.77(2H,d), 4.92(2H,s), 4.33(1H,q), 3.72(3H,s), 3.26(4H,t), 2.63(4H,t), 1.16(3H,d); m/e 384$(M+H)^+$; calculated for $C_{21}H_{25}N_3O_4$: C, 65.8; H, 6.6; N, 11.0. found C, 65.7; H, 6.8; N, 10.9%.

EXAMPLE 17: RS 4-[2-[4-(4-pyridyl)piperazin-1-yl]-2-methylacetyl]-phenoxyacetic acid sodium chloride adduct dihydrate

A stirred solution of the product of Example 16, (110mg) in methanol (1ml) was treated with a M sodium hydroxide solution (0.32ml) and stirring continued overnight. The methanol was removed in vacuo and the residue diluted with water and a M hydrochloric acid solution (0.32ml) added. The solvent was removed in vacuo to give a yellow foam which, on trituration with ether gave the title compound , 116mg: NMR (D_6DMSO) δ 8.17 (2H,d), 8.06(2H,d), 7.01(2H,d), 6.98(2H,d), 4.76(2H,s), 4.37(1H,q), 3.47(4H,t), 2.15(4H,), 1.16(3H,d), m/e 370 $(M+H)^+$; calculated for $C_{20}H_{23}N_3O_4$.NaCl. $2H_2O$: C, 51.8; H,5.8; N, 9.1. found: C,52.0; H, 5.6; N, 8.9%.

EXAMPLE 18: 2,2'-[4-[3-[4-(4-pyridyl)piperazin-1-yl]propanoyl]-phenylene-1,2-dioxy]diacetate, trifluoroacetate salt

Di-tertiary butyl 2,2'-[4-[3-[4-(4-pyridyl)-piperazin-1-yl]propanoyl]phenylene-1,2-dioxy]diacetate (555mg) was dissolved in 90% v/v trifluoroacetate acid/water (15ml) and the mixture stirred for one hour. The solvent was removed by evaporation in vacuo and the residual oil on trituration with ether gave the title compound, 608mg, as a solid: m.p. 42-44°C; NMR (d_6DMSO) δ 8.26(2H,d), 7.15(2H,d), 6.80(3H,m), 4.67(2H,s), 4.63(2H,s), 3.65(8H,b), 3.39(1H,q), 2.75(2H,m), 2.66(2H,m), 1.09(1.5H,t); m/e 444 $(M+H)^+$; calculated for $C_{22}H_{25}N_3O_7$. 1.3 CF_3COOH. $1H_2O$. 0.25 $C_4H_{10}O$: C, 48.9; H,

4.9; N, 6.7. found C, 49.1; H, 5.0; N, 6.3%; calculated CF_3COOH; 23.6. found 23.2%.

The necessary starting material was prepared as follows:-

(i) Solid sodium hydride (1.6g of a 60% w/w dispersion in mineral oil) was added to a stirred, cooled (4°C) solution of 3,4-dihydroxybenzaldehyde (2.76g) in THF (50ml). The mixture was then stirred for a further 15 minutes at ambient temperature, cooled to 4°C when tertiary butyl bromoacetate (6.5ml) was added followed by DMF (5ml). After one hour the mixture was diluted with ether (100ml), washed with water and brine, then dried ($MgSO_4$) and evaporated to give a solid. Recrystallisation from cyclohexane gave di-tertiary butyl 2,2'-([4-formyl])phenylene-1,2-dioxy)diacetate, 4.1g, as pale yellow crystals: m.p. 96°C; NMR (d_6DMSO) δ 9.82(1H,s), 7.54(1H,dd), 7.33(1H,d), 7.08(1H,d), 4.82(2H,s), 4.75(2H,s), 1.43(18H,s), m/e 366 (M+); calculated for $C_{19}H_{26}O_7$; C, 62.4; H, 7.3. found C, 62.3; H, 7.2%.

(ii) To a solution of the product of step (i) (10.0g) and malonic acid (42g) in pyridine (150ml) was added a few drops of piperidine and the mixture heated on a steam-bath for 4 hours. The pyridine was removed in vacuo, water 300ml added and the mixture extracted with ether (3 x 100ml). The combined extracts were washed with water, brine, dried ($MgSO_4$) then evaporated to give a gum. Recrystallisation from cyclohexane gave di-tertiary butyl 2,2'-([4-(3-propenoic acid)]phenylene-1,2-dioxy)diactate. 0.5 cyclohexane adduct, 6.6g, m.p. 104-106°C; NMR (d_6DMSO) δ 12.20(1H,b), 7.48(1H,d), 7.26(1H,s), 7.20(1H,d), 6.89(1H,d), 6.40(1H,d), 4.74(2H,s), 4.72(2H,s), 1.43(18H,s), 1.40(6H,s); m/e 408 (M+).

iii) 10% w/w palladium on charcoal (250mg) was added to a solution of the product of step (ii) (2.05g) in ethyl acetate (100ml) and the mixture hydrogenated at room temperature and pressure until the theoretical amount of hydrogen had been taken up. Charcoal was added, the mixture stirred for 5 minutes then filtered through diatomaneous earth and the filtrate evaporated to dryness giving

di-tertiary butyl 2,2'-(4-[1-(2-carboxyethyl)]phenylene--1,2-dioxy)diacetate, 1.9g, as a colourless gum: NMR ($CDCl_3$) δ 6.76(3H,m), 4.58(2H,s), 4.56(2H,s), 2.86(2H,t), 2.60(2H,t), 1.47(18H,s); m/e 410(M+). This gum slowly crystallised to give a white solid of m.p. 68 - 70°C; calculated for $C_{21}H_{30}O_8$: C, 61.5; H, 7.4. found: C,61.7; H, 7.7%.

(iv) To a stirred solution of the product of step (iii) (615mg) in dry DMF was added N,N'-diisopropylethylamine (0.78ml), HOBT (230mg), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (596mg). After 15 minutes 1-(4-pyridyl)piperazine (245mg) was added and stirring continued overnight. The DMF was removed in vacuo, the resulting oil partitioned between ethyl acetate (60ml), and water (20ml). The organic phase was separated, washed successively with water (20ml), M sodium hydroxide solution (20ml), brine (3 x 20ml) then dried and the solvent evaporated to give an oil. Purification of this oil by flash chromatography on silica, eluting with 6.5% v/v methanol in dichloromethane gave di-tertiary butyl 2,2'-[4-[3-[4-(4-pyridyl)piperazin-1-ylpropanoyl]phenylene-1,2-dioxy]-diacetate, 728mg, as a froth: m.p. 57 - 61°C, NMR (d_6DMSO) δ 8.16(2H,d), 6.80(5H,m), 4.63(2H,s), 4.59(2H,s), 3.58(4H,b), 3.32(4H,b), 2.73(2H,m), 2.61(2H,m), 1.45(18H,s); m/e 556$(M+H)^+$; calculated for $C_{30}H_{41}N_3O_7 . 0.5H_2O$: C, 63.8; H, 7.5; N, 7.4. found: C, 63.5; H, 7.4; N, 7.1%.

EXAMPLE 19: N-4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenyl-4-methylphenylsulphonamide

A mixture of 1-(4-pyridyl)piperazine (1.79g), N-(4-bromoacetylphenyl)-4-methylphenylsulphonamide (3.68g) and triethylamine (1.39ml) in isopropanol (50ml) was stirred for 18 hours. The precipitated solid was collected, triturated with dichloromethane, filtered and dried. This solid was further purified by flash chromatography on neutral alumina eluting successively with dichloromethane, 2.5% v/v methanol/dichloromethane then 5% v/v methanol/dichloromethane. Evaporation of the desired fractions to a

small volume followed by addition of dichloromethane gave a crystalline solid. This solid was collected, washed with dichloromethane to give the title compound, 440mg, as crystals: m.p. 168 - 170°C; NMR (d_6DMSO) δ 8.14(2H,d), 7.86(2H,d), 7.71(2H,d), 7.35(2H,d), 7.18(2H,d), 6.80(2H,d), 3.79(2H,s), 3.31(4H,t), 2.59(4H,t), 2.33(3H,s); m/e 451 $(M+H)^+$; calculated for $C_{24}H_{26}N_4O_3S$: C, 64.0; H, 5.8; N, 12.4. found C, 63.4; H, 5.7; N, 12.2%.

EXAMPLE 20: N-4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenyl-1-butanesulphonamide

A solution of N-(4-bromoacetylphenyl)1-butanesulphonamide (410mg) in acetonitrile (10ml) was added to a stirred solution of 1-(4-pyridyl)piperazine (400mg) in acetonitrile (10ml) and the mixture stirred for 18 hours. The solvent was removed in vacuo and the residue purified by flash chromatography on silica eluting with 20% v/v methanol/dichloromethane then on neutral alumina eluting with 2% v/v methanol/dichloromethane. The residue, after evaporation of the eluant fraction was triturated with ether to give N-(4-[(4-pyridylpiperazin-1-yl)acetyl]phenyl)1-butanesulphonamide, 166mg, as a white solid: m.p. 185-189°C dec.; NMR(d_6DMSO) δ 8.13(2H,d), 7.98(2H,d), 7.28(2H,d), 6.79(2H,d), 3.82(2H,d), 3.32(4H,t), 3.15(2H,m), 2.63(4H,t), 1.65(2H,m), 1.36(2H,m), 0.83(3H,t); m/e 417 $(M+H)^+$; calculated for $C_{21}H_{28}N_4O_3S$: C, 60.6; H, 6.8; N, 13.5. found C,60.5; H, 6.8; N, 13.1%.

EXAMPLE 21: N-[4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenyl]methyl-4-methylphenylsulphonamide

A solution of N-([4-bromoacetylphenyl]methyl)-4-methylphenylsulphonamide (470mg) in acetonitrile (10ml) was added to a stirred solution of 1-(4-pyridyl)piperazine (400mg) in acetonitrile (10ml) and the mixture stirred for 18 hours. The solvent was evaporated in vacuo and the residue purified by flash chromatography on silica, eluting with 10% v/v methanol/dichloromethane. On evaporation of the eluant fraction to a small volume crystallisation

occurred. These crystals, on filtration and washing with dichloromethane gave the title compound, 130mg, as a solid: m.p. 215-219°C dec.; NMR(d_6DMSO) δ 8.14(3H,m), 7.91(2H,d), 7.69(2H,d), 7.38(4H,d), 6.82(2H,d), 4.03(2H,d), 3.89(2H,s), 3.32(4H,t), 2.62(4H,t), 2.39(3H,s); m/e 465$(M+H)^+$; calculated for $C_{25}H_{28}N_4O_3S$: C, 64.6; N, 6.1; N, 12.1. found C, 64.7; H, 6.2; N, 12.0%.

The necessary starting material was prepared as follows:-

(i) To a stirred suspension under argon of 4-acetylbenzylamine hydrochloride (700mg) in dichloromethane (20ml) was added triethylamine (1.15ml) and stirring continued for 15 minutes. The mixture was cooled to 4°C, then 4-methylphenylsulphonyl chloride (790mg) in dichloromethane (5ml) added dropwise over 30 minutes. The reaction mixture was stirred for 18 hours at ambient temperature, then diluted with further dichloromethane (50ml), washed with water, dried ($MgSO_4$) and evaporated. Trituration of the residue gave N-([4-acetylphenyl]methyl)4-methylphenylsulphonamide (A), 1.02g., as an off-white solid: m.p. 125 - 128°C; NMR (d_6DMSO) δ 8.13(1H,t), 7.86(2H,d), 7.68(2H,d), 7.37(4H,dd), 4.03(2H,d), 2.55(3H,s), 2.39(3H,s); m/e304$(M+H)^+$.

(ii) A mixture of the product of step (i) (1.0g) and cupric bromide (1.47g) in ethyl acetate (3.0ml) was heated at reflux temperature for 16 hours. Additional cupric bromide (1.0g) was added and heating continued for a further 8 hours. The mixture was filtered and the filtrate concentrated to dryness in vacuo. This residue was purified by flash chromatography on silica, eluting with hexane/ethyl acetate (2:1v/v). Evaporation of the fractions gave N-([4-bromoacetylphenyl]methyl)-4-methylphenylsulphonamide, 1.13g, as a white solid: m.p. 116 - 117°C; NMR($CDCl_3$) δ 7.9(2H,d), 7.75(2H,d), 7.34(4H,m), 4.77(1H,t), 4.40(2H,s), 4.22(2H,d), 2.44(3H,s): m/e 382/384 $(M+H)^+$, 1 Br pattern.

EXAMPLE 22: N-[4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenyl]-methyl-1-butanesulphonamide

In a similar manner to Example 21 but starting from N-[4-bromoacetylphenyl]methyl1-butanesulphonamide the title compound was obtained as a solid in 25% yield: m.p. 158-160°C; NMR(d_6DMSO) δ 8.14(2H,d), 7.98(2H,d), 7.68(1H,t), 7.48(2H,d), 6.83(2H,d), 4.22(2H,d), 3.90(2H,s), 3.32(4H,t), 2.94(2H,m), 2.63(4H,t), 1.60(2H,m), 1.32(2H,m), 0.84(3H,t); m/e 431 $(M+H)^+$; calculated for $C_{22}H_{30}N_4O_3S$. 0.5 H_2O: C, 60.1; H, 7.1; N, 12.8. found: C,60.5; H, 7.2; N, 12.8%.

The necessary starting material was prepared as follows:-

(i) In a similar manner to Example 21(i) but starting from 1-butanesulphonyl chloride there was obtained, after flash chromatography on silica eluting with ethyl acetate/hexane (1:1 v/v), N-([4-acetylphenyl]methyl)1-butanesulphonamide in 89% yield as a white crystalline solid: m.p. 87 - 89°C; NMR (d_6DMSO) δ 7.93(2H,d), 7.67(1H,t), 7.49(2H,d), 4.22(2H,d), 2.95(2H,m), 2.56(3H,s), 1.61(2H,m), 1.32(2H,m), 0.86(3H,s); m/e 270 $(M+H)^+$.

ii) In a similar manner to 21(ii) but starting from the product of step (i) above, there was obtained, after chromatography on silica eluting with hexane/ethyl acetate (2:1v/v), N-([4-bromoacetylphenyl]methyl)1-butanesulphonamide as off-white crystals in 70% yield: m.p. 101-103°C; NMR(d_6DMSO) δ 7.99(2H,d), 7.69(1H,t), 7.52(2H,d), 4.49(2H,s), 4.23(2H,d), 2.96(2H,m), 1.60(2H,m), 1.33(2H,m), 0.86(3H,s); m/e 365/367 $(M+NH_4)^+$, 1 Br pattern.

EXAMPLE 23: N-[2-[4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenyl]-ethyl]-4-methylphenylsulphonamide

A solution of N-(2-[4-bromoacetylphenyl]ethyl)-4-methylphenylsulphonamide (485mg) in acetonitrile (10ml) was added to a stirred solution of 1-(4-pyridyl)piperazine (400mg) in acetonitrile

(10ml) and the mixture was stirred for 18 hours. The solvent was evaporated in vacuo and the residue purified by flash chromatography on silica, eluting with 10% v/v methanol/dichloromethane. On evaporation of the eluant fraction crystallisation occured. These crystals on filtration and washing with dichloromethane gave the title compound, 230mg, as an off-white solid: m.p. 133 - 135°C; NMR(d_6DMSO) δ 8.14(2H,bd), 7.90(2H,d), 7.65(2H,d), 7.59(1H,t), 7.35(2H,d), 7.29(2H,d), 6.81(2H,d), 3.37(2H,s), 3.33(4H,t), 2.98(2H,q), 2.76(2H,t), 2.63(4H,t), 2.38(3H,s); m/e 479$(M+H)^+$; calculated for $C_{26}H_{30}N_4O_3S$: C, 65.2; H, 6.3; N, 11.7; found. C 65.0; H, 6.3; N, 11.4%.

The necessary starting material was prepared as follows:-

(i) To a stirred suspension under argon of 4-acetylphenethylamine hydrochloride (1g) in dichloromethane (20ml) was added triethylamine (0.94ml) and stirring continued for 15 minutes. The mixture was cooled to 4°C, then 4-methylphenylsulphonyl chloride (1.29g) in dichloromethane (5ml) added dropwise over 30 minutes. The reaction mixture was stirred for 18 hours at ambient temperature, then diluted with further dichloromethane (50ml), washed with water, dried ($MgSO_4$) and evaporated. Trituration of the residue gave N-(2-[4-acetylphenyl]ethyl)4-methylphenylsulphonamide, 1.58g, as a yellow crystalline solid: m.p. 124-126°C; NMR(d_6DMSO) δ 7.84(2H,d), 7.63(3H,m), 7.37(2H,d), 7.29(2H,d), 2.98(2H,q), 2.75(2H,t), 2.55(3H,s), 2.39(3H,s); m/e 318$(M+H)^+$.

ii) A mixture of the product of step (i) (1.5g) and cupric bromide (2.1g) in ethyl acetate (50ml) was heated at reflux temperature for 16 hours. The mixture was filtered, and the filtrate concentrated to dryness in vacuo. This residue was purified by flash chromatography on silica, eluting with hexane/ethyl acetate (2:1 v/v). Evaporation of the fractions gave N-(2-[4-bromoacetylphenyl]ethyl)-4-methylphenylsulphonamide, 860mg, as a white crystalline solid: m.p. 133-136°C; NMR ($CDCl_3$) δ 7.90(2H,d), 7.70(2H,d,, 7.29(2H,d), 7.22(2H,d), 4.41(2H,s), 4.29(1H,t), 3.26(2H,q), 2.86(2H,t), 2.43(3H,s), m/e 396/398$(M+H)^+$, 1 Br pattern.

EXAMPLE 24: N-[2-[4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-phenyl]ethyl]-1-butanesulphonamide

In a similar manner to Example 23 but starting from N-(2-[4-bromoacetylphenyl]ethyl)1-butanesulphonamide the title compound was obtained, after trituration of the residual gum from flash chromatography with ether, in 22% yield: m.p. 74 - 80°C dec.; NMR(d_6DMSO) δ 8.15(2H,d), 7.94(2H,d), 7.39(2H,d), 7.10(1H,t), 6.64(2H,d), 3.70(2H,s), 3.37(4H,t), 3.21(2H,q), 2.85(4H,m), 2.64(4H,t), 1.52(2H,m), 1.31(2H,m), 0.84(3H,t); m/e 445 $(M+H)^+$; calculated for $C_{23}H_{32}N_4O_3$ S. 0.5 H_2O: C, 60.9; H, 7.3; N, 12.4. found: C, 60.5; H, 7.3; N, 12.1%.

The necessary starting material was prepared as follows:-

(i) In a similar manner to Example 23(i) but starting from 1-butanesulphonyl chloride there was obtained, after purification by flash chromatography on silica eluting with ethyl acetate hexane (1:1 v/v), N-(2-[4-acetylphenyl]ethyl)1-butanesulphonamide in 65% yield as a white crystalline solid: m.p. 75 - 76°C; NMR (d_6DMSO) δ 7.90(2H,d), 7.40(2H,d), 7.09(1H,t), 3.20(2H,q), 2.88(4H,m), 2.57(3H,s), 1.53(2H,m), 1.31(2H,m), 0.84(3H,s); m/e 284 $(M+H)^+$.

ii) In a similar manner to Example 23(ii) but starting from the product of step (i) above, there was obtained, after chromatography on silica eluting with hexane/ethyl acetate (2:1 v/v), N-(2-[4-bromoacetylphenyl]ethyl)1-butanesulphonamide in 54% yield as pale yellow crystals: m.p. 84 - 86°C; NMR ($CDCl_3$) δ 7.96(2H,d), 7.36(2H,d), 4.42(2H,s), 4.12(1H,t), 3.43(2H,q), 2.96(4H,m), 1.72(2H,m), 1.41(2H,m), 0.92(3H,t); m/e 379/381$(M+NH_4)^+$, 1 Br pattern.

EXAMPLE 25: Methyl 5-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]benzo-furan-2-carboxylate

To a solution of 1-(4-pyridyl)piperazine (262 mg) and triethylamine (0.1 ml) in acetonitrile (10 ml) was added dropwise over

40 minutes a solution of methyl 5-(2-bromoacetyl)benzofuran-2-carboxylate in acetonitrile (5 ml). The resulting mixture was stirred for 2 hours, concentrated and purified by flash column chromatography on grade III alumina, eluting with methanol/dichloromethane (1:99 to 4:96 v/v) to give the title compound as a solid (138 mg); m.p. 173-177 °C: NMR 2.66(4H,m), 3.8(4H,m), 3.91(3H,s), 4.00(2H,s), 6.82(2H,m), 7.8-8.5(6H,m); m/e 380 ($M+H^+$); calculated for $C_{21}H_{21}N_3O_4.0.5H_2O$: C, 64.9; H, 5.7; N, 10.8. Found: C, 65.2; H, 5.7; N, 10.9%.
The starting ester was prepared as follows:-

(a) Methyl 5-acetylbenzofuran-2-carboxylate

To a solution of 2-benzofuranoic acid methyl ester in carbon disulphide (240 ml) cooled to 5 °C was added acetyl chloride (70 ml) followed portionwise over 1 hour by aluminium trichloride (40 g). The mixture was heated under reflux for 42 hours before cooling and decanting the carbon disulphide. The residual complex was destroyed by the addition of iced water (50 ml) and 2N HCl (50 ml). The resulting mixture was extracted with ethyl acetate (3 x 200 ml). The organic layers were combined, washed with water (100 ml), dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography, eluting with ethyl acetate / hexane (10:90 to 40:60, v/v), to give methyl 5-acetylbenzofuran-2-carboxylate as a solid (3.099 g); NMR 2.68 (3H,s), 4.00(3H,s), 7.6-8.35(4H,m).

(b) Methyl 5-(2-bromoacetyl)benzofuran-2-carboxylate

To a suspension of cupric bromide (489mg) in ethyl acetate (5ml) at reflux was added dropwise a solution of the product of step (a) (272mg) in chloroform (5ml) and the resulting mixture was refluxed for a further 3hr. The resulting mixture was filtered, washed well with ethyl acetate and then concentrated. The residue was purified by flash column chromatography, eluting with ethyl acetate / hexane (20:80 v/v), to give methyl 5-(2-bromoacetyl)benzofuran-2-carboxylate as a solid (247mg); NMR 4.00(3H,s), 4.49(2H,s), 7.6-8.4(4H,m).

EXAMPLE 26: 5-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]benzofuran--2-carboxylic acid

To a solution of the product of Example 25 (93 mg) in methanol (5 ml) was added 1N sodium hydroxide (0.54 ml) and the resulting mixture was stirred for 2 hours. The mixture was filtered and washed with methanol to give the title compound as a solid (42 mg); NMR 2.66 (4H, m), 3.29 (4H, m), 3.97 (2H, s), 6.78-7.01 (3H, m), 7.58-8.33 (5H, m); m/e 366$(M+H)^+$; calculated for $C_{20}H_{19}N_3O_4.0.5H_2O$ C, 60.6; H, 4.8; N, 10.6; Found: C, 60.4; H, 4.5; N, 10.2%.

EXAMPLE 27: Ethyl 1-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]piperidin-4-carboxylate

A solution of ethyl-1-(bromoacetyl)-piperidin-4-carboxylate (0.84g, 3mMoles) in acetonitrile (10ml) was added dropwise to a stirred solution of 1-(4-pyridyl)piperazine (0.5g, 3mMoles) in acetonitrile (20ml) and the resulting mixture was allowed to stand for 3 hours. The white precipitate was removed by filtration and the mother liquors were concentrated under reduced pressure to give a yellow foam. The foam was purified by chromatography (flash column made with grade III neutral alumina and eluted with a gradient of 0 - 1% ethanol in dichloromethane) to give the title compound (350mg) as a colourless oil which was crystallised from cyclohexane to give colourless prisms; mp 102-104°C; Microanalysis, found: C,63.5; H,8.1; N, 15.5%; $C_{19}H_{28}N_4O_3$ requires C,63.3; H,7.8; N,15.5%; NMR (d_6DMSO + CD_3COOD): 1.2 (t,3H), 1.3-1.7 (m,2H), 1.8 (m,2H), 2.5-2.8 (m,6H), 3.0-3.4 (m,3H), 3.6 (br s,4H), 3.9 (d,1H), 4.0 (q,2H), 4.2 (d,1H), 7.1 (d,2H), 8.2 (d,2H); m/e 361 $(M+H)^+$.

The starting material was obtained as follows:

A solution of ethyl isonipecotate (5.1ml, 33mMoles) in triethylamine (4.7ml, 33mMoles) was added dropwise to a stirred ice-cooled solution of bromoacetyl bromide (2.9ml, 33mMoles) in ether (75ml) and stirring was continued for 1 hour. The resulting suspension was washed sequentially with water (2 X 20ml), dilute sodium bicarbonate solution (20ml), dilute citric acid solution

(20ml), water (20ml) and saturated brine (30ml), and then the organic fraction was dried ($MgSO_4$) and concentrated under reduced pressure to give ethyl 1-(bromoacetyl)-piperidin-4-carboxylate (4.6g) as a yellow oil which was used without further purification; NMR ($CDCl_3$): 1.2 (t,3H), 1.6-2.1 (m,4H), 2.5 (m,1H), 2.9 (m,1H), 3.2 (m,1H), 3.8 (s, 2H + m,1H), 4.15 (q,2H), 4.3 (m,1H); m/e 278/280 $(M+H)^+$.

EXAMPLE 28: 1-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]piperidin-4-carboxylic acid

A solution of the product of Example 27 (200mg, 0.56mMoles) in dioxan (10ml) and concentrated hydrochloric acid (5ml) was heated on a steam bath for 30 minutes. The solvent was evaporated under reduced pressure and the residue was triturated with ether to give a foam. The foam was dissolved in warm ethanol (10ml), filtered and allowed to cool. The title compound crystallised as colourless prisms (70mg); mp 280-282°C (decomposition); Microanalysis, found: C,50.0; H, 7.1; N,12.7; Cl,16.4; H_2O, 2.5%; $C_{17}H_{24}N_4O_3.2HCl.0.5H_2O.0.33C_2H_6O$ requires: C,49.4; H,6.8; N,13.0; Cl,16.5; H_2O,2.1%; NMR (d_6DMSO + CD_3COOD): 1.4-1.7 (m,2H), 2.0 (m,2H), 2.9 (t,1H), 3.2 (t,1H), 3.4-3.7 (m,5H), 3.9-4.2 (br s,4H), 4.3 (d,1H), 4.4 (q,2H), 7.25 (d,2H), 8.3 (d,2H), + signals due to ethanol (0.33 Mole eq); m/e 333 $(M+H)^+$.

EXAMPLE 29: Ethyl 2-[1-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]piperidin-4-yl]acetate

A solution containing 1-(4-pyridyl)-4-carboxymethylpiperazine dihydrochloride $1/4H_2O$(400mg, 1.33 mMoles), triethylamine (0.4ml, 2.66mMoles) and HOBT (0.2g, 1.46mMoles) in dry dimethylformamide (20ml) was treated with diisopropylcarbodiimide (0.23ml, 1.46mMoles) and the mixture was stirred for 5 minutes. Ethyl 4-carboxymethylpiperidine was added and the mixture was stirred for a further 4 hours. The mixture was concentrated to half volume under reduced pressure and then poured into water (50ml) and extracted with ethyl acetate (3 X 20ml) and dichloromethane (3 X 20ml). The combined organic extracts were concentrated under reduced pressure and the

residue was purified by chromatography (flash column made with grade III alumina and eluted with a gradient of 0 - 1% methanol in dichloromethane) to give the title compound (130mg) as a colourless oil; NMR (d_6DMSO): 0.9-1.1 (m,2H), 1.2 (t,3H), 1.65 (d,2H), 1.8-2.0 (m,1H), 2.2 (d,2H), 2.5 (m,2H), 2.9-3.4 (m,10H), 4.0 (q,2H + m,1H), 4.3 (d,1H), 6.8 (d,2H), 8.15 (d,2H); m/e 375 $(M+H)^+$.

The starting materials were prepared as follows:

a) 1-(4-pyridyl)-4-carboxymethylpiperazine, hydrochloride

A solution of tert-butyl bromoacetate (1.0ml, 6.1mMoles) in acetonitrile (20ml) was added to a stirred solution of 1-(4-pyridyl)-piperazine (2.0g, 12.3mMoles) in acetonitrile (30ml) and the mixture was stirred for 4 hours. The white precipitate was removed by filtration and the filtrate was concentrated under reduced pressure to give a yellow foam. The foam was purified by chromatography (flash column made with grade III alumina and eluted with a gradient of 0 - 1% methanol in dichloromethane) to give a colourless crystalline solid (900mg). Recrystallisation from cyclohexane gave tert-butyl 1-(4-pyridyl)-piperazine-4-acetic ester (500mg) as colourless prisms; mp 83-85 °C ; Microanalysis, found: C,65.2; H,8.6; N,15.0; $C_{15}H_{23}N_3O_2$ requires: C,65.0; H,8.4; N,15.1%; NMR (d_6DMSO): 1.4 (s,9H), 2.6 (t,4H), 3.2 (s,2H), 3.5 (t,4H), 6.8 (d,2H), 8.15 (d,2H); m/e 278 $(M+H)^+$.

A solution of tert-butyl 1-(4-pyridyl)-piperazine-4-acetic ester (400mg, 1.4mMoles) in concentrated hydrochloric acid (10ml) was allowed to stand for 1.5 hours and was then concentrated under reduced pressure. The residue was triturated with hot acetone, filtered and washed with acetone to give 1-(4-pyridyl)-4-carboxymethylpiperazine, hydrochloride (350mg) as a pale cream solid; Microanalysis, found: C,44.2; H,5.9; N,13.8; Cl,23.8; H_2O,1.4%; $C_{11}H_{15}N_3O_2.2HCl.0.25H_2O$ requires: C,44.2; H,5.9; N,14.1; Cl,23.7; H_2O 1.3%; NMR (d_6DMSO): 3.4-3.6 (br s,4H), 4.0-4.2 (br s,4H), 4.2 (s,2H), 7.3 (d,2H), 8.4 (d,2H); m/e 222 $(M+H)^+$.

b) Ethyl-4-carboxymethylpiperidine

A stirred suspension of sodium hydride (50% dispersion in mineral oil, 4.8g, 0.1Moles) in dimethoxyethane (300ml) was ice-cooled and treated under an atmosphere of argon with triethyl phosphonoacetate (19.82ml, 0.1Moles), added dropwise. Stirring was continued for 1 hour during which time the temperature of the mixture was maintained <5 °C. The cooling bath was removed and N-benzylpiperidone (17.85ml, 0.1Moles) was added dropwise. The mixture was stirred overnight at room temperature, then diluted with water (500ml) and extracted with ether (3 X 200ml). The combined organic extracts were washed with water (200ml) and saturated brine (100ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography (flash column, eluted with hexane/ethyl acetate; 3:2) to give ethyl 4-carboxymethylene-N-benzylpiperidine ester (5.52g) as a yellow oil; NMR ($CDCl_3$): 1.1 (t,3H), 2.2 (t,2H), 2.4 (m,4H), 3.4 (s,2H), 4.0 (q,2H), 5.6 (s,1H), 7.2 (m,5H); m/e 260 $(M+H)^+$.

A solution of ethyl 4-carboxymethylene-N-benzylpiperidine ester (5.5g, 21 mMoles) in ethanol (250ml)was stirred with 10% palladium on carbon under an atmosphere of hydrogen until a total of 950ml of hydrogen had been consumed. An additional quantity of 10% palladium on carbon (500mg) was added and stirring was continued for 4 hours to remove residual starting material. The mixture was filtered and concentrated under reduced pressure to give ethyl 4-carboxymethylpiperidine ester (3.31g) as a slightly green oil which was used without further purification; NMR ($CDCl_3$): 1.0-1.2 (m,2H), 1.25 (t,3H), 1.7 (s,2H), 1.9 (m,1H), 2.2 (d,2H), 2.6 (td,2H), 3.05 (dt,2H), 4.0 (q,2H); m/e 172 $(M+H)^+$.

EXAMPLE 30: 2-[1-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]piperidin-4-yl]acetic acid

In a similar manner to Example 28, but starting from the product of Example 29, the title compound was prepared as colourless prisms from isopropanol; mp 248-250°C (decomposition); Microanalysis, found: C,50.2; H,6.8; N,12.6; H_2O,3.4%; $C_{18}H_{26}N_4O_3.2HCl.0.8H_2O$ requires: C,49.8; H,6.9; N12.9; H_2O,3.3%; NMR (d_6DMSO + CD_3COOD): 0.9-1.3 (m,2H), 1.7 (m,2H), 1.9 (m,1H), 2.2 (d,2H), 2.7 (t,1H), 3.15(t,1H), 3.4-3.7 (m,5H), 3.8-4.2 (m,4H), 4.3-4.5(m,3H), 7.2 (d,2H), 8.3 (d,2H); m/e 347 $(M+H)^+$.

EXAMPLE 31: Tert-butyl 2-[1-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]-piperidin-4-yloxy]acetate

A solution of 1-(4-pyridyl)-carboxymethylpiperidine (400mg, 1.33mMoles) triethylamine (0.4ml, 2.66mMoles) and HOBT (0.2g, 1.46mMoles) in dry dimethylformamide (20ml) was treated with diisopropylcarbodiimide (0.23ml, 1.46mMoles) and the mixture was stirred for 5 minutes. Tert-butyl piperidine-4-oxyacetic ester (614mg, 2.8mMoles) was added and the mixture was stirred for a further 6 hours. The mixture was concentrated to half volume under reduced pressure and then poured into water (50ml) and extracted with dichloromethane (4 X 30ml). The combined organic extracts were washed with saturated brine and concentrated under reduced pressure. The residue was purified by chromatography (flash column made with grade III alumina and eluted with a gradient of 0 - 1% methanol in dichloromethane) to give the title compound (240mg) as a colourless oil; NMR (d_6DMSO): 1.3-1.7 (m,2H + s,9H), 1.7-1.9 (m,2H), 3.0-3.5 (m,12H), 3.55 (m,1H), 3.8 (m,2H), 4.0 (s,2H), 6.8 (d,2H), 8.15 (d,2H); m/e 419 $(M+H)^+$.

The starting material was prepared as follows:

An ice-cooled solution containing 4-piperidinol (5g, 50mMoles) and triethylamine (7ml, 50mMoles) in dichloromethane (50ml)

was cautiously treated with benzylchloroformate (7.5ml, 50mMoles) and allowed to stir for 2 hours. Dichloromethane (25ml) was added and the solution was washed sequentially with water (2 X 40ml) and saturated brine (50ml), then dried (MgSO4) and concentrated under reduced pressure. The residue was purified by vacuum flash chromatography, eluting with a gradient of 50-100% ether in hexane to give N-benzyloxycarbonyl piperidin-4-ol (7.5g) as a colourless oil; NMR (d_6DMSO): 1.2-1.4 (m,2H), 1.6-1 8 (m,2H), 3.0-3.2 (m,2H), 3.6-3.8 (m,3H), 4.7 (d,2H), 5.1 (2,2H), 7.3 (m,5H); m/e 236 $(M+H)^+$.

A solution of N-benzyloxycarbonyl piperidin-4-ol (7g, 30mMoles) in dry THF (100ml) was treated with sodium hydride (60% suspension in mineral oil, 1.3g, 32mMoles) and the resulting mixture was stirred until effervescence ceased (about 1 hour). Tert·butylbromoacetate (5.1ml, 32mMoles) was added and stirring was continued for a further 2 hours. The mixture was diluted with ether (200ml), washed with water (3 X 75ml) and saturated brine (75ml), dried (MgSO4) and concentrated under reduced pressure. The residual oil was purified by chromatography (flash column eluted first with hexane/ether 1:1 and then with ether alone) to give tert-butyl N-benzyloxycarbonyl-piperidine- 4-oxyacetic ester (3.0g) as a colourless oil;NMR (d_6DMSO): 1.3-1.5 (m,2H + s,9H), 1.7-1.9 (m,2H), 3.0-3.2 (m,2H), 3.5-3.8 (m,3H), 4.0 (s,2H), 5.1 (s,2H), 7.35 (m,5H); m/e 350 $(M+H)^+$.

A solution of tert-butyl N-benzyloxycarbonyl--piperidine-4-oxyacetic ester (1.0g, 2.9mMoles) in iso-propanol (40ml) was stirred with charcoal, filtered and stirred with 10% palladium on carbon (200mg) under an atmosphere of hydrogen. When 50ml of hydrogen had been consumed the mixture was filtered and the filtrate was concentrated under reduced pressure to give tert-butyl piperidine-4-oxyacetic ester (614mg) as a colourless oil which was used without further purification.

EXAMPLE 32: 2-[1-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]piperidin-4-yloxy]acetic acid

A solution of the product of Example 31 (220mg, 0.53mMoles) in a mixture of dichloromethane (5ml) and trifluoroacetic acid (5ml) was allowed to stand for 1.5 hours and was then concentrated under reduced pressure. The residue was triturated with ether and crystallised from isopropanol (12ml) to give the title compound (200mg) as colourless prisms; mp 198-200 °C; Microanalysis, found: C,45.0; H,4.8; N,9.4%; $C_{18}H_{26}N_4O_4.2CF_3COOH$ requires: C,44.8; H,4.8; N,9.5%; NMR (d_6DMSO): 1.3-1.7 (m,2H), 1.8-2.0 (m,2H), 3.0-4.2 (m,16H), 4.15 (s,2H), 7.25 (d,2H), 8.3 (d,2H); m/e 363 $(M+H)^+$.

EXAMPLE 33: Methyl 2-S-(n-butylsulphonylamino)-3-[4-[1-(4-pyridyl)-piperidin-4-yl]methoxyphenyl]propionate

n-Butylsulphonyl chloride (0.32ml) was added dropwise to a solution of methyl 2-Samino-3-[4-(1-(4-pyridyl)piperidin--4-yl)methoxyphenyl]-propionate (750mg) and triethylamine (0.5ml) in dichloromethane (15ml) cooled in an ice bath. The mixture was allowed to reach ambient temperature and stirred for 5 hours and then refluxed for 2 hours. The reaction mixture was washed with water (20ml) and saturated sodium chloride solution (15ml) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by flash chromatography eluting with methanol/dichloromethane (1:9v/v) to give the title compound (650mg) as a gum; NMR($CDCl_3$): 0.87(t,3H), 1.26-1.7(m,6H), 1.95(d,2H), 2.1(m,1H), 2.72-3.18(m,6H), 3.77(s,3H), 3.79(d,2H), 3.96(d,2H), 4.32(m,1H), 4.82(brd,1H), 6.69(d,2H), 6.83(d,2H), 7.1(d,2H), 8.25(brd,2H); mass spectrum (+ve FAB MeOH/NBA): 490 $(M+H)^+$ $[\alpha]_D^{22}$ = -14°C (c = 1, MeOH).

The starting macerial was prepared as follows:-

(i) Diethylazodicarboxylate (0.58ml) was added dropwise to a stirred mixture of 4-(4-hydroxymethylpiperidin-1-yl)pyridine (700mg), N-benzyloxycarbonyl-S-tyrosine methyl ester (1.2g), triphenylphosphine

(955mg) and THF (40ml) in an atmosphere of argon and cooled to 10 °C. The mixture was allowed to reach ambient temperature and stirred for 48 hours. The solvent was removed by evaporation and the residue purified by flash chromatography eluting with methanol/dichloromethane (1:9v/v) to give methyl 2S-(benzyloxycarbonylamino)-3-[4-(1-(4-pyridyl)piperidin-4-yl)methoxyphenyl]propionate (1.2g) as a solid m.p. 68-75 °C; NMR(d_6-DMSO): 1.2-1.4(m,2H), 1.84(d,d,2H), 1.92-2.1(m,1H), 2.7-3.02(m,4H), 3.6(s,3H), 3.8(d,2H), 3.98(d,2H), 4.14-4.28(m,1H), 4.98(s,2H), 6.78-6.88(m,4H), 7.13(d,2H), 7.20-7.4(m,5H), 7.75(d,1H), 8.13(d,2H); mass spectrum (+ve FAB, MeOH/NBA): 504$(M+H)^+$.

(ii) A solution of the product of step (i) (1g) in ethanol (40ml) and 10% palladium/carbon (200mg) was stirred in a stream of hydrogen for 4 hours at ambient temperature. The mixture was filtered through a pad of diatomaceous earth and the solvent removed by evaporation to give methyl 2-S-amino-3-[4-(1-(4'-pyridyl)piperidin-4-yl)-methoxyphenyl]propionate as an oil; NMR(d_6DMSO): 1.13-1.44(m,2H), 1.75-2.13(m,3H), 2.64-2.94(m,4H), 3.51(m,1H), 3.57(s,3H), 3.81(d,2H), 3.96(d,2H), 6.8(dd,2H), 6.83(d,2H), 7.08(d,2H), 8.12(dd,2H); mass spectrum(+ve FAB, MeOH/NBA): 370 $(M+H)^+$.

EXAMPLE 34: 2-S-(n-butylsulphonylamino)-3-[4-[1-(4-pyridyl)piperidin--4-yl]methoxyphenyl]propionic acid

Lithium hydroxide (285mg) was added to a solution of the product of Example 33 (520mg) in a mixture of methanol (9ml), THF (9ml) and water (9ml) and stirred at ambient temperature for 3.75 hours. The solvent was evaporated and water (5ml) added to the residue. A 10% aqueous solution of potassium hydrogen sulphate (8ml) was added and an oil separated. The oil was dissolved in methanol and filtered through diatomaceous earth. The solvent was evaporated, and the residue triturated with ethyl acetate gave the title compound (500mg) as an amorphous solid, NMR (d_6DMSO)): 0.81(t,3H), 1.1-1.6(m,6H), 1.85(d,2H), 2.0(brs,1H), 2.58-3.0(m,6H), 3.68(t,2H), 3.8(d,2H), 3.98(d,2H), 6.8(brs,4H), 7.13(d,2H), 8.12(brs,2H); mass spectrum(+ve FAB, methanol/m-nitrobenzyl alcohol(NBA)): 476$(M+H)^+$.

EXAMPLE 35: Methyl 2-S-(n-butylsulphonylamino)-3-[4-[2-[1-(4-pyridyl)-piperidin-4-yl]ethoxy]phenyl]propionate

n-Butylsulphonyl chloride (0.28ml) was added dropwise to a solution of methyl 2-S-amino-3-[4-[2-[1-(4-pyridyl)piperidin--4-yl]ethoxy]phenyl]propionate (630mg) and triethylamine (0.5ml) in dichloromethane (15ml) cooled in an ice-bath. The mixture was allowed to reach ambient temperature and stirred for 5 hours. The reaction mixture was diluted with dichloromethane (10ml) and washed with water (20ml), saturated sodium chloride solution (10ml) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by flash chromatography eluting with methanol/dichloromethane(1:9v/v) to give the title compound (680mg) as a gum; NMR($CDCl_3$): 0.9(t,3H), 1.25-1.45(m,4H), 1.55-1.95(m,7H), 2.72-3.15(m,6H), 3.78(s,3H), 3.9(brd,2H), 4.0(t,2H), 4.32(brs,1H), 4.84(brs,1H), 6.68(d,2H), 6.83(d,2H), 7.09(d,2H), 8.23(brs,2H); mass spectrum(+ve FAB, MeOH/NBA): 504 $(M+H)^+$.

The starting material was prepared as follows:-

(i) Following the method of Example 33, step (i), but using 4-(4-hydroxyethylpiperidin-1-yl)pyridine, methyl 2-S-(benzyloxycarbonylamino)-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]-propionate (900mg) was prepared as an oil; NMR (d_6DMSO): 1.05-1.35(m,2H), 1.6-1.9(m,5H), 2.7-3.05(m,4H), 3.63(s,3H), 3.92(d,2H), 4.0(t,2H), 4.21(m,1H), 4.98(s,2H), 6.8(d,2H), 6.84(d,2H), 7.14(d,2H), 7.3(m,4H), 7.75(d,1H), 8.12(d,2H); mass spectrum(+ve FAB, NBA/CH_2Cl_2): 518 $(M+H)^+$.

(ii) Following the method of Example 33, step (ii), but using the product of step (i) above, methyl 2-S-amino-3-[4-[2-[1-(4-pyridyl)-piperidin-4-yl]ethoxy]phenyl]propionate was prepared as a gum; NMR(d_6DMSO): 1.08-1.32(m,2H), 1.58-1.86(m,5H), 2.61-2.9(m,4H), 3.52(m,1H), 3.58(s,3H), 3.82-4.02(m,4H), 6.79(dd,2H), 6.81(d,2H), 7.07(d,2H), 8.1(dd,2H); mass spectrum(+ve FAB, MeOH/NBA): 384 $(M+H)^+$.

EXAMPLE 36: 2-S-(n-butylsulphonylamino)-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]propionic acid

Following the method of Example 34, but using the product of Example 35 the title compound (380mg) was prepared; NMR(d_6DMSO): 0.78(t,3H), 1.05-1.5(m,6H), 1.6-1.9(m,5H), 2.5-3.05(m,6H), 3.8-4.05(m,6H), 4.6(brs,1H), 6.85(m,4H), 7.19(d,2H), 8.13(brs,2H); mass spectrum(+ve FAB, MeOH/NBA): 490 $(M+H)^+$; microanalysis found: C, 57.7; H, 7.5; N, 8.0; H_2O, 7.1%; $C_{25}H_{35}N_3O_5S.2H_2O$ requires: C, 57.1; H, 7.4; N, 8.0; H_2O, 6.9%.

EXAMPLE 37: Methyl 2-S-(n-butylsulphonylamino)-3-[4-[1-(4-pyridyl)-piperidin-4-yl]oxyphenyl]propionate

Using a procedure similar to that described in Example 35, but starting from the appropriate amino acid ester, the title compound was prepared NMR($CDCl_3$): 0.9(t,3H), 1.25-1.45(m,2H), 1.55-1.8(m,2H), 1.8-2.15(m,4H), 2.6-2.88(m,2H), 2.9-3.2(m,2H), 3.3-3.45(m,2H), 3.55-3.74(m,2H), 3.78(s,3H), 4.27-4.4(m,1H), 4.45-4.6(m,1H), 4.8(brd,2H), 6.7(d,2H), 6.86(d,2H), 7.1(d,2H), 8.26(brd,2H); mass spectrum (+ve FAB, MeOH/NBA): 476 $(M+H)^+$.

The starting material was prepared using similar procedures to those described in Example 35. There were thus prepared the following intermediates starting from 4-(4-hydroxypiperidin-1-yl)pyridine:-

Methyl 2-S-(benzyloxycarbonylamino)-3-[4-(1-(4'-pyridyl)piperidin--4-yl)oxyphenyl]propionate; NMR(d_6DMSO): 1.5-1.72(m,2H), 1.9-2.1(m,2H), 2.7-3.02(m,2H), 3.18(d,2H), 3.2-3.35(m,1H), 3.48-3.77(m,1H), 3.62(s,3H), 4.13-4.28(m,1H), 4.5-4.65(m,1H), 4.97(s,2H), 6.8-6.94(m,4H), 7.14(d,2H), 7.77(d,1H), 8.15(d,2H); mass spectrum(+ve FAB, CH_2Cl_2/NBA): 518 $(M+H)^+$.

Methyl 2-S-amino-3-[4-(1-(4'-pyridyl)piperidin-4-yl)oxyphenyl]-propionate; NMR(d_6DMSO): 1.54-1.72(m,2H), 1.9-2.06(m,2H), 2.65-2.88(m,2H), 3.15-3.4(m,2H), 3.52(t,1H), 3.59(s,3H), 3.6-3.75(m,2H), 4.52-4.65(m,1H), 6.8-6.92(m,4H), 7.09(d,2H), 8.15(dd,2H); mass spectrum (+ve FAB, MeOH/NBA): 356 $(M+H)^+$.

EXAMPLE 38: 2-S-(n-butylsulphonylamino)-3-[4-[1-(4-pyridyl)piperidin--4-yl]oxyphenyl]propionic acid

Using a similar procedure to that described in Example 34 but starting from the product of Example 37, the title compound was obtained as a solid m.p.255-258°C dec.; NMR(d_6DMSO): 0.66 (t,3H), 0.98-1.04 (m,2H), 1.05-1.4(m,2H), 1.44-1.62(m,2H), 1.8-1.96(m,2H), 2.49(t,2H), 2.61(dd,1H), 2.87(dd,1H), 3.12-3.28(m,2H), 3.4-4.0(m,5H), 4.43-4.55(m,1H), 6.79(m,4H), 7.09(d,2H), 8.04(brd,2H); mass spectrum(+ve FAB, MeOH/NBA): 462 $(M+H)^+$; microanalysis found: C, 59.6; H 6.9; N, 9.0%; $C_{23}H_{31}N_3O_5S$ requires: C, 59.8; H, 6.8; N, 9.1%.

EXAMPLE 39: N-[N-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-L-aspartyl]-L-phenylalanine.

To a solution of O-benzyl-N-[O-benzyl-N-[2-[4-(4-pyridyl)-piperazin-1-yl]acetyl]-L-aspartyl]-L-phenylalanine (0.92 g) in methanol (125 ml) under argon was added 10% Pd on C (0.45 g). The mixture was covered with a blanket of hydrogen and stirred at room temperature until deprotection was complete. The catalyst was filtered off through a pad of kieselguhr and the filtrate was evaporated to dryness. The resultant white solid was dissolved in water and lyophilised overnight to yield the title compound (274 mg) as a white solid: m.p. 153°C (dec.); NMR (d_6DMSO + CD_3CO_2D) δ 2.65 (6H, m), 3.02 (4H, m), 3.63 (4H, m), 4.44 (1H, m), 4.67 (1H, m), 7.13 (2H, d), 7.23 (5H, m), 8.22 (2H, d); m/Z 484 $(M + H)^+$; calculated for $C_{24}H_{29}N_5O_6$. m/Z 484 $(M + H)^+$; amino acid analysis: found; Asp, 1.00; Phe 0.99; requires; Asp, 1.00; Phe, 1.00.

The necessary starting material was prepared as follows:-

(i) Boc-L-Asp(OBzl)-L-Phe-OBzl (9.91 g) was dissolved in a mixture of trifluoroacetic acid (50 ml) and dichloromethane (50 ml). The resultant solution was stored at room temperature for 2 hr. The reaction mixture was evaporated to dryness to yield a residue which was triturated with ether, collected, washed thoroughly with ether and dried under high vacuum to yield L-Asp(OBzl)-L-Phe-OBzl, trifluoroacetate salt (8.36 g) as a white solid: NMR ($CDCl_3$) δ 2.88 (2H, m), 3.07 (2H, m), 4.33 (1H, m), 4.78 (1H, m), 5.02 (2H, s), 5.06 (2H, q), 6.20 (3H, v. br), 7.04 (2H, m), 7.26 (13H, m), 7.65 (1H, d); m/Z 461 $(M + H)^+$.

(ii) To an ice-cold solution of 1-(4-pyridyl)-4-carboxymethylpiperazine dihydrochloride (307 mg), HOBt.H_2O (176 mg) and HBTU (436 mg) in DMF (8 ml) under argon was added diisopropylethylamine (1.07 ml), followed, after 5 minutes, by a solution of the product of step (i) (600 mg) in DMF (5 ml). The reaction mixture was allowed to warm to room temperature with stirring overnight under argon. The reaction mixture was diluted with ethyl acetate (100 ml) and washed with water, dilute $KHSO_4$ (aq.), dilute $NaHCO_3$ (aq.), water, dried ($MgSO_4$) and evaporated to yield O-benzyl-N-[O-benzyl-N-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-L- aspartyl]-L-phenylalanine (690 mg) as an off-white amorphous solid: NMR (d_6DMSO + CD_3CO_2D) δ 2.50 (4H, m), 2.69 (2H, m), 2.96 (4H, m), 3.54 (4H, m), 4.52 (1H, m), 4.72 (1H, m), 5.00 (4H, s), 7.03 (2H, d), 7.23 (15H, m), 8.10 (2H, m); m/Z 664 $(M + H)^+$.

EXAMPLE 40: N-[N-[N-2-[4-(4-pyridyl)piperazin-1-yl]acetyl]glycyl]-L-aspartyl]-L-phenylalanine

In a similar manner to Example 39, O-benzyl-N-[O-benzyl-N-[N-2-[4-(4-pyridyl)piperazin-1-yl]acetyl]glycyl]-L-aspartyl]-L-phenylalanine (0.42 g), 10% Pd on C (200 mg) and methanol (125 ml) under a blanket of hydrogen gave, after lyophilisation from water, the title compound (91 mg) as a white solid: m.p. 180°C (dec.); NMR (d_6DMSO + CD_3CO_2D) δ 2.50 (1H, m), 2.67 (5H, m), 2.96 (1H, m), 3.10 (3H, m), 3.72 (4H, m), 3.82 (2H, s), 4.44 (1H, m), 4.64 (1H, m), 7.13 (2H, d),

7.23 (5H, m), 8.18 (2H, d); m/Z 541 $(M + H)^+$; amino acid analysis: found; Asp, 1.00; Phe 1.04; Gly, 0.98; requires; Asp, 1.00; Phe, 1.00; Gly, 0.98.

The necessary starting material was prepared as follows:-

(i) In a similar manner to Example 39 (ii), Boc-Gly-OH (1.28 g), $HOBt.H_2O$ (1.23 g), HBTU (3.04 g), diisopropylethylamine (5 ml), L-Asp(OBzl)-L-Phe-OBzl, trifluoroacetate salt (4.18 g) and DMF (40 ml) gave Boc-Gly-L-Asp(OBzl)-L-Phe-OBzl (4.4 g) as a white solid: NMR ($CDCl_3$) δ 1.47 (9H, s), 2.63 (1H, m), 3.08 (3H, m), 3.69 (2H, m), 4.80 (2H, m), 5.10 (2H, s), 5.13 (2H, q), 6.97 (1H, d), 7.05 (2H, m), 7.28 (13H, m); m/Z 618 $(M + H)^+$.

(ii) In a similar manner to Example 39 (i), the product of step (i) (5.6 g), trifluoroacetic acid (30 ml) and dichloromethane (30 ml) gave Gly-L-Asp(OBzl)-L-Phe-OBzl, trifluoroacetate salt (5.6 g) as a colourless oil: NMR ($CDCl_3$ + CD_3CO_2D) δ 2.80 (2H, m), 3.09 (2H, m), 3.85 (2H, s), 4.83 (1H, m), 4.93 (1H, m), 5.07 (2H, s), 5.10 (2H, q), 7.05 (2H, m), 7.25 (13H, m); m/Z 518 $(M + H)^+$.

(iii) In a similar manner to Example 39 (ii), 1-(4-pyridyl)-4-carboxymethylpiperazine dihydrochloride (280 mg), $HOBt.H_2O$ (160 mg), HBTU (400 mg), diisopropylethylamine (0.98 ml), the product of step (ii) (600 mg) and DMF (10 ml) gave O-benzyl-N-[O-benzyl-N-[N-2-[4-(4-pyridyl)piperazin-1-yl]acetyl]glycyl]-L-aspartyl]-L-phenylalanine (0.42 g) as an off-white solid: NMR ($CDCl_3$) δ 2.68 (5H, m), 3.10 (5H, m), 3.49 (4H, m), 3.93 (2H, d), 4.81 (2H, m), 5.09 (2H, s), 5.10 (2H, q), 6.74 (2H, d), 7.07 (2H, m), 7.25 (15H, m), 7.64 (1H, t), 8.18 (2H, d); m/Z 721 $(M + H)^+$.

EXAMPLE 41: Methyl 4-[2-[4-(2-methyl-4-quinolinyl)piperazin-1-yl]acetyl]phenoxyacetate

In a similar manner to Example 1, methyl 4-bromoacetyl-phenoxyacetate (1.62 g), 2-methyl-4-(1-piperazinyl)quinoline

(preparation described in Sharma, M. et al (1981), Pol. J. Pharmacol. Pharm. 33(5), 539-44) (2.59 g) and acetonitrile (80 ml) yielded, after stirring at room temperature overnight, filtration and evaporation of the filtrate, an orange/brown oily residue which was purified by flash chromatography, first on neutral alumina by elution with 3% v/v methanol/dichloromethane, then on silica by elution with methanol/dichloromethane (0.5% v/v to 3% v/v), and finally by crystallisation from methanol/water, to yield the title compound (671 mg) as an off-white solid: NMR ($CDCl_3$) δ 2.68 (3H, s), 2.92 (4H, m), 3.32 (4H, m), 3.83 (3H, s), 3.90 (2H, s), 4.73 (2H, s), 6.74 (1H, s), 6.97 (2H, d), 7.42 (1H, m), 7.63 (1H, m), 7.98 (2H, m), 8.06 (2H, d); m/Z 434 $(M + H)^+$; calculated for $C_{25}H_{27}N_3O_4$: C, 69.3%; H, 6.28%; N, 9.69%; found: C, 69.2%; H,6.4%; N, 9.6%.

EXAMPLE 42: 4-[2-[4-(2-methyl-4-quinolinyl)piperazin-1-yl]acetyl]-phenoxyacetic acid

A mixture of the product of Example 41 (100 mg) and 0.5% v/v triethylamine/water (20 ml) was stirred at room temperature overnight, by which time all of the solids had dissolved. The pale yellow solution was washed with ether, filtered and lyophilised overnight to yield the title compound (107 mg) as an off-white solid: NMR (d_6-MSO) δ 1.13 (2.7H, t), 2.58 (3H, s), 2.83 (4H, m), 2.97 (1.8H, q), 3.18 (4H, m), 3.88 (2H, s), 4.70 (2H, s), 6.87 (1H, s), 6.99 (2H, d), 7.45 (1H, m), 7.63 (1H, m), 7.83 (1H, m), 7.94 (1H, m), 8.01 (2H, d); m/Z 420 $(M + H)^+$; calculated for $C_{24}H_{25}N_3O_4$. 0.3 Et_3N. 1 H_2O: C, 66.2%; H, 6.79%; N, 9.88%; found: C, 65.9%; H, 6.7%; N, 9.6%.

EXAMPLE 43: Methyl 4-[2-[4-(4-quinolinyl)piperazin-1-yl]acetyl]-phenoxyacetate

In a similar manner to Example 1, methyl 4-bromoacetylphenoxyacetate (1.60 g), 4-(1-piperazinyl)quinoline (Preparation described in EP 281309 A1) (2.39 g) and acetonitrile (75 ml) yielded, after stirring at room temperature overnight, filtration and evaporation of the filtrate, an orange/brown oily residue which

was purified by flash chromatography, first on neutral alumina by elution with 3% v/v methanol/dichloromethane, then on silica by elution with methanol/dichloromethane (0.5% v/v to 5% v/v), and finally by crystallisation from methanol/water, to yield the title compound (373 mg) as a yellow solid: NMR ($CDCl_3$) δ 2,91 (4H, m), 3.33 (4H, m), 3.82 (3H, s), 3.89 (2H, s), 4.72 (2H, s), 6.86 (1H, d), 6.96 (2H, d), 7.48 (1H, m), 7.65 (1H, m), 8.02 (2H, m), 8.06 (2H, d), 8.73 (1H, d); m/Z 420 $(M + H)^+$; calculated for $C_{24}H_{25}N_3O_4$. 0.25 H_2O: C, 68.0%; H, 6.06%; N, 9.91%; found: C, 67.9%; H, 6.0%; N, 9.7%.

EXAMPLE 44: 4-[2-[4-(4-quinolinyl)piperazin-1-yl]acetyl]phenoxyacetic acid, trifluoroacetate salt

In a similar manner to Example 42, the product of Example 43 (313 mg), and 1% v/v triethylamine/water (65 ml) gave, after 2 days stirring at room temperature, washing with ether, filtration and lyophilisation, an off-white solid which was purified by preparative rp-hplc on a DYNAMAX C-18, 60A [83-201-C] column using an acetonitrile/water mobile phase system containing 0.1% trifluoroacetic acid, to give, after lyophilisation, the title compound (200 mg) as a white solid: NMR (d_6DMSO) δ 3.45 (4H, m), 3.99 (4H, m), 4.85 (4H, s), 7.13 (2H, d), 7.32 (1H, d), 7.74 (1H, m), 8.01 (4H, m), 8.19 (1H, m), 8.83 (1H, d); m/Z 406 $(M + H)^+$; calculated for $C_{23}H_{23}N_3O_4$. 2.0 CF_3CO_2H: C, 51.2%; H, 3.98%; N, 6.63%; found: C, 50.9%; H, 3.9%; N, 6.5%.

EXAMPLE 45: Methyl 4-[2-[4-(5,6,7,8-tetrahydro-4-quinolinyl)-piperazin-1-yl]acetyl]phenoxyacetate

In a similar manner to Example 1, methyl 4-bromoacetylphenoxyacetate (1.23 g), a 1:1 mixture containing 4-(1-piperazinyl)quinoline and 4-(1-piperazinyl)-5,6,7,8-tetrahydroquinoline (1.84 g) and acetonitrile (56 ml) yielded, after stirring at room temperature overnight, filtration and evaporation of the filtrate, an orange/brown oily residue which was purified by flash chromatography, first on neutral alumina by elution with 5% v/v

methanol/dichloromethane, then on silica by elution with methanol/dichloromethane (0.5% v/v to 5% v/v), and finally by crystallisation of the lower Rf material from methanol/water, to yield the title compound (298 mg) as a cream solid: NMR ($CDCl_3$) δ 1.76 (2H, m), 1.89 (2H, m), 2.64 (2H, m), 2.76 (4H, m), 2.95 (2H, m), 3.07 (4H, m), 3.80 (2H, s), 3.81 (3H, s), 4.71 (2H, s), 6.68 (1H, d), 6.95 (2H, d), 8.03 (2H, d), 8.28 (1H, d); m/Z 424 $(M + H)^+$; calculated for $C_{24}H_{29}N_3O_4 \cdot 1.0\ H_2O$: C, 65.3%; H, 7.08%; N, 9.52%; found: C, 65.6%; H, 6.7%; N, 9.3%.

The necessary starting material was prepared as follows:-

(i) To a solution of 4-chloroquinoline (3 g) in mixed xylenes (b.p. 137-144°C) (25 ml) was added 1-benzylpiperazine (6.46 g). The mixture was heated to reflux with stirring for 20 hours then cooled to room temperature. The precipitate that formed was filtered and washed with xylene. To the combined filtrate and washings was added decolourising charcoal and the mixture was heated to reflux for 20 minutes, cooled and filtered through kieselguhr. The filtrate was evaporated to dryness to yield 1-benzyl-4-(4-quinolinyl)piperazine (4.55 g) as a yellow solid: m.p. 105-106°C; NMR ($CDCl_3$) δ 2.75 (4H, m), 3.26 (4H, m), 3.66 (2H, s), 6.84 (1H, d), 7.35 (5H, m), 7.45 (1H, m), 7.65 (1H, m), 8.03 (2H, m), 8.73 (1H, m); m/Z 304 $(M + H)^+$.

(ii) To a solution of the product of step (i) (3 g) and p-toluene sulphonic acid monohydrate (3.79 g) in methanol (300 ml) under argon was added 10% Pd on C (1.5 g). The mixture was covered with a blanket of hydrogen aded stirred vigorously at room temperature for 24 hours. The catalyst was filtered off through a pad of kieselguhr and the filtrate was evaporated to dryness. The oily residue was partitioned between water, ethyl acetate and a small volume of methanol, basified to pH 9-10 by addition of 1N NaOH (aq.) and the organic layer was separated. The aqueous layer was saturated with salt and re-extracted a number of times with dichloromethane. The organic extracts were dried ($MgSO_4$) and evaporated to yield a 1:1 mixture of 1-(4-quinolinyl)piperazine and 1-(5,6,7,8-tetrahydroquinolin-4-yl)-

piperazine (1.84 g) as a yellow solid which was used without further purification: m/Z 214 and 218 $(M + H)^+$ for two products.

EXAMPLE 46: 4-[2-[4-(5,6,7,8-tetrahydro-4-quinolinyl)piperazin-1-yl]-acetyl]phenoxyacetic acid

In a similar manner to Example 42, the product of Example 45 (180 mg), and 0.5% v/v triethylamine/water (40 ml) gave, after stirring overnight at room temperature, washing with ether, filtration and lyophilisation, the title compound (121 mg) as an off-white fluffy solid: NMR ($CDCl_3$) δ 1.75 (2H, m), 1.90 (2H, m), 2.61 (2H, m), 2.75 (4H, m), 3.08 (2H, m), 3.23 (4H, m), 3.78 (2H, s), 4.66 (2H, s), 6.79 (1H, d), 6.99 (2H, d), 7.98 (2H, d), 8.41 (1H, d); m/Z 410 $(M + H)^+$; calculated for $C_{23}H_{27}N_3O_4 \cdot 0.03\ Et_3N \cdot 1.0\ H_2O$: C, 64.7%; H, 6.89%; N, 9.86%; found: C, 64.4%; H, 6.6%; N, 9.5%.

EXAMPLE 47: Methyl 4-[2-[4-(4-pyrimidinyl)piperazin-1-yl]acetyl]-phenoxyacetate

To a mixture of 4-(1-piperazinyl)pyrimidine (preparation described in DE 2316920) (1.57 g) and triethylamine (3.87 g) in acetonitrile (40 ml) at room temperature was added dropwise over about 0.5 hour a solution of methyl 4-bromoacetylphenoxyacetate (2.73 g) in acetonitrile (25 ml). On completion of the addition the reaction mixture was stirred at room temperature for 2 days. The precipitated solid was filtered off, washed with acetonitrile and the combined filtrate and washings evaporated to dryness. The resultant red oil was purified by flash chromatography, first on silica by elution with 1-5% v/v methanol/dichloromethane, then on neutral alumina by elution with 3% v/v methanol/dichloromethane, to yield the title compound (0.92 g) as an off-white solid: NMR ($CDCl_3$) δ 2.69 (4H, m), 3.72 (4H, m), 3.80 (2H, s), 3.82 (3H, s), 4.71 (2H, s), 6.49 (1H, m), 6.94 (2H, d), 8.01 (2H, d), 8.20 (1H, d), 8.60 (1H, s); m/Z 371 $(M + H)^+$; calculated for $C_{19}H_{22}N_4O_4 \cdot 0.4\ H_2O$: C 60.4%; H, 6.09%; N, 14.8%; found: C, 60.7%; H, 6.2%; N, 14.7%.

EXAMPLE 48: 4-[2-[4-(4-pyrimidinyl)piperazin-1-yl]acetyl]phenoxyacetic acid

In a similar manner to Example 42, the product of Example 47 (200 mg), and 1% v/v triethylamine/water (40 ml) gave, after stirring overnight at room temperature, washing with ether, filtration and lyophilisation, the title compound (152 mg) as an off-white solid: NMR (d_6DMSO) δ 3.14 (4H, m), 3.93 (4H, m), 4.61 (2H, br, m), 4.83 (2H, s), 7.03 (1H, d), 7.09 (2H, d), 7.96 (2H, d), 8.31 (1H, d), 8.65 (1H, s); m/Z 357 $(M + H)^+$; calculated for $C_{18}H_{20}N_4O_4$. 0.34 H_2O: C, 59.6%; H, 5.75%; N, 15.5%; found: C, 59.2%; H, 6.0%; N, 15.0%.

EXAMPLE 49: [1-benzyl-3-[4-(4-pyridyl)piperazin-1-yl]-4-quinolon-7-yl]oxyacetic acid, trifluoroacetate salt

To a stirred suspension of sodium hydride (80 mg) in dry DMF (5 ml) under argon at room temperature was added 1-benzyl-3-[4-(4-pyridyl)piperazin-1-yl]-4-quinolon-7-ol (377 mg), followed, after 1 hour, by tert. butyl bromoacetate (0.13 ml). After stirring for a further 2 hours at room temperature under argon an extra aliquot of sodium hydride (40 mg) was added, followed, dropwise, by a further quantity of tert. butyl bromoacetate (0.13 ml). The reaction mixture was stirred at room temperature overnight then evaporated to dryness. The residue was purified by preparative rp-hplc on a DYNAMAX C-18, 60A [83-201-C] column using an acetonitrile/water mobile phase system containing 0.1% trifluoroacetic acid, to give, after lyophilisation, the de-esterified product as a gum, which, on trituration with water gave the title compound (22 mg) as an off-white solid: NMR (d_6DMSO) δ 3.30 (4H, m), 4.00 (4H, m), 4.83 (2H, s), 5.61 (2H, s), 7.00 (2H, m), 7.38 (7H, m), 7.96 (1H, s), 8.25 (1H, d), 8.38 (2H, d); m/Z 471 $(M + H)^+$; calculated for $C_{27}H_{26}N_4O_4$. 1.0 CF_3CO2H. 2.0 H_2O: C, 56.1%; H, 5.04%; N, 9.0%; found: C, 56.4%; H, 4.9%; N, 8.9%.

The necessary starting material was prepared as follows:-

(i) To a solution of 1-ethoxycarbonylpiperazine (20 g) and triethylamine (14.1 g) in dichloromethane (200 ml) at 0°C was added gradually with stirring over 10-15 minutes, methyl bromoacetate (20.3 g). On completion of the addition the reaction mixture was stirred at room temperature for 2 hours, washed with water and brine, dried ($MgSO_4$) and evaporated to yield 1-ethoxycarbonyl-4-methoxycarbonylmethylpiperazine (29.1 g) as a colourless oil: NMR ($CDCl_3$) δ 1.28 (3H, t), 2.56 (4H, m), 3.25 (2H, s), 3.52 (4H, m), 3.72 (3H, s), 4.14 (2H, q); m/Z 231 $(M + H)^+$.

(ii) To a solution of the product of step (i) (10 g) in dry DMF (80 ml) was added dimethylformamide dimethyl acetal (DMFDMA) (30 ml) and the reaction mixture was heated to reflux. After 2 days a further quantity of DMFDMA (30 ml) was added and refluxing was continued for a further 2 days. The reaction mixture was evaporated and the residue partitioned between aqueous ammonium chloride solution and ethyl acetate. The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica by elution with ethyl acetate to yield 1-ethoxycarbonyl-4-(1-dimethylamino-2-methoxycarbonylethen-2-yl)-piperazine (7 g) as an orange oil: NMR ($CDCl_3$) δ 1.28 (3H, t), 2.90 (4H, m), 3.14 (6H, s), 3.50 (4H, m), 3.64 (3H, s), 4.12 (2H, q), 7.01 (1H, s); m/Z 286 $(M + H)^+$.

(iii) A mixture of the product of step (ii) (6.3 g), m-anisidine (2.5 ml), ethanol (65 ml) and concentrated hydrochloric acid (2.2 ml) was stirred at room temperature for 2 hours then evaporated. The residue was basified by careful addition of aqueous sodium carbonate solution. The mixture was extracted with ethyl acetate and the organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography on silica by elution with 70% v/v ether/hexane to yield 1-ethoxycarbonyl-4-(1-(3-methoxyphenyl)amino-2-methoxycarbonylethen--2-yl)piperazine (5.15 g) as an off-white solid: m.p. 120-122°C; NMR

($CDCl_3$) δ 1.28 (3H, t), 2.90 (4H, m), 3.50 (4H, m), 3.71 (3H, s), 3.81 (3H, s), 4.18 (2H, q), 6.52 (3H, m), 7.21 (1H, t), 7.39 (1H, d), 7.80 (1H, d); m/Z 364 $(M + H)^+$.

(iv) A mixture of the product of step (iii) (8.5 g) and DOWTHERM (55 ml) was heated to 230-270°C for 1 hour. The dark coloured mixture was cooled to room temperature before excess hexane was added. Removal of the supernatant by decantation followed by washing gave a crude residue (4.66 g) which was used without further purification.

The residue (4.66 g) was added to a stirred mixture of 55% sodium hydride in mineral oil (0.67 g) and dry DMF under argon at room temperature. After stirring for 75 minutes benzyl bromide (1.86 ml) was added and the reaction mixture was stirred at room temperature overnight then evaporated and the residue partitioned between water and ethyl acetate. The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated to yield an oily residue which was purified by flash chromatography on silica by elution with ethyl acetate to give the higher Rf product, 1-benzyl-3-(1-ethoxycarbonyl-piperazin-4-yl)-7-methoxy-4-quinolone (1.8 g) as an off-white solid: m.p. 173-4°C; NMR ($CDCl_3$) δ 1.28 (3H, t), 3.05 (4H, m), 3.70 (4H, m), 3.75 (3H, s), 4.18 (2H, q), 5.27 (2H, s), 6.59 (1H, d), 6.89 (1H, dd), 7.10 (3H, m), 7.30 (3H, m), 8.41 (1H, d); m/Z 422 $(M + H)^+$.

(v) A mixture of the product of step (iv) (1.8 g), ethanol (40 ml) and 20% w/v aqueous potassium hydroxide solution (40 ml) was heated to reflux overnight, cooled and evaporated to dryness. The residue was partitioned between water and dichloromethane and the organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated to yield 1-benzyl-3-(piperazin-1-yl)-7-methoxy-4-quinolone (1.5 g) as a yellow foam: NMR ($CDCl_3$) δ 2.80 (1H, m), 3.20 (8H, m), 3.73 (3H, s), 5.28 (2H, s), 6.59 (1H, d), 6.88 (1H, dd), 7.15 (3H, m), 7.30 (3H, m), 8.41 (1H, d); m/Z 350 $(M + H)^+$.

(vi) A mixture of the product of step (v) (1.1 g). xylene (110 ml), isoamyl alcohol (11 ml), 4-chloropyridine hydrochloride (1.1 g) and triethylamine (11 ml) was heated to reflux and stirred for 30

hours. During this period extra aliquots of 4-chloropyridine hydrochloride (6 x 1.1 g) and triethylamine (3 x 11 ml) were added at intervals. The reaction mixture was evaporated to dryness and the residue was purified by flash chromatography on silica by elution with methanol/dichloromethane/concentrated ammonia (20:200:1) to give 1-benzyl-3-(4-(4-pyridyl)piperazin-1-yl)-7-methoxy-4-quinolone (780 mg) as an orange-red solid: NMR (d_6DMSO) δ 3.2 (4H, m), 3.75 (3H, s), 3.80 (4H, m), 5.55 (2H, s), 6.90 (2H, m), 7.30 (7H, m), 7.88 (1H, s), 8.13 (1H, d), 8.24 (2H, d); m/Z 427 $(M + H)^+$.

(vii) To a solution of the product of step (vi) (815 mg) in dry dichloromethane (10 ml) under argon was added a 1 M solution of boron tribromide in dichloromethane (10 ml). The reaction was stirred at room temperature for 14 days, extra aliquots of BBr_3 solution being added after 3 and 7 days. After 2 weeks, excess 1 M aqueous sodium hydroxide solution was added, dropwise at first, and the mixture stirred at room temperature for 3 hours. The precipitated material was filtered off and the aqueous layer of the filtrate separated. The pH of the aqueous layer was adjusted to 8 by addition of 2 N HCl (aq.) and 1 M $NaHCO_3$ (aq.) before being extracted with ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to dryness to yield 1-benzyl-3-(4-(4-pyridyl)piperazin-1-yl)-4-quinolon-7-ol (75 mg) as an off-white solid: m.p. 141-6°C; NMR (d_6DMSO) δ 3.10 (4H, m), 3.50 (4H, m), 5.40 (2H, s), 6.67 (1H, d), 6.72 (1H, dd), 6.90 (2H, m), 7.30 (5H, m), 7.76 (1H, s), 8.07 (1H, d), 8.15 (2H, s), 10.15 (1H, br, s); m/Z 413 $(M + H)^+$.

EXAMPLE 50: Ethyl 4-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]butyrate

A stirred suspension of 4-(4-(4-pyridyl)piperazin-1-yl)-phenol (1.34g) in dry DMF (20ml) was treated with sodium hydride (60% dispersion in mineral oil, 0.21g) and the mixture stirred for 1 hour. To the resulting solution was added ethyl 4-bromobutyrate and the mixture was stirred for 16 hours. Solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was washed with water, filtered through

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phase separating paper (Whatman 1PS) and evaporated. The residue was purified by flash chromatography on silica, eluting with 1.5/92.5/6 v/v/v methanol/ethyl acetate/aqueous ammonia (SG 0.89) and recrystallised from ethyl acetate/hexane to give the title compound (0.7g) as a solid: m.p. 84-85°C; NMR ($CDCl_3$) δ 8.3(2H,d); 6.86(4H,c); 6.72(2H,d); 4.12(2H,q); 4.0(2H,t); 3.47(4H,m); 3.20(4H,m); 2.5(2H,t); 2.1(2H,m); 1.26(3H,t); m/e 370$(M+H)^+$; calculated for $C_{21}H_{27}N_3O_3$ C, 68.3; H, 7.4; N, 11.4. Found: C, 68.1; H, 7.4; N, 11.1%.

The necessary starting material was prepared as follows:-

(i) 4-(piperazin-1-yl)anisole (4.24g) and 4-chloropyridine hydrochloride (3.35g) were intimately mixed and heated at 160-170°C (bath temperature) for 7 minutes. The solid obtained on cooling was dissolved in water (75ml) and the solution basified with aqueous ammonia. The solid precipitate was extracted into ethyl acetate and the organic extract washed with water, filtered through phase separating paper (Whatman 1PS) and evaporated. The residue was recrystallised from ethanol to give 4-[4-(4-pyridyl)-piperazin-1-yl]anisole (1.84g) as a solid: m.p. 165-167°C; NMR ($CDCl_3$) δ 8.3(2H,d); 6.86(4H,m); 6.71(2H,d); 3.78(3H,s); 3.46(4H,m); 3.2(4H,m).

(ii) The product from step (i) (1.5g) in concentrated hydrobromic acid (30ml) was heated under argon at 130-135°C for 2 1/2 hours. The solution was cooled, poured into water (150ml) and basified with aqueous ammonia. The precipitate was filtered, washed with water and dried to give 4-[4-(4-pyridyl)piperazin-1-yl]phenol (1.36g) as a solid: m.p. 310-312°C; NMR(d_6DMSO) δ 8.2(2H,d); 6.8(4H,m); 6.66(2H,d); 3.45(4H,m); 3.08(4H,m).

EXAMPLE 51: 4-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]butyric acid

A solution of the product of Example 50 (0.1g) in aqueous sodium hydroxide (1N, 0.8ml) and ethanol (2ml) was kept for 2 hours. The solution was evaporated and the residue dissolved in water (5ml). Hydrochloric acid (1N, 0.8ml) was added and the precipitate was filtered and washed with water and ether to give the title compound as a solid: m.p. 305-306°C; m/e 342$(M+H)^+$; NMR(d_6DMSO) δ 8.0(2H,d);

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6.72(6H,m); 3.74(2H,t); 3.3(4H,m); 2.94(4H,m); 2.19(2H,t); 1.72(2H,m); calculated for $C_{19}H_{23}N_3O_3$: C, 66.8; H, 6.8; N, 12.3. Found: C, 67.0; H, 6.8; N, 12.2%.

EXAMPLE 52: Ethyl 5-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]pentanoate

In a similar manner to Example 50, but starting from ethyl 5-bromopentanoate, was prepared the title compound in 41% yield (from ethyl acetate/hexane): m.p. 79-82°C; NMR($CDCl_3$) δ 8.2(2H,d), 6.88(4H,m), 6.7(2H,d), 4.13(2H,q), 3.47(4H,m), 3.17(4H,m), 2.36(2H,m), 1.8(4H,m), 1.33(3H,t); m/e 384$(M+H)^+$; calculated for $C_{22}H_{29}N_3O_3 \cdot 0.25H_2O$: C, 68.1; H, 7.6; N, 10.8. Found: C, 68.2; H, 7.8; N, 10.5%.

EXAMPLE 53: 5-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]pentanoic acid

In a similar manner to Example 51, but starting from the product of Example 52, the title compound was made in 50% yield: m.p. 237-241°C; NMR(d_6DMSO) δ 8.2(2H,d); 6.97(4H,m), 6.83(2H,d); 3.69(2H,t), 3.57(4H,m), 3.13(4H,m); 2.27(2H,t), 1.67(4H,m); m/e 356$(M+H)^+$; calculated for $C_{20}H_{25}N_3O_3$ $0.75H_2O$: C, 65.0; H, 7.2; N, 11.3. Found: C, 65.0; H, 6.9; N, 11.1%.

EXAMPLE 54: Ethyl 4-[4-(4-pyridyl)piperazin-1-yl]phenoxycrotonate

In a similar manner to Example 50, but starting from ethyl 4-bromocrotonate, was prepared the title compound in 3% yield (from ethyl acetate/hexane): m.p. 127-128°C; NMR($CDCl_3$) δ 8.3(2H,d), 7.1(1H,m), 6.9(4H,m), 6.7(2H,m), 6.18(2H,m), 4.66(2H,m), 4.25(2H,q), 3.49(4H,m), 3.2(4H,m), 1.3(3H,t); m/e 368$(M+H)^+$; calculated for $C_{21}H_{25}N_3O_3$: C, 68.6; H, 6.9; N, 11.4. Found C, 68.4; H, 6.9; N, 10.7%.

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EXAMPLE 55: 3-[3-[4-(4-pyridyl)piperazin-1-ylmethyl]]benzamido-3-phenylpropionic acid

Sodium hydroxide solution (1N, 0.5ml) was added to a solution of methyl 3-[3-[4-(4-pyridyl)piperazin-1-ylmethyl]]-benzamido-3-phenylpropionate (0.116g) in methanol (5ml) at room temperature. After 16 hours, hydrochloric acid (1N, 0.5ml) was added and the solution evaporated to dryness. The residue was warmed with dichloromethane (5ml) and the insoluble solid was isolated by decantation and heated in water (5ml) to give, after cooling a solid (0.062g); NMR (d_6DMSO/CD_3COOD) δ 8.13(2H,d), 7.77(2H,m), 7.14-7.5(7H, complex), 7.06(2H,d), 5.42(1H,m), 3.56(6H,d), 2.8(2H,m); m/e 445$(M+H)^+$; calculated for $C_{26}H_{28}N_4O_3$. $0.5H_2O$: C,68.9; H, 6.44; N, 12.35. Found: C, 68.7; H, 6.5; N, 12.2%.

The necessary starting material was prepared as follows:-

(i) A solution of 3-chloromethyl benzoyl chloride (0.189g) in DMF (2ml) was added to a mixture of methyl 3-amino-3-phenylpropionate hydrochloride (0.215g) and triethylamine (0.35ml) in DMF (15ml) with stirring at room temperature. After 3 hours, water (50ml) was added and the mixture was extracted with dichloromethane. The organic layer was dried ($MgSO_4$) and evaporated to give an oil which solidified under high vacuum to give methyl 3-(3-chloromethyl)benzamido-3-phenylpropionate in 100% yield; NMR ($CDCl_3$) δ 7.72-8.7(10H, complex), 5.62(1H,m), 4.6(2H,s), 3.66(3H,s), 3.0(2H,m).

ii) A solution of 1-(4-pyridyl)piperazine (0.33g) in acetonitrile (7.5ml) was added to a stirred solution of the product of step (i) in acetonitrile (5ml). After sixteen hours at room temperature, the mixture was filtered and the filtrate evaporated. The residue was dissolved in dichloromethane (75ml) and the solution washed with water (2 x 25ml), dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography, the product being eluted with 5% v:v methanol in dichloromethane to give methyl 3-[3-[4-(4-pyridyl)piperazin-1-ylmethyl]]benzamido-3-phenylpropionate as a solid (0.18g); NMR($CDCl_3$) δ 8.35(2H,d); 7.85(1H,s), 7.72(1H,m),

7.39(7H,m), 6.68(2H,d), 5.62(1H,m), 3.65(3H,s), 3.6(2H,s), 3.0(2H,m); m/e 459$(M+H)^+$; calculated for $C_{27}H_{38}N_4O_3 . 0.5H_2O$: C, 69.3; H,6.6; N,12. Found: C, 69.1; H, 6.6; N, 11.8%.

EXAMPLE 56: Methyl 3-[4-[4-(4-pyridyl)piperazin-1-yl]]benzamido-propionate

Methyl 3-aminopropionate hydrochloride (0.195g) and triethylamine (0.59ml) were added to a stirred suspension of 4-[(4-pyridyl)piperazin-1-yl]benzoyl chloride hydrochloride (0.473g) at room temperature. The mixture was stirred for two days and solvent removed under reduced pressure. The residue was purified by flash column chromatography. The product was obtained by elution with 1/9/0.1 v:v:v methanol/dichloromethane/0.88 S.G. aqueous ammonia as a solid which was recrystallised from ethyl acetate to give the title compound (0.2g): m.p. 197-199°C; NMR(d_6DMSO) δ 8.19(2H,d); 7.72(2H,d); 7.13(2H,d); 6.90(2H,d); 3.82(4H,m); 3.56(3H,s); 3.48(6H,m), 2.50(2H,t); m/e 369$(M+H)^+$; calculated for $C_{20}H_{24}N_4O_3 . 0.25H_2O$: C,64.4; H, 6.6; N, 15.0. Found: C,64.3; H, 6.6; N, 14.9%.

The necessary starting material was obtained as follows:-

(i) An intimate mixture of 1-(4-pyridyl)piperazine (1.63g) and 4-bromobenzoic acid (1.05g) was heated at 220°C for 6 hours. The resulting glass was cooled and triturated with methanol (50ml) to give, as an off-white solid, 4-((4-pyridyl)piperazin-1-yl)benzoic acid; m.p>350°C; IR(cm^{-1}) 1682, 1600, 1514, 1236, 1013.

(ii) Oxalyl chloride (0.5ml) was added to a stirred suspension of 4-((4-pyridyl)piperazin-1-yl)benzoic acid in dichloromethane (15ml), followed by DMF (1 drop). The mixture was stirred for 2 hours and evaporated to dryness to give 4-[(4-pyridyl)piperazin-1-yl]benzoyl chloride which was used immediately.

EXAMPLE 57: 3-[4-[4-(4-pyridyl)piperazin-1-yl]]benzamidopropionic acid

To a solution of the product of Example 56 (0.062g) in methanol (1ml) was added sodium hydroxide solution (1N, 0.17ml) and the solution kept for 4 days at room temperature. Hydrochloric acid

(1N, 0.17ml) was added to give the title compound as a solid (0.052g); m.p. >330°C; NMR(d_6DMSO 6.96(2H,d); 3.76(4H,m); 3.46(6H, complex); 2.5(2H,m); m/e 365 $(M+H)^+$; calculated for $C_{19}H_{22}N_4O_3$. 0.7 H_2O: C, 62.2; H, 6.4; N, 15.3. Found: C, 62.3; H, 6.4; N, 15.3%.

EXAMPLE 58: Methyl 3-[4-[4-(4-pyridyl)piperazin-1-yl]benzamido]-3-phenylpropionate

In a similar manner to Example 56, but starting from methyl 3-amino-3-phenylpropionate, was prepared the title compound in 26% yield as a solid (after trituration with hot ethyl acetate); NMR(d_6DMSO) δ 8.6(1H,d); 8.2(1H,broad s); 7.75(2H,d); 7.3(5H,m); 7.0(2H,d); 6.85(2H, broad s); 5.45(1H,m); 3.55(3H,s); 3.45(8H,m); 292(2H,m); m/e 445$(M+H)^+$; calculated for $C_{26}H_{28}N_4O_3$. 0.5H_2O: C, 68.9; H, 6.4; N, 12.4. Found. C, 68.7; H, 6.3; N, 12.3%.

EXAMPLE 59: 3-[4-[4-(4-pyridyl)piperazin-1-yl]benzamido]-3-phenylpropionic acid

In a similar manner to Example 51, but starting from the product of Example 58, was prepared the title compound in 73% yield as a solid; NMR(d_6DMSO) δ 8.61(1H,d); 8.2(2H,broad s); 7.78(2H,d); 7.3(5H,m); 7.0(2H,d); 6.9(2H,d); 5.43(1H,m); 3.45(8H,m); 2.82(1H,m); m/e 431(M+H)+; calculated for $C_{25}H_{26}N_4O_3$ 0.5H_2O: C, 68.3; H, 5.9; N, 12.8. Found: C, 68.3; H, 6.0; N, 12.9%.

EXAMPLE 60: Methyl 3-[4-[4-(4-pyridyl)piperazin-1-yl]benzamido]-butyrate

In a similar manner to Example 56, but starting from methyl 3-aminobutyrate, was prepared the title compound in 11% yield (recrystallised from ethyl acetate/hexane) as a solid; m.p. 130-132°C. NMR (d_6DMSO) δ 8.28(2H,d); 8.07(1H,d); 7.77(2H,d); 7.13(2H,d); 7.0(2H,d); 4.36(1H,m); 3.74(4H,m); 3.6(3H,s); 3.48(4H,m); 2.55(2H,m); 1.2(3H,d); m/e 383$(M+H)^+$; calculated for $C_{21}H_{26}N_4O_3$. 0.25H_2O: C, 65.2; H, 6.9; N, 14.5. Found: C, 65.3; H, 6.8; N, 14.4%.

EXAMPLE 61: Methyl 4-[2-[4-(4-pyridyl)piperazin-2-one-1-yl]acetyl]-phenoxyacetate

A dispersion of potassium hydride in mineral oil (35% w/w, 0.63g) was added to a stirred suspension of 4-(4-pyridyl)piperazin-2-one (0.885g) in DMF (10ml) and the mixture was stirred at room temperature for 2 hours.

To the anion thus formed, was added methyl 4-bromoacetylphenoxyacetate (1.44g) and the mixture was stirred at room temperature for 20 hours. Solvent was evaporated and the residue partitioned between dichloromethane (20ml) and water (20ml). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography, the product being eluted with 1/9/0.1 v:v:v methanol/dichloromethane/0.88 S.G aqueous ammonia. Recrystallisation from ethyl acetate gave the title compound, m.p. 164-165°C; NMR(d_6DMSO) δ 8.2(2H,d), 7.97(2H,d), 7.08(2H,d), 6.83(2H,d), 4.93(4H,d), 4.02(2H,s), 3.71(3H,s), 3.7(2H,m), 3.52(2H,m); m/e 384 $(M+H)^+$; calculated for $C_{20}H_{21}N_3O_5$: C, 62.7; H, 5.52; N, 11.0. Found: C, 62.6; H, 5.6; N, 10.9%.

The necessary starting material was prepared as follows:-

An intimate mixture of piperazinone (4.2g) and 4-chloropyridine hydrochloride (7.33g) was stirred and heated at 200°C for 10 minutes and allowed to cool. The product was purified by flash column chromatography and eluted with 1/9/0.1 v:v:v methanol/methylene chloride/0.88 S.G. aqueous ammonia.

The solid thus obtained was recrystallised from ethanol to give 4-(4-pyridyl)piperazin-2-one (1.75g); m.p. 268-270°C; NMR(D_6DMSO) δ 8.2(3H,m); 6.8(12H,m); 3.85(2H,s); 3.52(2H,m); 3.31(2H,m); m/e 178$(M+H)^+$.

EXAMPLE 62: 4-[2-[4-(4-pyridyl)piperazin-2-one-1-yl]acetyl]-phenoxyacetic acid.

In a similar manner to Example 51, but starting from the product of Example 61, was prepared the title compound in 20% yield as

a solid NMR(d_6DMSO) δ 8.22(2H,d), 7.97(2H,d), 7.04(2H,d), 6.89(2H,d); 4.93(2H,s), 4.77(2H,s), 4.07(2H,s), 3.72(2H,m), 3.49(2H,m); m/e 370$(M+H)^+$); calculated for $C_{19}H_{19}N_3O_5$. 2.5H_2O: C, 55.1; H, 5.8; N, 10.1. Found: C, 55.1; H, 5.3; N, 10.6%.

EXAMPLE 63: Methyl 4-[[4-(4-pyridyl)piperazin-1-yl]carboxamido]phenoxy acetate

To a solution of 1-(4-pyridyl)piperazine (0.4g) in dichloromethane (10ml) was added a solution of methyl 4-isocyanatophenoxyacetate (0.5g) in dichloromethane (5ml). The resulting solution was stirred for 3 hours at room temperature. Solvent was evaporated and the residue triturated with ethanol to give the title compound as a solid (0.155g); NMR(d_6DMSO) δ 8.55(1H,s), 8.22(2H,d), 7.28(2H,d), 7.02(2H,d), 6.82(2H,d), 4.72(2H,s), 3.7(3H,s), 3.58(8H,m); m/e 371$(M+H)^+$; calculated for $C_{19}H_{22}N_4O_4$. H_2O: C, 58.8; H, 6.2; N, 14.4 Found: C, 58.7; H, 5.8; N, 14.8%.

The necessary starting material was prepared as follows:-

Methyl 4-aminophenoxyacetate (2.2g) in ethyl acetate (dried with calcium chloride) (50ml) was added dropwise to a stirred solution of phosgene in toluene (115ml, ~2M) at 75°C. After addition the mixture was stirred at 75°C for 1.5 hours and at 95-105°C for 16 hours. Solvent was evaporated to give an oil (2.5g); IR shows a strong band at 2273cm^{-1}.

EXAMPLE 64: 4-[[4-(4-pyridyl)piperazin-1-yl]carboxamido]phenoxyacetic acid

In a similar manner to Example 51, but starting from the product of Example 63, was prepared the title compound in 86% yield as a solid; NMR(d_6DMSO) δ 8.45(1H,s); 8.2(2H,d), 7.35(2H,d), 6.35(4H,m), 4.55(2H,s), 3.49(8H,m), m/e 357$(M+H)^+$; calculated for $C_{18}H_{20}N_4O_4$. 0.75 H_2O: C, 58.5; H, 5.8; N, 15.2. Found: C, 58.5; H, 5.9; N, 15.1%.

EXAMPLE 65: 1-Ethyl-7-[4-(4-pyridyl)piperazin-1-yl]-4-quinolon-3-ylcarboxylic acid

A mixture of 1-ethyl-7-chloro-4-quinolon-3-ylcarboxylic acid (182 mg) and 1-(4-pyridyl) piperazine (125 mg) was heated to 200°C for 20 minutes. The mixture was cooled and methanol (5 ml) was added. The resulting solid was filtered and washed with methanol (10ml) to give the title compound (68 mg), as a solid: NMR (d_6DMSO) δ 1.4(t,3H), 3.75-3.85(m,4H), 3.9-4.0(m,4H), 4.55(q,2H), 6.9(d,1H), 7.2(d,2H), 7.3(dd,1H), 8.2(d,1H), 8.3(d,2H), 8.9(s,1H); m/e 379$(M+H)^+$

EXAMPLE 66: Methyl 2-RS-(n-butylsulphonylamino)-3-[4-[2-[4-(4-pyridyl)-piperazin-1-yl]acetyl]phenyl]propionate

To a solution of 1-(4-pyridyl) piperazine (296mg) and triethylamine (0.25ml) in acetonitrile (10ml) was added, dropwise, over 30 minutes a solution of methyl-2-RS-(n-butylsulphonylamino)-3-(4-bromoacetylphenyl) propionate (382mg) in acetonitrile (8ml). The mixture was stirred for an additional 4 hours. The solvent was removed by evaporation to give an oil which was purified by flash column chromatography on silica, eluting with methanol/dichloromethane (5:95 to 10:90 v/v) to give the title compound as a solid (202mg): NMR(d_6DMSO) 0.7(t,3H), 1.05-1.4(m,4H), 2.55-2.7(m,4H), 2.8-3.2(m,4H), 3.25-3.4(m,4H), 3.65(s,3H), 3.9(s,2H), 4.1-4.25(m,1H), 6.85(d,2H), 7.45(d,2H), 7.95(d,1H), 7.95(d,2H), 8.15(d,2H); m/e 503$(M+H)^+$; calculated for $C_{25}H_{34}N_4O_5S.0.5H_2O$: C, 58.7; H, 6.85; N, 10.9. Found: C, 58.8; H, 6.9; N, 10.6.

The necessary starting material was prepared as follows:-

(i) Methyl 2-amino-3-(4-acetylphenyl)propionate was prepared by the method described by M.P.Doyle JOC (1977), 42, 2431 and G,H.Cleland JOC (1969), 34, 744.

(ii) n-Butylsulphonyl chloride(0.6ml) was added dropwise over 15 minutes to a solution of the product of step (i) (926mg) and triethylamine (0.7ml) in dichloromethane (20ml). The resulting mixture was stirred for a further 3 hours before it was poured into water (10ml) and extracted with dichloromethane (3 x 20ml). The organic extracts were combined, dried ($MgSO_4$) and then evaporated to give a gum. Purification by flash column chromatography on silica, eluting with ethyl acetate/hexane (40:60 v/v) gave methyl 2-RS-(n-butylsulphonylamino)-3-(4-acetylphenyl)propionate (794mg) as a solid: NMR (d_6DMSO) δ 0.75(t,3H), 1.0-1.4(m,4H), 2.55(s,3H), 2.65(s,3H), 2.8-2.95(m,2H), 3.05-3.2(m,2H), 3.65(s,3H), 4.1-4.25(m,1H), 7.45(d,2H), 7.85(d,1H), 7.9(d,2H); m/e 342$(M+H)^+$.

(iii) To a suspension of $CuBr_2$ (822mg) in ethyl acetate (8ml) at reflux was added, dropwise over 10 minutes, a solution of the product from step (ii) in chloroform (8ml). The resulting mixture was refluxed for 3 hours. The mixture was cooled, filtered and the solvent was removed by evaporation to give an oil. Purification by flash column chromatography on silica, eluting with ethyl acetate/hexane (10:90 to 50:50 in 10% increments v/v) gave methyl 2-RS-(n-butylsulphonylamino)-3-(4-bromoacetylphenyl) propionate (387mg) as an oil: NMR ($CDCl_3$) δ 0.9(t,3H), 1.25-1.4(m,2H), 1.6-1.75(m,2H), 2.75-2.85(m,2H), 3.05-3.3(m,2H), 3.8(s,3H), 4.35-4.45(m,1H), 4.4(s,2H), 4.8(d,1H), 7.35(d,2H), 7.95(d,2H); m/e 420/422 $(M+H)^+$, Br pattern.

EXAMPLE 67: 2-RS-(n-butylsulphonylamino)-3-[4-[2-[4-(4-pyridyl)-piperazine-1-yl]acetyl]phenyl]propionic acid

To a solution of the product of Example 66 (105mg) in methanol (4ml) was added 2N sodium hydroxide (0.25ml) and the resulting solution was stirred for 3 hour. The mixture was concentrated, dissolved in water (2ml) and acidified with acetic acid. The resulting solution was transferred to a reverse phase hplc column (Dynamax C18 83-201-C 60A) and eluted with 0.1% TFA in water/acetonitrile. The pure fractions, on freeze drying, gave the title compound (89mg) as a solid: NMR (d_6DMSO) δ 0.8(t,3H),

1.15-1.6(m,4H), 2.75(t,2H), 2.9-3.05(m,1H), 3.2-3.3(m,1H), 3.4-3.5(m,4H), 3.95-4.2(m,5H), 4.95(s,2H), 7.25(d,2H), 7.55(d,2H), 8.0(d,2H), 8.35(d,2H); m/e 489$(M+H)^+$; calculated for $C_{24}H_{32}N_4O_5S.3CF_3COOH$: C, 43.4 ; H, 4.2 ; N, 6.7 ; TFA, 41.2. Found C, 43.7 ; H, 4.3; N, 6.8; TFA, 42.7.

EXAMPLE 68: 2-RS-(n-Butylsulphonylamino)-3-[4-(4-pyridyl)piperazin-1-yl methylene]phenylpropionic acid

To a solution of ethyl 2-RS-(n-butylsulphonylamino)-3-[4-(4-pyridyl)piperazin-1-yl methylene]phenylpropionate in methanol (3ml) was added 2N sodium hydroxide (0.3ml). The mixture was stirred for 3 hours and then concentrated. The resulting slurry was dissolved in water (2ml) and acidified with acetic acid. The resulting solution was transfered to a reverse phase hplc column (Dynamax C18 83-201-C 60 A) and eluted with 0.1% TFA in water/acetonitrile. The pure product fractions, on freeze drying, gave the title compound (165mg) as a solid: NMR (d_6DMSO) δ 0.8(t,3H), 1.1-1.6(m,4H), 2.65-2.95(m,4H), 3.2-3.3(m,4H), 3.85-4.0(m,4H), 4.05-4.15(m,1H), 4.3(s,2H), 7.2(d,2H), 7.4(s,5H), 8.3(d,2H); m/e 461$(M+H)^+$; calculated for $C_{23}H_{32}N_4O_4S.H_2O.2CF_3COOH$: C, 45.9 ; H, 5.1 ; N, 7.9. Found C, 45.5 ; H, 4.8 ; N, 7.5.

The starting material was prepared as follows:-

(i) To a solution of α,α'-dibromo-p-xylene (6.59g),N-(diphenylmethylene) glycine ethyl ester (4.76g) and potassium iodide in 1,4-dioxane (120ml), cooled to 10°C, was added 40% aq. benzyltrimethylammonium hydroxide(7.45ml) over 1 hour. The mixture was allowed to warm to room temperature and then to stir for 2.5 hours. The mixture was partitioned between water (50ml) and ethyl acetate (100ml). The organic layer was separated, dried ($MgSO_4$) and evaporated to give an oil. Purification by flash column chromatography on silica, eluting with ether/hexane (10:90 v/v) gave ethyl RS-N-(diphenylmethylene)-4-(bromomethyl)phenylalanine ethyl ester

(3.58g) as an oil: NMR (d_6DMSO) δ 1.5(t,3H), 3.0-3.2(m,2H), 4.05-4.15(m,3H), 4.65(s,2H), 6.55-6.65(m,2H), 7.0(d,2H),7.25(d,2H), 7.3-7.5(m,8H); m/e 450/452$(M+H)^+$ Br pattern.

(ii) To a warm solution of 1-(4-pyridyl)piperazine (296mg) and triethylamine (0.14ml) in acetonitrile (15ml) was added slowly over 40 minutes a solution of the product from step (i) (409mg) in acetonitrile (5ml). The resulting mixture was stirred at room temperature for 18 hours. The mixture was concentrated and purified by flash column chromatography on silica, eluting with methanol/dichloromethane (3:97 to 10:90 v/v) to give RS-N-(diphenylmethylene)-4-[4-(4-pyridyl)piperazin-1-ylmethylene]phenylalanine ethyl ester (305mg) as a solid: NMR (d_6DMSO) δ 1.15(t,3H), 2.4-2.5(m,4H), 3.0-3.2(m,2H), 3.25-3.35(m,4H), 3.45(s,2H), 4.05-4.15(m,3H), 6.65(d,2H), 6.75(d,2H), 7.0(d,2H), 7.15(d,2H), 7.35-7.5(m,8H), 8.1(d,2H); m/e 533$(M+H)^+$.

(iii) To a suspension of the product from step (iii) in ether (5ml) was added 1N hydrochloric acid (2.2ml) and the resulting mixture was stirred for 1 hour. The mixture was partitioned between ether (20ml) and 1N hydrochloric acid(10ml). The acid layer was separated, basified with aqueous sodium bicarbonate and extracted with dichloromethane (3x 20ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to give RS-4-[4-(4-pyridyl)-piperazin-1-ylmethylene]phenylalanine ethyl ester as an oil: NMR (d_6DMSO) δ 1.1 (t,3H), 2.4-2.5(m,4H), 2.7-2.9(m,2H), 3.2-3.35(m,4H), 3.5(s,2H), 3.5-3.6(m,1H), 4.0(q,2H), 6.8(m,2H), 7.2(dd,4H), 8.1(bm,2H); m/e 369$(M+H)^+$.

(iv) To a solution of the product of step (iii) (137mg) and triethylamine (0.11ml) in tetrahydrofuran (5ml) was added 0.75ml of a stock solution of n-butylsulphonyl chloride (0.2ml in 3ml of tetrahydrofuran) and the resulting mixture was stirred for 3 hours. The solvent was removed by evaporation to give a gum. Purification by flash column chromatography on silica, eluting with methanol/dichloromethane (5:95 to 10:90 v/v) gave ethyl

2-(RS)-(n-butylsulphonylamino)-3-[4-(4-pyridyl)piperazin-1-yl-methylene]phenylpropionate as a solid which was used without further purification.

EXAMPLE 69: Methyl 3-[6-[4-(4-pyridyl)piperazin-1-yl]pyrid-3-yl-carboxamido] propionate

To 6-[4-(4-pyridyl)piperazin-1-yl]nicotinic acid was added dimethylformamide (0.1ml) and thionyl chloride (5ml)and the resulting mixture was refluxed for 2 hour. The excess thionyl chloride was removed by evaporation and the resulting solid was suspended in dichloromethane (10ml) to which was added methyl-3-aminopropionate hydrochloride (546mg). The resulting mixture was cooled to 5°C and triethylamine(3ml) was added dropwise over 15 minutes. The mixture was stirred at room temperature for 18 hours. The mixture was partitioned between dichloromethane(50ml) and aqueous sodium bicarbonate(25ml). The organic layer was separated, dried ($MgSO_4$), and evaporated to give a gum. Purification by flash column chromatography on silica, eluting with methanol/dichloromethane (6:94 to 15:85 v/v), gave the title compound (339mg) as a gum: NMR (d_6DMSO) δ 2.6(t,2H), 3.4-3.5(m.2H), 3.5-3.6(m,4H), 3.6(s,3H), 3.7-3.8(m,4H), 6.9-7.0(m,3H), 8.0(dd,1H), 8.2(d,2H), 8.35(t,1H), 8.6(d,1H); m/e 370$(M+H)^+$; calculated for $C_{19}H_{23}N_5O_3.1.5H_2O$: C, 57.6; H, 6.5; N, 17.6. Found: C 57.3; H,5.9; N,17.5.

The necessary starting material was prepared as follows:-

(i) A mixture of 6-chloronicotinic acid (3.21g) and 1-(4-pyridyl) piperazine (3.32g) was heated to 220°C for 3 minutes. The mixture was cooled and methanol (10ml)was added. The resulting suspension was boiled for 10 minutes, cooled and filtered to give o-[4-(4-pyridyl)piperazin-1-yl] nicotinic acid (2.51g) which was used without further purification.

EXAMPLE 70: 3-[6-[4-(4-pyridyl)piperazin-1-yl]pyrid-3-ylcarboxamido]-propionic acid

To a solution of the product of Example 69 (136mg) in methanol (8ml) was added 2N sodium hydroxide (0.9ml). The mixture was stirred for 3h and then concentrated. The resulting gum was dissolved in water (4ml) and acidified with acetic acid. The precipitate was filtered and washed with water to give the title compound (83mg) as a solid: NMR (d_6DMSO + TFA) δ 2.5-2.6(m,2H), 3.45-3.55(m,2H), 3.95-4.1(m,8H), 7.2(d,2H), 7.4(d,1H), 8.3-8.4(m,3H), 8.55(d,1H); m/e 356$(M+H)^+$; calculated for $C_{18}H_{21}N_5O_3.H_2O$: C, 57.9; H, 6.1; N, 18.75. Found : C, 57.7; H, 5.8; N, 18.5.

EXAMPLE 71: 4-[[4-(4-pyridyl)piperazin-1-yl]quinolin-6-yl]oxyacetic acid

To a solution of methyl 4-[4-(4-pyridyl)piperazin-1-yl]-quinolin-6-yloxyacetate (146mg) in methanol (5ml) was added 2N sodium hydroxide (0.7ml). The mixture was stirred for 3 hours before evaporation to dryness. The resulting gum was dissolved in water (3ml) and acidified with acetic acid. This was transfered to a reverse phase hplc column (Dynamax C18 83-201-C 60A) and eluted with 0.1% TFA in water/acetonitrile. The pure fractions, on freeze drying, gave the title compound (261mg) as a solid: NMR (d_6DMSO) δ 3.9-4.1(m,8H), 4.9(s,2H), 7.15(d,1H), 7.2(d,2H), 7.45(d,1H), 7.7(dd,1H), 8.0(d,1H), 8.35(d,2H), 8.65(d,1H); m/e 365$(M+H)^+$; calculated for $C_{20}H_{20}N_4O_3.2TFA.0.5H_2O$: C,47.9; H, 3.8; N, 9.3. Found : C, 48.1; H, 3.6; N, 9.2.

The necessary starting material was prepared as follows:-

To a solution of methyl 4-bromoquinolin 6-yloxyacetate (169mg) in isopropanol(10ml) was added 1-(4-pyridyl)piperazine (93mg) followed by 2 drops of saturated ethereal HCl. The resulting mixture was refluxed for 18 hours. The mixture was filtered and concentrated. Purification by flash column chromatography on silica, eluting with

methanol/dichloromethane (10% to 15% v/v in 1% increments) gave methyl 4-[4-(4-pyridyl)piperazin-1-yl]quinolin-6-yloxyacetate (74mg) as a solid: NMR(d_6DMSO) δ 3.2-3.4(m,4H), 3.6-3.7(m,4H), 3.75(s, 3H), 5.0(s,2H), 6.95(d,2H), 7.05(d,1H), 7.25(d,1H), 7.45(dd,1H), 7.9(d,1H), 8.25(d,2H), 8.6(d,1H); m/e 379$(M+H)^+$.

EXAMPLE 72: 9:6 mixture of isopropyl 2-[4-(4-pyridyl)piperazin-1-yl]-quinolin-6-yloxyacetate and methyl 2-[4-(4-pyridyl)piperazin-1-yl]-oxyacetate

In a similar manner to Example 71, step (i) the title mixture of compounds was obtained. NMR (d_6MDMSO) δ 1.2(d,4H, 0.6 isopropyl ester), 3.5-3.6(m,4H), 3.7(s,1.2H, 0.4 methyl ester), 3.73-3.85(m,4H), 4.8 and 4.85(s, 2H), 5.0(m,0.6 isopropyl ester), 6.97.0(m,2H),7.15-7.35(m,3H), 7.55(d,1H), 8.0(dd,1H), 8.15-8.25(m,2H); m/e 427/429$(M+H)^+$.

EXAMPLE 73: 2-[4-(4-pyridyl)piperazin-1-yl]quinolin-6-yloxyacetic acid

To a solution of the product of Example 72 (145mg) in methanol (5ml) was added 2N sodium hydroxide (0.7ml). The mixture was stirred for 3 hours before evaporating to (dryness. The resulting gum was dissolved in water (3ml) and acidified with acetic acid. The resulting precipitate was filtered and washed with water to give the title compound (47mg): NMR (d_6DMSO) δ 3.6-3.7(m,4H), 3.8-3.9(m,4H), 4.75(s,2H), 7.0(d,2H), 7.15(d,1H), 7.2-7.3(m,2H), 7.55(d,1H), 8.0(d,1H), 8.25(d,2H); m/e 365$(M+H)^+$; calculated for $C_{20}H_{20}N_4O_3.0.25H_2O$: C,65.1; H, 5.6; N, 15.2. Found : C, 65.1; H, 5.4; N, 15.0.

EXAMPLE 74: 3-[6-[4-(4-pyridyl)piperazin-1-yl]pyrid-2-yl]carboxamido-propionic acid

To a solution of isoamyl 3-[6-[4-(4-pyridyl]piperazin-1-yl]-pyrid-2-yl]carboxamidopropionate (140mg) in methanol (10ml) was added 1N sodium hydroxide and the resulting solution was stirred for 18

hours. The mixture was filtered and the solvent was removed by evaporation to give the title compound as a white solid: NMR (d_6DMSO+CD_3COOD) δ 2.5-2.6(m,2H), 3.55(t,2H), 3.8(s,8H), 6.9(d,1H), 7.05(d,2H), 7.35(d,1H), 7.6-7.7(m,1H), 8.15(d,2H); m/e 356$(M+H)^+$.

The starting material was prepared as follows:-

(i) A suspension of 2,6-dibromopyridine (19g) in diethylether (200ml) was added to a mixture of n-butyl lithium (130ml of a 1.6M solution in hexane) and diethylether (200ml) cooled to -50°C. The resulting solution was stirred at -50°C for 10 minutes before pouring onto a slurry of diethyl ether(100ml) and dry-ice. The mixture was allowed to warm to room temperature and filtered. The resulting solid was dissolved in 2N sodium hydroxide (350ml) and extracted with diethyl ether (2x300ml). The aqueous layer was separated and acidified with 2N hydrochloric acid. The resulting precipitate was filtered and washed with water to give 6-bromo-2-pyridine carboxylic acid (7.25g): NMR (d_6DMSO) δ 7.69(d,1H), 7.95(d,1H), 8.05(dd,1H); m/e 202$(M+H)^+$.

(ii) In a similar manner to Example 69 but starting from 6-bromo-2-pyridine carboxylic acid was prepared methyl 3-(6-bromo-pyridin-2-carboxamido)propionate; NMR (d_6DMSO), δ 2.65(t,2H), 3.5-3.6(m,2H), 3.6(s,3H), 7.7-8.05(m,3H), 8.7(b,1H); m/e 287/289 $(M+H)^+$ Br pattern.

(iii) To a solution of the product of step (ii) (770mg) in isoamyl alcohol (2.5ml) was added 1-(4-pyridyl)piperazine (540mg) and 2 drops of saturated ethereal HCl. The resulting mixture was refluxed for 18 hours. The mixture was concentrated and purified by flash column chromatography on silica, eluting with methanol / dichloromethane (3:97 v/v), to give isoamyl 3-[6-[4-(4-pyridyl]piperazin-1-yl]-pyrid-2-yl]carboxamidopropionate as a gum: NMR (d_6DMSO) δ 1.25-1.35(m,6H), 1.4-1.7(m,3H), 2.6(t,2H), 3.35-3.6(m,8H), 3.7-3.75(m,2H), 4.05(t,2H), 6.85(d,2H), 7.05(d,1H), 7.3(d,1H), 7.7(dd,1H), 8.2(d,2H), 8.6(t,1H); m/e 426$(M+H)^+$.

EXAMPLE 75: 4-[4'-[N-methyl-N-(4-pyridyl)]aminomethyl]biphenyloxy-acetic acid

To a solution of Methyl 4-[4'-[N-methyl-N-(4-pyridyl)]-aminomethyl]biphenyloxyacetate (50mg) in methanol (5ml) was added 1N sodium hydroxide (0.45ml) and the resulting mixture was stirred for 18 hours. The resulting precipitate was riltered to give the title compound (29 mg) ; NMR (d_6DMSO) δ 2.9(s,3H), 4.05(s,2H), 5.35(s,2H), 6.8-6.95(m,4H), 7.35-7.55(dd,4H), 7.6(d,2H), 8.2(d,1H), 8.45(d,1H); m/e 349$(M+H)^+$; calculated for $C_{21}H_{20}N_2O_3.2.25H_2O$: C,64.9; H, 6.05; N, 7.2. Found : C, 65.2; H, 6.4; N, 7.2.

The starting material was prepared as follows:-

(i) To a solution of 4-hydroxy-4-biphenylcarboxylic acid (2.14g) in tetrahydrofuran (25ml) under an argon atmosphere was added slowly 1M borane-THF complex (50ml). The resulting mixture was stirred for 18 hours before the addition of ethyl acetate (10ml) and water (100ml). The resulting mixture was acidified with 2N hydrochloric acid and stirred for 30 minutes. The aqueous layer was extracted with ethyl acetate (2x100ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated . Recrystallisation from a small volume of ethyl acetate gave 4-hydroxy-4-biphenylmethanol (580mg): NMR (d_6DMSO),δ 4.5(s,2H), 6.85(d,2H), 7.35(d,2H), 7.45-7.55(dd,4H), 9.45(s,1H); m/e 201$(M+H)^+$.

(ii) To a solution of 4-hydroxy-4-biphenylmethanol (580mg) in acetone (15ml) was added anhydrous potassium carbonate (1.2g) followed by methyl bromoacetate (0.3ml). The resulting mixture was stirred for 72 hours and filtered. The solvent was removed by evaporation to give a solid which was recrystallised from ethyl acetate to give methyl 4-(4'-hydroxymethyl)biphenyloxyacetate (316mg); NMR (d_6DMSO) δ 3.7(s,3H), 4.5(s,2H), 4.85(s,2H), 7.0(d,2H), 7.35(d,2H), 7.5-7.6(dd,4H); m/e 273$(M+H)^+$

(iii) To a solution of the product from step (ii) (300mg) in dichloromethane (15ml) cooled to 5°C was added triethylamine (0.17ml) followed by methanesulphonyl chloride (0.19ml). The resulting mixture was stirred for 72 hours. Water (10ml) was added and the mixture was extracted with dichloromethane (3x50ml). The organic extracts were combined, dried (MgSO4) and evaporated to give a gum. Purification by flash column chromatography on silica, eluting with ethyl acetate / hexane (25:75 v/v) gave methyl 4-(4'-chloromethyl)biphenyloxyacetate (230mg) as a solid: NMR (d_6DMSO) δ 3.75(s,3H), 4.8(s,2H), 4.85(s,2H), 7.05(d,2H), 7.5(d,2H), 7.6-7.65(dd,4H); m/e 290 M^+.

(iv) To a solution of 4-methylaminopyridine (142mg) in acetonitrile (5ml) was added slowly a solution of the product of step (iii) (230mg) in acetonitrile (5ml). Triethylamine (0.18ml) was added and the resulting mixture was stirred for 72 hours. The mixture was partitioned between water (20ml) and dichloromethane (50ml). The organic layer was separated, dried ($MgSO_4$) and evaporated to give a solid, which was recrystallised from isopropanol to give methyl 4-[4'-[N-methyl-N-(4-pyridyl)aminomethyl]biphenyloxyacetate (50mg): NMR (d_6DMSO) δ 2.9(d,3H), 3.7(s,3H), 4.85(s,2H), 5.4(s,2H), 6.85-6.95(m,2H),7.0(d,2H), 7.45(d,2H), 7.55-7.7(dd,4H), 8.25(d,1H), 8.5(d,1H); m/e 363$(M+H)^+$

EXAMPLE 76: 5-[[4-(4-pyridyl)piperazin-1-yl]methylene]naphth-2-yloxyacetic acid

In a similar manner to Example 67, but starting from methyl 5-[[4-(4-pyridyl)piperazin-1-yl]methylene]naphth-2-yloxyacetate was prepared the title compound: NMR (d_6DMSO) δ 2.75(m,4H), 3.7(m,4H), 4.1(s,2H), 4.8(s,2H), 7.15-7.5(m,6H), 7.8(d,1H), 8.2-8.3(m,3H); m/e 378$(M+H)^+$.

The starting material was prepared as follows:-

(i) A solution of 6-methoxy-1-tetralone (15g) in diethyl ether (250ml) was added slowly to a mixture of methyl magnesium iodide (37ml

of a 3M solution in diethyl ether) and diethyl ether(100ml) whilst maintaining the temperature below 10°C. After stirring at 5°C for 30 minutes, the mixture was refluxed for 2 hours. The reaction was quenched with saturated ammonium chloride. The organic layer was separated, dried($MgSO_4$) and evaporated. Purification by flash column chromatography, eluting with ethyl acetate/hexane (1:99 v/v) gave 1-methyl-7-methoxy-1,2-dehydrodecalin (11.58g) as an oil: NMR (d_6DMSO) δ 1.95(m,3H), 2.1-2.25(m,2H), 2.7(d,2H), 3.75(s,3H), 5.65-5.75(m,1H), 6.7-6.8(m,2H), 7.1(d,1H); m/e 175$(M+H)^+$.

(ii) 2,3-dichloro 5,6 dicyano-1,4 benzoquinone (17.85g) was added in one portion to a solution of the product from step (i) (11.56g) in toluene (500ml). After stirring for 1 hour the mixture was filtered and an equal volume of hexane was added. The diluted filtrate was passed down a short alumina column. Removal of the solvent gave 6-methoxy-1-methylnaphthalene (6.4g) as an oil: NMR (d_6DMSO) δ 2.6(s,3H), 3.7(s,3H), 7.15-7.25(m,2H), 7.3-7.35(m,2H), 7.65(d,1H), 7.9(d,1H); m/e 173$(M+H)^+$

(iii) To a solution of 6-methoxy-1-methylnaphthalene (6.4g) in dichloromethane (500ml), cooled to -60°C, was added boron tribromide (45ml of a 1M solution in dichloromethane). The resulting mixture was stirred at -60°C for 3 hours. The reaction was quenched with water (500ml) and extracted with dichloromethane (2x500ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to give a solid. Purification by flash column chromatography on silica, eluting with ethyl acetate/hexane (5:95 v/v) gave 6-methyl-2-naphthol (3.76g) as a white solid. This was used without further characterisation.

(iv) To a solution of 6-methyl-2-naphthol (3.15g) in acetone (100ml) was added anhydrous potassium carbonate (6.0g) followed by methyl bromoacetate (2.0ml). The mixture was stirred for 18 hours and then filtered. The solvent was removed by evaporation to give an oil. Purification by flash column chromatography on silica, eluting with ethyl acetate/hexane (5:95 v/v) gave methyl 2-(5-methyl)naphthoxy-

acetate (3.8g) as a white solid: NMR (d_6DMSO) δ 2.6(s,3H), 3.7(s,3H), 4.9(s,2H), 7.15-7.4(m,4H), 7.65(d,1H), 7.95(d,1H); m/e 231$(M+H)^+$.

(v) To a solution of the product from step (iv) (1.5g) in carbon tetrachloride (100ml) was added N-bromosuccinimide (1.16g) followed by a catalytic amount of AIBN. The resulting mixture was refluxed for 2 hours. The solvent was removed by evaporation to give an oil, which was purified by flash column chromatography on silica, eluting with ethyl acetate/hexane (5:95 v/v) to give methyl 2-(5-bromomethyl)naphthoxyacetate (1.16g) as a gum: NMR (d_6DMSO) δ 3.75(s,3H), 4.95(s,2H), 5.2(s,2H), 7.3-7.6(m,4H), 7.8(d,1H), 8.15(d,1H); m/e 309/311 $(M+H)^+$ Br pattern.

(vi) In a similar manner to Example 66, but starting from the product of step (v) was prepared methyl 5-[[4-(4-pyridyl)-piperazin-1-yl]methylene]naphth-2-yloxyacetate: NMR (d_6DMSO) δ 3.2-3.35(m,8H), 3.7(s,3H), 3.9(s,2H), 4.9(s,2H), 6.8(d,2H), 7.2-7.45(m,4H), 7.75(d,1H), 8.15(d,2H), 8.25(d,1H); m/e 392$(M+H)^+$.

EXAMPLE 77: 4-[[4-(4-pyridyl)piperazin-1-yl]methylene]cinnamic acid

^{t}Butyl 4-[[4-(4-pyridyl)piperazin-1-yl]methylene] cinnamate (200mg) was stirred in trifluoroacetic acid (5ml) for 2 hours. The solvent was removed by evaporation and the resulting oil was titriated with anhydrous ether to give the title compound (210mg) as a white solid: NMR (d_6DMSO) δ 3.05-3.25(m,4H), 3.7-4.1(bm,4H), 4.25(s,2H), 6.6(d,1H), 7.25(d,2H), 7.5(d,2H), 7.6(d,1H), 7.75(d,2H), 8.35(d,2H); m/e 324$(M+H)^+$; calculated for $C_{19}H_{21}N_3O_2.2CF_3COOH.0.5H_2O$: C, 49.5; H, 4.25; N, 7.4. Found: C, 49.1; H, 4.2; N, 7.1.

The necessary starting material was prepared as follows:-

(i) In a similar to Example 66, but starting from ^{t}butyl 4-bromomethyl cinnamate was prepared ^{t}butyl 4-[[4-(4-pyridyl)-piperazin-1-yl]methylene] cinnamate: NMR (d_6DMSO) δ 1.45(s,9H), 3.55(s,2H), 6.5(d,1H), 6.8(d,2H), 7.35(d,2H), 7.55(d,1H), 7.65(d,2H), 8.15(d,2H).

EXAMPLE 78: Dimethyl 4-[2-[(4-(4-pyridyl)piperazin-1-yl)-2-methyl]-acetyl]-1,2-diphenoxydiacetate

In a similar manner to Example 66, but starting from dimethyl 4-[(2'-bromopropionyl)-phenylene-1,2-dioxy]diacetate was prepared the title compound: NMR (d_6DMSO) δ 1.15(d,3H), 2.55-2.7(m,4H), 3.2-3.35(m,4H), 3.68(s,3H),3.70(s,3H), 4.25(q,1H), 4.9(s,2H), 4.95(s,2H), 6.75(d,2H), 7.0(d,1H), 7.65(d,1H), 7.75(dd,1H), 8.15(d,2H); m/e 472$(M+H)^+$.

The starting material was prepared as follows:-

(i) To a solution of 3,4 dihydroxypropiophenone (1.24g) in DMF (15ml) was added anhydrous potassium carbonate (3.09g) followed by methyl bromoacetate (1.4ml). The resulting mixture was stirred for 24 hours. Water (50ml) was added and the mixture was extracted with ethyl acetate (3x100ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to give a gum. Purification by flash column chromatography on silica, eluting with ethyl acetate/hexane (1:1 v/v) gave dimethyl 4-propionyl-phenylene-1,2-dioxydiacetate (1.79g) as an oil: NMR (d_6DMSO) δ 1.05(t,3H), 3.0(q,2H), 3.7(s,6H), 4.9(s,2H),4.95(s,2H), 7.05(d,d,1H), 7.45(d,1H), 7.6(dd,1H),; m/e 311$(M+H)^+$.

(ii) To a solution of the product from step (i) (1.79g) in chloroform (15ml) was added dropwise a solution of bromine (0.3ml) in chloroform (5ml) and the resulting mixture was stirred for 3 hours. The solvent was removed by evaporation to give a gum which was purified by flash column chromatography on silica, eluting with ethyl acetate/hexane (2:3 v/v) to give dimethyl 4-[(2'-bromopropionyl)-phenylene-1,2-dioxy)diacetate (1.95g), which solidified on standing:

NMR (d_6DMSO) δ 1.75(d,3H), 3.7(s,6H), 4.9(s,2H), 4.95(s,2H), 5.8(q,1H), 7.05(d,1H), 7.5(d,1H), 7.7(dd,1H); m/e 389/391 $(M+H)^+$ Br pattern.

EXAMPLE 79: 4-[2-[(4-pyridyl)piperazin-1-yl]-2-methyl]acetyl-1,2-diphenoxydiacetic acid

In a similar manner to Example 67, but starting from the product of Example 78 was prepared the title compound: NMR (d_6DMSO) δ 1.4(d,3H), 3.0-3.2(m,4H), 3.75-3.9(m,4H), 4.75.5.0(m,1H), 4.8(s,2H), 4.85(s,2H), 7.05(d,1H), 7.25(d,2H), 7.55(d,1H), 7.75(dd,1H), 8.3(d,2H); m/e 444$(M+H)^+$. Calculated for $C_{22}H_{25}N_3O_7.2.25CF_3COOH.H_2O$ C, 44.3; H, 4.1; N, 5.85; TFA, 35.7. Found C, 44.2; H, 3.9; N, 5.7; TFA, 36.2.

EXAMPLE 80: Methyl 2-[4-(4-pyridyl)piperazin-1-yl]tetralone-6-oxyacetate

In a similar manner to Example 66, but starting from methyl 2-bromotetralone-6-oxyacetate was prepared the title compound: NMR (d_6DMSO+CD_3COOD) δ 2.05-2.4(m,2H), 2.9-3.05(m,2H), 3.1-3.25(m,4H), 3.6(s,3H), 3.75-3.9(m,4H), 4.05(dd,1H), 4.75(s,2H), 6.75(d,1H), 6.85(dd,1H), 7.05(d,2H), 7.85(d,1H), 8.1(d,2H); m/e 396$(M+H)^+$.

The starting material was prepared as follows:-

(i) A solution of 6-methoxy-1-tetralone (5.0g) in 48% hydrobromic acid (62ml) was refluxed for 8 hours. The mixture was cooled, filtered and washed with water (50ml) to give 6-hydroxy-1-tetralone (3.9ig). NMR δ (d_6DMSO) 1.9-2.05(m,2H), 2.4-2.55(m,2H), 2.8-2.9(m,2H), 6.65(d,1H), 6.7(dd,1H), 7.75(d,1H),; m/e 163$(M+H)^+$.

(ii) To a solution of 6-hydroxy-1-tetralone (2.62g) in acetone (50ml) was added anhydrous potassium carbonate (2.23g) followed by methyl bromoacetate (1.52ml) and the resulting mixture was stirred for

18 hours. The mixture was filtered and the solvent was evaporated to give a yellow solid. Recrystallisation from ethyl acetate gave methyl tetralone-6-oxyacetate (2.28g): NMR (d_6DMSO) δ 1.95-2.05(m,2H), 2.45-2.55(m,2H), 2.9(t,2H), 3.7(s,3H), 4.9(s,2H), 6.85-6.9(m,2H), 7.8(d,1H); m/e 235$(M+H)^+$.

(iii) To a solution of the product from step (ii) (1.3g) in chloroform (15ml) was added dropwise a solution of bromine (0.29ml) in chloroform (1ml) and the resulting mixture was stirred for 4 hours. The solvent was evaporated to give an oil. Purification by flash column chromatography on silica, eluting with ethyl acetate/hexane (30:70 v/v) gave methyl 2-bromotetralone-6-oxyacetate (1.55g) as an oil: NMR (d_6DMSO) δ 2.3-2.6(m,2H), 2.9-3.1(m,2H), 3.7(s,3H), 4.9(s,2H), 4.9-5.0(m,1H), 6.9-7.0(m,2H), 7.9(d,1H); m/e 313/315$(M+H)^+$ Br pattern.

EXAMPLE 81: Methyl 2-S-(n-butylsulphonylamino)-3-[4-[3-[1-(4-pyridyl)-piperidin-4-yl]propoxy]phenyl]propionate.

Using a procedure similar to that described in Example 35, but starting from the appropriate amino ester, the title compound was prepared; NMR(d_6DMSO): 0.75(t,3H), 1.0-1.44(m,8H), 1.44-1.64(m,1H), 1.75(brd,4H), 2.5-3.02(m,6H), 3.64(s,3H), 3.85-4.1(m,5H), 6.81(d,2H), 6.84(d,2H), 7.19(d,2H), 7.78(d,1H), 8.12(d,2H); mass spectrum(+ve FAB, MeOH/NBA): 518 $(M+H)^+$.

The starting material was prepared using similar procedures to those described in Example 33. There was thus prepared the following intermediates (i) and (ii) which were themselves prepared starting from 4-(4-hydroxypropylpiperidin-1-yl) pyridine(iii).

(i) Methyl 2-S-(benzyloxycarbonylamino)-3-[4-[3-[1-(4-pyridyl)piperidin-4-yl] propoxy]phenyl]propionate; NMR(d_6DMSO): 1.18-1.24(m,2H), 1.3-1.43(m,2H), 1.44-1.65(m,1H), 1.65-1.83(m,4H), 2.7-2.88(m,3H), 2.96(dd,1H), 3.61(s,3H), 3.92(t,4H), 4.14-4.25(m,1H), 4.98(s,2H), 6.8(d,2H), 6.82(d,2H), 7.14(d,2H), 7.2-7.4(m,5H), 7.74(d,1H), 8.12(d,2H); mass spectrum(+ve FAB, MeOH/NBA): 532$(M+H)^+$.

(ii) Methyl 2-S-amino-3-[4-[3-[1-(4-pyridyl)piperidin-4-yl]-propoxy]phenyl] propionate; NMR(d_6DMSO): 1.03-1.2(m,2H), 1.28-1.40(m,2H), 1.42-1.62(m,1H), 1.64-1.80(m,4H), 2.65-2.9(m,4H), 3.58(s,3H), 3.45-3.6(m,1H), 3.85-3.98(m,4H), 6.78(d,2H), 6.8(d,2H), 7.06(d,2H), 8.11(d,2H); mass spectrum(+ve FAB, MeOH/NBA): 398$(M+H)^+$.

(iii) 4-(4-Hydroxypropylpiperidin-1-yl)pyridine.

A solution of N-(2-carbamoylethyl)-4-cyanopyridinium chloride (2.1g) in water (5ml) was added dropwise to a stirred mixture of 4-hydroxypropylpiperidine (2.4g), water (10ml) and 2.5M sodium hydroxide solution (4.6ml) cooled in an ice-bath. The mixture was stirred at 0-5°C for 1 hour. 2.5M sodium hydroxide solution (7ml) was added and the mixture heated at reflux for 3 hours. The mixture was cooled in an ice-bath and gummy solid separated out. The aqueous layer was decanted off and the gummy solid dissolved in dichloromethane (75ml). The solution was washed with saturated sodium chloride solution (10ml) and dried ($MgSO_4$). The solvent was removed by evaporation to give a gummy solid (880mg) which on trituration with ether gave a solid; NMR(d_6DMSO): 1.0-1.35(m,4H), 1.35-1.6(m,3H), 1.7(dd,2H), 2.70-2.88(dt,2H), 3.38(t,2H), 3.89(brd,2H), 4.35(brs,1H), 6.78(d,2H), 8.1(d,2H); mass spectrum(CI^+): 221$(M+H)^+$.

EXAMPLE 82: 2-S-(n-butylsulphonylamino)-3-[4-[3-[1-(4-pyridyl)-piperidin-4-yl]propoxy]phenyl]propionic acid.

Using a similar procedure to that described in Example 34, but starting from the product of Example 81, the title compound was obtained as an amorphous solid; NMR(d_6DMSO/CD_3CO_2D): 0.73(t,3H), 1.0-1.5(m,8H), 1.55-1.85(m,5H), 2.54-2.78(m,3H), 2.9-3.2(m,3H), 3.8-3.98(m,3H), 4.15(brd,2H), 6.8(d,2H), 7.09(d,2H), 7.15(d,2H), 8.1(d,2H); mass spectrum(+ve FAB, MeOH/NBA): 504$(M+H)^+$; microanalysis found C,60.3; H,7.2; N,7.9%; $C_{26}H_{37}N_3O_5S.H_2O$ requires C,59.9; H,7.5; N,8.1%.

EXAMPLE 83: Methyl 2-S-(butylsulphonylamino)-3-[4-[4-[1-(4-pyridyl)piperidin-4-yl]butoxy]phenyl]propionate.

Using a similar procedure to that described in Example 35, but starting from the appropriate amino ester, the title compound was prepared; NMR($CDCl_3$): 0.87(t,3H), 1.14-1.4(m,6H), 1.42-1.7(m,5H), 1.7-1.9(m,4H), 2.7-3.18(m,6H), 3.78(s,3H), 3.9(brd,2H), 3.93(t,2H), 4.32(brs,1H), 4.82(brs,1H), 6.66(d,2H), 6.83(d,2H), 7.09(d,2H), 8.22(d,2H); mass spectrum(+ve FAB, MeOH/NBA): 532 $(M+H)^+$.

The starting material was prepared using similar procedures to those described in Example 33 and 81(iii). There was thus prepared the following intermediates:-

(i) 4-(4-hydroxybutylpiperidin-1-yl)pyridine; NMR(d_6DMSO): 0.97-1.58(m,9H), 1.7(dd,2H), 2.78(dt,2H), 3.38(m,2H), 3.88(brd,2H), 4.29(t,1H), 6.78(d,2H), 8.10(d,2H); mass spectrum(CI^+): 235$(M+H)^+$.

(ii) Methyl 2-S-(benzylcarbonylamino)-3-[4-[4-[1-(4-pyridyl)-piperidin-4-yl]butoxy]phenyl]propionate; NMR(d_6DMSO): 1.0-1.35(m,4H), 1.35-1.60(m,3H), 1.62-1.80(m,4H), 2.8(dt,3H), 2.96(dd,1H), 3.62(s,3H), 3.85-3.97(m,4H), 4.15-4.28(m,1H), 4.99(s,2H), 6.78(d,2H), 6.81(d,2H), 7.13(d,2H), 7.2-7.4(m,5H), 7.74(d,1H), 8.11(d,2H); mass spectrum(CI^+): 546$(M+H)^+$.

(iii) Methyl 2-S-amino-3-[4-[4-[1-(4-pyridyl)-piperidin-4-yl]-butoxy]phenyl]propionate; NMR(d_6DMSO): 1.05-1.35(m,4H), 1.35-1.58(m,3H), 1.6-1.8(m,4H), 2.65-2.9(m,4H), 3.51(t,1H), 3.58(s,3H), 3.8-3.98(m,4H), 6.78(dd,2H), 6.81(d,2H), 7.05(d,2H), 8.1(dd,2H); mass spectrum(CI^+): 412$(M+H)^+$.

EXAMPLE 84: 2-S-(n-butylsulphonylamino)-3-[4-[4-[1-(4-pyridyl)-piperidin-4-yl]butoxy]phenyl]propionic acid.

Using a similar procedure to that described in Example 34 but starting from the product of Example 83, the title compound was obtained as an amorphous solid; NMR(d_6DMSO): 0.78(t,3H), 1.0-1.6(m,11H), 1.6-1.82(brt,4H), 2.5-3.04(m,6H), 3.8-4.0(m,5H), 6.8(m,4H), 7.19(d,2H), 8.1(brd,2H); mass spectrum(+ve FAB,MeOH/NBA):

518$(M+H)^+$; microanalysis found C,62.4; H,7.8; N,7.9%; $C_{27}H_{39}N_3O_5S$ requires C,62.6; H,7.6; N,8.1%.

EXAMPLES 85-87:

Using a procedure similar to that described in Example 35, but starting from the appropriate substituted sulphonyl chloride and methyl 2-S-amino-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]-phenyl]propionate there was obtained the following compounds:-

Example 85: Methyl 2-S-(methylsulphonylamino)-3-[4-[2-[1-(4-pyridyl)-piperidin-4-yl]ethoxy]phenyl]propionate NMR(d_6DMSO): 1.08-1.34(m,2H), 1.6-1.85(m,5H), 2.6(s,3H), 2.7-3.0(m,4H), 3.63(s,3H), 3.84-4.2(m,5H), 6.80(d,2H), 6.85(d,2H), 7.18(d,2H), 8.12(d,2H); mass spectrum(+ve FAB, MeOH/NBA): 462$(M+H)^+$.

Example 86: Methyl 2-S-(benzylsulphonylamino)-3-[4-[2-[1-(4-pyridyl)-piperidin-4-yl]ethoxy]phenyl]propionate NMR(d_6DMSO): 1.05-1.28(m,2H), 1.57-1.82(m,5H), 2.68-2.95(m,4H), 3.58(s,3H), 3.8-4.15(m,7H), 6.79(d,2H), 6.38(d,2H), 7.12(d,2H), 7.17(m,2H), 7.3(m,3H), 7.79(brd,1H), 8.1(d,2H) mass spectrum(+ve FAB, MeOH/NBA): 538$(M+H)^+$.

Example 87: Methyl 2-S-(4-methylphenylsulphonylamino)-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]propionate NMR(d_6DMSO): 1.1-1.33(m,2H), 1.6-1.88(m,5H), 2.35(s,3H), 2.6-2.75(dd,1H), 2.75-2.92(m,3H), 3.38(s,3H), 3.8-4.1(m,5H), 6.76(d,2H), 6.81(d,2H), 7.0(d,2H), 7.28(d,2H), 7.47(d,2H), 8.12(d,2H), 8.32(d,1H); mass spectrum(+ve FAB, MeOH/NBA): 538$(M+H)^+$.

EXAMPLES 88-90:

Following the method of Example 34, but using the products of Examples 85-87, there was obtained the following compounds:-

EXAMPLE 88: 2-S-(Methylsulphonylamino)-3-[4-[2-[1-(4-pyridyl)-piperidin-4-yl]ethoxy]phenyl]propionic acid NMR(d_6DMSO): 1.05-1.35(m,2H), 1.6-1.95(m,5H), 2.61(s,3H), 2.65-3.1(m,4H), 3.88-4.1(m,5H), 6.84(d,2H), 6.9(d,2H), 7.18(d,2H), 8.14(d,2H); mass spectrum(+ve FAB, MeOH/NBA): 448$(M+H)^+$.

EXAMPLE 89: 2-S-(Benzylsulphonylamino)-3-[4-[2-[1-(4-pyridyl)-piperidin-4-yl]ethoxy]phenyl]propionic acid NMR(d_6DMSO/CD_3CO_2D): 1.07-1.35(m,2H), 1.60-1.88(m,5H), 2.7-3.2(m,4H), 3.85-4.25(m,7H), 6.87(d,2H), 7.1(d,2H), 7.13-7.45(m,7H), 8.15(d,2H); mass spectrum(+ve FAB,MeOH/NBA): 524$(M+H)^+$; microanalysis found C,61.8; H,6.8; N,7.6%; $C_{28}H_{33}N_3O_5S.H_2O$ requires C,62.1; H,6.5; N,7.8%.

EXAMPLE 90: Lithium 2-S-(4-methylphenylsulphonylamino)-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]propionate NMR(d_6DMSO/CD_3CO_2D): 1.15-1.38(m,2H), 1.67-1.78(m,2H), 1.82-2.0(m,3H), 2.36(s,3H), 2.65-2.8(dd,1H), 2.85-2.95(dd,1H), 3.14(t,2H), 3.78(m,1H), 4.0(t,2H), 4.18(d,2H), 6.77(d,2H), 7.04(d,2H), 7.11(d,2H), 7.24(d,2H), 7.51(d,2H), 8.15(d,2H); mass spectrum(+ve FAB, MeOH/NBA): 536$(M+Li)^+$; microanalysis found C,63.2; H,6.5; N,7.9%; $C_{28}H_{32}N_3O_5SLi$ requires C,63.5; H,6.1; N,7.9%.

EXAMPLE 91: Methyl 2-S-(pentanoylamino)-3-[4-[2-[1-(4-pyridyl)-piperidin-4-yl]ethoxy]phenyl]propionate.

Valeryl chloride (0.25ml) was added dropwise to a solution of methyl 2-S-amino-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]-phenyl]propionate (640mg) and triethylamine (0.7ml) in dichloromethane (17ml) at ambient temperature. The reaction mixture was stirred for 5 hours and then diluted with dichloromethane (20ml) and washed with water (20ml), saturated sodium chloride solution (10ml) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by flash chromatography eluting with methanol/dichloromethane (1:9v/v) to give the title compound (660mg) as a gum; NMR(d_6DMSO): 0.81(t,3H), 1.05-1.3(m,4H), 1.3-1.45(m,2H), 1.60-1.85(m,5H), 2.04(t,2H), 2.7-3.0(m,4H), 3.6(s,3H), 3.92(d,2H), 3.99(t,2H), 4.35-4.48(m,1H),

6.8(d,2H), 6.83(d,2H), 7.11(d,2H), 8.12(d,2H), 8.18(d,1H); mass spectrum(+ve FAB,MeOH/NBA): 468$(M+H)^+$.

EXAMPLE 92: Methyl 2-S-(pentanoylamino)-3-[4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenyl]propionate.

Using a procedure similar to that described in Example 91, but starting from the appropriate amino ester, the title compound was prepared, NMR(d_6DMSO): 0.8(t,3H), 1.05-1.45(m,6H), 1.83(dd,2H), 1.9-2.1(m,1H), 2.04(t,2H), 2.7-3.0(m,4H), 3.59(s,3H), 3.82(d,2H), 3.96(d,2H), 4.35-4.48(m,1H), 6.80(d,2H), 6.83(d,2H), 7.10(d,2H), 8.12(d,2H), 8.17(d,1H); mass spectrum(+ve FAB, MeOH/NBA): 454$(M+H)^+$.

EXAMPLE 93: 2-S-(Pentanoylamino)-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]propionic acid.

Using a procedure similar to that described in Example 34, but starting from the product of Example 91, the title compound was prepared, NMR(d_6DMSO): 0.8(t,3H), 1.08-1.3(m,4H), 1.3-1.45(m,2H), 1.6-1.87(m,5H), 2.05(t,2H), 2.7-3.05(m,4H), 3.9-4.05(m,4H), 4.3-4.43(m,1H), 6.82(d,2H), 6.85(d,2H), 7.11(d,2H), 7.97(d,1H), 8.12(brd,2H); mass spectrum(+ve FAB, MeOH/NBA): 454$(M+H)^+$; microanalysis found C,63.1; H,7.8; N,8.3%; $C_{26}H_{35}N_3O_4.2H_2O$ requires C,63.8; H,8.0; N,8.6%.

EXAMPLE 94: 2-S-(Benzyloxycarbonylamino)-3-[4-[2-[1-(4-pyridyl) piperidin-4-yl]ethoxy]phenyl]propionic acid.

Using a procedure similar to that described in Example 34, but starting from the product of Example 35, step (i), the title compound was prepared, NMR(d_6DMSO): 1.1-1.35(m,2H), 1.6-1.9(m,5H), 2.65-3.1(m,4H), 3.85-4.2(m,5H), 4.96(s,2H), 6.75-6.9(m,4H), 7.14(d,2H), 7.2-7.35(m,5H), 7.5(d,1H), 8.1(d,2H); mass spectrum(+ve FAB, MeOH/NBA): 504$(M+H)^+$.

EXAMPLE 95: Methyl-2-S-(n-butylsulphonylamino)-3-[3-(N-methyl-N-4-pyridyl)aminopropoxy]phenylpropionate.

Using a procedure similar to that described in Example 33, but starting from methyl 2-S-amino-3-[3-(N-methyl-N-4-pyridyl)-aminopropoxy]phenylpropionate, the title compound was prepared, NMR($CDCl_3$): 0.89(t,3H), 1.25-1.4(m,2H), 1.55-1.75(m,2H), 2.0-2.15(m,2H), 2.80(dd,2H), 2.9-3.15(m,2H), 3.05(s,3H), 3.63(t,2H), 3.77(s,3H), 3.95(t,2H), 4.28-4.38(m,1H), 6.57(d,2H), 6.80(d,2H), 7.10(d,2H), 8.14(d,2H); mass spectrum (CI^+): $464(M+H)^+$.

The necessary starting material was prepared as follows:-

(i) Using a procedure similar to that described in Example 33, step (i), but starting from N-methyl-N-(4-pyridyl)aminopropanol and N-t-butyloxycarbonyl-S-tyrosine methyl ester, there was obtained, methyl 2-S-(t-butyloxycarbonylamino)-3-[3-N-methyl-N-(4-pyridyl)-aminopropoxy]phenyl propionate, as a gum, NMR($CDCl_3$): 1.43(s,9H), 2.0-2.15(m,2H), 3.04(s,3H), 2.95-3.10(m,2H), 3.62(t,2H), 3.73(s,3H), 3.98(t,2H), 4.54(brd,1H), 4.98(brd,1H), 6.56(d,2H), 6.80(d,2H), 7.04(d,2H), 8.17(d,2H).

(ii) The product from step (i) (500mg) and 5M methanolic hydrochloric acid solution (4ml) was stirred at ambient temperature for 16 hours. The solvent was evaporated to give the corresponding amino compound as the dihydrochloride salt which was used without further purification.

EXAMPLE 96: 2-S-(n-Butylsulphonylamino)-3-[3-(N-4-pyridyl-N-methyl)aminopropoxy]phenyl propionic acid

Using a procedure similar to that described in Example 34, but starting from the product of Example 95, the title compound was prepared, NMR(d_6DMSO/CD_3CO_2D): 0.8(t,3H), 1.1-1.28(m,2H), 1.28-1.55(m,2H), 2.0-2.15(m,2H), 2.6-2.8(m,3H), 2.93-3.08(dd,1H), 3.18(s,3H), 3.75(t,2H), 3.9-4.05(m,3H), 6.86(d,2H), 7.0(d,2H),

7.2(d,2H), 8.15(d,2H); mass spectrum (+ve FAB,MeOH/NBA): 450$(M+H)^+$; microanalysis found C,53.9; H,6.9; N,8.4%; $C_{22}H_{31}N_3O_5S.2H_2O$ requires C,54.4; H,7.2; N,8.6%.

EXAMPLE 97: Methyl 3-(n-butylsulphonylamino)-3-[4-[1-(4-pyridyl) piperidin-4-yl]methoxyphenyl]propionate.

Using a procedure similar to that described in Example 33, but starting from methyl 3-amino-3-[4-[1-(4-pyridyl)piperidin-4-yl]-methoxyphenyl]propionate, dihydrochloride, the title compound was prepared; NMR($CDCl_3$): 0.84(t,3H), 1.2-1.4(m,2H), 1.4-1.55(m,2H), 1.55-1.75(m,2H), 1.97(brd,2H), 2.02-2.2(m,1H), 2.65-2.85(m,2H), 2.88(d,2H), 3.0(dt,2H), 3.67(s,3H), 3.84(d,2H), 4.0(brd,2H), 4.85(q,1H), 5.40(d,1H), 6.71(d,2H), 6.86(d,2H), 7.27(d,2H), 8.25(d,2H); mass spectrum(+ve FAB,MeOH/NBA): 490$(M+H)^+$.

The starting material was prepared as follows:-

(i) Thionyl chloride (4.3ml) was added to methanol (50ml) cooled in an ice-salt bath. 3-Amino-3-(4-hydroxyphenyl)propionic acid (9.7g) was added and the mixture allowed to reach ambient temperature and then refluxed for 2 hours. The solvent was removed by evaporation in vacuo to give a gummy solid (12.8g) which was used without further purification. A solution of di-t-butyldicarbonate (5.8g) in dichloromethane (50ml) was added to a stirred mixture of the gummy solid (5.75g) and potassium hydrogen carbonate (6.2g) in water (20ml). The mixture was stirred at ambient temperature for 4 hours. The organic layer was separated and washed with water (10ml), 1M hydrochloric acid solution (10ml), saturated sodium hydrogen carbonate solution (10ml), water (10ml) and dried ($MgSO_4$). The solvent was evaporated to give methyl 3-(t-butyloxycarbonylamino)-3-(4-hydroxyphenyl)propionate as a solid; m.p. 119-120°C; NMR(d_6DMSO) : 1.34(s,9H), 2.54-2.78(m,2H), 3.53(s,3H), 4.7-4.9(q,1H), 6.67(d,2H), 7.08(d,2H), 7.28(brd,1H), 9.24(brs,1H).

(ii) Using a procedure similar to that described in Example 33, step (i), but using the product of step (i), methyl 3-(t-butyloxycarbonylamino)-3-[4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenyl]-propionate was prepared as a gum; NMR($CDCl_3$): 1.33-1.55(m,2H), 1.44(s,9H), 1.95(brd,2H), 1.95-2.15(m,1H), 2.7-3.0(m,4H), 3.61(s,3H), 3.80(d,2H), 3.95(brd,2H), 4.95-5.1(m,1H), 5.25-5.40(m,1H), 6.68(d,2H), 6.85(d,2H), 7.2(d,2H), 8.25(d,2H).

(iii) The product of step (ii) (550mg) and 5M methanolic hydrochloric acid solution (4ml) was stirred at ambient temperature for 18 hours. The solvent was evaporated to give methyl 3-amino-3-[4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenyl] propionate dihydrochloride as a foam; NMR(d_6DMSO/CD_3CO_2D): 1.23-1.45(m,2H), 1.92(brd,2H), 2.05-2.25(m,1H), 3.0-3.25(m,4H), 3.52(s,3H), 3.85(d,2H), 4.2(brd,2H), 4.54(t,1H), 6.92(d,2H), 7.1(d,2H), 7.39(d,2H), 8.10(d,2H).

EXAMPLE 98: 3-(n-Butylsulphonylamino)-3-[4-[1-(4-pyridyl)-piperidin-4-yl]methoxyphenyl]propionic acid.

Using a procedure similar to that described in Example 34, but using the product of Example 97, the title compound was prepared; NMR(d_6DMSO/CD_3CO_2D): 0.78(t,3H), 1.05-1.3(m,2H), 1.3-1.57(m,4H), 1.98(brd,2H), 2.1-2.33(m,1H), 2.45-2.85(m,4H), 3.25(t,2H), 3.89(d,2H), 4.25(brd,2H), 4.68(t,1H), 6.90(d,2H), 7.14(d,2H), 7.33(d,2H), 8.14(d,2H); mass spectrum(+ve FAB,MeOH/NBA): $490(M+H)^+$.

EXAMPLE 99: Methyl 3-(4-methylphenylsulphonylamino)-3-[4-[1-(4-pyridyl)-piperidin-4-yl]methoxyphenyl]propionate.

Using a procedure similar to that described in Example 33, but starting from the product of Example 97, step (iii) and p-toluenesulphonyl chloride, the title compound was prepared; NMR($CDCl_3$): 1.34-1.55(m,2H), 1.95(d,2H), 2.0-2.2(m,1H), 2.38(s,3H), 2.62-3.05(m,4H), 3.55(s,3H), 3.78(d,2H), 3.96(d,2H), 4.65(m,1H),

5.65(brs,1H), 6.7(d,2H), 6.72(d,2H), 7.05(d,2H), 7.2(d,2H), 7.65(d,2H), 8.25(d,2H); mass spectrum(+ve FAB,MeOH/NBA): 524$(M+H)^+$.

EXAMPLE 100: Methyl 2-R-(n-butylsulphonylamino)-3-[4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenyl]propionate.

Using a procedure similar to that described in Example 33, but starting from methyl 2-R-amino-3-[4-[1-(4-pyridyl)piperidin-4-yl]-methoxyphenyl]propionate, the title compound was prepared; NMR($CDCl_3$): 0.88(t,3H), 1.2-1.7(m,6H), 1.96(d,2H), 2.0-2.2(m,1H), 2.7-2.83(m,2H), 2.85-3.15(m,4H), 3.77(s,3H), 3.79(d,2H), 3.96(d,2H), 4.32(m,1H), 4.85(brd,1H), 6.7(d,2H), 6.83(d,2H), 7.08(d,2H), 8.25(brd,2H); mass spectrum(+ve FAB,MeOH/NBA): 490$(M+H)^+$.

The necessary starting material was prepared as follows:-

(i) Using a similar procedure to that described in Example 33, step (i), but starting from N-t-butyloxycarbonyl-S-tyrosine methyl ester, there was obtained, methyl 2-R-(t-butyloxycarbonylamino)-3-[4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenyl]propionate as a gum, NMR($CDCl_3$): 1.43(s,9H), 1.36-1.55(m,2H), 1.96(brd,2H), 2.0-2.15(m,1H), 2.95(dt,2H), 3.03(d,2H), 3.71(s,3H), 3.81(d,2H), 3.95(brd,2H), 4.52(brd,1H), 4.95(brd,1H), 6.70(d,2H), 6.80(d,2H), 7.01(d,2H), 8.24(d,2H).

(ii) Using a similar procedure to that described in Example 95, step (ii), but starting from the product obtained in step (i), there was obtained, methyl 2-R-amino-3-[4-[1-(4-pyridyl)-piperidin-4-yl]methoxyphenyl]propionate dihydrochloride as a foam, NMR(d_6DMSO/CD_3CO_2D): 1.26-1.48(m,2H), 1.96(brd,2H), 2.1-2.3(m,1H), 3.09(dd,2H), 3.21(t,2H), 3.70(s,3H), 3.84(d,2H), 4.15-4.3(m,3H), 6.88(d,2H), 7.14(m,4H), 8.1[illegible](d,2H).

EXAMPLE 101: 2-R-(n-Butylsulphonylamino)-3-[4-[1-(4-pyridyl)-piperidin-4-yl]-methoxyphenyl]propionic acid.

Following the method of Example 34, but using the product of Example 100, the title compound was prepared; NMR(d_6DMSO): 0.75(t,3H), 1.03-1.45(m,6H), 1.87(d,2H), 1.95-2.2(m,1H), 2.45-2.78(m,3H), 2.88-3.08(m,3H), 3.82(d,2H), 3.8-3.95(m,1H), 4.05(brd,2H), 6.84(d,2H), 6.92(d,2H), 7.18(d,2H), 8.13(brs,2H); mass spectrum(-ve FAB,MeOH/NBA): 474$(M-H)^-$; microanalysis found C,55.1; H,6.8; N,7.8%; $C_{24}H_{33}N_3O_5S.2.5H_2O$ requires C,55.4; H,7.3; N,8.1%.

EXAMPLE 102: cis-1-Hydroxy-4-[4-(4-pyridyl)piperazin-1-yl]cyclohexane-acetic acid.

A mixture of cis-1,1-dimethylethyl 1-hydroxy-4-[4-(4-pyridyl)piperazin-1-yl]cyclohexane acetate (120mg), water(0.2ml) and trifluoroacetic acid (2ml) was stirred for 30 minutes at ambient temperature. The mixture was concentrated in vacuo to give a gum which was triturated with ether to give the title compound as a white solid; m.p. 197-200°C(dec.); NMR(d_6DMSO/CD_3CO_2D): 1.45-1.68(m,2H), 1.8-2.0(m,6H), 2.43(s,2H), 3.15-3.34(m,1H), 3.48(brs,4H), 4.0(brs,4H), 7.23(d,2H), 8.3(d,2H); mass spectrum(+ve FAB,MeOH/NBA): 320$(M+H)^+$; microanalysis found C,45.6; H,5.0; N,7.2; CF_3CO_2H,42.6%; $C_{17}H_{25}N_3O_3.2.1CF_3CO_2H$ requires C,45.6; H,4.9; N,7.5; CF_3CO_2H,42.8%.

The starting material was prepared as follows:-

(i) Sodium cyanoborohydride (280mg) was added to a stirred mixture of 1,1-dimethylethyl 1-hydroxy-4-oxocyclohexane acetate (1.0g), 1-(4-pyridyl)piperazine (830mg), 1M hydrochloric acid solution in methanol (1.5ml) and 3A molecular sieve (500mg) in methanol (25ml) at ambient temperature. The mixture was stirred for 72 hours, filtered and the filtrate concentrated in vacuo. Saturated sodium hydrogen carbonate solution (10ml) and saturated sodium chloride solution (10ml) was added to the residue and extracted with ethyl acetate (2x25ml). The combined ethyl acetate extracts were washed with saturated sodium chloride solution (10ml) and dried($MgSO_4$). The

solvent was removed by evaporation and the residue (1.7g) purified by flash chromatography eluting with methanol/dichloromethane/triethylamine (1:9:0.2v/v/v) to give cis-1,1-dimethylethyl-1-hydroxy-4-[4-(4-pyridyl)piperazin-1-yl]cyclohexane acetate as a white amorphous solid; NMR($CDCl_3$): 1.25-1.4(m,2H), 1.47(s,9H), 1.6-1.9(m,6H), 2.35(s,2H), 2.26-2.42(m,1H), 2.69-2.73(m,4H), 3.31-3.35(m,4H), 3.56(brs,1H), 6.65(d,2H), 8.25(d,2H).

EXAMPLE 103: Tert-butyl 1-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-piperidin-3-yloxyacetate

A solution of t-butyl 1-(bromoacetyl)piperidin-3-yloxyacetate (1.2g) in acetonitrile (20ml) was added dropwise to a stirred solution of 1-(4-pyridyl)piperazine (1.6g) in acetonitrile (30ml) and stirring was continued for 1 hour. The mixture was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography, eluting with triethylamine (1%) in ethyl acetate, to give a colourless gum, which on crystallisation from cyclohexane, afforded the title compound (350mg) as colourless prisms m.p. 93-95°; NMR(d_6DMSO): δ 1.4(9H,d); 1.3-2.0(4H,m); 2.7(4H,br.s); 3.2-3.9(11H,m); 4.0(2H,d); 7.1(2H,d); 8.2(2H,d); m/e 419$(M+H)^+$; calculated for $C_{22}H_{34}N_4O_4$: C, 63.1; H, 8.2; N, 13.4; found: C, 63.4; H, 8.2; N, 13.3%.

The starting material was prepared as follows:-

(i) Benzylchloroformate (15ml) was added dropwise to a stirred suspension of 3-hydroxypiperidine hydrochloride (13.7g) and triethylamine (30ml) in dichloromethane (150ml), maintaining the temperature below 15°C throughout. Stirring was continued for three hours, then the solution was washed with water (4 x 100ml) and saturated aqueous sodium chloride (100ml), dried (PS paper) and concentrated. The residual oil was dissolved in ether (300ml), washed with dilute hydrochloric acid (2 x 100ml) and water (100ml), dried (PS paper) and concentrated. The residue was purified by flash column chromatography, eluting first with hexane/ether (1:1) then ether to give 1-benzyloxycarbonylpiperidine-3-ol (7.1g) as a colourless oil.

NMR(d_6DMSO): δ 1.2-1.4(2H,m); 1.6-1.9(1H,m + 1H,m); 2.8(1H,br s); 2.95(1H,m); 3.45(1H,m); 3.65(1H,br.d); 3.8(1H,dd); 4.85(1H,d); 5.1(2H,s); 7.3(5H,m); m/e 236$(M+H)^+$.

(ii) A solution of the product of step (i) (4.7g) in THF (100ml) was cooled to -30°C and treated with a solution of lithium hexamethyldisilazide (22ml, 1M in THF). The mixture was stirred for 2 minutes, cooled to -70°C, treated with t-butylbromoacetate (3.5ml) and allowed to warm to room temperature over four hours. The mixture was diluted with ether (100ml) and washed with water (3 x 100ml) and saturated aqueous sodium chloride (100ml), dried (PS paper) and concentrated. The residual oil was purified by flash column chromatography, eluting with hexane/ethyl acetate (first 90:10 then 85:15) to give t-butyl 1-benzyloxycarbonyl-piperidin-3-yloxyacetate (1.6g) as a pale yellow oil, NMR (d_6DMSO): δ 1.4(9H,s); 1.3-1.6(2H,m), 1.65(1H,m); 1.85(1H,m); 3.25(2H,m); 3.4(2H,m); 3.6(1H,d); 4.0(2H,s); 5.0(2H,s); 7.2-7.4(5H,m); m/e 350 $(M+H)^+$.

(iii) A solution of the product of step (ii) (1.6g) in isopropanol (50ml) was hydrogenolysed over palladium on carbon catalyst (10%, 200mg). The mixture was filtered and the filtrate was concentrated to give t-butyl piperidin-3-yloxyacetate as an oil which was used without further purification.

(iv) The product of step (iii) was dissolved in ether (25ml), treated with triethylamine (0.65ml) and added to a stirred cooled solution of bromoacetylbromide (0.42ml) in ether (25ml). Stirring was continued for two hours and the mixture was allowed to warm to room temperature. Ether (50ml) was added and the solution was washed sequentially with water (50ml), dilute aqueous sodium hydrogen carbonate (50ml), water (50ml) and saturated aqueous sodium chloride (50ml) then dried (PS paper) and concentrated to give t-butyl (1-bromoacetyl)piperidin-3-yloxyacetate (1.2g) as a pale brown oil which was used without further purification. NMR($CDCl_3$): δ 1.5(9H,s); 1.4-2.0(4H,m); 3.2-4.0(9H,m); m/e 336$(M+H)^+$.

EXAMPLE 104: 1-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]piperidin-3-yloxyacetic acid.

The product of Example 103 (340mg) was dissolved in a mixture of trifluoroacetic acid (10ml) and dichloromethane (10ml) and the solution was allowed to stand for 1.5 hours. The solution was concentrated and the residue was azeotroped successively with dichloromethane and ether, then concentrated. The residual gum was passed down a Mega-bond elut column, eluting with dichloromethane/methanol/water (5:4:1), concentrated, dissolved in water (25ml) and freeze-dried to give the title compound (250mg) as a foam. NMR(d_6DMSO); δ 1.2-1.8(4H,m); 3.0-4.2(15H,m); 4.35(2H,d); 7.2(2H,d); 8.2(2H,d); m/e 363$(M+H)^+$.

EXAMPLE 105: 3RS, 4RS 1-[2-[4-(4-pyridyl)piperazin-1-yl]-acetylpiperidin-3,4-dioxydiacetic acid

In a similar manner to Example 104 there was obtained the title compound as a pale yellow solid. NMR(d_6DMSO + d_4AcOH): δ 1.6(1H,m); 1.8(1H,m); 3.1-4.5(20H,m); 7.2(2H,d); 8.25(2H,d); m/e 437$(M+H)^+$.

The starting material was obtained using similar procedures to those described in Example 103. The following intermediates were prepared:

1-benzyloxycarbonylpiperidine-3,4-diol. NMR (d_6DMSO): δ 1.2-1.4(1H,m); 1.7-1.9(1H,m); 2.8-3.4(5H,m); 3.6-3.8(2H,m); 4.8(1H,d); 4.9(1H,d); 5.1(2H,s); 7.3(5H,m); m/e 252$(M+H)^+$.

di-t-butyl 1-benzyloxycarbonylpiperidin-3,4-dioxydiacetate NMR(d_6DMSO + d_4ACOH): δ 1.4(18H,s); 1.4-1.5(1H,m); 1.9(1H,m); 3.2-3.7(6H,m); 4.0(4H,d); 5.1(2H,s); 7.3(5H,m); m/e 480$(M+H)^+$ and 502$(M+Na^+)$.

di-t-butyl-1-bromoacetylpiperidine-3,4-dioxydiacetate m/e 466$(M+H)^+$ and 356(s) (M- 2^{t}Bu).

di-t-butyl 1-[2-[4-(4-pyridyl)piperazin-1-yl]acetylpiperidin-3,4-dioxydiacetate: used immediately without characterisation.

EXAMPLE 106: t-butyl 1-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl-piperidin-4-yloxyacetate

In a similar manner to Example 103 there was obtained the title compound as a gum. NMR(d_6DMSO): δ 1.3(9H,s); 1.3-1.5(2H,m); 1.6-1.8(2H,m); 3.0-3.3(6H,m); 3.5(3H,m); 3.6-3.9(7H,m); 3.9(2H,s); 7.05(2H,d); 8.1(2H,d). m/e 419 $(M+H)^+$.

The starting material was obtained using similar procedures to those described in Example 103. The following intermediates were obtained:

1-benzyloxycarbonylpiperidine-4-ol

NMR (d_6DMSO): δ 1.2-1.4(2H,m); 1.6-1.8(2H,m); 3.0-3.2(2H,m); 3.6-3.8(3H,m); 4.7(1H,d); 5.1(2H,s); 7.35(5H,m). m/e 236$(M+H)^+$.

t-butyl 1-benzyloxycarbonylpiperidine-4-oxyacetate NMR: (d_6DMSO): δ 1.3-1.5(2H,m); 1.4(9H,s); 1.7-1.9(2H,m); 3.0-3.2(2H,m); 3.5-3.6(1H,m); 3.6-3.8(2H,m); 4.0(2H,s); 5.1(2H,s); 7.3(5H,m). m/e 350$(M+H)^+$.

t-butyl 1-bromoacetylpiperidine-4-oxyacetate NMR: ($CDCl_3$): δ 1.45(9H,s); 1.6-2.0(4H,m); 3.4(1H,m); 3.5(1H,m); 3.6-3.8(3H,m); 3.9(2H,s); 4.0(2H,s). m/e 336/338$(M+H)^+$; 358/360$(M+Na)^+$; 280/282 $(M-^tBu)^+$.

EXAMPLE 107: N-2-methoxyethyl 1-[2-[4-(4-pyridyl)piperazin-1-yl]-acetyl]-piperidin-4-yloxyacetamide

A solution of N-2-methoxyethyl 1-bromoacetylpiperidine-4-oxyacetamide (350mg) in acetonitrile (10ml) was added to a stirred solution of N-(4-pyridyl)piperazine (400mg) in acetonitrile (10ml) and the mixture was allowed to stand for 16 hours. The precipitate was removed by filtration and the filtrate was concentrated. The residue was dissolved in ethyl acetate, (15ml) and extracted with water (3 x 10ml). The combined aqueous extracts were extracted with dichloromethane (3 x 15ml) and the combined organic extracts were dried (PS paper) and concentrated. The residual gum was purified by flash column chromatography (grade II alumina) eluting first with dichloromethane and then with methanol/dichloromethane (1:200) to give the title compound (110mg) as a colourless gum.

NMR: (d_6DMSO): δ 1.3-1.6(2H,m); 1.6-1.9(2H,m); 3.0(4H,m); 3.05-3.25(2H,m); 3.15(3H,s); 3.25-3.4(5H,m); 3.7-3.9(7H,m); 3.9(2H,s); 7.0(2H,d); 8.1(2H,d) m/e 420 $(M+H)^+$; m/e 442$(M+Na)^+$.

The starting material was obtained as follows:

A mixture of ethyl 1-benzyloxycarbonylpiperidine-4-oxyacetate (2.4g) and 2-methoxyethylamine (5ml) was heated on a steam bath for 6 hours. The amine was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (10ml), washed sequentially with dilute citric acid solution (5ml), water (5ml) and saturated aqueous sodium chloride (5ml), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography, eluting with hexane/ethyl acetate (1:3) to give N-2-methoxyethyl-1-benzyloxy-carbonylpiperidine-4-oxyacetamide (500mg) as a colourless oil. NMR: (d_6DMSO): δ 1.4-1.5(2H,m); 1.75-1.9(2H,m); 3.[illegible]3.4(9H,m); 3.55(1H,m); 3.65-3.8(2H,m); 3.9(2H,s); 5.1(2H,s); 7.3(5H,m); 7.6(1H, br. t); m/e 351$(M+H)^+$, 373 $(M+Na)^+$.

In a similar manner to that described in Example 103, N-2-methoxyethyl 1-benzyloxycarbonylpiperidine-4-oxyacetamide was converted to N-2-methoxyethyl-1-bromoacetylpiperidine-4-oxyacetamide . NMR ($CDCl_3$): δ 1.5-2.0(4H,m); 3.2-3.5(5H,m); 3.5(4H,m); 3.6-3.8(2H,m); 3.8-4.0(1H,m); 3.9(2H,s); 4.0(2H,s); 6.9(1H, br. s), m/e 337/339 $(M+H)^+$ 359/361$(M+Na)^+$.

EXAMPLE 108: 4-[2-[3-[4-(1-pyrrolidinyl)pyridin-3-yl]methylidene]-pyrrolidin-1-yl]acetylphenoxyacetic acid

A solution of methyl 4-[2-[3-[4-(1-pyrrolidinyl)pyridin-3-yl]-methylidene]pyrrolidin-1-yl]acetyl]phenoxyacetate (300mg) in a mixture of concentrated hydrochloric acid (2ml) and dioxan (8ml) was heated and stirred at 50°C for 30 minutes. The solution was concentrated and the residue was dissolved in water (20ml), washed with ether (2 x 5ml), treated with decolourising charcoal, filtered and concentrated to give the title compound (161mg) as a pale brown foam. NMR: (d_6DMSO) + d_4AcOH): δ 2.0(4H,br.s); 2.6-4.6(10H,m); 4.85(2H,s); 5.15(2H,s); 6.8(1H,m); 6.85(1H,d); 7.1(2H,d); 8.0(2H,d); 7.9-8.1(1H,m); 8.1(1H,d); m/e 422 $(M+H)^+$.

The starting material was obtained as follows:

(i) A mixture of 4-chloropyridine-3-carboxaldehyde (10g, prepared according to the method described in J.Het.Chem, 25, 81), pyrrolidine (25ml) and ethanol (100ml) was heated under reflux for 5 hours, then concentrated. The residue was purified by flash column chromatography (grade II alumina) eluting first with dichloromethane and then with methanol/dichloromethane (1:200) to give 3-[[4-(pyrrolidin-1-yl)pyridin-3-yl]methylidene]-1-pyrroline (900mg) as a white solid. NMR (d_6DMSO): δ 1.8(4H,m); 2.5(2H,m); 3.3(4H,m); 3.95(2H,m); 6.6(1H,d); 7.0(1H,t), 7.9(1H,t), 8.0(1H,d); 8.15(1H,s); m/e 228$(M+H)^+$; calculated for $C_{14}H_{17}N_3$: C, 74.0; H, 7.5; N, 18.5; found C, 74.1; H, 7.7; N, 18.4%.

(ii) A solution of the product of step (i) (650mg) in ethanol (20ml) was treated with sodium borohydride (150mg) and the mixture was stirred for 4 hours. Glacial acetic acid (2ml) was added and the mixture was concentrated. The residue was treated with saturated aqueous sodium chloride (20ml) and saturated sodium hydrogen carbonate solution (10ml) and extracted with ethyl acetate (2 x 10ml). The aqueous solution was basified with aqueous sodium hydroxide (2.5M) and extracted with dichloromethane (4 x 20ml). The combined organic extracts were concentrated to give 3-[[4-(pyrrolidin-1-yl)pyridin-3-yl]methylidine]pyrrolidine (350mg) as a yellow paste which was used without further purification. Conversion to the hydrochloride salt using hydrogen chloride in ether/ethanol followed by crystallisation from iso-propanol gave pale yellow prisms, m.p. 250°, NMR(d_6DMSO): δ 1.95(4H,br.s); 2.55(2H,m); 3.3(2H,m); 3.5-3.7(4H,br.s); 3.95(2H,br.s); 6.75(1H,br.s); 6.85(1H,d); 8.0(1H,s); 8.15(1H,dd); 9.6-10.0(2H,br.s); m/e 230$(M+H)^+$; calculated for $C_{14}H_{19}N_3$. 2HCl. 0.1 H_2O: C, 55.3; H,7.0; N,13.8; H_2O, 0.6; found: C, 55.7; 55.5; H, 7.2, 7.1; N, 13.6; 13.5; H_2O 0.8%.

(iii) A solution of methyl 4-bromoacetyl-phenoxyacetic ester (1.2g) in acetonitrile (20ml) was added dropwise to a stirred mixture of the product of step (ii) (1.0g) and triethylamine (0.6ml) in acetonitrile (20ml), and stirring was continued for 3 hours. The mixture was concentrated and the residue was dissolved in ethyl acetate (50ml). The solution was washed with water (3 x 20ml) and

saturated sodium chloride solution (10ml), dried ($MgSO_4$) and concentrated to give a gum. Methanol (20ml) was added and the solution was acidified with ethereal HCl. Concentration gave methyl 4-[2-[3-(4-[1-pyrrolidinyl)pyridin-3-yl]methylidene]pyrrolidin-1-yl]-acetyl]phenoxyacetate (650mg) as an orange solid which was used without further purification.

EXAMPLE 109: 3-[1-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-piperidin-4-yl]propanoic acid

A mixture containing ethyl 3-[1-[2-[4-(4-pyridyl)-piperazin-1-yl]acetyl]piperidin-4-yl]propanoate (50mg), concentrated hydrochloric acid (1ml) and dioxan (4ml) was stirred at 50-60°C for 1 hour, then concentrated to give a foam which was triturated with hot isopropanol. Filtration gave the title compound (48mg) as pale cream prisms, m.p. 188-190°C. NMR (d_6DMSO+d_4AcOH): δ 1.0-1.3(2H,m); 1.5-1.6(3H,m); 1.8(2H,d); 2.3(2H,t); 2.6-2.8(1H,m); 2.95-3.15(1H,m); 3.5(4H,br.s); 3.6-3.7(1H,m); 4.0-4.2(4H,br.s); 4.3-4.5(3H,m); 7.25(2H,d); 8.35(2H,d); m/e 361$(M+H)^+$; calculated for $C_{19}H_{28}N_4O_3$. 2HCl. H_2O: C, 50.6; H, 7.2; N, 12.4; H_2O, 4.0; found: C, 50.3; H, 7.2; N, 12.2; H_2O, 4.0%.

The starting material was prepared as follows.

(i) Diethylazodicarboxylate (24.6ml) was added dropwise to a stirred solution of triphenylphosphine (39.3g) in THF (120ml) at 0°C under argon. The mixture was stirred for 20 minutes, then treated sequentially with lithium bromide (26.1g) and a solution of 1-benzyloxycarbonylpiperidine-4-ol (7.1g) in THF (50ml). The mixture was allowed to warm to room temperature and stirring was continued for 1 hour. The mixture was concentrated, the residue treated with ether (100ml) and silica (60ml), and the solvent was evaporated under reduced pressure. The resulting powder was added to the top of a flash column and the column was eluted with hexane/ether (4:1) to give 1-benzyloxycarbonyl-4-bromopiperidine (3.6g) as a colourless oil. NMR: ($CDCl_3$): δ, 1.8-2.0(2H,m); 2.0-2.2(2H,m); 3.3-3.5(2H,m); 3.6-3.8(2H,m); 4.35(1H,m); 5.1(2H,s); 7.3(5H,m). m/e 298/300$(M+H)^+$; 320/322$(M+Na)^+$.

(ii) A solution of the product of step (i) (2.6g) in toluene (100ml) was stirred at 95°C under argon and treated with a solution of tributyltin hydride (5.9ml) in toluene (50ml), added via a syringe pump over 6 hours. Samples of ethyl acrylate (4.7ml each) and azoisobutyronitrile (10mg) were added at periods of 0h, 2h and 4h after the addition of the tin hydride. The mixture was cooled, concentrated and purified by flash column chromatography, eluting with hexane/ethyl acetate (4:1) to give ethyl 3-(1-benzyloxycarbonyl) piperidin-4-yl)propanoate (1.7g). NMR: (d_6DMSO): δ 0.9-1.1(2H,m); 1.15(3H,t); 1.3-1.5(3H,m); 1.6-1.7(2H,m); 2.3(2H,t); 2.6-2.8(2H,br.t); 3.9-4.1(2H, br.t + 2H,q); 5.05(2H,s); 7.3(5H,m). m/e 320 $(M+H)^+$, 342$(M+Na)^+$,

and ethyl 3-(1-benzyloxycarbonylpiperidin-4-yl)-2-(2-ethoxycarbonylethyl)propanoate (0.7g) NMR: (d_6DMSO): δ, 1.2(6H,2t); 1.0-1.8(9H,m); 2.3(2H,t); 2.45(1H,m); 2.6-2.9(2H,br.t): 3.8-4.0(2H,br.t); 4.0-4.2(4H,2q); 5.05(2H,s); 7.3(5H,m); m/e 420$(M+H)^+$, 442$(M+Na)^+$.

(iii) In a similar manner to that described in Example 103, ethyl 3-(1-benzyloxycarbonylpiperidin-4-yl)propanoate was converted to ethyl 3-[1-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]piperidin-4-yl]propanoate. The following intermediates were isolated:

ethyl-1-bromoacetylpiperidin-4-ylpropanoate. NMR($CDCl_3$): δ, 1.1-1.4(2H,m); 1.25(3H,t); 1.5-1.7(3H,m); 1.7-1.9(2H,t); 2.3(2H,t); 2.5-2.7(1H,td); 3.0-3.2(1H,td); 3.8-4.0(2H,d + 1H,m); 4.15(2H,q); 4.55(1H,m); m/e 306/308$(M+H)^+$,

ethyl 3-[1-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]piperidin-4-yl]propanoate. m.p. 90-92°C; NMR(d_6DMSO): δ, 0.85-1.0(1H,m); 1.05-1.2(1H,m); 1.2(3H,t); 1.5(3H,m); 1.7(2H,m); 2.3(2H,t); 2.5(4H,br.s); 2.8-3.0(1H,t); 3.1(1H,d); 4.05(2H,q + 1H,m); 4.3(1H,d); 6.8(2H,d); 8.15(2H,d); m/e 389 $(M+H)^+$ 411 $(M+Na)^+$; calculated for $C_{21}H_{32}N_4O_3$; C, 64.9; H, 8.3; N, 14.4; found: C, 65.0; H, 8.5; N, 14.4%.

EXAMPLE 110: Ethyl 2RS-(n-butylsulphonylamino)-3-[1-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]piperidin-4-yl]propanoate

A mixture containing ethyl (2-n-butylsulphonylamino)-3-[1-(2-bromoacetyl)piperidin-4-yl]propanoate (330mg), 1-(4-pyridyl)piperazine (150mg), triethylamine (0.13ml) and acetonitrile (20ml) was stirred for 16 hours. The mixture was concentrated and the residue was dissolved in ethyl acetate (50ml). The solution was washed with water (2 x 20ml) and saturated aqueous sodium chloride (20ml), dried ($MgSO_4$) and concentrated. The residue was dissolved in ethanol (20ml), treated with decolourising charcoal, filtered and concentrated to give the title compound (136mg) as a colourless glass. NMR (d_6DMSO+d_4AcOH): δ 0.8(3H,t); 1.0(1H,m); 1.1(3H,t); 1.3(2H,m); 1.5-1.8(8H,m); 2.9(4H,m); 3.2(4H,br.s); 3.65(1H,m); 3.8-4.1(4H,br.s + 3H,m +2H,q); 4.35(1H,m); 7.1(2H,d); 8.1(2H,d); m/e 524$(M+H)^+$.

The starting material was prepared as follows:

(i) A solution of methanesulphonylchloride (7.7ml) in dichloromethane (50ml) was added dropwise to a stirred solution of 1-benzyloxycarbonyl-4-hydroxymethylpiperidine (23.4g) in dichloromethane (350ml) cooled to 5°C. Stirring was continued for 1 hour, then the solution was washed with water (4 x 150ml) and saturated aqueous sodium chloride (100ml), dried and concentrated. The residue was crystallised from tetrachloromethane (250ml) to give 1-benzyloxycarbonyl-4-methanesulphonyloxymethylpiperidine (20g) as colourless prisms, m.p. 72-74°C. NMR ($CDCl_3$): δ 1.1-1.4(2H,m); 1.7-1.8(2H,d); 1.9-2.1(1H,m); 2.7-2.9(2H,t); 3.0(3H,s); 4.05(2H,d); 4.1-4.4(2H,d); 5.1(2H,s); 7.3(5H,m); m/e 328$(M+H)^+$ 350 $(M+Na)^+$; calculated for $C_{15}H_{21}N_5O_5$: C, 55.0; H, 6.5; N, 4.3; found: C, 54.8; H, 6.6; N, 4.2%.

(ii) A mixture containing triethylbenzylammonium bromide (0.3g), the product of step (i) (3.27g), ethyl N-diphenylmethylidene glycine ester (3.0g), potassium carbonate (4.2g) and acetonitrile (45ml) was heated under reflux for 48 hours, concentrated, and the residue was partitioned between ethyl acetate (100ml) and water (100ml). The ethyl acetate fraction was washed with water (2 x 50ml) and saturated

aqueous sodium chloride (50ml), dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography, eluting with hexane/ether (3:1) to give ethyl 2RS-(diphenylmethylidene amino)-3-(1-benzyloxycarbonylpiperidin-4-yl)propanoate (650mg) as a pale yellow oil. NMR(d_6DMSO): δ 0.8-1.6(5H,m); 1.2(3H,t); 1.8(2H,t); 2.6-2.8(2H,m); 3.8-4.0(3H,m); 4.1(2H,q); 5.05(2H,s); 7.1-7.6(15H,m); m/e 499$(M+H)^+$; 421$(M+Na)^+$.

(iii) A mixture of the product of step (ii) (1.1g), saturated hydrogen chloride in ether solution (15ml) and ethanol (50ml) was allowed to stand for 1 hour. The solution was concentrated and the residue was stirred with ether (30ml) to give a colourless solid. The solid was filtered off, washed with ether (30ml) and dried to give ethyl 2RS-amino-3-(1-benzyloxycarbonylpiperidin-4-yl)propanoate hydrochloride (700mg) as a colourless solid which was used without further purification. A sample (50mg) was recrystallised from ethyl acetate (10ml) to give colourless prisms (30mg), m.p. 122°. NMR(d_6DMSO): δ 0.9-1.1(2H,br.m); 1.25(3H,t); 1.6-1.8(5H,br.m); 2.6-2.9(2H,br.m); 3.9-4.1(3H,br.m); 4.2(2H,dq); 5.1(2H,s); 7.3(5H,m); 8.4-8.7(3H,br.s); m/e 335$(M+H)^+$; calculated for $C_{18}H_{26}N_2O_4$. HCl: C, 58.3; H, 7.3; N, 7.6; found: C, 58.2; H, 7.7; N, 7.5%.

(iv) A mixture of the product of step (iii) (650mg), n-butylsulphonylchloride (0.25ml), triethylamine (0.55ml) and dichloromethane (30ml) was stirred for 4 hours at room temperature, then diluted with dichloromethane (50ml), washed with water (3 x 50ml) and saturated aqueous sodium chloride (50ml), dried (PS paper) and concentrated. The residue was purified by flash column chromatography, eluting with hexane/ethyl acetate (3:1) to give ethyl 2RS-(n-butylsulphonylamino)-3-(1-benzyloxycarbonyl-piperidin-4-yl)propanoate (400mg) as a colourless gum. NMR (d_6DMSO): δ 0.9(3H,t); 1.0-1.2(2H,m); 1.25(3H,t); 1.3-1.5(2H,m); 1.5-1.8(7H,m); 2.6-2.9(2H,m); 2.8-3.1(2H,m); 3.8-4.1(3H,m); 4.15(2H,q); 5.1(2H,s); 7.3(5H,m); 7.7(1H,d); m/e 455 $(M+H)^+$; 477$(M+Na)^+$.

In a similar manner to that described in Example 103, the carbonyl-protected piperidine was converted to the N-bromoacetyl analogue, which was isolated as a colourless gum and used without further purification.

EXAMPLE 111: 2-RS-(n-butylsulphonylamino)-3-[1-[2-[4-(4-pyridyl)-piperazin-1-yl]acetyl]piperidin-4-yl]propanoic acid.

A mixture of the product of Example 110 (50mg), concentrated hydrochloric acid (1ml) and dioxan (4ml) was stirred at 50°C for one hour, then concentrated, triturated with acetone and dried under vacuum. The residual solid was stirred with dioxan (3ml) and concentrated hydrochloric acid (2ml) at 70°C for 1 hour then concentrated and dried under vacuum to give the title compound (34.3mg) as a pale yellow solid. NMR(d_6DMSO + d_4 AcOH): δ, 0.8(3H,t); 1.0-1.2(1H,m); 1.3(2H,m); 1.5-1.8(8H,m); 2.8-3.0(4H,m); 3.4-3.6(6H,m); 4.0(4H,br.s); 4.1-4.4(3H,m); 7.1(2H,d); 8.1(2H,d); m/e 496 $(M+H)^+$; 518 $(M+Na)^+$.

EXAMPLE 112: 3-[1-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-piperidin-4-yl]-3-[2-(2-carboxyethyl)]propanoic acid

A mixture containing ethyl 3-[1-[2-[4-(4-pyridyl)-piperazin-1-yl]acetyl]piperidin-4-yl]-3-[2-(2-ethoxycarbonylethyl)]-propanoate, concentrated hydrochloric acid (2ml) and dioxan (3ml) was stirred at 70°C for 1 hour, concentrated and dried under vacuum. The residue was triturated with acetone and redried to give the title compound (52mg) as a pale yellow foam. NMR(d_6DMSO + d_4AcOH); δ, 0.9-1.1(1H,m); 1.2-1.3(1H,m); 1.5(3H,m); 1.7(2H,t +2H,m); 2.2(2H,t); 2.35(1H,m); 2.6(1H,m); 2.7-3.0(2H,m); 3.2(1H,m); 3.5(4H,m); 4.0(4H,m); 4.8(2H,d); 7.1(2H,d); 8.2(2H,d); m/e 433$(M+H)^+$.

The starting material was prepared as a pale yellow gum from ethyl 3-(1-benzyloxycarbonylpiperidin-4-yl)-2-(2-ethoxycarbonylethyl)-propanoate using a similar procedure to that described for the monoester in Example 109.

EXAMPLE 113: 4-[4-[(4-dimethylaminopyrid-3-yl)methoxy]-phenoxy]butanoic acid

A mixture containing ethyl 4-[4-[(4-dimethylaminopyrid-3-yl)methoxy]phenoxy]butanoate (25mg), aqueous sodium hydroxide (1M, 0.2ml), methanol (0.5ml) and water (0.5ml) was stirred for 3 hours then neutralised with hydrochloric acid (1M, 0.2ml) and concentrated. The residue was dissolved in dichloromethane (5ml), filtered, and the filtrate was concentrated to give the title compound (17mg) as a colourless gum. NMR (d_6DMSO + d_4AcOH): δ 2.0(2H,q); 2.4(2H,t); 3.35(6H,s); 3.95(2H,t); 5.1(2H,s); 6.8-7.0(4H, dd + 1H,m); 8.15(1H,dd); 8.3(1H,d); m/e 331$(M+H)^+$.

The starting material was prepared as follows:-

(i) A solution of 4-dimethylaminopyridine-3-carboxaldehyde (J. Het. Chem, 25, 81) (1.5g) in ethanol (25ml) was treated with sodium borohydride (200mg) and the mixture was stirred for 4 hours. Concentrated hydrochloric acid (1ml) was added and the mixture was concentrated. The residue was treated with saturated aqueous sodium chloride (40ml) and concentrated aqueous sodium hydroxide (2ml) and the mixture was extracted with dichloromethane (4 x 20ml). The combined organic extracts were washed with saturated aqueous sodium chloride (40ml), dried (PS paper) and concentrated. The residue was dissolved in methanol, treated with decolourising charcoal, filtered and concentrated to give 4-dimethylaminopyridine-3-methanol (1.1g) as a pale yellow oil. NMR: (d_6DMSO): δ 2.9 (6H,s); 4.5(2H,s); 4.0-4.8(1H,br.s); 6.7(1H,d); 8.15(1H,d); 8.3(1H,s); m/e 153 $(M+H)^+$; 135$(M+H-H_2O)^+$.

(ii) A mixture containing the product of step (i) (300mg), ethyl 4-(4-hydroxyphenoxy)butanoate (450mg), triphenylphosphine (0.58g) and dichloromethane (5ml) was stirred for 30 minutes then treated dropwise with diethylazodicarboxylate (0.35ml). The mixture was stirred for 2 hours then diluted with ether (50ml), washed with water (2 x 25ml) and saturated aqueous sodium chloride (25ml), dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography eluting with ethanol/dichloromethane (3:97) to give ethyl 4-[4-(4-dimethylaminopyrid-3-yl)methoxy]phenoxybutanoate (200mg) as a

colourless solid. NMR(d_6DMSO + d_4 AcOH); δ 1.1(3H,t); 1.9(2H,q); 2.3(2H,t); 3.2(6H,s); 3.8(2H,t); 3.95(2H,q); 5.0(2H,s); 6.7-6.9(2H,d + 1H d + 2H,d); 8.0(1H,dd); 8.15(1H,d); m/e 359 $(M+H)^+$.

EXAMPLE 114: Methyl 3-[4-(4-dimethylaminopyrid-3-yl)methoxyphenoxy]-2-benzyloxycarbonylaminopropanoate

A stirred mixture containing 4-dimethylaminopyridine-3-methanol (700mg), triphenylphosphine (1.3g), N-benzyloxycarbonyltyrosine methyl ester (1.66g) and THF (50ml) was treated dropwise with diethylazodicarboxylate (1.3g) and the mixture was stirred for 4.5 hours and concentrated. The residue was purified by flash column chromatography eluting with methanol/dichloromethane (first 1:99, then 2:98) to give the title compound (900mg) as a colourless foam. NMR(d_6DMSO): δ 2.7-3.1(2H,m); 2.9(6H,s); 3.6(3H,s); 4.2(1H,m); 4.95(2H,s); 5.05(2H,s); 6.8(1H,d); 6.9(2H,d); 7.15(2H,d); 7.2-7.4(5H,m); 7.75(1H,d); 8.3(1H,s); m/e 464$(M+H)^+$.

EXAMPLE 115: N-[1-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]piperidin-4-ylmethyl]-1-butanesulphonamide

A mixture containing 4-n-butylsulphonylaminomethyl-N-bromoacetylpiperidine (250mg), 1-(4-pyridyl)piperazine (125mg), triethylamine (0.11ml) and acetonitrile (10ml) was stirred for 16h and concentrated. The residue was purified by flash column chromatography, eluting with dichloromethane/methanol/triethylamine (95:5:0.5), to give a colourless solid (280mg). The solid was dissolved in water (5ml) and extracted with ethyl acetate (3 x 5ml). The combined organic extracts were washed with saturated aqueous sodium chloride (5ml), dried ($MgSO_4$) and concentrated to give the title compound (90mg) as a colourless oil. NMR(d_6DMSO + d_4 AcOH): δ 0.8(3H,t); 1.4(2H,m); 0.9-1.8(2H,m + 2H,m + 2H,m + 1H,m); 2.6(1H,t); 2.7-3.0(2H,d + 2H,m + 1H,t); 3.3(4H,br.s); 3.6(1H,br.d); 3.9(4H,br.s); 3.9-4.2(2H,dd); 4.3(1H,br.d); 7.1(2H,d); 8.15(2H,d); m/e 438$(M+H)^+$.

The starting material was prepared as follows:-

(i) A solution of n-butylsulphonamide (500mg) in DMF (5ml) was added dropwise to a suspension of sodium hydride (150mg, 60% dispersion in mineral oil) in DMF (10ml) and the mixture was stirred for 10 minutes. 4-Methanesulphonyloxymethyl-N-benzyloxy-carbonylpiperidine (1.09g) was added and the mixture heated at 80°C for 16 hours. The mixture was cooled, poured into water (100ml) and extracted with ethyl acetate (3 x 50ml). The combined organic extracts were washed with water (3 x 50ml) and saturated aqueous sodium chloride (50ml), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography, eluting with methanol/dichloromethane (1:99) to give a colourless semi-solid. This mixture was dissolved in warm tetrachloromethane (6ml) and cooled to give 4-n-butylsulphonylaminomethyl-N-benzyloxycarbonylpiperidine (230mg) as colourless prisms, mp 83-85°C. NMR (d_6DMSO): δ 0.9(3H,t); 0.9-1.1(2H,m); 1.3-1.5(2H,m); 1.5-1.8(5H,m); 2.7-2.9(4H,m); 2.95(2H,m); 4.0(2H,d); 5.1(2H,s); 7.0(1H,t); 7.3(5H,m). m/e 369$(M+H)^+$; 391$(M+Na)^+$; calculated for $C_{18}H_{28}N_2SO_4$: C, 58.7; H, 7.7; N, 7.6; found: C, 58.5; H, 7.8; N, 7.6%.

The N-benzyloxycarbonyl-protected piperidine was converted to the N-bromoacetyl analogue using a similar procedure to that described in Example 103. The N-bromoacetyl compound was used immediately in the preparation of product.

EXAMPLE 116 : Methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-2,6-dichlorophenoxyacetate.

Prepared in a similar manner to Example 5, but starting from methyl 4-bromoacetyl-2,6-dichlorophenoxyacetate, however stirring for only 6 hours and purification by flash chromatography on silica, eluting first with dichloromethane then successively 2,3,4 and 5% v/v methanol/dichloromethane. Concentration of the fractions in vacuo and recrystallisation of the residue from methanol gave the title compound in 24% yield as a pale orange solid: m.p. 149-150°C;
NMR (d_6DMSO) δ 8.14 (2H, d), 8.06 (2H, s), 6.81 (2H, d), 4.82 (2H, s), 4.05 (0.5H, b), 3.94 (2H, s), 3.73 (3H, s), 3.32 (4H, t), 3.18 (1.5H, s), 2.64 (4H, t); m/e 438 $(M+H)^+$, 2xCl pattern;

calculated for $C_{20}H_{21}Cl_2N_3O_4.0.5CH_3OH$: C, 54.1; H, 5.1; N, 9.2. found: C, 53.7; H, 5.4; N, 8.9%.

The starting material was prepared as follows:-

(i) Sodium hydride (50% w/w dispersion in mineral oil, 1.32 g) was treated under argon with repeated washes of hexane. The oil-free residue was suspended in dry DMF (10 ml) and, with stirring and cooling (ice-bath), a solution of 3,5-dichloro-4-hydroxyacetophenone (5.13 g) in dry DMF (15 ml) was added dropwise. Stirring was continued for 30 minutes when methyl bromoacetate (3.06 ml) was added dropwise and stirring was continued for a further 18 hours at ambient temperature. The reaction mixture was added to water, the mixture was extracted twice with ethyl acetate, the organic phases dried ($MgSO_4$), filtered and then evaporated. The residue, after recrystallisation from hexane (250 ml), gave methyl 4-acetyl-2,6-dichlorophenoxyacetate, 4.25 g, as white crystals: NMR (d_6DMSO) δ 8.00 (2H, s), 4.80 (2H, s), 3.73 (3H, s), 2.59 (3H, s).

(ii) A solution of bromine (0.77 ml) in chloroform (10 ml) was added dropwise over 15 minutes to a stirred solution of the product from step (i) (4.16 g) in chloroform (40 ml) at 25°C. The temperature was raised to 40°C for 1 hour and then stirring continued for a further 18 hours at ambient temperature. The solvent was removed in vacuo and the residual oil purified by flash chromatography on silica, eluting with dichloromethane, to give a crystalline solid. Recrystallisation from methanol gave methyl 4-bromoacetyl-2,6-dichlorophenoxyacetate, 1.88 g, as white crystals: m.p. 89-90°C; NMR (d_6DMSO) δ 8.06 (2H, s), 4.93 (2H, s), 4.82 (2H, s), 3.72 (3H, s); m/e 355/357 $(M+H)^+$, 1 Br pattern; calculated for $C_{11}H_9BrCl_2O_4$: C, 37.1; H, 2.3. found: C, 36.8; H, 2.4%.

EXAMPLE 117 : Methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-1-naphthoxyacetate.

Prepared in a similar manner to Example 5, but starting from methyl 4-bromoacetylnaphthoxyacetate and purification by flash chromatography on silica, eluting with dichloromethane then increasing

concentrations of methanol to 5% v/v methanol/dichloromethane. Trituration with ether gave the title compound in 13% yield, as a solid: m.p. 140-142°C; NMR (d_6DMSO) δ 8.70 (1H, dd), 8.32 (1H, dd), 8.23 (1H, d), 8.16 (2H, bd), 7.64 (2H, m), 7.00 (1H, d), 6.80 (2H, d), 5.14 (2H, s), 3.92 (2H, s), 3.75 (3H, s), 3.31 (4H, t), 2.67 (4H, t); m/e 420 $(M+H)^+$; calculated for $C_{24}H_{25}N_3O_4 \cdot 0.25\ H_2O$: C, 67.9; H, 6.0; N, 9.9. found: C, 67.8; H, 6.0; N, 9.7%.

The starting material was prepared as follows:-

(i) In a similar manner to Example 116 step (i), but starting from 4-acetyl-1-naphthol, there was obtained methyl 4-acetyl-1-naphthoxyacetate in 62% yield as a white crystalline solid: m.p. 123-125°C; NMR (d_6DMSO) δ 8.89 (1H, dd), 8.31 (1H, dd), 8.19 (1H, d), 7.63 (2H, m), 7.00 (1H, d), 5.14 (2H, s), 3.76 (3H, s), 2.68 (3H, s); m/e 259 $(M+H)^+$; calculated for $C_{15}H_{14}O_4$: C, 69.8; H, 5.5. found: C, 69.7; H, 5.4%.

(ii) A mixture of the product from step (i) above (2.0 g) and cupric bromide (3.45 g) in ethyl acetate (35 ml) was heated at reflux temperature for 24 hours. On cooling, the mixture was filtered, concentrated in vacuo and the residue purified by flash chromatography on silica eluting with dichloromethane. Evaporation of the fractions gave methyl 4-bromoacetyl-1-naphthoxyacetate as a white solid: m.p. 99-101°C; NMR (d_6DMSO) δ 8.73 (1H, d), 8.34 (1H, d), 8.26 (1H, d), 7.59 to 7.82 (2H, m), 7.02 (1H, d), 5.15 (2H, s), 4.97 (2H, s), 3.76 (3H, s); m/e 337/339 $(M+H)^+$, 1 Br pattern.

EXAMPLE 118 : Methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-3-methylphenoxyacetate.

In a similar manner to Example 5, but starting from methyl 4-bromoacetyl-3-methylphenoxyacetate and with purification by flash chromatography on silica, eluting with 0 to 5% v/v methanol/dichloromethane, and then by flash chromatography on neutral alumina, eluting first with dichloromethane and then 1% v/v methanol/dichloromethane there was obtained the title compound in 9%

yield as a yellow oil: NMR (d_6DMSO) δ 8.15 (2H, d), 7.38 (1H, d), 6.82 (4H, m), 4.88 (2H, s), 3.75 (2H, s), 3.71 (3H, s), 3.32 (4H, t), 2.61 (4H, t), 2.43 (3H, s), m/e 384 $(M+H)^+$; calculated for $C_{21}H_{25}N_3O_4.0.5H_2O.0.1\ CH_2Cl_2$: C, 63.1; H, 6.5; N, 10.5. found: C, 62.6; H, 6.6; N, 10.2%.

The starting material was prepared as follows:-

(i) A mixture of 4-hydroxy-2-methylacetophenone (4.8 g), anhydrous potassium carbonate (5.3 g) and methyl bromoacetate (3.55 ml) in anhydrous acetone (100 ml) was stirred for 2 days. The mixture, after filtration and evaporation of the solvent, gave methyl 4-acetyl-3-methylphenoxyacetate, 6.6 g, as a crystalline solid: m.p. 49-50°C; NMR (d_6DMSO) δ 7.84 (1H, d), 6.83 (2H, m), 4.87 (2H, s), 3.71 (3H, s), 2.50 (3H, s), 2.45 (3H, s).

(ii) Prepared in a similar manner to Example 117 step (ii), but starting from the product of (i) above and purification by flash chromatography on silica eluting with 10 to 17.5% v/v ethyl acetate/hexane. Recrystallisation from ethanol gave methyl 4-bromoacetyl-3-methylphenoxyacetate, in 35% yield, as white needles: NMR (d_6DMSO) δ 7.90 (1H, d), 6.90 (1H, s), 6.88 (1H, d), 4.90 (2H, s), 4.78 (2H, s), 3.71 (3H, s), 2.43 (3H, s).

EXAMPLE 119 : Methyl 3-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-phenoxyacetate.

Prepared in a similar manner to Example 5, but starting from methyl 3-bromoacetylphenoxyacetate and with purification by flash chromatography on silica, eluting with 10% v/v methanol/dichloromethane. Trituration with ether gave the title compound in 20% yield: m.p. 114-116°C; NMR (d_6DMSO) δ 8.15 (2H, b), 7.61 (1H, dd), 7.50 (1H, m), 7.43 (1H, t), 7.21 (1H, dd), 6.83 (2H, d), 4.87 (2H, s), 3.91 (2H, s), 3.70 (3H, s), 3.35 (4H, t), 2.64 (4H, t); m/e 370 $(M+H)^+$; calculated for $C_{20}H_{23}N_3O_4.0.5H_2O$: C, 63.5; H, 6.4; N, 11.1. found: C, 63.5; H, 6.5; N, 10.6%.

The starting material was prepared as follows:-

(i) In a similar manner to Example 116 step (ii), but starting from the methyl 3-acetylphenoxyacetate and purification by flash chromatography on silica, eluting with ethyl acetate/hexane (1:1 v/v) there was obtained methyl 3-bromoacetylphenoxyacetate in 64% yield as a pale fawn solid: NMR ($CDCl_3$) δ 7.61 (1H, d), 7.50 (1H, m), 7.43 (1H, t), 7.20 (1H, dm), 4.70 (2H, s), 4.44 (2H, s), 3.82 (3H, s); m/e 287/289 $(M+H)^+$, 1 Br pattern.

EXAMPLE 120 : Mixture of methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]-acetyl]-2-methylphenoxyacetate and ethyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-2-methylphenoxyacetate (3:2).

A mixture of methyl 4-acetyl-2-methylphenoxyacetate (3.33 g) and cupric bromide (7.0 g) in ethyl acetate (50 ml) was heated on a steam bath for 18 hours. After filtration, the solvent was evaporated and the residual solid purified by flash chromatography on silica eluting with 10% v/v ethyl acetate/hexane to give an off-white solid. Recrystallisation from ethanol gave white needles, 2.37 g, shown by NMR (d_6DMSO) to be a mixture of methyl 4-bromoacetyl-2-methylphenoxy-acetate and ethyl 4-bromoacetyl-2-methylphenoxyacetate which was used without further purification. The mixture (2.25 g) was added portionwise to a stirred solution of 1-(4-pyridyl)piperazine (2.45 g) in acetonitrile (50 ml) and the mixture stirred for 18 hours. The reaction mixture was filtered and the filtrate evaporated to give an orange oil. Purification by flash chromatography on silica eluting with dichloromethane then 1 to 3% v/v methanol/dichloromethane gave the title mixture of compounds, 0.87 g, as a solid: m.p. 136-138°C; NMR (d_6DMSO) δ 8.04 (2H, d), 7.85 (1H, d), 7.82 (1H, s), 6.95 (1H, d), 6.81 (2H, d), 4.96 and 4.93 (2H, s,s), 4.18 (0.7H, q), 3.84 (2H, s), 3.72 (1.7H, s), 3.30 (4H, t), 2.60 (4H, t), 2.25 (3H, s), 1.21 (1.3H, t). [Ratio of methyl to ethyl ester 3:2]; m/e 384 $(M+H)^+$ for methyl ester, 398 $(M+H)^+$ for ethyl ester; calculated for $C_{21}H_{25}N_3O_4$: $C_{22}H_{27}N_3O_4$ (3:2): C, 66.1; H, 6.6; N, 10.8. found: C, 65.8; H, 6.7; N, 10.5%.

The starting material was prepared as follows:-
(i) A mixture of 4-hydroxy-3-methylacetophenone (5 g), methyl bromoacetate (3.70 ml) and anhydrous potassium carbonate (5.52 g) in acetone (100 ml) was stirred for 66 hours. The mixture was filtered and the filtrate evaporated to give an oil which crystallised on standing giving methyl 4-acetyl-2-methylphenoxyacetate, 7.2 g: m.p. 51-53°C; NMR (d_6DMSO) δ 7.79 (1H, s), 7.77 (1H, d), 6.94(1H,d), 4.93 (2H, s), 3.71 (3H, s), 2.50 (3H, s + DMSO), 2.24 (3H, s).

EXAMPLE 121 : Mixture of methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]-acetyl]-3-methoxyphenoxyacetate and ethyl4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-3-methoxyphenoxyacetate (3:1).

In a similar manner to Example 120, but starting from methyl 4-acetyl-3-methoxyphenoxyacetate there was prepared, after flash chromatography on silica eluting with dichloromethane, a mixture of methyl 4-bromoacetyl-3-methoxyphenoxyacetate and ethyl 4-bromoacetyl-3- methoxyphenoxyacetate in 60% yield: m.p. 84-86°C. Treatment of this mixture, as in Example 120, followed by chromatography on silica eluting with 1 to 5% v/v methanol/dichloromethane gave the title mixture of compounds in 24% yield as a solid: NMR (d_6DMSO) δ 8.13 (2H, d), 7.63 (1H, d), 6.80 (2H, d), 6.67 (1H, d), 6.59 (1H, dd), 4.90 and 4.88 (2H, 2s), 4.18 (0.5, q), 3.88 (3H, s), 3.75 (2H, s), 3.71 (2.3H, s), 3.32 (4H, t), 2.62 (4H, t), 1.22 (0.7 H, t) [Ratio of methyl to ethyl ester 3:1]; m/e 400 $(M+H)^+$ for methyl ester, 414 $(M+H)^+$ for ethyl ester; calculated for $C_{21}H_{25}N_3O_5$: $C_{22}H_{27}N_3O_5$ (3:1): C, 63.3; H, 6.5; N, 10.4. found C, 63.1; H, 6.5; N, 10.3%.

The starting material was prepared as follows:-

(i) In a similar manner to Example 120 step (i), but starting from 4-hydroxy-2-methoxy-acetophenone there was obtained, after evaporation of the solvent and trituration with diethyl ether, methyl 4-acetyl-3-methoxyphenoxyacetate in 91% yield as a white solid: m.p. 95-96°C; NMR (d_6DMSO) δ 7.64 (1H, d), 6.70 (1H, d), 6.60 (1H, dd), 4.91 (2H, s), 3.89 (3H, s), 3.72 (3H, s), 2.49 (3H, s).

EXAMPLE 122 : Mixture of dimethyl 2,2′-[4-[2-[4-(4-pyridyl)piperazin--1-yl]acetyl]-phenylene-1,3-dioxy]diacetate and diethyl 2,2′-[4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenylene-1,3-dioxy]-diacetate(1:1).

In a similar manner to Example 120, but starting from dimethyl 2,2′-[(4-acetyl)phenylene-1,3-dioxy]diacetate there was prepared, after flash chromatography on silica eluting with dichloromethane, a mixture of dimethyl 2,2′-[(4-bromoacetyl)phenylene-1,3-dioxy]diacetate and diethyl 2,2′-[(4-bromoacetyl)phenylene-1,3-dioxy] diacetate in 28% yield. Treatment of the mixture, as in Example 120, followed by chromatography on silica eluting with 1 to 5% v/v methanol/dichloromethane gave the title mixture of compounds in 44% yield as a solid: NMR (d_6DMSO) δ 8.14 (2H, d), 7.63 (1H, d), 6.82 (2H, d), 6.65 (2H, d), 4.96 and 4.93 (2H, 2s), 4.49 and 4.47 (2H, 2s), 4.20 (2H, m), 3.91 (2H, s), 3.75 and 3.71 (3H, 2s), 3.32 (4H + H_2O), 2.61 (4H, t), 1.23 (3H, m) [Ratio of methyl to ethyl esters 1:1]; m/e 458 $(M+H)^+$ for dimethyl ester and 486 $(M+H)^+$ for diethyl ester; calculated for $C_{23}H_{27}N_3O_7$: $C_{25}H_{31}N_3O_7$ (1:1). H_2O:C,60.0; H, 6.3; N, 8.7. found: C, 60.3; H, 6.2; N, 8.5%.

The starting material was prepared as follows:-

(i) In a similar manner to Example 120 step (i), but starting from 2,4-dihydroxy- acetophenone and using 2.4 equivalents of methyl bromoacetate and 2.4 equivalents of anhydrous potassium carbonate there was obtained, after evaporation and trituration with diethyl ether/hexane (1:1 v/v), dimethyl 2,2′- [(4-acetyl)phenylene-1,3-dioxy]diacetate in 82% yield as a white solid: m.p. 119-120°C; NMR (d_6DMSO) δ 7.64 (1H, d), 6.56 (2H, m), 4.99 (2H, s), 4.90 (2H, s), 3.73 (3H, s), 3.71 (3H, s), 2.57 (3H, s).

EXAMPLE 123 : 4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]-2,6-dichlorophenoxyacetic acid, dihydrochloride.

A solution of the product of Example 116 (190 mg) in dioxane (1.7 ml) was treated with 1N hydrochloric acid (1.7 ml) and the mixture heated at 100°C for 1.5 hours. The mixture was cooled, diluted with water and freeze-dried. The solid residue, on treatment with a small volume of ethanol, gave the title compound, 120 mg, as a white solid: m.p. 174-176°C; NMR (D_2O) δ 8.42 (2H, d), 8.26 (2H, s), 7.41 (2H, d), 5.24 (2H, s), 4.98 (2H, s), 4.34 (4H, t), 3.90 (4H, t); m/e 424 $(M+H)^+$, 2xCl pattern; calculated for $C_{19}H_{19}Cl_2N_3O_4.2HCl.H_2O$: C, 44.4; H, 4.5; N, 8.2. found: C, 44.8; H, 4.2; N, 8.1%.

EXAMPLES 124 to 129

In a similar manner to Example 123, but starting from the product of Examples 117 to 122 the following compounds were prepared:-

EXAMPLE 124 : 4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]naphthoxyacetic acid, dihydrochloride.

The title compound was prepared from the product of Example 117 in 84% yield: m.p. 253-255°C; NMR (D_2O) δ 9.16 (1H, d), 8.63 (1H, d), 8.42 (2H, d), 8.28 (1H, d), 8.00 (1H, t), 7.78 (1H, t), 7.41 (2H, d), 7.08 (1H, d), 5.27 (2H, s), 5.15 (2H, s), 4.34 (4H, bs), 3.94 (4H, bs); m/e 406 $(M+H)^+$; calculated for $C_{23}H_{23}N_3O_4.2HCl.0.5H_2O$: C, 56.7; H, 5.4; N, 8.6. found: C, 56.8; H, 5.6; N, 8.1%.

EXAMPLE 125 : 4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]-3-methylphenoxyacetic acid, dihydrochloride.

The title compound was prepared from the product of Example 118 in 78% yield: m.p. 242-244°C; NMR (D_2O) δ 8.38 (2H, d), 8.00 (1H, d), 7.36 (2H, d), 7.14 (1H, s), 7.10 (1H, d), 5.12 (2H, s), 4.97 (2H, s), 4.30 (4H, bs), 3.84 (4H, bs), 2.75 (3H, s); m/e 370 $(M+H)^+$; calculated for $C_{20}H_{23}N_3O_4.2HCl.0.5H_2O$: C, 53.4; H, 5.3; N, 9.3. found C, 53.2; H, 5.8; N, 8.8%.

EXAMPLE 126 : 3-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]phenoxyacetic acid, dihydrochloride.

The title compound was prepared from the product of Example 119 in 57% yield: m.p. 190-193°C; NMR (D_2O) δ 8.41 (2H, d), 7.86 (1H, dt), 7.75 (1H, t), 7.72 (1H, t), 7.57 (1H, dm), 7.40 (2H, d), 5.26 (2H, s), 4.98 (2H, s), 4.98 (2H, s), 4.32 (4H, bs), 3.89 (4H, t); m/e 356 $(M+H)^+$; calculated for $C_{19}H_{21}N_3O_4.2HCl.0.75H_2O$: C, 51.7; H, 5.6; N, 9.5. found: C, 51.6; H, 5.8; N, 9.3%.

EXAMPLE 127 : 4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]-2-methyl-phenoxyacetic acid, dihydrochloride.

The title compound was prepared from the product of Example 120 in 98% yield: m.p. 259 to 263°C; NMR (d_6DMSO+D_2O) δ 8.46 (2H, d), 7.95 (2H, m), 7.38 (2H. d), 7.15 (1H, d), 5.17 (2H, s), 5.00 (2H, s), 4.19 (4H, s), 3.62 (4H, s), 2.39 (3H, s); m/e 370 $(M+H)^+$; calculated for $C_{20}H_{23}N_3O_4.2HCl.0.5H_2O$: C, 53.5; H, 5.8; N, 9.4. found: C, 53.6; H, 5.7; N, 9.5%.

EXAMPLE 128 : 4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]-3-methoxy-phenoxyacetic acid, dihydrochloride.

The title compound was prepared from the product of Example 121 in 69% yield: m.p. 168-170°C; NMR (d_6DMSO+d_4 acetic acid) δ 8.36 (2H, d), 7.93 (1H, d), 7.28 (2H, d), 6.76 (1H, d), 6.72 (1H, dd), 4.86 (2H, s), 4.78 (2H, s), 4.08 (4H, bs), 3.98 (3H, s), 3.54 (4H, bs); m/e 386 $(M+H)^+$; calculated for $C_{20}H_{23}N_3O_5.2HCl.2H_2O$: C, 48.7; H, 5.9; N, 8.5. found: C, 48.5; H, 5.7; N, 8.3%.

EXAMPLE 129 : 2,2'-[4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]-phenylene-1,3-dioxy]diacetic acid, dihydrochloride.

The title compound was prepared from the product of Example 122 in 79% yield: m.p. 257-258°C; NMR (D_2O) δ 8.39 (2H, d), 8.18 (1H, d), 7.48 (2H, d), 6.94 (1H, dd), 6.76 (1H, d), 5.18 (2H, s), 5.09 (2H, s), 5.01 (2H, s), 4.29 (4H, b), 3.34 (4H, b); m/e 430 $(M+H)^+$; calculated for $C_{21}H_{24}N_3O_7.2HCl.0.5H_2O$: C, 49.5; H, 5.3; N, 8.2. found C, 49.4; H, 5.3; N, 7.8%.

EXAMPLE 130 : 4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]-2,6-di-tert-butylphenoxyacetic acid.

A solution of methyl 4-(2-[4-(4-pyridyl)piperazin-1-yl]-acetyl)-2,6-di-tert-butylphenoxyacetate (24[illegible] mg) in dioxane (2.0 ml) was treated with 1N hydrochloric acid and the mixture heated at 100°C for 20 hours. The mixture was cooled, diluted with water, filtered and the filtrate freeze-dried. The solid residue was purified by flash chromatography on silica eluting with toluene/ethyl acetate/0.880 ammonia/ethanol (60:20:10:35 v/v/v/v). The fractions containing the desired product were evaporated, the residue treated with dioxane, filtered and the filtrate diluted with water and freeze dried to give a white foam, which on drying at 55°C gave the title compound, 90 mg: NMR (d_6DMSO) δ 8.16 (2H, d), 7.97 (2H, s), 6.84 (2H, d), 4.22 (2H, s), 3.86 (2H, s), 3.37 (4H, t), 2.64 (4H, t), 1.39 (18H, s); m/e 468 $(M+H)^+$; calculated for $C_{27}H_{37}N_3O_4.2H_2O$: C, 64.4; H, 8.2; N, 8.3. found C, 64.6; H, 7.9; N, 7.9%.

The starting material was prepared as follows:-

(i) In a similar manner to Example 116 step (i), but starting from 2,5-di-tert-butyl-4-hydroxyacetophenone there was obtained from the ethyl acetate extracts a brown oil. Flash chromatography on silica, eluting with successively hexane, then 2% v/v ethyl acetate/hexane and finally 5% v/v ethyl acetate/hexane gave methyl 4-acetyl-2,6-di-tert-butylphenoxyacetate in 50% yield as an oil: NMR (d_6DMSO) δ 7.84 (2H, s), 4.38 (2H, s), 3.76 (3H, s), 2.55 (3H, s), 1.40 (18H, s); m/e 321 $(M+H)^+$; calculated for $C_{19}H_{28}O_4$: C, 71.2; H, 8.8. found C, 71.5; H, 9.0%.

(ii) In a similar manner to Example 117 step (ii), but starting from the product of step (i) above and with purification by flash chromatography on silica eluting with 5% v/v ethyl acetate/hexane there was obtained methyl 4-bromoacetyl-2,6-di-tert butylphenoxyacetate in 82% yield as a yellow oil: NMR (d_6DMSO) δ 7.90 (2H, s), 4.92 (2H, s), 4.40 (2H, s), 3.76 (3H, s), 1.41 (18H, s).

(iii) In a similar manner to Example 5, but starting from the product

of step (ii) above and with purification by flash chromatography on silica eluting successively with dichloromethane then 2 to 5% v/v methanol/dichloromethane there was obtained a solid. Trituration with ether gave methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-2,6-di-tert-butylphenoxyacetate in 33% yield: m.p. 140-142°C; NMR (d_6DMSO) δ 7.97 (2H, s), 6.82 (2H, d), 4.39 (2H, s), 3.85 (2H, s), 3.75 (3H, s), 3.33 (4H, t), 2.64 (4H, t), 1.39 (18H, s); m/e 482 $(M+H)^+$; calculated for $C_{28}H_{39}N_3O_4$: C, 69.8; H, 8.2; N, 8.7. found: C, 69.7; H, 8.6; N, 8.1%.

EXAMPLE 131 : Ethyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]benzoate.

Prepared in a similar manner to Example 5, but starting from ethyl 4-bromoacetylbenzoate; recrystallisation from methanol gave the title compound in 32% yield as pale yellow crystals: m.p. 147-149°C; NMR (d_6DMSO) δ 8.14 (2H, d), 8.08 (4H, q), 6.78 (2H, d), 4.35 (4H, q, AB pattern), 3.98 (2H, s), 3.31 (4H, t), 2.63 (4H, t), 1.35 (3H, t); m/e 354 $(M+H)^+$; calculated for $C_{20}H_{23}N_3O_3$: C, 68.0; H, 6.6; N, 11.9. found: C, 68.0; H, 6.5; N, 11.7%.

EXAMPLE 132 : Sodium 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-benzoate.

A stirred suspension of the product of Example 131 (353 mg) in methanol (5 ml) was treated with a 1 molar sodium hydroxide solution (3 ml). After 2 hours, the cream coloured solid was collected, washed with a little methanol and dried to give the title compound, 240 mg, m.p. >300°C; NMR (d_6DMSO) δ 8.15 (2H, d), 8.05 (4H, t, AB pattern), 6.85 (2H, d), 3.97 (2H, s), 3.38 (4H, t), 2.65 (4H, t), m/e 348 $(M+H)^+$; calculated for $C_{18}H_{18}N_3NaO_3 . 0.25H_2O$: C, 61.4; H, 5.3; N, 11.9. found: C, 61.3; H, 5.2; N, 11.7%.

EXAMPLE 133 : Dimethyl 2,2'-[5-[2-[4-(4-pyridyl)piperazin-1-yl]-acetyl]phenylene-1,3-dioxy]diacetate.

In a similar manner to Example 5, but starting from dimethyl 2,2'-[(5-bromoacetyl)phenylene-1,3-dioxy]diacetate and with purification by flash chromatography on silica, eluting with 10% v/v methanol/dichloromethane, there was obtained a gum. Trituration with

diethyl ether gave the title compound in 14% yield as a yellow solid: m.p. 105-108°C; NMR (d_6DMSO) δ 8.16 (2H, d), 7.15 (2H, d), 6.82 (3H, m), 4.87 (4H, s), 3.89 (2H, s), 3.70 (6H, s), 3.31 (4H, t), 2.63 (4H, t); m/e 458 $(M+H)^+$; calculated for $C_{23}H_{27}N_3O_7.0.75H_2O$:C, 58.7; H, 6.1; N, 8.9. found C, 58.6; H, 6.0; N, 8.5%.

The starting material was prepared as follows:-

(i) In a similar manner to Example 116 step (i), but starting from 3,5-dihydroxyacetophenone and using 2.2 equivalents of sodium hydride and methyl bromoacetate there was obtained, after recrystallisation from iso-propanol, dimethyl 2,2'-[(5-acetyl)phenylene-1,3-dioxy]-diacetate in 56% yield as a fawn solid: m.p. 96-98°C; NMR ($CDCl_3$) δ 7.14 (2H, d), 6.70 (1H, t), 4.66 (4H, s), 3.81 (6H, s), 2.56 (3H, s); m/e 296 (M^+), calculated for $C_{14}H_{16}O_7$: C, 56.8; H, 5.4. found: C, 57.0; H, 5.7%.

(ii) In a similar manner to Example 116 step (ii) but starting from the product of step (i) above and with purification by flash chromatography on silica eluting with ethyl acetate/hexane (1:2 v/v) there was obtained dimethyl 2,2'-[5-(bromoacetyl)phenylene-1,3-dioxy]diacetate in 47% yield as a sticky solid: NMR ($CDCl_3$) δ 7.14 (2H, d), 6.73 (1H, t), 4.66 (4H, s), 4.38 (2H, s), 3.81 (6H, s); m/e 375/377 $(M+H)^+$, 1 Br pattern.

EXAMPLE 134 : Disodium 2,2'-[5-[2-[4-(4-pyridyl)piperazin-1-yl]-acetyl]phenylene-1,3-dioxy]diacetate.

A stirred solution of the product from Example 133 (100 mg) in methanol (5 ml) was treated with 1 molar sodium hydroxide solution (0.44 ml) and stirring continued for 18 hours. Evaporation of the solvent in vacuo and trituration of the residue with diethyl ether gave the title compound, 86 mg, as a yellow solid: m.p. 184-206°C; NMR (D_2O) δ 8.36 (2H, d), 7.29 (2H, d), 7.12 (2H, d), 6.98 (1H, t), 4.72 (4H, s), 4.28 (2H, s), 3.71 (4H, bt), 2.98 (4H, bt); m/e 474 $(M+H)^+$.

EXAMPLE 135 : 2-[4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]phenoxy]-isobutyric acid, dihydrobromide.

A mixture of methyl 2-[4-[2-[4-(4-pyridyl)piperazin-1-yl]-acetyl]phenoxy]isobutyrate (50 mg), 48% w/v hydrobromic acid (0.74 ml), dioxane (1 ml) and water (3 ml) was heated at 95°C for 4 hours. The solution was cooled, diluted with water and freeze-dried to give the title compound, 40 mg, as a pale yellow solid: m.p. 163-167°C; NMR (D_2O) δ 8.40 (2H, d), 8.16 (2H, d), 7.40 (2H, d), 7.21 (2H, d), 5.21 (2H, s), 4.32 (4H, b), 3.89 (4H, bt), 1.86 (6H, s); m/e 384 $(M+H)^+$; calculated for $C_{21}H_{25}N_3.2HBr.2H_2O$: C, 43.3; H, 5.3; N, 7.2. found: C, 43.6; H, 5.3; N, 7.3%.

The starting material was prepared as follows:-

(i) In a similar manner to Example 116 step (ii) but starting from methyl 2-(4-acetylphenoxy)isobutyrate and purification by flash chromatography on silica, eluting with ethyl acetate/hexane (1:2 v/v), there was obtained methyl 2-(4-bromoacetylphenoxy)isobutyrate in 45% yield as an orange oil: NMR ($CDCl_3$) δ 7.91 (2H, d), 6.85 (2H, d), 4.48 (2H, s), 3.76 (3H, s), 1.67 (6H, s). m/e 315/317 $(M+H)^+$ 2 Br pattern.

(ii) The product from step (i) above (2.00 g) in acetonitrile (10 ml) was added dropwise over 15 minutes to a stirred solution of 1-(4-pyridyl)piperazine (1.04 g) and triethylamine (0.89 ml) in acetonitrile (15 ml) and the mixture stirred overnight. The precipitated solid was removed by filtration and the filtrate evaporated. Purification of the residue by flash chromatography on silica, eluting with 0 to 5% v/v methanol/dichloromethane, gave a yellow gum. Trituration of this gum with diethyl ether gave methyl 2-[4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenoxy]isobutyrate, 170 mg, as a white solid: m.p. 88-90°C; NMR (d_6DMSO) δ 8.15 (2H, d), 7.96 (2H, d), 6.82 (4H, m), 3.92 (2H, s), 3.70 (3H, s), 3.33 (4H, t), 2.63 (4H, t), 1.60 (6H, s); m/e 398 $(M+H)^+$; calculated for $C_{22}H_{27}N_3O_4.0.25H_2O$: C, 65.8; H, 6.8; N, 10.5. found: C, 65.8; H, 7.1; N, 10.4%.

EXAMPLE 136 : Ethyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-phenoxyacetate.

Ethyl 4-bromoacetylphenoxyacetate (6.0 g) was added to a stirred, cooled (4°C) solution of 1-(4-pyridyl)piperazine (6.5 g) in acetonitrile (225 ml). Stirring was continued for 1 hour at 4°C, then overnight at ambient temperature when the precipitated solid was removed by filtration. The filtrate was evaporated in vacuo and the solid residue triturated with water, filtered, then washed with water and dried. Recrystallisation from a small volume of ethanol gave the title compound, 1.71 g, as a cream coloured solid: m.p. 113-114°C; NMR (d_6DMSO) δ 8.15 (2H, d), 7.98 (2H, d), 7.02 (2H, d), 6.80 (2H, d), 4.89 (2H, d), 4.17 (2H, q), 3.84 (2H, s), 3.32 (4H, t), 2.62 (4H, t), 1.22 (3H, t); m/e 384 $(M+H)^+$; calculated for $C_{21}H_{25}N_3O_4$: C, 65.8; H, 6.6; N, 11.0. found: C, 65.5; H, 6.6; N, 10.8%.

The starting material was prepared as follows:-

(i) In a similar manner to Example 118 step (i), but starting from ethyl bromoacetate there was prepared ethyl 4-acetylphenoxyacetate as a crystalline solid in quantitative yield. The product was used without further purification.

(ii) In a similar manner to Example 117 step (ii), but starting from the product of step (i) above there was prepared ethyl 4-bromoacetylphenoxyacetate in 47% yield as a solid: m.p. 41-42°C; NMR (d_6DMSO) δ 7.90 (2H, d), 7.05 (2H, d), 4.90 (2H, s), 4.72 (2H, s), 4.18 (2H, q), 1.33 (3H, t).

EXAMPLE 137 : iso-Propyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-phenoxyacetate.

iso-Propyl 4-bromoacetylphenoxyacetate (6.3 g) was added to a stirred, cooled (4°C) solution of 1-(4-pyridyl)piperazine (6.5 g) in acetonitrile (225 ml). Stirring was continued for 1 hour at 4°C, then overnight at ambient temperature when the precipitated solid was removed. The filtrate was evaporated in vacuo and the residue partitioned between ethyl acetate and water. The organic phase was

dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica, eluting firstly with 0 to 10% v/v methanol/dichloromethane and then toluene/ethyl acetate/.880 ammonium hydroxide/ethanol (60:20:10:35 v/v/v/v), gave a cream solid. Recrystallisation from iso-propanol gave the title compound, 2.1 g: m.p. 121-122°C; NMR (d_6DMSO) δ 8.14 (2H, d), 7.98 (2H, d), 7.02 (2H, d), 6.80 (2H, d), 4.99 (1H, m), 4.85 (2H, s), 3.84 (2H, s), 3.33 (4H, t), 2.62 (4H, t), 1.22 (6H, d); m/e 398 $(M+H)^+$; calculated for $C_{22}H_{27}N_3O_4$: C, 66.5; H, 6.9; N, 10.6. found: C, 65.8; H, 6.8; N, 10.4%.

The starting material was prepared as follows:-

(i) In a similar manner to Example 118 step (i), but starting from iso-propyl bromoacetate there was prepared iso-propyl 4-acetylphenoxyacetate as a crystalline solid in quantitative yield. The product was used without further purification.

(ii) In a manner similar to Example 117 step (ii), but starting from the product of step (i) above and using iso-propyl acetate in place of ethyl acetate as solvent, there was prepared iso-propyl 4-bromoacetylphenoxyacetate as a crystalline solid in 69% yield: m.p. 64-66°C; NMR (d_6DMSO) δ 7.98 (2H, d), 7.06 (2H, d), 4.99 (1H, m), 4.88 (2H, s), 4.83 (2H, s), 1.22 (6H, d).

EXAMPLE 138 : tert-Butyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-phenoxyacetate.

Prepared in a similar manner to Example 136, but starting from tert-butyl 4-bromoacetylphenoxyacetate. After evaporation of the acetonitrile solution the residue was purified by column chromatography on silica, eluting with 0 to 5% v/v methanol/dichloromethane, to give a yellow oil. Trituration with diethyl ether gave the title compound in 35% yield as a solid: m.p. 103-104°C; NMR (d_6DMSO) δ8.15 (2H, d), 7.98 (2H, d), 7.00 (2H, d), 6.82 (2H, d), 4.76 (2H, s), 3.84 (2H, s), 3.37 (4H, t), 2.62 (4H, t), 1.43 (9H, s); m/e 412 $(M+H)^+$ calculated for $C_{23}H_{29}N_3O_4$: C, 67.1; H, 7.1; N, 10.2. found: C, 66.9; 7.3; N, 10.0%.

The starting material was prepared as follows:-

(i) In a similar manner to Example 118 step (i), but starting from tert-butyl bromoacetate there was prepared tert-butyl 4-acetylphenoxyacetate as a crystalline solid in 90% yield: m.p. 59-61°C; NMR (d_6DMSO + d_4 acetic acid) δ 7.94 (2H, d), 6.98 (2H, d), 4.21 (2H, s), 2.52 (3H, s), 1.44 (9H, s).

(ii) A solution of the product from step (i) above (3.3 g) and N-bromosuccinimide (2.35 g) in carbon tetrachloride was heated at reflux temperature for 80 hours. After cooling, the precipitate was removed by filtration and the filtrate concentrated in vacuo. Purification of the residual oil by flash chromatography on silica, eluting with 5% v/v ethyl acetate/toluene, gave tert-butyl 4-bromoacetylphenoxyacetate, 1.9 g, as a crystalline solid: m.p. softens at 110-116°C; NMR (d_6DMSO) δ 7.97 (2H, d), 7.04 (2H, d), 4.84 (2H, s), 4.80 (2H, s), 1.43 (9H, s).

EXAMPLE 139 : Neopentyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-phenoxyacetate.

Prepared in a similar manner to Example 136, but starting from neopentyl 4-bromoacetylphenoxyacetate. After evaporation of the acetonitrile filtrate, the residue was purified by flash chromatography on silica, eluting with 0 to 5% v/v methanol dichloromethane, to give an oil. Trituration with diethyl ether/hexane gave the title compound in 23% yield as a solid: m.p. 88-90°C; NMR (d_6DMSO) δ 8.14 (2H, d), 7.98 (2H, d), 7.04 (2H, d), 6.81 (2H, d), 4.97 (2H, s), 3.83 (4H, s), 3.32 (4H, t), 2.61 (4H, t), 0.86 (9H, s); m/e 426 $(M+H)^+$; calculated for $C_{24}H_{31}N_3O_4$: C, 67.7; H, 7.3; N, 9.9. found: C, 68.1; H, 7.4; N, 9.9%.

The starting material was prepared as follows:-

To a stirred suspension of 4-acetylphenoxyacetic acid (4.36 g) in dichloromethane (50 ml) was added oxalyl chloride (2.36 ml) and DMF (one drop). The mixture was stirred for one hour and then the

solvent removed in vacuo to give a yellow oil (4.8 g). A solution of this oil in diethyl ether was added dropwise to a stirred solution of neopentyl alcohol (2.18 g) and triethylamine (3.4 ml) in diethyl ether (50 ml). After the addition, stirring was continued for a further 18 hours when the precipitated solid was removed by filtration. Evaporation of the filtrate and purification of the residue by flash chromatography on silica, eluting with dichloromethane, gave neopentyl 4-acetylphenoxyacetate, 5.1 g, as a pale yellow oil: NMR ($CDCl_3$) δ 7.94 (2H, d), 6.95 (2H, d), 4.72 (2H, s), 3.91 (2H, s), 2.56 (3H, s), 0.93 (9H, s).

(ii) To a stirred solution of the product of step (i) above (2.64 g) in chloroform (25 ml), was added slowly over 10 minutes, a solution of bromine (0.52 ml) in chloroform (10 ml). Stirring was continued for a further hour and the solvent removed in vacuo. Trituration of the residue with diethyl ether/hexane gave neopentyl 4-bromoacetylphenoxyacetate, 2.3 g, as a crystalline solid: m.p. 85-87°C.

EXAMPLE 140 : Dimethyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-phenoxymalonate.

Prepared in a similar manner to Example 136, but starting from dimethyl 4-bromoacetylphenoxymalonate and after evaporation of the acetonitrile filtrate the residue was partitioned between water/dichloromethane. The organic solution was dried ($MgSO_4$), concentrated and purification by flash chromatography, eluting with 0 to 5% v/v methanol/dichloromethane, then trituration with diethyl ether gave the title compound in 31% yield as a pale yellow solid: m.p. 115-116°C; NMR (d_6DMSO) δ 8.16 (2H, d), 8.02 (2H, d), 7.09 (2H, d), 6.82 (2H, d), 5.95 (1H, s), 3.86 (2H, s), 3.80 (6H, s), 3.34 (4H, t), 2.63 (4H, t); m/e 428 $(M+H)^+$; calculated for $C_{22}H_{25}N_3O_6$: C, 61.8; H, 5.9; N, 9.8. found C, 61.3; H, 5.9; N, 9.2%.

The starting material was prepared as follows:-

(i) In a similar manner to Example 118 step (i), but starting from dimethyl bromomalonate and purification by flash chromatography on silica, eluting with 50 to 75% v/v diethyl ether/hexane, there was prepared dimethyl 4-acetylphenoxymalonate in 53% yield as a white crystalline solid: m.p. 71-72°C; NMR (d_6DMSO) δ 7.95 (2H, d), 7.09 (2H, d), 5.95 (1H, s), 3.78 (6H, s), 2.53 (3H, s); m/e 267 $(M+H)^+$; calculated for $C_{13}H_{14}O_6$: C, 58.6; H, 5.3. found: C, 58.9; H, 5.3%.

(ii) In a similar manner to Example 117 step (ii), but starting from the product of step (i) above and using methyl acetate in place of ethyl acetate as solvent, there was prepared methyl 4-bromoacetylphenoxymalonate in 59% yield as a white crystalline solid: m.p. 114-115°C; NMR (d_6DMSO) δ 7.99 (2H, d), 7.12 (2H, d), 5.99 (1H, s), 4.86 (2H, s), 3.80 (6H, s).

EXAMPLE 141 : 5-[4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]phenoxymethyl]tetrazole

A mixture of 5-(4-chloroacetylphenoxymethyl)tetrazole (166 mg) and 1-(4-pyridyl)piperazine (214 mg) in acetonitrile (10 ml) was stirred overnight. The precipitate was collected, washed with acetonitrile and dried. A solution of this material in a small volume of 50% v/v acetic acid/water was transfered to a 1 inch preparative reverse phase hplc column (DYNAMAX (Trade Mark) C18 83-221-C) and eluted with water/acetonitrile/trifluoroacetic acid in a gradient from 98:2:0.1 v/v/v to 60:40:0.1 v/v/v. The pure fractions, on freeze-drying, gave the title compound, 8.1 mg, as a white powder: NMR (D_2O) δ 8.39 (2H, d), 8.18 (2H, d), 7.40 (4H, m), 5.84 (2H, s), 5.20 (2H, s), 4.31 (4H, bt), 3.87 (4H, bt); m/e 380 $(M+H)^+$.

The starting material was prepared as follows:-

(i) A mixture of phenoxyacetonitrile (26.6 g), sodium azide 13.0 g and ammonium chloride (10.6 g) in DMF (80 ml) was heated at reflux temperature for 18 hours. The solvent was removed in vacuo and the black solid triturated with diethyl ether, collected and dissolved in 4 molar sodium hydroxide solution. This solution was extracted with

diethyl ether, then treated with charcoal and filtered. The filtrate, on acidification with concentrated hydrochloric acid, gave a white precipitate. Recrystallisation from toluene gave 5-(phenoxymethyl) tetrazole, 12.05 g, as white plates: m.p. 128-131°C; NMR (d_6DMSO) δ 7.31 (2H, m), 7.02 (3H, m), 5.47 (2H, s); m/e 177 $(M+H)^+$; calculated for $C_8H_8N_4O$: C, 54.5; H, 4.6; N, 31,8. found: C, 54.6; H, 4.6; N, 32.0%.

(ii) Aluminium chloride (30.3 g) was added to a stirred mixture of the product of step (i) above (10 g) and chloroacetyl chloride (19.3 g) in dry 1,2-dichloroethane and stirring continued overnight. The mixture was concentrated to about half volume on the steam bath, cooled and added to an ice/hydrochloric acid mixture. After stirring for 15 minutes the solid was collected and, on recrystallisation from methanol/water, gave 5-(4-chloroacetylphenoxymethyl)tetrazole, 7.5 g: m.p. 194-196°C; NMR (d_6DMSO) δ 7.99 (2H, d), 7.20 (2H, d), 5.61 (2H, s), 5.11 (2H, s); m/e 251 $(M-H)^-$, 1 Cl pattern; calculated for $C_{10}H_9ClN_4O_2$: C, 47.5; H, 3.6; N, 22.2. found: C, 47.3; H, 3.7; N, 22.2%.

EXAMPLE 142 : 4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]phenoxy-acetamide.

A solution of the product of Example 1 (200 mg) in methanol (10 ml), prepared under argon, was cooled to 4°C and saturated with dry ammonia gas, then sealed in a pressure bottle and kept for 2 days. The orange crystals which formed, after filtration and washing with a little methanol, gave the title compound, 140 mg: m.p. 247 to 248°C; NMR (d_6DMSO) δ 8.16 (2H, d), 7.99 (2H, d), 7.55 (1H, bs), 7.37 (1H, bs), 7.02 (2H, d), 6.81 (2H, d), 4.54 (2H, s), 3.85 (2H, s), 3.33 (4H, t), 2.60 (4H, t); m/e 355 $(M+H)^+$; calculated for $C_{19}H_{22}N_4O_3$: C, 64.4; H, 6.3; N, 15.8. found: C, 64.4; H, 6.4; N, 15.6%.

EXAMPLE 143 : 2-[4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]phenoxy]-N-methylacetamide.

A suspension of the product of Example 1 (100 mg) in a 33% w/v solution of methylamine in ethanol (3 ml) was stirred for 18

hours. The solid formed, after filtration and washing with a little ethyl acetate, gave the title compound, 65 mg: m.p. 169-171°C; NMR (d_6DMSO) δ 8.14 (2H, d), 8.06 (1H, bq), 8.00 (2H, d), 7.05 (2H, d), 6.80 (2H, d), 4.56 (2H, s), 3.82 (2H, s), 3.30 (4H, t), 2.66 (3H, d), 2.61 (4H, t); m/e 369 $(M+H)^+$; calculated for $C_{20}H_{24}N_4O_3$: C, 65.2; H, 6.6; N, 15.2. found: C, 65.0; H, 6.8; N, 15.1%.

EXAMPLE 144 : 2-[4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]phenoxy]-N-(2-methoxyethyl)acetamide.

A suspension of the product of Example 1, (100 mg) in 2-methoxyethylamine (1 ml) was stirred for 18 hours. Filtration of the solid and washing with ethyl acetate gave the title compound, 70 mg, as a white crystalline solid: m.p. 142-145°C; NMR (d_6DMSO + d_4 acetic acid) δ 8.20 (2H, d), 8.00 (2H, d), 7.14 (2H, d), 7.06 (2H, d), 4.62 (2H, s), 3.72 (4H, t), 3.38 (4H, m), 3.26 (3H, s), 2.78 (4H, t); m/e 413 $(M+H)^+$; calculated for $C_{22}H_{28}N_4O_4$: C, 64.1; H, 6.8; N, 13.6. found: C, 63.9; H, 6.8; N, 13.3%.

EXAMPLE 145 : 2-[4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]phenoxy]-N-(phenylmethyl)acetamide.

A solution of 2-[4-(bromoacetyl)phenoxy]-N-(phenylmethyl)-acetamide (1.40 g) (preparation described in EPO 052442) in acetonitrile (5 ml) was added to a stirred solution of 1-(4-pyridyl)piperazine (1.14 g) in acetonitrile (20 ml). After stirring overnight the liquors were decanted from the residual gum, then concentrated in vacuo. Purification by flash chromatography on silica, eluting with 2 to 5% v/v methanol/dichloromethane, gave a solid. Trituration of this solid with diethyl ether gave the title compound, 95 mg: m.p. 150-151°C; NMR (d_6DMSO) δ 8.67 (1H, bt), 8.15 (2H, d), 8.00 (2H, d), 7.26 (5H, m), 7.06 (2H, d), 6.81 (2H, d), 4.66 (2H, s), 4.34 (2H, d), 3.84 (2H, s), 3.33 (4H, t), 2.54 (4H, t); m/e 445 $(M+H)^+$; calculated for $C_{26}H_{28}N_4O_3 . 0.25H_2O$: C, 69.5; H, 6.4; 12.5. found: C, 69.6; H, 6.4; N, 12.3%.

EXAMPLE 146 : Methyl N-[4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-phenoxyacetyl]glycinate.

A solution of methyl N-[4-(bromoacetyl)phenoxyacetyl]-glycinate (0.85 g) in acetonitrile (10 ml) was added to a stirred solution of 1-(4-pyridyl)piperazine (0.81 g) in acetonitrile (30 ml). After stirring overnight the solvent was removed in vacuo and the residue partitioned between water/ethyl acetate. The organic phase was washed with water, then dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica, eluting with 0 to 7.5% v/v methanol/dichloromethane. Evaporation of the fractions gave the title compound, 130 mg, as a foam: NMR (d_6DMSO) δ 8.58 (1H, t), 8.16 (2H, d), 8.01 (2H, d), 7.08 (2H, d), 6.83 (2H, d), 5.75 (1H, s), 4.68 (2H, s), 3.92 (2H, d), 3.84 (2H, s), 3.65 (3H, s), 3.34 (4H, t+H_2O), 2.65 (4H, t); m/e 427 $(M+H)^+$; calculated for $C_{22}H_{26}N_4O_5$. $0.5CH_2Cl_2$: C, 57.6; H, 5.8; N, 11.9. found: C, 57.8; H, 5.7; N, 12.0%.

The starting material was prepared as follows:-

(i) To a stirred suspension of 4-(acetyl)phenoxyacetic acid (3.00 g) in dichloromethane (40 ml) was added oxalyl chloride (1.62 ml) and 1 drop of DMF. Stirring was continued for 1.5 hours and the clear solution on evaporation gave an oil (I). Triethylamine (4.30 ml) was added slowly to a stirred, cooled (4°C) suspension of methyl glycinate hydrochloride (1.95 g) in dichloromethane (25 ml) under argon. After stirring for 10 minutes, a solution of (I) in dichloromethane (10 ml) was added and stirring continued for a further 2 hours. The precipitate was removed by filtration and the filtrate concentrated in vacuo. Purification of the residue by flash chromatography on silica, eluting with 2% v/v methanol/dichloromethane, gave a solid. Trituration with ether/hexane gave methyl N-[4-(acetyl)-phenoxyacetyl]glycinate, 3.1 g, as white crystals: m.p. 120-121°C; NMR (d_6DMSO) δ 8.57 (1H, t), 7.94 (2H, d), 7.07 (2H, d), 4.66 (2H, s), 3.92 (2H, s), 3.64 (3H, s), 2.52 (3H, s); m/e 266 $(M+H)^+$; calculated for $C_{13}H_{15}NO_5$: C, 58.9; H, 5.7; N, 5.3. found C, 58.4; H, 5.5; N, 5.0%.

(ii) The product of step (i) (3.00 g) and N-bromosuccinimide (2.02 g) in carbon tetrachloride (50 ml) was heated at reflux temperature for 64 hours. The solvent was evaporated and the black residue dissolved in methanol/ethyl acetate, treated with charcoal, filtered and then evaporated. The resulting brown oil was purified by flash chromatography on silica, eluting with dichloromethane. Trituration with hexane gave methyl N-[4-(bromoacetyl)phenoxyacetyl]glycinate, 0.85 g, as a solid: mp softens 109-111°C; NMR (d_6DMSO) δ 8.60 (1H, bt), 7.99 (2H, d), 7.09 (2H, d), 4.84 (2H, s), 4.69 (2H, s), 3.91 (2H, d), 3.64 (3H, s).

EXAMPLE 147 : Methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]ethyl]-phenoxyacetate.

A mixture of methyl 4-[1-(2-methanesulphonyloxyethyl)]-phenoxyacetate (2.0 g) and 1-(4-pyridyl)piperazine (2.26 g) in acetonitrile was heated at reflux temperature for 25 hours. The solvent was removed in vacuo and the residue purified by flash chromatography on silica, eluting with successively 2.5, 3, 3.5, and 4% v/v methanol/dichloromethane. Isolation of the desired fractions and trituration with diethyl ether gave the title compound, 600 mg: recrystallisation from methanol gave white crystals, m.p. 104-105°C; NMR (d_6DMSO) δ 8.15 (2H, d), 7.15 (2H, d), 6.86 (2H, d), 6.82 (2H, d), 4.74 (2H, s), 3.69 (3H, s), 3.30 (4H, t. 2H, m. + H_2O), 2.71 (2H, m), 2.54 (4H, t), m/e 356 $(M+H)^+$, calculated for $C_{20}H_{25}N_3O_3$. $0.25H_2O$: C, 66.7; H, 7.1; N, 11.7. found: C, 67.0; H, 7.2; N, 11.4%.

The starting material was prepared as follows:-

(i) A mixture of 4-hydroxyphenethyl alcohol (5.37 g), anhydrous potassium carbonate (5.37 g) and methyl bromoacetate (3.80 ml) in anhydrous acetone (50 ml) was stirred for 18 hours. The mixture, after filtration, was evaporated and the residue after purification by flash chromatography on silica, eluting with 2% v/v methanol/dichloromethane, gave methyl 4-[1-(2-hydroxyethyl)]-phenoxyacetate, 5.05 g, as an oil: NMR ($CDCl_3$) δ 7.15 (2H, d), 6.86 (2H, d), 4.62 (2H, s), 3.84 (2H, m), 3.80 (3H, s), 2.81 (2H, t), 1.40

(1H, bt); m/e 210 $(M)^+$; calculated for $C_{11}H_{14}O_4$: C, 62.8; H, 6.7. found: C, 62.8; H, 6.8%

(ii) Methanesulphonyl chloride (0.98 ml) was added dropwise, over 30 minutes, to a stirred, cooled (4°C) solution of the product from step (i) (2.22 g) and triethylamine (1.91 ml) in dichloromethane (35 ml) under argon. After 2 hours, the solvent was evaporated and the residue partitioned between ethyl acetate (75 ml) and water (20 ml). The organic phase was separated, washed with saturated sodium chloride solution (3x15 ml), dried and evaporated. The residue on purification by flash chromatography on silica, eluting with 45% v/v ethyl acetate/hexane, gave methyl 4-[1-(2-methanesulphonyloxyethyl)]-phenoxyacetate, 2.85 g, as an oil: NMR ($CDCl_3$) δ 7.16 (2H, d), 6.87 (2H, d), 4.62 (2H, s), 4.38 (2H, t), 3.81 (3H, s), 3.00 (2H, t), 2.85 (3H, s); m/e 288 (M^+); calculated for $C_{12}H_{16}O_6S$: C, 50.0; H, 5.6; S, 11.1. found: C, 50.1; H, 5.5; S, 11.0%.

EXAMPLE 148 : 4-[2-[4-(4-pyridyl)piperazin-1-yl]ethyl]phenoxyacetic acid dihydrochloride.

In a similar manner to Example 123, but starting from the product of Example 147, there was obtained the title compound in 95% yield: m.p. 270-273°C; NMR (d_6DMSO + d_4 acetic acid) δ 8.34 (2H, d), 7.30 (2H, d), 7.22 (2H, d), 6.91 (2H, d), 4.67 (2H, s), 4.06 (4H, b), 3.46 (4H, b), 3.35 (2H, m), 3.05 (2H, m); m/e 342 $(M+H)^+$; calculated for $C_{19}H_{22}N_3O_3.2HCl$: C, 55.0; H, 6.5; N, 10.1. found: C, 54.8; H, 6.2; N, 9.8%.

EXAMPLE 149: Tertiary butyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]carbonylmethyl]phenoxyacetate.

In a similar manner to Example 18 step (iv), but starting from tertiary butyl 4-(carboxymethyl)phenoxyacetate, there was obtained after flash chromatography on silica, eluting with 0 to 5% v/v methanol/dichloromethane, a gum. Further purification by flash chromatography on neutral alumina, eluting with 1% v/v methanol/dichloromethane followed by trituration with diethyl ether

gave the title compound in 17% yield as a white solid: m.p. 110-112°C; NMR (d_6DMSO) δ 8.22(2H, d), 7.15(2H, d), 7.06(2H, d), 6.83(2H, d), 4.60(2H, s), 3.70(2H, s), 3.62(4H, bt), 3.38(4H, bt + H_2O), 1.42(9H, s); m/e 412 $(M+H)^+$; calculated for $C_{23}H_{29}N_3O_4.0.25H_2O$: C, 66.4; H, 7.1; N, 10.1. found: C, 66.4; ", 7.2; N, 10.1%.

The starting material was prepared as follows:-

(i) Sodium hydride (50% w/w dispersion in mineral oil, 3.7g) was treated under argon with repeated washes of hexane. The oil-free residue was suspended in dry DMF (100 ml) and 4-hydroxyphenylacetic acid (13.0g) was added portionwise to the stirred cooled (4°C) mixture. After 30 minutes, benzyl bromide (9.2ml) was added dropwise and, after a further 1 hour at 4°C, stirring was continued overnight at ambient temperature. The solvent was evaporated in vacuo and the residue partitioned between ethyl acetate and water. The aqueous phase was re-extracted with further ethyl acetate and the combined organic extracts washed with water and brine, then dried ($MgSO_4$) and evaporated. The crystalline residue gave benzyl 4-hydroxyphenylacetate, 17.8g, as off-white crystals: m.p. 70-72°C; NMR ($CDCl_3$) δ 7.32(5H, m), 7.14(2H, d), 6.76(2H, d), 5.12(2H, s), 3.59(2H, s); m/e 242 $(M^{\cdot})^+$.

(ii) Sodium hydride (50% w/w dispersion in mineral oil, 2.1g) was treated under argon with repeated washes of hexane. The oil-free residue was suspended in dry DMF (130 ml) and the product from step (i) (10g) added in three portions to the cooled (4°C) stirred mixture. Stirring was continued for a further 15 minutes when tertiary butyl bromoacetate (7.0 ml) was added dropwise over 15 minutes. After 1 hour at 4°C, the mixture was stirred for 6 hours at ambient temperature. The solvent was evaporated in vacuo and the residue partitioned between ethyl acetate and water. The aqueous phase was re-extracted with further ethyl acetate and the combined organic phases washed with water and brine, then dried ($MgSO_4$) and evaporated. The residue, after purification by flash chromatography on silica eluting with dichloromethane, gave tertiary butyl

4-(benzyloxycarbonylmethyl)phenoxyacetate, 7.5g, as a colourless oil: NMR ($CDCl_3$) d 7.31(5H, m), 7.20(2H, m), 6.85(2H, m), 5.12(2H, s), 4.49(2H, s), 3.60(2H, s), 1.48(9H, s); m/e 356 $(M^{\cdot})^+$.

(iii) In a similar manner to Example 18 step (iii) but starting from the product of step (ii) above was prepared tertiary butyl 4-(carboxymethyl)phenoxyacetate in 96% yield as a white crystalline solid: m.p.78-80°C; NMR (d_6DMSO) δ 7.15(2H, d), 6.82(2H, d), 4.60(2H, s), 3.48(2H, s), 1.43(9H, s); m/e 266 $(M^{\cdot})^+$; calculated for $C_{14}H_{18}O_5.0.75H_2O$: C, 60.1; H, 7.0. found: C, 59.9; H, 7.2%.

EXAMPLE 150: 4-[2-[4-(4-pyridyl)piperazin-1-yl]carbonylmethyl]phenoxyacetic acid, dihydrochloride.

A solution of the product from Example 149 (50 mg) in a mixture of dioxane (1 ml), water (2 ml) and 1 molar hydrochloric acid solution (0.61 ml) was heated overnight at 90°C. The resulting solution, on dilution with water and freeze-drying, gave the title compound, 30mg, as a yellow foam: NMR (d_6DMSO + d^4 acetic acid) δ 8.31(2H, d), 7.24(2H, d), 7.18(2H, m), 6.87(2H, m), 4.64(2H, s), 3.96(4H, t), 3.72(2H, s), 3.32(4H, t); m/e 356 $(M+H)^+$; calculated for $C_{19}H_{21}N_3O_4.2HCl.2.5H_2O$: C, 48.2; H, 5.9; N, 8.9. found C, 48.5; H, 6.0; N, 8.8%.

EXAMPLE 151: Methyl 4-[2-[4-(2-methylpyrid-4-yl)piperazin-1-yl]acetyl]phenoxyacetate

Methyl 4-bromoacetylphenoxyacetate (1.72g) was added to a stirred mixture of 1-[4-(2-methylpyridyl)]piperazine dihydrochloride (1.5g) and triethylamine (2.5 ml) in acetonitrite (25 ml). Stirring was continued overnight when the solvent was removed in vacuo. Purification by flash chromatography, first on silica eluting with 10% v/v methanol/dichloromethane and then on neutral alumina eluting with 1% v/v methanol/dichloromethane, gave the title compound, 418 mg, as a white solid: m.p. 155-157°C; NMR (d_6DMSO) δ 8.00(3H, m), 7.04(2H, d), 6.70(1H, d), 6.64(1H, dd), 4.92(2H, s), 3.83(2H, s), 3.71(3H, s),

3.30(4H, b+ H_2O), 2.61(4H, t), 2.32(3H, s); m/e 384 $(M+H)^+$; calculated for $C_{21}H_{25}N_3O_4$: C, 65.8; H, 6.6; N, 11.0. found: C, 65.4; H, 6.8; N, 10.9%.

The starting material was prepared as follows:-

(i) A mixture of 4-chloro-2-picoline (5 g) and 1-benzylpiperazine (13.6 ml) in xylene (50 ml) was heated at reflux temperature for 18 hours. The solution was cooled and the solid precipitate removed by filtration and the filtrate concentrated in vacuo. Purification by flash chromatography on silica, eluting with 20% v/v methanol/dichloromethane gave 4-[4-(2-picolyl)]-1-benzylpiperazine, 9.54g, as a light fawn crystalline solid: m.p. 94-95°C; NMR ($CDCl_3$) δ 8.15(1H, d), 7.30(5H, m), 6.51(2H, m), 3.57(2H, s), 3.44(4H, t), 2.57(4H, t), 2.46(3H, s); m/e 268 $(M+H)^+$; calculated for $C_{17}H_{21}N_3$: C, 76.4; H, 7.9; N, 15.7. found: C, 75.7; H, 8.1; N, 15.7%.

(ii) 10% w/w Palladium on charcoal (1.5 g) was added to a stirred solution of the product of step (i) (9.00g) and 2 molar hydrochloric acid (34 ml) in methanol (180 ml) and the mixture was hydrogenated at room temperature and pressure until the theoretical amount of hydrogen had been taken up. Charcoal was added, the mixture stirred for 5 minutes then filtered through diatomaceous earth and the filtrate on evaporation to dryness gave 1-[4-(2-methylpyridyl)]piperazine dihydrochloride, 10.6 g, as a fawn solid: m.p. 64-68°C; NMR (d_6DMSO) δ 8.20(1H, d), 7.18(1H, d), 7.12(1H, dd), 3.92(4H, t), 3.19(4H, t), 2.51(3H, s + DMSO); m/e 178 $(M+H)^+$; calculated for $C_{10}H_{15}N_3.2HCl.0.75H_2O$: C, 45.5; H, 7.0; N, 15.9. found: C, 45.3; H, 7.0; N, 15.8%.

EXAMPLE 152:4-[2-[4-(2-methylpyrid-4-yl)piperazin-1-yl]acetyl]-phenoxyacetic acid, dihydrobromide.

A mixture of the product of Example 151 (160 mg), 48% w/v hydrobromic acid (0.25 ml) and dioxane (1 ml) in water (3 ml) were

heated at 90°C for 30 minutes. The solution was cooled, further water added and the mixture freeze-dried. Trituration of the residue with absolute ethanol gave the title compound, 50 mg, as a fawn solid: m.p. 146-148°C; NMR (d_6DMSO + d_4 acetic acid) δ 8.17(1H, d), 7.95(2H, d), 7.09(4H, m), 4.94(2H, s), 4.78(2H, s), 3.99(4H, b), 3.07(1H, q), 2.46(3H, s), 1.17(1.5H, t); m/e 370 $(M+H)^+$; calculated for $C_{20}H_{23}N_3O_4.2HBr.H_2O.0.5C_2H_5OH$: C, 44.1; H, 5.3; N, 7.3. found: C, 44.0; H, 5.4; N, 7.2%.

EXAMPLE 153: Methyl 4-[2-[4-(2,6-dimethylpyrid-4-yl)piperazin-1-yl]acetyl]phenoxyacetate, hydrobromide

Prepared in a similar manner to Example 151, but starting from 1-[4-(2,6-dimethylpyridyl)]piperazine and using only one equivalent of triethylamine. Purification by flash chromatography on silica, eluting with 0 to 5% v/v methanol/dichloromethane, followed by trituration with diethyl ether, gave the title compound in 64% yield as a white solid: m.p. 212-215°C; NMR (d_6 DMSO) δ 13.0(1H, b), 7.96(2H, d), 7.04(2H, d), 6.96(2H, s), 3.90(2H, s), 3.71(3H, s), 3.65(4H, bt), 2.65(4H, bt), 2.42(6H, s); m/e 398 $(M+H)^+$; calculated for $C_{22}H_{27}N_3O_4.1HBr$: C, 55.2; H, 5.9; N, 8.8. found: C, 55.3; H, 5.9; N, 8.6%.

The starting material was prepared as follows:-

(i) In a similar manner to Example 151 step (i), but starting from 4-chloro-2,6-lutidine there was obtained 4-[4-(2,6-dimethylpyridyl)]-1-benzylpiperazine in 59% yield as a yellow oil: NMR ($CDCl_3$) δ 7.31(5H, m), 6.37(2H, s), 3.55(2H, s), 3.32(4H, t), 2.55(4H, t), 2.44(6H, s); m/e 282 $(M+H)^+$.

(ii) In a similar manner to Example 151 step (ii) but starting from the product of step (i) above there was prepared the solid dihydrochloride. This was dissolved in water, two equivalents of 2 molar potassium hydroxide added and the solvent evaporated. Purification of the residue by flash chromatography on alumina,

eluting with 2% v/v methanol/dichloromethane gave 1-[(4-[2,6-dimethylpyridyl)]piperazine in 51% yield as a white crystalline solid: m.p. 123-124°C; NMR ($CDCl_3$) δ 6.40(2H, s), 3.27(4H, t) 2.98(4H, t), 2.43(6H, s); m/e 198 $(M+H)^+$; calculated for $C_{11}H_{17}N_3$: C, 69.1; H, 9.0; N, 22.0. found: C, 69.2; H, 9.2; N, 21.6%.

EXAMPLE 154: 4-[2-[4-(2,6-dimethylpyrid-4-yl)piperazin-1-yl]acetyl]-phenoxyacetic acid, dihydrobromide

Following the method of Example 152, but starting from the product of Example 153, the title compound was prepared in 78% yield as a fawn solid: m.p. 210-212°C; NMR (d_6 DMSO + d_6 acetic acid) δ 7.99(2H, d), 7.16(2H, d), 7.08(2H, s), 5.09(2H, s), 4.87(2H, s), 4.07(4H, b), 3.52(4H, b), 2.49(6H, s); m/e 384 $(M+H)^+$; calculated for $C_{21}H_{25}N_3O_4.2HBr.2.5H_2O$: C, 42.7; H, 5.4; N, 7.1. found: C, 42.7; H, 5.1; N, 6.9%.

EXAMPLE 155: Methyl 4-[1-(4-pyridyl)piperidin-4-yl]oxyphenoxyacetate

Diethylazodicarboxylate (0.47 ml) was added dropwise over 30 minutes to a stirred mixture of 1-(4-pyridyl)-4-piperidinol (534 mg), methyl 4-hydroxyphenoxyacetate (546 mg), triphenylphosphine (787 mg) and dry THF (30 ml) in an atmosphere of argon and cooled to 4°C. After 1 hour at 4°C, the mixture was allowed to reach ambient temperature and stirred for 48 hours. The solvent was removed by evaporation and the residue purified by flash chromatography on silica eluting with 5% v/v methanol/dichloromethane. Recrystallisation from ethyl acetate/hexane gave the title compound, 532 mg, as a white solid: m.p. 74-76°C; NMR (d_6DMSO) δ 8.15(2H, bd), 6.89(6H, m), 4.71(2H, s), 4.50(1H, m), 3.70(2H, m), 3.69(3H, s), 3.23(2H, m), 1.96(2H, m), 1.62(2H, m); m/e 343 $(M+H)^+$; calculated for $C_{19}H_{22}N_2O_4$: C, 66.7; H, 6.5; N, 8.2. found: C, 66.2; H, 6.7; N, 8.2%.

EXAMPLE 156: 4-[1-(4-pyridyl)piperidin-4-yl]oxyphenoxyacetic acid

Following the method of Example 2, but starting from the product of Example 155, the title compound was prepared in 85% yield: m.p. 288-291°C; NMR (NaOD + d_6 DMSO) δ 7.97(2H, d), 6.77(4H, m), 6.69(2H, d), 4.35(1H, m), 4.19(2H, s), 3.53(2H, m), 3.08(2H, m), 1.82(2H, m), 1.49(2H, m); m/e 329 $(M+H)^+$; calculated for $C_{18}H_{20}N_2O_4$: C, 65.8; H, 6.1; N, 8.5. found: C, 65.7; H, 6.3; N, 8.4%.

EXAMPLE 157: Methyl 4-[1-(4-pyridyl)piperidin-4-yl]-methoxyphenoxyacetate

Following the method of Example 155, but starting from 4-(4-hydroxymethylpiperidin-1-yl)pyridine, the title compound was prepared in 18% yield: m.p. 127-129°C; NMR (d_6DMSO) δ 8.12(2H, d), 6.84(4H, s), 6.81(2H, d), 4.70(2H, s), 3.96(2H, bd), 3.79(2H, d), 3.70(3H, s), 2.88(2H, dt), 2.01(1H, m), 1.82(2H, bd), 1.30(2H, m), m/e 357 $(M+H)^+$; calculated for $C_{20}H_{24}N_2O_4.0.5H_2O$: C, 65.7; H, 6.9; N, 7.7. found: C, 66.1; H, 6.9; N, 7.8%.

EXAMPLE 158: 4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenoxyacetic acid.

Following the method of Example 2 but starting from the product of Example 157, the title compound was prepared in 86% yield: m.p. 278-281°C; NMR (d_6 DMSO + TFA) δ 8.09(2H, t), 7.08(2H, d), 6.78(4H, s), 4.50(2H, s), 4.20(2H, bd), 3.74(2H, d), 3.17(2H, bt), 2.12(1H, m), 1.91(2H, dm), 1.32(2H, m); m/e 343 $(M+H)^+$; calculated for $C_{19}H_{22}N_2O_4.0.25H_2O$: C, 65.8; H, 6.5; N, 8.1. found: C, 66.0; H, 6.6; N, 8.0%.

EXAMPLE 159: Methyl 4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenoxy-acetate

Following the method of Example 155, but starting from 4-(4-hydroxyethylpiperidin-1-yl)pyridine, the title compound was prepared in 65% yield: m.p. 86-88°C; NMR (d_6DMSO) δ 8.11(2H, d),

6.85(4H, s), 6.79(2H, d), 4.70(2H, s), 3.96(2H, t), 3.92(2H, bd), 3.69(3H, s), 2.81(2H, dt), 1.78(2H, bd), 1.73(1H, m), 1.65(2H, q), 1.20(2H, m); m/e 371 $(M+H)^+$; calculated for $C_{21}H_{26}N_2O_4$: C, 68.1; H, 7.1; N, 7.6. found: C, 67.5; H, 7.3; N, 7.5%.

EXAMPLE 160: 4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenoxyacetic acid

Following the method of Example 2, but starting from the product of Example 159, the title compound was prepared in 74% yield: m.p. 247-249°C; NMR (d_6 DMSO + TFA) δ 8.19(2H, t), 7.19(2H, d), 6.38(4H, s), 4.60(2H, s), 4.25(2H, bd), 4.01(2H, t), 3.20(2H, dt), 1.93(3H, m), 1.70(2H, q), 1.28(2H, m); m/e 357 $(M+H)^+$; calculated for $C_{20}H_{24}N_2O_4$: C, 67.4; H, 6.8; N, 7.9. found: C, 67.0; H, 6.8; N, 7.7%.

EXAMPLE 161: Methyl 3-[4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenyl]-propionate

Following the method of Example 155, but starting from 4-(4-hydroxymethylpiperidin-1-yl)pyridine and methyl 3-(4-hydroxyphenyl)propionate, the title compound was prepared in 14% yield:
m.p. 96.5-98.5°C; NMR (d_6DMSO) δ 8.13(2H, d), 7.11(2H, d), 6.83(4H, m), 3.97(2H, dm), 3.81(2H, d), 3.56(3H, s), 2.87(2H, dt), 2.77(2H, t), 2.57(2H, t), 2.01(1H, m), 1.84(2H, m), 1.30(2H, m); m/e 355 $(M+H)^+$; calculated for $C_{21}H_{26}N_2O_3.0.75H_2O$: C, 68.5; H, 7.2; N, 7.8. found: C, 68.5; H, 7.5; N, 7.6%.

EXAMPLE 162: 3-[4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenyl]propionic acid

Following the method of Example 2, but starting from the product of Example 161, the title compound was prepared in 80% yield: m.p. 303-307°C; NMR (d_6 DMSO + TFA) δ 8.20(2H, d), 7.25(6H, m), 4.31(2H, dm), 3.88(2H, d), 3.27(2H, bt), 2.82(2H, t), 2.52(2H, t),

2.25(1H, m), 2.00(2H, bd), 1.40(2H, m); m/e 341 $(M+H)^+$; calculated for $C_{20}H_{24}N_2O_3.0.25H_2O$: C, 69.6; H, 7.2; N, 8.1. found: C, 69.6; H, 7.2; N, 8.0%.

EXAMPLE 163: Methyl 4-[[1-(4-pyridyl)piperidin-4-yl]carboxamido]-phenoxyacetate, hydrochloride

Thionyl chloride (5 ml) was added dropwise over ten minutes to a stirred suspension of 1-(4-pyridyl)-4-piperidinecarboxylic acid (2.06 g) in dry dichloromethane (20 ml) at 4°C. After 1 hour at 4°C, the mixture was allowed to reach ambient temperature and stirred for 16 hours. The solvent was removed by evaporation and the residue dried under high vacuum to give a solid foam (2.84 g).

Triethylamine (0.70 ml) was added to a stirred suspension of methyl 4-aminophenoxyacetate hydrochloride (544 mg) in dry dichloromethane (10 ml). After stirring for 1 hour, the mixture was cooled to 4°C, and the foam (0.71 g) added. After 1 hour at 4°C the mixture was allowed to reach ambient temperature and stirred for 16 hours. The precipitated solid was collected, washed with dichloromethane and, on recrystallisation from water, gave the title compound, 744 mg: m.p. 233-234.5°C; NMR (d_6DMSO) δ 13.56(1H, b), 9.98(1H, s), 8.21(2H, d), 7.51(2H, d), 7.20(2H, d), 6.85(2H, d), 4.72(2H, s), 4.25(2H, bd), 3.69(3H, s), 3.27(2H + H_2O), 2.78(1H, m), 1.97(2H, m), 1.67(2H, m); m/e 370 $(M+H)^+$; calculated for $C_{20}H_{23}N_3O_4.HCl$: C, 59.2; H, 6.0; N, 10.4. found: C, 58.8; H, 6.1; N, 10.3%.

EXAMPLE 164: 4-4-[[1-([1-(4-pyridyl)piperidin-4-yl]carboxamido]-phenoxyacetic acid

Following the method of Example 2, but starting from the product of Example 163, the title compound was prepared in 69% yield: m.p. 285-287°C; NMR(NaOD) δ 8.30(2H,d), 7.44(2H,d), 7.07(2H,d), 7.04(2H,d), 4.60(2H,s), 4.14(2H,bd), 3.11(2H,dt), 2.81(1H,m),

2.11(2H,bd), 1.88(2H,dq); m/e 356$(M+H)^+$; calculated for $C_{19}H_{21}N_3O_4 \cdot H_2O$: C, 61.1; H, 6.2; N, 11.3. found: C, 60.9; H, 6.2; N, 11.0%.

EXAMPLE 165: Methyl 4-[2-[(1-(4-pyridyl)piperidin-4-yl]-acetamido]phenoxyacetate.

To a stirred solution of 1-(4-pyridylpiperidin-4-yl)acetic acid hydrochloride (400mg) in dry DMF (5ml) was added N,N'-diisopropylethylamine (1.1ml), HOBT (240mg), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (600mg). After 15 minutes methyl 4-aminophenoxyacetate (280mg) was added and stirring continued overnight. The reaction mixture was added to ethyl acetate (100ml) and this mixture washed with water, 10% w/v sodium hydrogen sulphate solution and brine, then dried ($MgSO_4$) and evaporated. Purification of the resulting gum by flash chromatography, first on silica eluting with 0 to 5% v/v methanol/dichloromethane and then on neutral alumina eluting with 2% v/v methanol/dichloromethane gave, on trituration with diethyl ether the title compound, 55mg, as an off-white solid: m.p. 155-157°C; NMR(d_6DMSO) δ 9.74(1H,s), 8.11(2H,d), 7.48(2H,d), 6.86(2H,d), 6.79(2H,d), 4.73(2H,s), 3.91(2H,bd), 3.70(3H,s), 2.84(2H,dt), 2.21(2H,d), 2.03(1H,m), 1.72(2H,bd), 1.22(2H,dq); m/e 384$(M+H)^+$; calculated for $C_{21}H_{25}N_3O_4 \cdot 0.5\ H_2O$: C, 64.5; H, 6.6; N, 10.7. found: C, 64.7; H, 6.8; N, 10.8%.

The starting material was prepared as follows:-

(i) A mixture of ethyl 4-carboxymethylpiperidine (from Example 29 step (b) (3.25g), triethylamine (5.28ml), 4-chloropyridine hydrochloride (2.85g) and xylene (100ml) was heated at reflux temperature overnight. The mixture was cooled, the precipitate removed by filtration and the filtrate evaporated. A solution of the residue in dichloromethane was washed with water, then dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica, eluting with 10% v/v methanol/dichloromethane, gave ethyl 1-(4-pyridylpiperidin-4-yl)acetate, 2.15g, as an oil: NMR($CDCl_3$) δ

8.23(2H,d), 6.64(2H,d), 4.26(2H,q), 3.88(2H,dm), 2.89(2H,dt), 2.27(2H,d), 2.05(1H,m), 1.83(2H,dm), 1.36(2H,dq), 1.27(3H,t); m/e 249$(M+H)^+$.

(ii) A mixture of the product from step (i) (2.20g), 1 molar hydrochloric acid (35.5ml) and dioxane (100ml) was heated at 95°C for 3 hours. The resulting solution, on freeze-drying, gave 1-(4-pyridylpiperidin-4-yl)acetic acid hydrochloride, 2.3g, as a light-brown powder: m.p. 105-108°C; NMR(d_6DMSO) δ 13.57(1H,b), 8.18(2H,d), 7.17(2H,d), 4.21(2H,bd), 3.17(2H,dt), 2.21(2H,d), 2.09(1H,m), 1.83(2H,dm); 1.22(2H,dq); m/e 221$(M+H)^+$; calculated for $C_{12}H_{16}N_2O_2$. HCl. 1.25 H_2O: C, 51.6; H, 7.0; N, 10.0; Cl,12.7. found C, 51.7; H, 7.0; N, 9.8; Cl,12.2%.

EXAMPLE 166: 4-[2-[1-(4-pyridyl)piperidin-4-yl]acetamido]phenoxyacetic acid dihydrochloride

A mixture of the product from Example 165 (30mg), 1 molar hydrochloric acid (0.40ml), water (2ml) and dioxane (1ml) was heated at 95°C for 1 hour. The resulting solution, on freeze-drying and trituration of the residue with ether, gave the title compound, 25mg, as a light brown solid: m.p. 158-162°C; NMR(d^6DMSO + d^4 acetic acid) 8.17(2H,d), 7.49(2H,d), 7.20(2H,d), 6.85(2H,d), 4.61(2H,s), 4.23(2H,bd), 3.21(2H,bt), 2.21(3H,m); 1.86(2H,bd + acetic acid), 1.28(2H,bq); m/e 370 $(M+H)^+$; calculated for $C_{20}H_{23}N_3O_4$. 2HCl. 1.25 H_2O: C, 51.7; H, 5.9; N, 6.0. found: C, 51.6; H, 6.0; N, 9.2%.

EXAMPLE 167: 4-[[1-(4-pyridyl)piperidin-4-yl]aminocarbonyl]-phenoxyacetic acid dihydrochloride

Following the method of Example 166, but starting from tertiary butyl 4-[[1-(4-pyridyl)piperidin-4-yl]aminocarbonyl]-phenoxyacetate (50mg), but with the removal of the insoluble precipitate before freeze-drying, the title compound was prepared in 50% yield: m.p. 278-280°C; NMR(d_6DMSO + d_4 acetic acid) δ 8.19(2H,d), 7.82(2H,d), 7.20(2H,d), 6.98(2H,d), 4.74(2H,s), 4.23(3H,m), 3.38(2H,bt), 2.04(2H,m), 1.64(2H,m); m/e 356 $(M+H)^+$; calculated for

$C_{19}H_{21}N_3O_4$. 2HCl. 1.25 H_2O: C, 50.6; H, 5.7; N, 9.3. found: C, 50.6; H, 5.7; N, 9.2%.

The starting material were prepared as follows.

(i) Acetyl chloride (3.95ml) was added dropwise to a stirred solution of 4-aminol-benzylpiperidine (10.0g) and triethylamine (7.7ml) in dry dichloromethane (100ml) at 4°C. The mixture was allowed to reach ambient temperature and stirred for 16 hours. Water was then added, the organic phase separated and dried ($MgSO_4$), and removal of the solvent by evaporation gave 4-acetylamino-1-benzylpiperidine, 10.23g, as a light brown solid which was used without further purification: NMR ($CDCl_3$) δ 7.29(5H,m), 5.29(1H,b), 3.79(1H,m), 3.49(2H,s), 2.80(2H,dm), 2.12(2H,dt), 1.95(3H,s), 1.91(2H,dm), 1.46(2H,dq); m/e 233 $(M+H)^+$.

(ii) 10% w/w Palladium on charcoal (1.5g) was added to a solution of the product from step (i) (10.0g), 1 molar hydrochloric acid (21.5ml) and methanol (150ml) and the mixture hydrogenated at room temperature and pressure until the theoretical amount of hydrogen had been taken up. Charcoal was added, the mixture stirred for 1 hour then filtered through diatomaceous earth and the filtrate evaporated to dryness giving 4-acetylaminopiperidine hydrochloride, 8.64g, as a sticky foam: NMR ($CDCl_3$ + d_6DMSO). δ 9,72(1H,b), 9.02(1H,b), 7.40(1H,bd), 3.87(1H,m), 3.30(2H,m), 2.81(2H,m), 1.86(4H,m), 1.80(3H,s); m/e 143 $(M+H)^+$.

(iii) A mixture of the product from step (ii) (1.79g), 4-chloropyridine hydrochloride (1.50g), sodium hydrogen carbonate (2.86g) in 3-methyl 1-butanol (25ml) was heated at reflux temperature for 16 hours. The cooled mixture was filtered and the filtrate concentrated <u>in vacuo</u>. Purification of the residue by flash chromatography on silica, eluting with methanol/dichloromethane (1:2 v/v) gave 4-acetylamino-1-(4-pyridyl)piperidine as a foam, 0.69g: NMR(d_6DMSO) δ 8.10(2H,d), 7.80(1H,bd), 6.80(2H,dd), 3.82(3H,m), 2.93(2H,dt), 1.78(3H,s), 1.77(2H,m), 1.33(2H,dq); m/e 220 $(M+H)^+$.

(iv) The product from step (iii) (0.52g) in 1 molar hydrochloric acid (11.9ml) was heated at 95°C for 5 hours. The solvent was evaporated and the residue, on drying over potassium hydroxide <u>in vacuo</u> gave 4-amino-1-(4-pyridyl)piperidine trihydrochloride hydrate,

0.70g as a light brown solid: m.p. >300°C; NMR (d_6DMSO) δ 8.28(4H,m), 7.22(2H,d), 4.27(2H,bd), 3.5 to 3.15(3H + H_2O), 2.09(2H,m), 1.59(2H,dq); m/e 178$(M+H)^+$; calculated for $C_{10}H_{15}N_3$. 3HCl. 0.75 H_2O: C, 40.0; H, 6.5; N, 14.0. found: C, 40.4; H, 6.3; N, 13.5%.

(v) A mixture of benzyl 4-hydroxybenzoate (4g), t-butyl bromoacetate (3.7g), powdered anhydrous potassium carbonate (2.4g) and acetone (100ml) was heated at reflux for 3 days. The reaction mixture was cooled and then filtered and the filtrate evaporated to dryness to give a viscous oil (6.37g). A portion of this oil (3.4g) was dissolved in methanol (30ml) and ammonium formate (4g) was added. The resultant solution was covered with a blanket of argon before a slurry of 10% Pd on C (100mg) in methanol (5ml), also under argon, was added. The reaction mixture was stirred at room temperature for 18 hours then the catalyst was filtered off through a pad of kieselguhr and washed with ethanol and water. The combined filtrate and washings were evaporated to dryness and the residue was partitioned between dichloromethane and aqueous sodium bicarbonate. The aqueous layer was separated, washed with dichloromethane and then carefully acidified with dilute aqueous citric acid solution. A solid precipitated which was collected, washed with water and air-dried to give 4-t-butoxycarbonylmethoxybenzoic acid (1.45g), as a white crystalline solid: m.p. 119-121°C.

(vi) Following the method of Example 165, but starting from the product of step (v) and the product from step (iv) and purification by flash chromatography on silica eluting with 0-5% v/v methanol/dichloromethane there was obtained tertiary butyl 4-[[1-(4-pyridyl)piperidin-4-yl]aminocarbonyl]phenoxyacetate hexafluorophosphate in 49% yield as a white solid: m.p. 196-198°C; NMR(d_6DMSO) δ 8.21(2H,d), 8.18(1H,d), 7.80(2H,d), 7.19(2H,d), 6.95(2H,d), 4.72(2H,s), 4.20(3H,m), 3.5-3.1(4H + H_2O), 1.98(2H,m), 1.59(2H,m), 1.42(9H,s); m/e 412 $(M+H)^+$; calculated for $C_{23}H_{29}N_3O_4$. HPF_6: C, 49.6; H, 5.4; N, 7.5. found: C, 49.1; H, 5.5; N, 7.3%. The free base was generated by flash chromatography on neutral alumina eluting with 1% v/v methanol dichloromethane and used in the preparation of the acid.

EXAMPLE 168: 4-[[1-(4-pyridyl)piperidin-4-yl]methylaminocarbonyl]-phenoxyacetic acid

Following the method of Example 166, but starting from tertiary butyl 4-[[1-(4-pyridyl)piperidin-4-yl]methylaminocarbonyl]-phenoxyacetate, the title compound was prepared in 95% yield: m.p. 84-86°C; NMR (d_6DMSO) δ 8.38(1H,t), 8.18(2H,d), 7.81(2H,d), 7.19(2H,d), 6.95(2H,d), 4.73(2H,s), 4.20(2H,bd), 3.8 to 3.0(H_2O), 1.99(1H,m), 1.84(2H,bd), 1.21(2H,m); m/e 370 $(M+H)^+$.

The starting material was prepared as follows:-

(i) Following the method of Example 167 step (i), but starting from 1-tertiarybutyloxycarbonylpiperidin-4-ylmethylamine tosylate there was prepared N-[(1-tertiarybutyloxycarbonylpiperidin-4-yl)-methyl]acetamide in 95% yield as an oil which slowly crystallised: NMR ($CDCl_3$) δ 5.52(1H,b), [illegible]2H,bd), 3,14(2H,m), 2.68(2H,dt), 1.98(3H,s), 1.67(3H,m), 1.44(9H,s), 1.12(2H,dq); m/e 257 $(M+H)^+$.

The product was used in step (ii) without further purification.

(ii) A solution of the product from step (i) (6.50g) in trifluoroacetic acid (50ml) was stirred overnight. The solvent was evaporated and the residue, on purification by flash chromatography on neutral alumina, eluting with 10% v/v methanol/dichloromethane gave N-[4-piperidinylmethyl]acetamide, 3.78g, as a yellow oil: NMR (d^4 acetic acid) δ 3.22(2H,bd), 2.96(2H,d), 2.81(2H,dt), 1.83(3H,s), 1.76(2H,bd), 1.67(1H,m), 1.26(2H,dq); m/e 157 $(M+H)^+$.

(iii) Following the method of Example 165 step (i), but starting from the product of (ii) above and purification by flash chromatography on silica eluting with 20 to 33% v/v methanol/dichloromethane there was obtained 4-(4-acetylaminomethylpiperidin-1-yl)pyridine in 28% yield as a gummy solid: NMR (d_6DMSO) δ 8.18(2H,d), 7.90(1H,t), 7.07(2H,d), 4.12(2H,bd), 3.05(2H,dt), 2.95(2H,t), 1.80(3H,s), 1.77(3H,m), 1.13(2H,m); m/e 234 $(M+H)^+$.

(iv) Following the method of Example 167 step (iv), but starting from the product of (iii) above, there was obtained 4-(4-aminomethylpiperidin-1-yl)pyridine in 95% yield as a yellow gum:

NMR (d_6DMSO) δ 8.26(4H,m), 7.21(2H,d), 4.26(2H,bd), 3.19(2H,dt), 2.74(2H,t), 2.05(1H,m), 1.92(2H,bd), 1.26(2H,dq); m/e 192 $(M+H)^+$.

(v) Following the method of Example 165, but starting from the product of Example 167 step (v) and the product from step (iv) above and purification by flash chromatography on silica, eluting with 0 to 5% v/v methanol/dichloromethane and trituration with diethyl ether there was obtained tertiary butyl 4-[[1-(4-pyridyl)piperidin-4-yl)]-methylaminocarbonyl]phenoxyacetate hexafluorophosphate in 35% yield as a white solid: m.p. 182-184°C; NMR (d_6DMSO) δ 13.11(1H,b), 8.37(1H,t), 8.17(2H,d), 7.80(2H,d), 7.19(2H,d), 6.95(2H,d), 4.72(2H,s), 4.21(2H,bd), 3.19(4H,m), 2.00(1H,m), 1.86(2H,m), 1.43(9H,s), 1.21(2H,m); m/e 426$(M+H)^+$; calculated for $C_{24}H_{31}N_3O_4 . HPF_6 . 0.5\ H_2O$: C, 49.6; H, 5.7; N, 7.2; P, 5.4. found: C, 49.6; H, 5.7; N, 7.1; P, 5.8%.

EXAMPLE 169: 4-[[1-(4-pyridyl)piperidin-4-yl]carboxamido]phenylacetic acid

Following the method of Example 2, but starting from methyl 4-[[1-(4-pyridyl)piperidin-4-yl]carboxamido]phenylacetate hydrochloride the title compound was prepared in 93% yield: m.p. 281-282°C; NMR (d_6DMSO) δ 9.87(1H,s), 8.13(2H,d), 7.51(2H,d), 7.16(2H,d), 6.83(2H,dd), 4.00(2H,dm), 3.49(2H,s), 2.90(2H,dt), 2.61(1H,m), 1.87(2H,dd), 1.66(2H,dq); m/e 340 $(M+H)^+$; calculated for $C_{19}H_{21}N_3O_3$: C, 67.2; H, 6.2; N, 12.4. found: C, 67.4; H, 6.2; N, 12.4%.

The starting material was prepared as follows:-

(i) Following the method of Example 163, but starting from methyl 4-aminophenylacetate hydrochloride, methyl 4-[[1-(4-pyridyl)piperidin-4-yl]carboxamido]phenylacetate hydrochloride was prepared in 78% yield: m.p. 235-236.5°C; NMR (d_6DMSO) δ 13.61(1H,b), 10.10(1H,s), 8.21(2H,d), 7.55(2H,d), 7.21(2H,d), 7.16(2H,d), 4.28(2H,dm), 3.60(5H,s), 3.30(2H,m + H_2O), 2.81(1H,m), 1.98(2H,m), 1.67(2H,m); m/e 354$(M+H)^+$; calculated for $C_{20}H_{23}N_3O_3 .$ HCl: C, 61.6; H, 6.2; N, 10.8. found: C, 61.7; H, 6.3; N, 10.6%.

EXAMPLE 170: N-[4-[4-[1-(4-pyridyl)piperidin-4-yl]carboxamidophenyl]-methyl]-1-butanesulphonamide

4-[1-(4-pyridyl)piperidin-4-ylcarboxamido]benzylamine dihydrochloride, hydrate (1.09g) was dissolved in water and treated with 1 molar sodium hydroxide and the mixture stirred for 3 hours. The solid precipitate was collected, washed with water and dried to give 4-[1-(4-pyridyl)piperidin-4-ylcarboxamido]benzylamine (840mg). 1-Butanesulphonyl chloride (0.08ml) was added to a stirred solution under argon of the amine (160mg) and triethylamine (0.09ml) in dry DMF at 4°C. After 2 hours, the solvent was evaporated in vacuo. The residue was dissolved in water, 1 molar sodium hydroxide added and the precipiate collected and dried. Purification of this solid by flash chromatography on silica, eluting with 15% v/v methanol/dichloromethane and recrystallisation from methanol gave the title compound, 146mg: m.p. 98-101°C; NMR(d_6DMSO) δ 9.90(1H,s), 8.24(2H,d), 7.56(2H,d), 7.50(1H,t), 7.24(2H,d), 6.82(2H,d), 4.06(2H,d), 3.99(2H,dm), 2.89(4H,m), 2.61(1H,m), 1.85(2H,dd), 1.62(4H,m), 1.30(2H,m), 0.82(3H,t); m/e 431 $(M+H)^+$; calculated for $C_{22}H_{30}N_4O_3S.\ H_2O$: C, 58.9; H, 7.2; N, 12.5. found: C, 58.5; H, 7.3; N, 12.3%.

The starting material was prepared as follows:-

(i) A mixture of 4-nitrobenzylamine hydrochloride (5.00g), triethylamine (25ml), dry DMF (25ml) and di-tertiary-butyl dicarbonate (6.07g) was stirred for 16 hours then the solvent was evaporated in vacuo. The residue was partitioned between ethyl acetate (200ml) and water (50ml), separated and the organic phase washed successively with water, 0.5 molar sodium hydroxide, water and brine, dried ($MgSO_4$) and evaporated. Recrystallisation of the solid residue from ethyl acetate/hexane gave N-tertiary-butyloxycarbonyl 4-nitrobenzylamine, 5.65g: m.p. 110-111°C; NMR(d_6DMSO) δ 8.19(2H,d), 7.52(1H,bt), 7.51(2H,d), 4.24(2H,d), 1.40(9H,s); m/e 253$(M+H)^+$; calculated for $C_{12}H_{16}N_2O_4$: C, 57.1; H, 6.4; N, 11.1. found: C, 56.9; H, 6.3; N, 10.9%.

(ii) 10% w/w palladium on charcoal (250mg) was added to a solution of the product from step (i) (5.37g) in ethanol (100ml) and the mixture hydrogenated at room temperature and pressure until the theoretical amount of hydrogen had been taken up. Charcoal was added, the mixture stirred for 10 minutes then filtered through diatomaceous earth and the filtrate evaporated to dryness. The solid residue, on recrystallisation from ethyl acetate/hexane gave 4-(N-tertiary-butyloxycarbonylaminomethyl)aniline, 4.20g: m.p. 80-81°C; NMR (d_6DMSO) δ 7.10(1H,bt), 6.88(2H,d), 6.49(2H,d), 4.92(2H,s), 3.92(2H,d), 1.38(9H,s); m/e 223$(M+H)^+$; calculated for $C_{12}H_{18}N_2O_2$: C, 64.8; H, 8.2; N, 12.6. found: C, 65.4; H, 8.3; N, 13.0%.

(iii) Thionyl chloride (5ml) was added dropwise over ten minutes to a stirred suspension of 1-(4-pyridyl)-4-piperidinecarboxylic acid (5.15g) in dry dichloromethane (20ml) at 4°C. After 1 hour at 4°C, the mixture was allowed to reach ambient temperature and stirred for 16 hours. The solvent was removed by evaporation and the residue dried under high vacuum to give a solid foam (7.06g).

The foam (4.31g) was added, under argon, to a stirred solution of the product from step (ii) (3.55g) and triethylamine (4.59ml) in dry dichloromethane (150ml) at 4°C. After 1 hour at 4°C, the mixture was allowed to reach ambient temperature and stirred for 16 hours. Dichloromethane (150ml) was added and the mixture washed with water (3 x 30ml), dried ($MgSO_4$) and evaporated. The solid residue on recrystallisation from ethyl acetate gave N-tertiary-butyloxycarbonyl 4-[1-(4-pyridyl)piperidin-4-ylcarboxamido]benzylamine, 4.22g: m.p. 215-217°C. NMR(d_6DMSO) δ 9.88(1H,s), 8.15(2H,d), 7.52(2H,d), 7.30(1H,t), 7.14(2H,d), 6.82(2H,d), 4.02(4H,m), 2.90(2H,dt), 2.61(1H,m), 1.87(2H,dd), 1.65(2H,dq); m/e 411 $(M+H)^+$; calculated for $C_{23}H_{30}N_4O_3$: C, 67.3; H, 7.4; N, 13.6. found: C, 67.3; H, 7.4; N, 13.5%.

(iv) A hydrogen chloride solution in dry ether (40ml) was added to a stirred suspension of the product of step (iii) (4.10g) in acetonitrile (100ml) under argon. After 2.5 hours, the solid was collected, washed with dry ether and dried over potassium hydroxide to give 4-[1-(4-pyridyl)piperidin-4-ylcarboxamido]benzylamine

dihydrochloride, 3.78g, as a white solid: m.p. 286-289°C; NMR(d_6DMSO) δ 13.69(1H,b), 9.96(1H,s), 8.39(3H,b), 8.23(2H,d), 7.66(2H,d), 7.40(2H,d), 7.22(2H,d), 4.27(2H,bd), 3.93(2H,m), 3.26(2H,m), 2.86(1H,m), 2.00(2H,bd), 1.69(2H,bq); *m/e* 311 $(M+H)^+$; calculated for $C_{18}H_{22}N_4O$. 2HCl. 0.5 H_2O: C 55.1; H, 6.4; N, 14.3. found. C, 54.9; H, 6.4; 13.9%.

EXAMPLE 171: N-[4-[4-[1-(4-pyridyl)piperidin-4-yl]carboxamidophenyl]-methyl]-4-methylphenylsulphonamide

4-Methylphenylsulphonyl chloride (419mg) was added to a stirred mixture of the product of Example 170 step (iv) (766mg), triethylamine (0.86ml) and dry DMF (15ml) at 4°C. After 1 hour, the mixture was allowed to attain ambient temperature and stirred for 16 hours. Then further 4-methylphenylsulphonyl chloride (210mg) and triethylamine (0.17ml) were added and stirring continued for 24 hours. The precipitated solid was collected, washed with dichloromethane and water. This solid was suspended in 1 molar sodium hydroxide, the mixture stirred for 3 hours. The solid was collected, washed well with water and on drying, gave the title compound, 734mg: m.p. 124-127°C; NMR (d_6DMSO) δ 9.37(1H,s), 8.15(2H,b), 7.94(1H,t), 7.67(2H,d), 7.48(2H,d), 7.36(2H,d), 7.12(2H,d),6.32(2H,bd), 3.99(2H,bd), 3.87(2H,d), 2.90(2H,bt), 2.58(1H,m), 2.48(3H,s), 1.84(2H,bd), 1.63(2H,dq); m/e 465 $(M+H)^+$; calculated for $C_{25}H_{28}N_4O_3S$. 1.25 H_2O: C, 61.6; H, 6.3; N, 11.5; S, 6.6. found: C, 61.5; H, 6.1; N, 11.2; S, 7.0%.

EXAMPLE 172: 4-Methyloxycarbonylmethylaminophenyl [1-(4-pyridyl)-piperidin-4-yl]acetate

Thionyl chloride (1ml) was added dropwise to a stirred suspension of [1-(4-pyridyl)piperidin-4-yl]acetic acid (300mg) in dry dichloromethane (5ml) and the mixture stirred for 4 hours. The solvent was evaporated and the residue triturated with hexane and dried under high vacuum over potassium hydroxide to give a solid foam.

A solution of the foam in dry dichloromethane (5ml) was added dropwise to a stirred solution of methyl N-(4-hydroxyphenyl)-glycinate (210mg) and triethylamine (0.33ml) in dry dichloromethane (10ml) and the mixture stirred for 16 hours. The mixture was diluted with dichloromethane, washed with water, dried and evaporated. Purification by flash chromatography on silica, eluting with 0 - 10% v/v methanol/dichloromethane and trituration of the resulting gum with diethyl ether gave the title compound, 80mg, as a white solid: m.p. 120-122°C; NMR(d_6DMSO), δ 8.13(2H,d), 6.84(2H,d), 6.81(2H,d), 6.54(2H,d), 6.01(1H,t), 3.96(2H,bd), 3.90(2H,d), 3.66(3H,s), 2.90(2H,dt), 2.50(2H,d + DMSO), 2.07(1H,m), 1.81(2H,bd), 1.30(2H,dq); m/e 384$(M+H)^+$; calculated for $C_{21}H_{25}N_3O_4$. 0.5 H_2O: C, 64.3; H, 6.6; N, 10.7. found: C, 64.2; H, 6.3; N, 10.7%.

EXAMPLE 173: Methyl 4-[2-[1-(4-pyridyl)piperidin-4-yl]acetyl]-phenoxyacetate

Oxalyl chloride (2.40 ml) was added to a stirred suspension of [1-(4-pyridyl)piperidin-4-yl]acetic acid hydrochloride hydrate (1.25 g) in dry dichloromethane under argon. A few drops of dry DMF were added and the mixture stirred for 30 minutes to give a clear solution. The solvent was removed in vacuo and the residue dried. The resulting solid foam was suspended in dichloroethane (40 ml), the suspension cooled to 4°C and with stirring, aluminium chloride (3.21 g) added. After 30 minutes the mixture was allowed to warm to ambient temperature when methyl phenoxyacetate (1.16 ml) was added and stirring continued for a further 2.5 hours. The mixture was added to an ice-water mixture to which was added dichloromethane. The aqueous phase was adjusted to pH7 and the solid removed by filtration. The filtrate was extracted three times with dichloromethane and the extracts dried ($MgSO_4$). Evaporation of the solvent gave a clear oil which crystallised on addition of ether. The solid was collected and on recrystallisation from methyl acetate gave the title compound, 1.06 g: m.p. 137-138°C; NMR (d_6DMSO) δ 8.11 (2H, b). 7.94 (2H, d), 7.03 (2H, d), 6.78 (2H, bd), 4.91 (2H, s), 3.90 (2H, d), 3.71 (3H, s), 2.91 (2H, d), 2.85 (2H, dt), 2.12 (1H, m), 1.75 (2H, bd), 1.26 (2H, dq);

m/e 369 $(M+H)^+$; calculated for $C_{21}H_{24}N_2O_4$: C, 68.5; H, 6.6; N, 7.6. found C, 68.2; H, 6.5; N, 7.5%.

The starting [1-(4-pyridyl)piperidin-4-yl]acetic acid hydrochloride hydrate is described in Example 165 steps (i) and (ii).

EXAMPLE 174: 4-[2-[1-(4-pyridyl)piperidin-4-yl]acetyl]phenoxyacetic acid hydrochloride.

A mixture of the product of Example 173 (300 mg), dioxan (10 ml) and 1 molar hydrochloric acid (2.7 ml) were stirred for 80 hours at ambient temperature. The solvent was removed in vacuo and a little water added. The resulting solid was collected, washed with water and, after drying, gave the title compound, 170 mg: m.p. 239-241°C; NMR (D_2O) δ 8.17 (2H, d), 8.15 (2H, d), 7.36 (2H, d), 7.20 (2H, d), 5.01 (2H, s), 4.33 (2H, d), 3.38 (2H, dt), 3.16 (2H, d), 2.48 (1H, m), 2.08 (2H, d), 1.54 (2H, dq); m/e 355 $(M+H)^+$; calculated for $C_{20}H_{22}N_2O_4.HCl.1.5H_2O$: C, 57.4; H, 6.1; N, 6.7. found: C, 57.3; H, 6.1; N, 6.4%.

EXAMPLE 175: Methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]-2,2-dimethylacetyl]phenoxyacetate.

Methyl 4-(2,2-dimethylbromoacetyl)phenoxyacetate (1.58 g) was added to a stirred solution of 1-(4-pyridyl)piperazine (1.63 g) in acetonitrile (40 ml). After 34 days, the solid formed was removed by filtration and the filtrate evaporated to give an oil. Purification by flash chromatography on silica, eluting with 0.5 to 4.0% v/v methanol/ dichloromethane gave the title compound, 240 mg, as a white foam:
NMR (d_6DMSO) δ 8.49 (2H, d), 8.12 (2H, d), 6.96 (2H, d), 6.77 (2H, d), 4.87 (2H, s), 3.69 (3H, s), 3.28 (4H, t), 2.58 (4H, t), 1.25 (6H, s); m/e 398 $(M+H)^+$; calculated for $C_{22}H_{27}N_3O_4.0.25H_2O$: C, 65.7; H, 6.8; N, 10.4. found: C, 65.3; H, 6.9; N, 10.4%.

The necessary starting material was prepared as follows:-

(i) Following the method of Example 118 step (i) but starting from 4-(2,2-dimethylacetyl)phenol and only stirring for 18 hours

instead of 2 days. there was obtained methyl 4-(2,2-dimethylacetyl)-phenoxyacetate, in 90% yield, as an off-white crystalline solid: m.p. 45-46°C; NMR (d_6DMSO) δ 7.92 (2H, d), 7.02 (2H, d), 4.90 (2H, s), 3.71 (3H, s), 3.60 (1H, m), 1.09 (6H, d).

(ii) Bromine (2.09 ml) was added dropwise over ten minutes to a stirred solution of the product of step (i) above (9.44 g) in carbon tetrachloride (200 ml). The solution was stirred for 16 hours, then the solvent was evaporated in vacuo to give an orange oil. A solution of this oil, in a small volume of dichloromethane, was filtered through silica and the clear filtrate, on evaporation, gave methyl 4-(2-bromo-2,2-dimethylacetyl)phenoxyacetate, 11.3 g, as a white crystalline solid: m.p. 46-50°C; NMR (d_6DMSO) δ 8.09 (2H, d), 7.05 (2H, d), 4.92 (2H, s), 3.72 (3H, s), 2.00 (6H, s).

EXAMPLE 176: 4-[2-[4-(4-pyridyl)piperazin-1-yl]-2,2-dimethylacetyl]-phenoxyacetic acid.

Following the method of Example 2 but starting from the product of Example 175 and stirring for 16 hours instead of 2 hours, the title compound was obtained in 76% yield, as a white crystalline solid: m.p. 278-279°C; NMR (D_2O) δ 8.72 (2H, d), 8.20 (2H, d), 7.16 (4H, d), 4.76 (2H, s), 3.80 (4H, bt), 2.91 (4H, bt), 1.55 (6H, s); m/e 406 $(M+Na)^+$, 384 $(M+H)^+$; calculated for $C_{21}H_{25}N_3O_4.0.5NaCl$: C, 61.1; H, 6.1; N, 10.2. found: C, 60.8; H, 5.9; N, 10.0%.

EXAMPLE 177: RS Methyl 4-[3-[4-(4-pyridyl)piperazin-1-yl]-2-methyl-propanoyl]phenoxyacetate.

A stirred mixture of methyl 4-(2,2-dimethylbromoacetyl)-phenoxyacetate (3.15 g), and 1-(4-pyridyl)piperazine (3.26 g) in acetonitrile (200 ml) was heated at reflux temperature for 4 days. The solvent was removed in vacuo and the residue partioned between dichloromethane/water. The organic phase was dried ($MgSO_4$), evaporated and then purified by flash chromatography on silica, eluting with 2 to 5% v/v methanol/dichloromethane. Further purification by flash chromatography on neutral alumina, eluting with

dichloromethane, gave the title compound, 350 mg, as a clear oil: NMR (d_6DMSO) δ 8.12 (2H, d), 7.98 (2H, d), 7.04 (2H, d), 6.75 (2H, d), 4.92 (2H, s), 3.86 (1H,m), 3.71 (3H, s), 3.19 (4H, t), 2.70 (1H, q), 2.49 (DMSO+4H), 2.36 (1H, q), 1.09 (3H, s), trace of dichloromethane; m/e 398 $(M+H)^+$; calculated for $C_{22}H_{27}N_3O_4.0.1\ CH_2Cl_2$: C, 65.3; H, 6.7; N, 10.3. found: C, 65.1; H, 6.9; N, 10.1%.

EXAMPLE 178: Methyl 4-[4-[4-(4-pyridyl)piperazin-1-yl]methylphenyl]-butyrate.

1-(4-Pyridyl)piperazine (1.63 g) was dissolved in warm acetonitrile (25 ml), the solution cooled to 30°C and with stirring, a solution of methyl 4-(4-bromomethylphenyl)butyrate in acetonitrile (5 ml) added. After 30 minutes the resulting precipitate was removed by filtration and the filtrate concentrated in vacuo to give a yellow oil. Purification by flash chromatography on silica, eluting with 0 to 4% v/v methanol/dichloromethane gave a solid. Trituration with ether and removal of the insoluble solid gave a clear solution. Concentration of this solution gave the title compound, 0.90 g, as a white fluffy solid: m.p. 126-127°C; NMR (d_6DMSO) δ 8.14 (2H, d), 7.24 (2H, d), 7.14 (2H, d), 6.77 (2H, d), 3.59 (3H, s), 3.48 (2H, s), 3.30 (4H, t), 2.59 (2H, t), 2.47 (4H, t), 2.32 (2H, t), 1.63 (2H, m); m/e 354 $(M+H)^+$; calculated for $C_{21}H_{27}N_3O_2.0.25H_2O$: C, 70.4; H, 7.7; N, 11.7. found: C, 70.6; H, 7.6; N, 11.7%.

EXAMPLE 179: Methyl 5-[4-[4-(4-pyridyl)piperazin-1-yl]methylphenyl]-pentanoate.

A mixture of methyl 5-(4-bromomethylphenyl)pentanoate and 5-(2-bromomethylphenyl)pentanoate, 70:30 w/w by NMR, prepared according to the method for the starting material in Example 178 (2.14 g) was reacted in a similar manner to Example 178. The crude mixture of esters was purified by flash chromatography on silica, eluting with 0-5% v/v methanol/dichloromethane. Evaporation of the appropriate fractions gave the title compound, 605 mg, as a waxy solid: m.p. 53-54°C; NMR (d_6DMSO) δ 8.13 (2H, d), 7.23 (2H, d), 7.14 (2H, d), 6.79

(2H, d), 3.58 (3H, s), 3.47 (2H, s), 3.30 (4H, t + H_2O), 2.57 (2H, t), 2.46 (4H, t), 2.32 (2H, t), 1.56 (4H, m); m/e 368 $(M+H)^+$; calculated for $C_{22}H_{29}N_3O_2.0.5H_2O$: C, 70.1; H, 8.0; N, 11.2. found: C, 70.3; H, 8.2; N, 11.0%.

EXAMPLE 180: 4-[4-[4-(4-pyridyl)piperazin-1-yl]methylphenyl]butyric acid, dihydrochloride.

Following the method of Example 123 but starting from the product of Example 178 and heating at 100°C for 4 hours instead of 1.5 hours the title compound was prepared in 88% yield: m.p. 236-238°C; NMR (D_2O) δ 8.40 (2H, d), 7.66 (2H, d), 7.61 (2H, d), 7.36 (2H, d), 4.61 (2H, s), 4.19 (4H, b), 3.69 (4H, b), 2.94 (2H, t), 2.61 (2H, t), 2.15 (2H, m); m/e 340 $(M+H)^+$; calculated for $C_{20}H_{25}N_3O_2.2HCl.0.5H_2O$: C, 57.0; H, 6.6; N, 10.0. found: C, 57.2; H, 6.9; N, 9.8%.

EXAMPLE 181: Mixture of 5-[4-[4-(4-pyridyl)piperazin-1-yl]-methylphenyl]pentanoic acid and 5-[2-[4-(4-pyridyl)piperazin-1-yl]-methylphenyl]pentanoic acid, dihydrochloride (4:1).

Following the method of Example 180, but starting from the crude mixture of esters in Example 179, there was obtained the title mixture of compounds in 59% yield, as a white solid: NMR (D_2O) δ 8.38 (2H, d), 7.62 (4H, m), 7.35 (2H, d), 4.70 (0.4H, s), 4.61 (1.6H, s), 4.18 (4H, b), 3.68 (4H, b), 2.98 (0.4H, t), 2.91 (1.6H, t), 2.59 (2H, t), 1.82 (4H, m); m/e 354 $(M+H)^+$; calculated for $C_{21}H_{27}N_3O_2.2HCl.0.5H_2O$: C, 57.9; H, 6.9; N, 9.7. found: C, 59.6; H, 7.2; N, 9.4%.

EXAMPLE 182: N-[[4-[1-(4-pyridyl)piperidin-4-yl]carboxamidophenyl]-methyl]-methanesulphonamide.

Following the method of Example 170 but starting from methanesulphonyl chloride instead of 1-butanesulphonyl chloride there was obtained after evaporation of the reaction solvent an oily solid. This residue was partitioned between ethyl acetate and a dilute

hydrochloric acid solution. Separation and then neutralisation of the aqueous phase with sodium hydroxide solution gave a solid. This was collected by filtration, washed with water and, on drying, gave the title compound in 93% yield: m.p. 238-240°C; NMR (d_6DMSO) δ 9.91 (1H, s), 8.13 (2H, d), 7.08 (2H, d), 7.47 (1H, bt), 7.25 (2H, d), 6.82 (2H, d), 4.08 (2H, d), 3.98 (2H, bd), 2.89 (2H, bt), 2.82 (3H, s), 2.59 (1H, m), 1.87 (2H, bd), 1.65 (2H, dq); m/e 389 $(M+H)^+$; calculated for $C_{19}H_{24}N_4O_3S.0.25H_2O$: C, 58.1; H, 6.3; N, 14.3. found: C, 58.2; H, 6.5; N, 14.3%.

EXAMPLE 183: N-[2-[4-[1-(4-pyridyl)piperidin-4-yl]carboxamido-phenyl]ethyl]-methanesulphonamide.

Following the method of Example 182, but starting from 4-[1-(4-pyridyl)piperidin-4-ylcarboxamido]phenethylamine, the title compound was prepared in 90% yield: m.p. 193-195°C; NMR (d_6DMSO) δ 9.85 (1H, s), 8.16 (2H, d), 7.51 (2H, d), 7.15 (2H, d), 7.03 (1H, t), 6.82 (2H, d), 4.00 (2H, bd), 3.13 (2H, q), 2.90 (2H, dt), 2.83 (3H, s), 2.72 (2H, t), 2.60 (1H, m), 1.87 (2H, dd), 1.65 (2H, dq); m/e 403 $(M+H)^+$; calculated for $C_{20}H_{26}N_4O_3S.0.25H_2O$: C, 59.0; H, 6.6; N, 13.8. found, C, 59.0; H, 6.7; N, 13.7%.

The necessary starting material was prepared as follows:-

(i) Following the method of Example 170 step (i), but starting from 4-nitrophenethylamine, there was obtained N-tertiary-butyloxycarbonyl 4-nitrophenethylamine in 82% yield: m.p. 94-95°C; NMR (d_6DMSO) δ 8.14 (2H, d), 7.46 (2H, d), 6.89 (1H, bt), 3.20 (2H, q), 2.82 (2H, t), 1.33 (9H, s); m/e 267 $(M+H)^+$; calculated for $C_{13}H_{18}N_2O_4$: C, 58.6; H, 6.81; N, 10.5. found: C, 58.3; H, 6.9; N, 10.5%.

(ii) Following the method of Example 170 step (ii), but starting from the product of step (i) above, there was obtained 4-(N-tertiary-butyloxycarbonyl 2-aminoethyl)aniline in 78% yield: m.p. 74-75°C; NMR (d_6DMSO) δ 6.81 (2H, d), 6.73 (1H, m), 6.47 (2H, d), 4.82 (2H, s), 3.02 (2H, m), 2.50 (2H, m+DMSO), 1.37 (9H, s); m/e 237 $(M+H)^+$; calculated for $C_{13}H_{20}N_2O_2$: C, 66.1; H, 8.5; N, 11.9. found C, 65.9; H, 8.9; N, 11.8%.

(iii) Following the method of Example 170 step (iii), but starting from the product of step (ii) above, was obtained after recrystallisation from methanol, N-tertiary-butyloxycarbonyl 4-[1-(4-pyridyl)piperidin-4-ylcarboxamido]phenethylamine in 62% yield: m.p. 242-244°C; NMR (d_6DMSO) δ 9.82 (1H, s), 8.15 (2H, d), 7.50 (2H, d), 7.09 (2H, d), 6.82 (2H, d), 6.78 (1H, m), 3.99 (2H,bd), 3.10 (2H, q), 2.90 (2H, dt), 2.63 (2H, t), 2.56 (1H, m), 1.86 (2H, dd), 1.65 (2H, dq), 1.48 (9H, m); m/e 425 $(M+H)^+$; calculated for $C_{24}H_{32}N_4O_3.0.5H_2O$: C, 66.5; H, 7.7; N, 12.9. found: C, 66.5; H, 7.7; N, 12.9%.

(iv) Following the method of Example 170 step (iv) but starting from the product of step (iii) above there was obtained the dihydrochloride salt, m.p. 286-289°C. To a stirred solution of the salt in water was added 3 equivalents of 1 molar sodium hydroxide. After 1 hour the precipitated solid was collected by centrifugation, washed with water and on drying, gave 4-[1-(4-pyridyl)piperidin-4-ylcarboxamido]phenethylamine in 92% yield: m.p. 207-211°C; NMR (d_6DMSO+d_4 acetic acid) δ 8.18 (2H, d), 7.58 (2H, d), 7.18 (4H, m), 4.22 (2H, d), 3.28 (2H, t), 3.05 (2H, m), 2.83 (3H, m), 2.00 (2H, dd), 1.76 (2H, dq); m/e 325 $(M+H)^+$; calculated for $C_{19}H_{24}N_4O.0.5H_2O$: C, 68.4; H, 7.6; N, 16.8. found: C, 68.2; H. 7.6; N, 16.7%.

EXAMPLE 184: N-[2-[4-[1-(4-pyridyl)piperidin-4-yl]carboxamido-phenyl]ethyl]-4-methylphenylsulphonamide.

Following the method of Example 183, but starting from 4-methylphenylsulphonyl chloride instead of methanesulphonyl chloride, the title compour was obtained 81% yield: m.p. 175-178°C; NMR (d_6DMSO) δ 9.81 (1H, s), 8.15 (2H, bd), 7.64 (2H, d), 7.55 (1H, t), 7.46 (2H, d), 7.36 (2H, d), 7.03 (2H, d), 6.82 (2H, d), 3.98 (2H, bd), 3.90 (4H, m), 2.60 (3H, m), 2.37 (3H, s), 1.85 (2H, dd), 1.65 (2H, dq), m/e 479 $(M+H)^+$; calculated for $C_{26}H_{30}N_4O_3S.H_2O$: C, 62.9; H, 6.5; N, 11.3. found: C, 63.1; H, 6.3; N, 11.1%.

EXAMPLE 185: N-[4-[2-[4-(4-pyridyl)piperazin-1-yl]ethyl]phenyl]methyl-1-butanesulphonamide.

Triethylamine (0.41 ml) was added to a stirred suspension of 4-[2-[4-(4-pyridyl)piperazin-1-yl]ethyl]benzylamine, trihydrochloride (300 mg) in dry dichloromethane (20 ml). After 5 minutes, 1-butanesulphonyl chloride (0.10 ml) was added and the mixture stirred overnight. Dichloromethane (80 ml) was added and the solution washed with water (2x25 ml), dried ($MgSO_4$) and the solvent removed in vacuo. Trituration of the residue with a small volume of ethyl acetate gave the title compound, 50 mg, as an off-white solid: m.p. 154-156°C; NMR (d_6DMSO) δ 8.16 (2H, d), 7.53 (1H, t), 7.22 (4H, m), 6.37 (2H, d), 4.10 (2H, d), 3.35 (6H, m + H_2O), 2.81 (4H, m), 2.54 (4H, m + DMSO), 1.56 (2H, m), 1.29 (2H, m), 0.82 (3H, t); m/e 417 $(M+H)^+$; calculated for $C_{22}H_{32}N_4O_2S.0.75H_2O$: C, 61.5; H, 7.8; N, 13.0. found: C, 61.5; H, 7.6; N, 12.7%.

The necessary starting material was prepared as follows:-

(i) A suspension of di-tert-butyl iminodicarboxylate (4.25 g) and finely powdered anhydrous potassium hydroxide (1.1 g) in dry THF (60 ml) was stirred for 2 hours. 2-(4-Bromomethylphenyl)ethanol (4.2 g) dissolved in THF (40 ml) was added and the mixture stirred for 16 hours when further anion [prepared from di-tert-butyl iminodicarboxylate (4.25 g) and finely powdered anhydrous potassium hydroxide (1.1 g) in dry THF (40 ml)] was added and stirring continued for 3 days. Ether (300 ml) was added and the mixture washed with water and saturated sodium chloride solution, then dried ($MgSO_4$) and evaporated to give a colourless oil. Purification by flash chromatography on silica, eluting with 1% v/v methanol/dichloromethane gave N-di-tert-butyloxy- carbonyl 4-[1-(2-hydroxyethyl)]benzylamine, 6.1 g, as a clear oil: NMR ($CDCl_3$) δ 7.25 (2H, d), 7.17 (2H, d), 4.75 (2H, s), 4.37 (1H, b), 3.35 (2H, bt), 2.85 (2H, t), 1.46 (18H, s); m/e 352 $(M+H)^+$.

(ii) A stirred, cooled (4°C), solution of the product from step (i) above (6.1 g) in dry dichloromethane (100 ml) was treated under argon with triethylamine (3.1 ml), then methanesulphonyl chloride (1.6 ml) was added dropwise over 15 minutes and stirring continued for 1

hour at 4°C and 2 hours at ambient temperature. The dichloromethane was removed by evaporation and the residue dissolved in ethyl acetate (250 ml). This solution was washed with water and saturated sodium chloride solution, then dried ($MgSO_4$). Evaporation of the solvent gave N-di-tert-butyloxycarbonyl 4-[1-(2-methanesulphonyloxyethyl)]-benzylamine, 6.53 g, as an off-white solid: m.p. 66-68°C; NMR ($CDCl_3$) δ 7.26 (2H, d), 7.17 (2H, d), 4.75 (2H, s), 4.40 (2H, t), 3.03 (2H, t), 2.84 (3H, s), 1.46 (18H, s); m/e 452 $(M+Na)^+$.

(iii) A mixture of the product from step (ii) above, (6.5 g) and 1-(4- pyridyl)piperazine (4.95 g) in acetonitrile (100 ml) was heated and stirred at reflux temperature for 16 hours. The solvent was removed in vacuo, the residue dissolved in dichloromethane (300 ml) and this solution washed with water, then dried ($MgSO_4$) and evaporated. The residue, after purification by flash chromatography on silica, eluting with 10% v/v methanol/dichloromethane gave N-di-tert-butyloxycarbonyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]-ethyl]benzylamine, 2.25 g, as a coloured gum: NMR (d_6DMSO) δ 8.14 (2H, d), 7.21 (2H, d), 7.12 (2H, d), 6.81 (2H, d), 4.63 (2H, s), 3.30 (6H, m + H_2O), 2.75 (2H, t), 2.53 (4H, t + DMSO), 1.40 (18H, s); m/e 497 $(M+H)^+$.

(iv) A solution of the product from step (iii) above (2.0 g) dissolved in methanol (40 ml) was treated with a 5 molar solution of dry hydrogen chloride gas in methanol (8.0 ml) and the mixture stirred for 16 hours. The solvent was removed in vacuo and the residue, on trituration with ether, gave 4-[2-[4-(4-pyridyl)piperazin-1-yl]ethyl]-benzylamine, trihydrochloride, 1.86 g, as a pale yellow solid: m.p. 297-299°C dec.; NMR (d_6DMSO) δ 13.92 (2H, b), 12.01 (1H, b), 8.49 (4H, m), 7.47 (2H, m), 7.31 (4H, m), 4.46 (2H, b), 4.00 (2H, q), 3.70 (4H, b), 3.30 (6H, m + H_2O); m/e 297 $(M+H)^+$; calculated for $C_{18}H_{24}N_4.3HCl.3.5H_2O$: C, 46.1; H, 7.3; N, 11.9. found: C, 45.8; H, 7.1; N, 11.8%.

EXAMPLE 186: N-[4-[2-[4-(4-pyridyl)piperazin-1-yl]ethyl]phenyl]methyl-4-methylphenylsulphonamide.

Following the method of Example 185, but starting from 4-methylphenylsulphonyl chloride instead of 1-butanesulphonyl chloride the title compound was obtained in 69% yield, as a white solid: m.p. 180-182°C; NMR (d_6 DMSO+d_4 acetic acid) δ 8.21 (2H, d), 7.70 (2H, d), 7.47 (2H, d), 7.19 (6H, m), 3.96 (2H, s), 3.80 (4H, bt), 2.94 (4H, bt), 2.86 (4H, bs), 2.40 (3H, s); m/e 451 $(M+H)^+$; calculated for $C_{25}H_{30}N_4O_2S.H_2O$: C, 64.1; H, 6.8; N, 11.9. found: C, 63.9; H, 6.6; N, 11.6%.

EXAMPLE 187: Ethyl 6-[4-(4-pyridylamino)phenoxy]hexanoate.

Trifluoroacetic acid (3 ml) was added to a stirred solution of ethyl 6-[4-[N-(4-pyridyl)-N-tertiary-butyloxycarbonylamino]phenoxy]-hexanoate (260 mg) dissolved in dichloromethane (3 ml). After 18 hours the solvents were removed in vacuo and the residual gum dissolved in dichloromethane. This solution was treated with a saturated solution of sodium hydrogen carbonate. The organic phase was washed with water, dried and evaporated. Trituration of the residue with hexane gave the title compound, 120 mg, as a white solid: m.p. 104-106°C; NMR ($CDCl_3$) δ 8.22 (2H, d), 7.12 (2H, d), 6.90 (2H, d), 6.64 (2H, dd), 5.82 (1H, s), 4.13 (2H, q), 3.97 (2H, t), 2.34 (2H, t), 1.80 (2H, m), 1.70 (2H, m), 1.53 (2H, m), 1.27 (3H, t); m/e 329 $(M+H)^+$; calculated for $C_{19}H_{24}N_2O_3.0.25H_2O$:C, 68.6; H, 7.4; N, 8.4. found: C, 68.8; H, 7.3; N, 8.2%.

The necessary starting material was prepared as follows:-

(i) A stirred mixture of 4-chloropyridine hydrochloride (2 g) and 4-methoxyaniline (4.9 g) was heated at 140°C for 5 hours. After cooling the residue was dissolved in dichloromethane (250 ml), the solution extracted with water (2x100 ml). The aqueous extracts were treated with sodium hydroxide solution and then extracted with ethyl acetate (4x100 ml). The combined organic extracts were washed with

water, and saturated sodium chloride solution, then dried and the solvent evaporated. Purification by flash chromatography on silica, eluting with 10% v/v methanol/dichloromethane gave 4-(4-pyridylamino)-methoxybenzene, 2 g, as a fawn solid: m.p. 159-160°C; NMR (d_6DMSO) δ 8.47 (1H, s), 8.09 (2H, d), 7.10 (2H, d), 6.92 (2H, d), 6.70 (2H, dd), 3.73 (3H, s); m/e 201 $(M+H)^+$; calculated for $C_{12}H_{12}N_2O_3$: C, 72.0; H, 6.0; N, 14.0. found: C, 71.4; H, 6.1; N, 13.8%.

(ii) A mixture of the product from step (i) above (2.0 g) and 48% w/v hydrobromic acid (30 ml) was heated at 140°C for 4 hours. The cooled solution was neutralised with 0.880 ammonia solution and then extracted four times with ethyl acetate. The combined organic extracts were washed with water and saturated sodium chloride solution, then dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica, eluting with 10 to 20% v/v methanol/dichloromethane gave 4-(4-pyridylamino)phenol, 0.78 g as an off-white solid: m.p. 246-248°C; NMR ($CDCl_3$+d_6DMSO) δ 8.92 (1H, b), 8.09 (2H, d), 7 31 (1H, s), 7.00 (2H, d), 6.79 (2H, d), 6.67 (2H, dd); m/e 187 $(M+H)^+$.

(iii) A mixture of the product from step (ii) above (0.78 g), di-tertiary-butyl dicarbonate (0.91 g), triethylamine (0.59 ml), 1,2-dimethoxymethane (20 ml) and water (10 ml) was stirred for 18 hours. The solvents were removed <u>in vacuo</u> and the residue partitioned between ethyl acetate and water. The aqueous phase was extracted two times with further ethyl acetate and the combined organic extracts washed with water and brine, dried ($MgSO_4$) and evaporated to a small volume when crystallisation occurred. Collection by filtration gave 4-[N-(4-pyridyl)-N-tertiary-butyloxycarbonylamino]phenol, 1.07 g as a white crystalline solid: m.p. 192-194°C (dec); NMR ($CDCl_3$) δ 8.28 (2H, dd), 7.18 (4H, s), 6.76 (2H, dd), 6.03 (1H, bs), 1.57 (9H, s); m/e 287 $(M+H)^+$.

(iv) Sodium hydride (50% w/w dispersion in mineral oil, 55 mg) was added under argon to a stirred solution of the product from step (iii) above (300 mg) in dry DMF (5 ml). After five minutes, ethyl 6-bromohexanoate (0.20 ml) was added and the mixture stirred for 16 hours. The DMF was evaporated <u>in vacuo</u> and the residue partitioned between dichloromethane and water. The aqueous phase was extracted

with further dichloromethane. The combined organic extracts were washed with water then dried, and evaporated. The residue was purified by chromatography on alumina, eluting with dichloromethane and then 1% v/v methanol/dichloromethane. Evaporation of the appropriate fractions gave ethyl 6-[4-[N-(4-pyridyl)-N-tertiary-butyloxycarbonylamino]-phenoxy]hexanoate, 260 mg, as a yellow gum: NMR ($CDCl_3$) δ 8.40 (2H, dd), 7.16 (2H, dd), 7.07 (2H, m), 6.90 (2H, m), 4.13 (2H, q), 3.98 (2H, t), 2.34 (2H, t), 1.78 (4H, m), 1.57 (2H, m), 1.44 (9H, s), 1.26 (3H, t); m/e 429 $(M+H)^+$.

EXAMPLE 188: 6-[4-(4-pyridylamino)phenoxy]hexanoic acid hydrochloride.

Following the method of Example 123, but starting from the product of Example 187 and heating at 100°C for 16 hours instead of 1.5 hours, the title compound was obtained in 80% yield as a freeze-dried solid: NMR (d_6DMSO) δ 13.63 (1H, b), 11.95 (1H, b), 10.49 (1H, s), 8.21 (2H, d), 7.26 (2H, d), 6.98 (4H, m), 4.00 (2H, t), 2.23 (2H, t), 1.70 (2H, m), 1.55 (2H, m), 1.45 (2H, m); m/e 301 $(M+H)^+$; calculated for $C_{17}H_{20}N_2O_2.HCl.\ 1.25H_2O$: C, 56.8; H, 6.6; N, 7.8. found: C, 56.8; H, 6.6; N, 7.4%.

EXAMPLE 189: N-[4-[(4-pyridyl)piperazin-1-yl]benzoyl]-N-methylglycine, trifluoroacetate

To a solution of ethyl N-[4-[(4-pyridyl)piperazin-1-yl]-benzoyl]-N-methylglycinate (78 mg) in methanol (2 ml) was added sodium hydroxide solution (1N, 0.4 ml) and the resultant mixture was stored at room temperature for 1 hour. The pH of the reaction mixture was adjusted to 2 by addition of 2N HCl (aq) (0.45 - 0.5 ml) and the resultant solution was purified by preparative rp-hplc on a DYNAMAX C-18, 60A [83-201-C] column using an acetonitrile/water mobile phase containing 0.1% trifluoroacetic acid, to give, after lyophilisation, the title compound (46 mg) as a glass: NMR (d_6-DMSO) δ 2.98 (3H, s), 3.45 (4H, m), 3.86 (4H, m), 4.07 (2H, s), 6.97 (2H, d), 7.23 (2H, d), 7.31 (2H, m), 8.27 (2H, d); m/Z 355 (M + H)$^+$; calculated for

$C_{19}H_{22}N_4O_3$. 1.0 CF_3CO_2H. 1.25 H_2O: C, 51.4%; H, 5.24%; N, 11.4%; found: C, 51.2%; H, 4.9%; N, 11.2%.

The necessary starting material was prepared as follows:-

(i) To a stirred mixture of 4-[(4-pyridyl)piperazin-1-yl]benzoic acid (prepared as in Example 56(i)) (311 mg), HOBt.H_2O (170 mg) and HBTU (416 mg) in DMF (5 ml) at 0-5°C under argon was added diisopropylethylamine (0.75 ml). The ice-bath was removed and the reaction mixture was stirred at room temperature for 15 minutes before solid sarcosine, ethyl ester hydrochloride (154 mg) was added. The reaction mixture was stirred at room temperature under argon overnight then diluted with dichloromethane (30 ml) and water (30 ml). The organic layer was separated and the aqueous layer was re-extracted with dichloromethane (30 ml). The combined organic extracts were washed with water, saturated sodium bicarbonate solution, water, dried ($MgSO_4$) and evaporated. The residue was purified by filtration through a short bed of activated (grade II) alumina by elution with ethyl acetate/methanol, 5:1, to give ethyl N-(4-[(4-pyridyl)piperazin-1-yl]benzoyl)-N-methylglycinate (92 mg) as an amorphous solid: NMR (d_6-DMSO + CD_3CO_2D) δ 1.18 (3H, t), 2.98 (3H, s), 3.44 (4H, m), 3.79 (4H, m), 4.11 (4H, m), 6.94 (2H, d), 7.12 (2H, d), 7.31 (2H, br, d), 8.19 (2H, d); m/Z 383 $(M + H)^+$.

EXAMPLE 190: N-[4-[(4-pyridyl)piperazin-1-yl]benzoyl]-L-phenylalanine, methyl ester

In a similar manner to Example 189 (i), 4-[(4-pyridyl)piperazin-1-yl]benzoic acid (311 mg), p-toluene sulphonic acid, monohydrate (418 mg), HOBt.H_2O (170 mg), HBTU (416 mg), DMF (5 ml), diisopropylethylamine (1.13 ml) and L-phenylalanine, methyl ester hydrochloride (216 mg) gave, after filtration through a bed of neutral alumina and elution with ethyl acetate/methanol, 6:1, the title compound as a white crystalline solid (336 mg): m.p. 139-143.5°C; NMR ($CDCl_3$) δ 3.26 (2H, m), 3.50 (8H, m), 3.76 (3H, s), 5.09 (1H, m), 6.46 (1H, d), 6.70 (2H, m), 6.90 (2H, d), 7.13 (2H, m),

7.28 (3H, m), 7.68 (2H, d), 8.31 (2H, m); m/z 445 $(M + H)^+$; calculated for $C_{26}H_{28}N_4O_3$. 1.0 H_2O: C, 67.5%; H, 6.54%; N, 12.1%; found: C, 67.6%; H, 6.4%; 12.1%.

EXAMPLE 191: N-[4-[(4-pyridyl)piperazin-1-yl]benzoyl]-L-phenylalanine

To a solution of the product of Example 190 (100 mg) in methanol (2.2 ml) was added sodium hydroxide solution (1N, 0.44 ml). The resultant mixture was stored at room temperature with occasional swirling for 2.5 hr, then the pH was adjusted to 5 by addition of 2N HCl (aq) (0.22 ml) and 50% aqueous acetic acid (3 drops). The mixture was filtered and evaporated to dryness. The residue was crystallised from hot water containing a trace of methanol to give the title compound as a pale yellow crystalline solid (47 mg): NMR (d_6-DMSO + CD_3CO_2D) δ 3.05 (1H, m), 3.15 (1H, m), 3.45 (4H, m), 3.77 (4H, m), 4.58 (1H, m), 6.90 (2H, d), 7.12 (2H, d), 7.22 (5H, m), 7.70 (2H, d), 8.19 (2H, d); m/Z 431 $(M + H)^+$; calculated for $C_{25}H_{26}N_4O_3$. 0.75 H_2O: C, 67.6%; H, 6.24%; N, 12.6%; found: C, 67.6%; H, 6.0%; N, 12.5%.

EXAMPLE 192: (S)-3-[N-[2-phenethyl]carboxamido]-3-[4-[4-(4-pyridyl)piperazin-1-yl]]benzamidopropionic acid

To a stirred suspension of benzyl (S)-3-[N-[2-phenethyl]-carboxamido]-3-[4-[4-(4-pyridyl)piperazin-1-yl]]benzamidopropionate (120 mg) in methanol (3 ml) was added sodium hydroxide solution (1N, 0.5 ml). Within 15 minutes all the solids had dissolved, and the reaction mixture was stirred at room temperature for a further 2 hr. The pH was then adjusted to 5 by addition of 2N HCl (aq) (0.25 ml) and 50% aqueous acetic acid (3 drops). The mixture was filtered and evaporated to dryness. The residue was crystallised from hot water containing a trace of methanol to give the title compound as a pale yellow crystalline solid (66 mg): NMR (d_6-DMSO + CD_3CO_2D) δ 2.70 (4H, m), 3.30 (2H, t), 3.56 (4H, m), 3.85 (4H, m), 4.73 (1H, m), 6.99 (2H, d), 7.20 (7H, m), 7.80 (2H, d), 8.25 (2H, d); m/Z 502 $(M + H)^+$; calculated for $C_{28}H_{31}N_5O_4$. 1.25 H_2O: C, 64.2%; H, 6.44%; N, 13.4%; found: C, 64.2%; H, 6.4%; N, 13.6%.

The necessary starting material was prepared as follows:-

i) Boc-L-aspartic acid, 2-phenethylamide, β-benzyl ester (preparation described in Samanen, J. et al (1991), J. Med. Chem. 34, 3114-25) (2 g) was dissolved in a mixture containing dichloromethane (10 ml) and trifluoroacetic acid (10 ml). The resultant pale yellow solution was stored at room temperature for 2 hr after which time the mixture was evaporated to dryness. The oily product was dissolved in dry ether and re-evaporated. This procedure was repeated twice more to give a viscous oily residue containing the trifluoroacetate salt of L-aspartic acid, 2-phenethylamide, β-benzyl ester (2.07 g) which was used without further purification.

ii) In a similar manner to Example 189 (i), 4-[(4-pyridyl)piperazin-1-yl]benzoic acid (311 mg), p-toluene sulphonic acid, monohydrate (627 mg), HOBt.H_2O (170 mg), HBTU (416 mg), DMF (15 ml), diisopropylethylamine (1.5 ml) and L-aspartic acid, 2-phenethylamide, β-benzyl ester (440 mg) gave, after purification by flash chromatography on silica, eluting solvent, ethyl acetate/methanol, 4:1 to 2:1, benzyl (S)-3-(N-[2-phenethyl]-carboxamido)-3-[4-[4-(4-pyridyl)piperazin-1-yl]]benzamidopropionate (268 mg) as a white crystalline solid: NMR (d_6-DMSO) δ 2.70 (2H, t), 2.76 (1H, m), 2.88 (1H, m), 3.25 (2H, m), 3.44 (4H, m), 3.50 (4H, m), 4.84 (1H, m), 5.08 (2H, s), 6.89 (2H, d), 7.02 (2H, d), 7.20 (5H, m), 7.31 (5H, m), 7.78 (2H, d), 7.90 (1H, t), 8.20 (2H, d), 8.36 (1H, d); m/Z 592 $(M + H)^+$; calculated for $C_{35}H_{37}N_5O_4 \cdot 0.25\ H_2O$: C, 70.5%; H, 6.34%; N, 11.7%; found: C, 70.5%; H, 6.3%; N, 11.7%.

EXAMPLE 193: (R)-3-[N-[2-phenethyl]carboxamido]-3-[4-[4-(4-pyridyl)piperazin-1-yl]]benzamidopropionic acid

Following the method of Example 192, but starting from benzyl (R)-3-[N-[2-phenethyl]carboxamido]-3-[4-[4-(4-pyridyl)-piperazin-1-yl]]benzamidopropionate instead of the corresponding (S)-isomer, the title compound was obtained as a pale yellow crystalline solid in 33% yield: NMR (d_6-DMSO + CD_3CO_2D) δ 2.71 (4H,

m), 3.29 (2H, t), 3.53 (4H, m), 3.83 (4H, m), 4.72 (1H, m), 6.99 (2H, d), 7.17 (7H, m), 7.77 (2H, d), 8.24 (2H, d); m/Z 502 $(M + H)^+$; calculated for $C_{28}H_{31}N_5O_4 \cdot 1.25\ H_2O$: C, 64.2%; H, 6.44%; N, 13.4%; found: C, 64.2%; H, 6.4%; N, 13.3%.

The necessary starting material was prepared as follows:-

i) Boc-D-aspartic acid, 2-phenethylamide, β-benzyl ester (preparation described in Rodriguez, M. et al (1989), J. Med. Chem. 32, 522-8) (1 g) was dissolved in acetonitrile (5 ml) with gentle warming, then cooled to room temperature before excess ethereal HCl (5 ml) was added. The reaction mixture was stored at room temperature overnight then evaporated to dryness. The pale yellow oily residue was triturated with dry ether and re-evaporated. This procedure was repeated twice more to give a hygroscopic oily residue containing the hydrochloride salt of D-aspartic acid, 2-phenethylamide, β-benzyl ester (0.55 g) which was used without further purification.

ii) In a similar manner to Example 56, the hydrochloride salt of D-aspartic acid, 2-phenethylamide, β-benzyl ester (363 mg), 4-[(4-pyridyl)piperazin-1-yl]benzoyl chloride (377 mg), diisopropylethylamine (0.87 ml) and DMF (5 ml) gave benzyl (R)-3-[N-[2-phenethyl]carboxamido]-3-[4-[4-(4-pyridyl)-piperazin-1-yl]]benzamidopropionate (510 mg) as an off-white, amorphous solid: m/Z 592 $(M + H)^+$.

EXAMPLE 194: (S)-3-[N-(2-phenethyl)carboxamido]-3-[N-[N-2-[4-(4-pyridyl)piperazin-1-yl]acetyl]glycyl]aminopropionic acid, trifluoroacetate

In a similar manner to Example 189, benzyl (S)-3-[N-(2-phenethyl)carboxamido]-3-[N-[N-2-[4-(4-pyridyl)piperazin-1-yl]acetyl]glycyl]aminopropionate (240 mg), sodium hydroxide solution (1N, 1.4 ml) and methanol (4 ml) gave, after 6 hr, followed by acidification to pH 4, preparative rp-hplc and lyophilisation, the title compound (224 mg) as a colourless glass: NMR (d_6-DMSO + CD_3CO_2D)

δ 2.58 (2H, m), 2.74 (2H, t), 3.17 (4H, m), 3.31 (2H, t), 3.70 (2H, m), 3.91 (6H, m), 4.62 (1H, m), 7.21 (7H, m), 8.25 (2H, d); m/Z 497 (M + H)$^+$; calculated for $C_{25}H_{32}N_6O_5$. 2.0 CF_3CO_2H. 1.0 H_2O: C, 46.9%; H, 4.89%; N, 11.3%; found: C, 46.7%; H, 4.8%; N, 11.1%.

The necessary starting material was prepared as follows:-

i) In a similar manner to Example 192 (i), N-(N'-Boc-glycyl)-L-aspartic acid, 2-phenethylamide, β-benzyl ester (preparation described in Samanen, J. et al (1991), J. Med. Chem. 34, 3114-25) (370 mg), dichloromethane (2 ml) and trifluoroacetic acid (2 ml) gave a hygroscopic oil containing the trifluoroacetate salt of N-glycyl-L-aspartic acid, 2-phenethylamide, β-benzyl ester (340 mg), which was used without further purification.

ii) In a similar manner to Example 189 (i), 1-(4-pyridyl)-4-carboxymethylpiperazine dihydrochloride (220 mg), HBTU (284 mg), HOBt.H_2O (115 mg), DMF (3 ml), diisopropylethylamine (0.53 ml) and the trifluoroacetate salt of N-glycyl-L-aspartic acid, 2-phenethylamide, β-benzyl ester (340 mg) gave, after purification by flash chromatography on silica, eluting solvent, dichloromethane/methanol, 9:1 to 4:1, benzyl (S)-3-(N-[2-phenethyl]carboxamido)-3-[N-[N-2-[4-(4-pyridyl)piperazin-1-yl]acetyl]glycyl]aminopropionate (249 mg) as a colourless foam: NMR (d_6-DMSO + CD_3CO_2D) δ 2.63 (4H, m), 2.69 (2H, t), 2.72 (2H, m), 3.06 (2H, s), 3.25 (2H, m), 3.64 (4H, m), 3.78 (2H, q), 4.62 (1H, m), 5.05 (2H, s), 7.06 (2H, d), 7.10-7.35 (10H, m), 8.15 (2H, d); m/Z 587 (M + H)$^+$.

EXAMPLE 195: 3-[4-[4-(4-pyridyl)piperazin-1-yl]butyryl]aminopropionic acid, trifluoroacetate

In a similar manner to Example 189, methyl 3-[4-[4-(4-pyridyl)piperazin-1-yl]butyryl]aminopropionate (163 mg), and sodium hydroxide solution (1N, 1.5 ml) gave, after preparative rp-hplc and lyophilisation, a glassy solid which was crystallised from hot acetonitrile/ether to give the title compound, trifluoroacetate

salt (165 mg) as a colourless cystalline solid: m.p. 129-131°C; NMR (d_6-DMSO + CD_3CO_2D) δ 1.89 (2H, m), 2.19 (2H, t), 2.37 (2H, t), 3.08 (2H, m), 3.25 (2H, t), 3.32 (4H, m), 3.91 (4H, m), 7.26 (2H, d), 8.32 (2H, d); m/Z 321 $(M + H)^+$; calculated for $C_{16}H_{24}N_4O_3$. 1.9 CF_3CO_2H: C, 44.3%; H, 4.86%; N, 10.4%; found: C, 44.5%; H, 4.9%; N, 10.3%.

The necessary starting material was prepared as follows:-

(i) To a stirred suspension of 1-(4-pyridyl)piperazine (5 g) in dry DMF (30 ml) under argon at 0-5°C was added, in portions, a solid dispersion of sodium hydride (60%) in mineral oil (1.23 g). On completion of the addition, the ice-bath was removed and the reaction was stirred vigorously at room temperature. After 45 min, a solution of ethyl 4-bromobutyrate (5.85 g) in dry DMF (5 ml) was added and the reaction mixture was stirred at room temperature for 2 hr then diluted carefully with water (50 ml) and poured into dichloromethane (50 ml). The organic layer was separated and the aqueous layer was re-extracted with dichloromethane (50 ml). The combined organic extracts were washed with water, then extracted with 1N HCl(aq) (40 ml). The acidic extract was washed with dichloromethane (40 ml) and the aqueous layer was basified by addition of sodium hydroxide solution (1N, 40 ml) and saturated sodium bicarbonate solution (10 ml). This mixture was then extracted with dichloromethane (50 ml) and the organic extract was washed with water, dried ($MgSO_4$) and evaporated. The resultant pale yellow oil was dissolved in ether (50 ml) and to this solution was added excess ethereal HCl. An amorphous solid precipitated immediately, which was triturated, collected and washed with dry ether to give ethyl 4-[(4-pyridyl)piperazin-1-yl]butyrate, dihydrochloride salt (5.09 g) as a white hygroscopic solid: NMR (d_6-DMSO + CD_3CO_2D) δ 1.13 (3H, t), 1.95 (2H, m), 2.38 (2H, t), 3.10 (2H, m), 3.35 (4H, br, m), 3.97 (4H, br, m), 4.02 (2H, q), 7.19 (2H, d), 8.25 (2H, d); m/Z 278 $(M + H)^+$.

(ii) A mixture of the product of step (i) (5 g) and conc. HCl (50 ml) was heated at 100°C for 45 min. The resultant solution was evaporated to dryness and the residue dissolved again in conc. HCl and

heated to 100°C for a further 45 min. The reaction mixture was evaporated to dryness, and the residue was twice triturated with toluene, and evaporated to dryness, collected and washed with ether. The crude product was crystallised from hot methanol/ether to give 4-[(4-pyridyl)piperazin-1-yl]butyric acid, dihydrochloride as an off-white crystalline solid (3.45 g): m.p. 280-300°C (dec); NMR (d_6-DMSO) δ 2.00 (2H, m), 2.36 (2H, t), 3.12 (2H, m), 3.00-3.70 (4H, v. br, m), 3.50-4.50 (4H, v. br, m), 7.30 (2H, d), 8.35 (2H, d), 12.2 (1H, v. br); m/Z 250 $(M + H)^+$; calculated for $C_{13}H_{19}N_3O_2$. 2.0 HCl. 0.5 H_2O: C, 47.1%; H, 6.69%; N, 12.7%; found: C, 47.5%; H, 6.7%; N, 12.5%

(iii) In a similar manner to Example 189 (i), the product of step (ii) (403 mg), HBTU (474 mg), HOBt.H_2O (190 mg), DMF (5 ml), diisopropylethylamine (1.31 ml) and methyl 3-aminopropionate, hydrochloride (175 mg) gave, after purification by flash chromatography on silica, eluting solvent dichloromethane/methanol, 4:1 to 3:1, methyl 3-[4-[4-(4-pyridyl)piperazin-1-yl]butyryl]-aminopropionate (168 mg) as an amorphous solid: NMR (d_6-DMSO + CD_3CO_2D) δ 1.74 (2H, m), 2.14 (2H, t), 2.42 (2H, t), 2.50 (2H, t), 2.62 (4H, m), 3.33 (2H, t), 3.65 (7H, m), 7.12 (2H, d), 8.22 (2H, d); m/Z 335 $(M + H)^+$.

EXAMPLE 196: 5-[(4-pyridyl)piperazin-1-yl]pentanoic acid, dihydrochloride salt

Following the method of Example 195 (ii), but starting from ethyl 5-[(4-pyridyl)piperazin-1-yl]pentanoate, dihydrochloride salt instead of ethyl 4-[(4-pyridyl)piperazin-1-yl]butyrate, dihydrochloride salt, the title compound was isolated, after recrystallisation from wet ethanol, as an off-white crystalline solid in 59% overall yield: m.p. 294-297°C (dec); NMR (d_6-DMSO + CD_3CO_2D) δ 1.62 (2H, m), 1.80 (2H, m), 2.32 (2H, t), 3.18 (2H, m), 3.41 (4H, m), 4.05 (4H, m), 7.29 (2H, d), 8.34 (2H, d); m/Z 264 $(M + H)^+$; calculated for $C_{14}H_{21}N_3O_2$. 2.0 HCl: C, 50.0%; H, 6.89%; N, 12.5%; found: C, 50.5%; H, 7.2%; N, 12.2%.

The necessary starting material was prepared as follows:-

(i) Following the method of Example 195 (i), but starting from ethyl 5-bromovalerate instead of ethyl 4-bromobutyrate, ethyl 5-[(4-pyridyl)piperazin-1-yl]pentanoate, dihydrochloride salt was isolated as a white hygroscopic solid in 43% overall yield: NMR (d_6-DMSO + CD_3CO_2D) δ 1.21 (3H, t), 1.62 (2H, m), 1.77 (2H, m), 2.38 (2H, t), 3.16 (2H, m), 3.42 (4H, m), 4.05 (4H, m), 4.08 (2H, q), 7.29 (2H, d), 8.34 (2H, d); m/Z 292 $(M + H)^+$.

EXAMPLE 197: Methyl 3-[5-[4-(4-pyridyl)piperazin-1-yl]-pentanoyl]aminopropionate

In a similar manner to Example 189 (i), the product of Example 196 (840 mg), HBTU (950 mg), HOBt.H_2O (380 mg), DMF (10 ml), diisopropylethylamine (2.6 ml) and methyl 3-aminopropionate, hydrochloride (280 mg) gave, after purification by flash chromatography on neutral alumina, eluting solvent ethyl acetate/methanol, 50:1 to 4:1,the title compound (303 mg) as a white crystalline solid: m.p. 118-122°C; NMR (d_6-DMSO) δ 1.45 (4H, m), 2.05 (2H, t), 2.27 (2H, t), 2.42 (6H, m), 3.26 (6H, m), 3.58 (3H, s), 6.78 (2H, m), 7.83 (1H, br, t), 8.12 (2H, m); m/Z 349 $(M + H)^+$; calculated for $C_{18}H_{28}N_4O_3$: C, 62.0%; H, 8.1%; N, 16.1%; found: C, 62.2%; H, 8.4%; N, 16.0%.

EXAMPLE 198: 3-[5-[4-(4-pyridyl)piperazin-1-yl]pentanoyl]-aminopropionic acid

In a similar manner to Example 189, the product of Example 197 (160 mg), methanol (5 ml) and sodium hydroxide solution (1N, 1.4 ml) gave, after preparative rp-hplc and lyophilisation, a glassy solid which was crystallised from hot acetonitrile/ether to give the title compound, trifluoroacetate salt (160 mg) as a colourless cystalline solid: m.p. 176-180°C; NMR (d_6-DMSO + CD_3CO_2D) δ 1.64 (4H, m), 2.18 (2H, t), 2.45 (2H, t), 3.12 (2H, t), 3.30 (2H, t), 3.37 (4H, m), 3.97 (4H, m), 7.26 (2H, d), 8.33 (2H, d); m/Z 335 $(M + H)^+$; calculated for

$C_{17}H_{26}N_4O_3 \cdot 2.0\ CF_3CO_2H$: C, 44.8%; H, 5.02%; N, 9.96%; found: C, 44.6%; H, 5.0%; N, 9.8%.

EXAMPLE 199: 4-oxo-4-[4-[4-(4-pyridyl)piperazin-1-yl]phenyl]-aminobutyric acid

To a solution of 1-(4-aminophenyl)-4-(4-pyridyl)piperazine (100 mg) in DMF (8 ml) was added succinic anhydride (79 mg). The reaction mixture was stirred at room temperature for 2.5 hr and a precipitate was collected, washed with DMF and ethanol, then dried to give the title compound (106 mg) as a beige-coloured solid: m.p. 263-264°C; NMR (d_6-DMSO + CF_3CO_2H) δ 2.68 (4H, m), 3.80 (4H, m), 4.19 (4H, m), 7.20 (2H, d), 7.56 (2H, d), 7.82 (2H, d), 8.21 (2H, d), 9.62 (1H, s); m/Z 355 $(M + H)^+$; calculated for $C_{19}H_{22}N_4O_3 \cdot 0.4\ H_2O$: C, 63.1%; H, 6.36%; N, 15.5%; found: C, 63.1%; H, 6.4%; N, 15.7%.

The necessary starting material was prepared as follows:-

(i) To an intimate mixture of 4-[(4-pyridyl)piperazin-1-yl]-benzoic acid (Example 56(i)) (500 mg) and hydroxylamine hydrochloride (13.5 mg) was added polyphosphoric acid (16 g). The resultant mixture was heated to 160°C and maintained at that temperature with stirring for 30 min. The mixture was then allowed to cool to approximately 100°C before crushed ice, followed by 15% potassium hydroxide solution to give a pH 11 of were added. The suspension was allowed to cool to room temperature and the precipitate was collected, washed with water and air-dried to give 1-(4-aminophenyl)-4-(4-pyridyl)piperazine (159 mg) as a light brown solid: m.p. 204-208°C; NMR (d_6-DMSO) δ 3.00 (4H, m), 3.41 (4H, m), 4.65 (2H, br. s), 6.51 (2H, d), 6.73 (2H, m), 6.85 (2H, d), 8.18 (2H, d); m/Z 255 $(M + H)^+$.

EXAMPLE 200: 4-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]butyric acid, hydrochloride salt

A mixture of the product from Example 51 (1.5 g) and methanol (80 ml) was heated to reflux with stirring, and solid

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pyridine hydrochloride (0.5 g) was added. Heating was stopped and ethyl acetate (10 ml) was added. The reaction mixture was evaporated until a slight turbidity was observed. On further cooling, a precipitate formed which was collected, washed with ethyl acetate and dried to give the title compound (1.33 g) as a beige solid: m.p. >240°C (dec); NMR (d_6-DMSO) δ 1.90 (2H, m), 2.36 (2H, t), 3.17 (4H, m), 3.83 (4H, m), 3.91 (2H, t), 6.89 (4H, q), 7.26 (2H, d), 8.25 (2H, d), 12.1 (1H, br), 13.75 (1H, br); m/Z 342 $(M + H)^+$; calculated for $C_{19}H_{23}N_3O_3 \cdot 1.0$ HCl: C, 60.4%; H, 6.4%; N, 11.1%; found: C, 60.0%; H, 6.4%, N, 10.8%.

EXAMPLE 201: N-2-methoxyethyl-4-[4-[4-(4-pyridyl)piperazin-1-yl]-phenoxy]butyramide, trifluoroacetate

A solution of methoxyethylamine (0.9 ml) in dry dichloromethane (5 ml) was added dropwise to a stirred solution of trimethylaluminium, 2M in toluene (5 ml) at 5-10°C under argon. On completion of the addition, the ice-bath was removed and the reaction mixture was stirred at room temperature for 1 hr before a solution of the product of Example 50 (0.62 g) in dichloromethane (5 ml) was added dropwise. The reaction mixture was heated to reflux under argon and stirred at reflux for 2 hr. The reaction mixture was then cooled to room temperature and diluted with dichloromethane (20 ml). A solution of methanol/dichloromethane, 1:1 (3 ml) was then added dropwise with stirring. The reaction mixture was further diluted with dichloromethane (10 ml), methanol, (3 ml) and water (5 ml). The organic layer was separated, dried (Na_2SO_4) and evaporated to dryness. The residue was purified by preparative rp-hplc on a DYNAMAX C-18, 60A [83-201-C] column using an acetonitrile/water mobile phase containing 0.1% trifluoroacetic acid, to give, after lyophilisation, the title compound (56 mg) as an off-white solid: NMR (d_6-DMSO) δ 1.89 (2H, m), 2.22 (2H, t), 3.18 (6H, m), 3.23 (3H, s), 3.32 (2H, t), 3.85 (6H, m), 6.90 (4H, q), 7.28 (2H, d), 7.88 (1H, br. t), 8.25 (2H, d); m/Z 399 $(M + H)^+$; calculated for $C_{22}H_{30}N_4O_3 \cdot 1.7$ CF_3CO_2H: C; 51.5%; H, 5.4%; N, 9.5%; found: C, 51.4%; H, 5.6%; N, 9.3%.

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AMENDED SHEET

EXAMPLE 202 4-[2-[4-(4-pyridyl)piperazin-2-one-1-yl]acetyl]-phenoxyacetic acid monohydrochloride

A solution of methyl 4-[2-(piperazin-2-one-1-yl)acetyl]-phenoxyacetate (0.347g), 4-chloropyridine hydrochloride (0.19g) and triethylamine (0.178g) in water (8ml) and dioxan (1ml) was heated on a steam bath for 2 hours and then evaporated to dryness. The residue was triturated with water (2ml) and filtered. The solid thus obtained was recrystallised from water to give the title compound (0.187g), m.p. 275-277°C; NMR(d_6DMSO δ8.33(2H,d), 8.0(2H,d), 7.21(2H,d), 7.1(2H,d), 4.97(2H,s), 4.81(2H,s), 3.94(2H,m), 3.59(2H,m); m/e 370$(M+H)^+$; calculated for $C_{19}H_{20}N_3O_5Cl$. 0.75 H_2O: C, 54.4; H, 5.0; N, 10.0. Found: C, 54.5; H, 5.3; N, 9.5%.

The necessary starting material was made as follows:-

(i) To a vigorously stirred mixture of piperazinone (3.23g), potassium carbonate (4.46g) in water (15ml) and tert butanol (15ml) at room temperature, was added portionwise over 5 minutes, di tert butyl dicarbonate (7.75g). The mixture was stirred for 2 hours. Ethyl acetate (20ml) was added to extract the solid thus formed and the organic layer separated, filtered through phase separating paper and evaporated. The oily residue was recrystallised from ethyl acetate to give 4-tert butoxycarbonylpiperazin-2-one (5.31g), m.p. 157-159°C; NMR(d_6DMSO) δ 8.0(1H,broad), 3.81(2H,s), 3.45(2H,t), 3.17(2H,m), 1.4(9H,s); m/e 207 $(M+H)^+$.

(ii) To a stirred suspension of the product of step i) (0.5g) in dry DMF (3ml) under an argon atmosphere, was added sodium hydride (60% dispersion in mineral oil, 0.1g). After 1 hour at room temperature, methyl 4-bromoacetylphenoxyacetate (0.72g) was added and the solution stirred for 1 1/2 hours. The mixture resulting was partitioned between water and ethyl acetate. The organic layer was separated, washed with water and filtered through phase separating paper. Evaporation of the solvent gave an oil which was purified by flash column chromatography, the product being eluted with 1/1 v:v ethyl acetate/hexane to give methyl 4-([2-(4-tert-butoxycarbonyl)piperazin-2-one-1-yl]acetyl)phenoxyacetate as a solid (0.32g), m.p. 81-82°C;

NMR($CDCl_3$) δ7.97(2H,m), 6.98(2H,m), 4.83(2H,s), 4.71(2H,s), 4.18(2H,s), 3.81(3H,s), 3.72(2H,t), 3.42(2H,t), 1.47(9H,s).

(iii) A solution of the product from step (ii) (2.2g) in TFA (10ml) was kept at room temperature for 1 hour and then evaporated to dryness. The residue was partitioned between ethyl acetate and aqueous sodium carbonate. The organic layer was filtered through phase separating paper and solvent evaporated. The residue was triturated with ethyl acetate to give a solid, m.p. 128 - 132°C. NMR(d_6DMSO) δ 7.95(2H,d), 7.06(2H,d), 4.9(2H,s), 3.7(3H,s), 3.3(2H,m), 2.9(2H,m).

EXAMPLE 203: RS 3-Methyl-4-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]-butyric acid, trifluoroacetate

To a stirred suspension of 4-[4-(4-pyridyl)piperazin-1-yl]phenol (1.02g) in dry DMF (10ml) was added sodium hydride (60% dispersion in mineral oil, 0.16g) and the mixture stirred for 1 hour at room temperature. To the resulting solution was added ethyl-4-bromo-3-methylbutyrate and the mixture stirred for 16 hours. Solvent was evaporated and the residue partitioned between water and dichloromethane. Insoluble material was removed by centrifugation. The organic layer was filtered through phase separating paper (Whatman IPS) and the residue was purified by flash chromatography on silica gel by elution with methanol/dichloromethane/concentrated ammonia (50/950/5) to give ethyl 3-methyl-4-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]butyrate (0.27g) which was hydrolysed in methanol (3ml) and aqueous sodium hydroxide (1N, 2ml) for 2 hours at room temperature. The solution was evaporated and the residue purified by reverse phase h.p.l.c (water/acetonitrile/0.1% TFA gradient) to give a glass which crystallised on trituration with ether to give the title compound (0.08g): m.p. 169-171°C; NMR(d_6DMSO) δ 13.45(1H,broad), 12.07(1H,broad) 8.27(2H,d), 7.28(2H,d), 6.9(4H,m), 3.80(6H,m), 3.16(4H,t), 2.45(1H,m), 2.37(1H,m), 2.12(1H,m), 1.0(3H,d); m/e 356$(M+H)^+$; calculated for $C_{22}H_{25}N_3O_4F_3$. 0.5 H_2O: C. 55.2; H, 5.6; N, 8.9. Found: C, 55.3; H, 5.6; N, 8.7%.

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EXAMPLE 204: RS-4-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]-3-vinyl-butyric acid, sodium salt

A solution of RS methyl 4-[4-[4-(4-pyridyl)piperazin-1-yl]-phenoxy]-3-vinylbutyrate (0.29g) in 1N sodium hydroxide solution (2.3ml) and methanol (5ml) was kept at room temperature for 4 hours. The solution was evaporated and water (2ml) added to the solid residue. The solid thus obtained was filtered and washed with acetone and ether to give the title compound (0.042g): m.p. 293-295°C; NMR (d_6-DMSO) δ 8.18(2H,d), 6.9(6H,m), 5.88(1H,m), 4.96(2H,m), 4.0(1H,m), 3.77(1H,t), 3.41(2H,m), 3.10(2H,m), 2.84(1H,m), 1.98(2H,d), m/e 470$(M+H)^+$; calculated for $C_{21}H_{24}N_3O_3Na.\ H_2O$: C, 61.9; H, 6.4; N, 10.3. Found: C, 62.1; H, 6.4; N, 10.5%.

The necessary starting material was made as follows:-

(i) A solution of RS 3-vinylbutyrolactone (3.5g) and sodium acetate (2.56g) in methanol (30ml) was kept for 20 hours. Solvent was evaporated and the residue was partitioned between water and ether. The aqueous layer was extracted twice more with ether and the extracts combined, filtered through phase separating paper and evaporated. The residue was purified by filtration chromatography on silica gel (Merck 7736) starting with 1/9 ethyl acetate/hexane and progressing to 4/6 ethyl acetate/hexane as eluent to give methyl 4-hydroxy-3-vinylbutyrate as an oil; NMR($CDCl_3$) δ 5.73(1H,m), 5.15(2H,m), 3.68(3H,s), 3.60(2H,t), 2.76(1H,m), 2.48(2H,m), 1.69(1H,t); m/e 145$(M+H)^+$.

(ii) To a stirred suspension of 4-[4-(4-pyridyl)piperazin-1-yl]phenol (1.98g) in dichloromethane (30ml) at 15°C was added triphenylphosphine (2.04g) followed by dropwise addition of diethyl azodicarboxylate (1.35g). The mixture was stirred until complete solution was obtained. Methyl-4-hydroxy-3-vinylbutyrate (1.12g) was added dropwise and the mixture stirred for 4 hours. The solid which had precipitated during the reaction was the starting phenol and was filtered off. The filtrate was evaporated and the residue treated with ethyl acetate (20ml) and filtered. The filtrate was extracted

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with 2N hydrochloric acid (2 x 10ml) and the aqueous layer separated and basified with 0.89 S.G. ammonium hydroxide. The precipitate was extracted twice into ethyl acetate and the combined extracts filtered through phase separating paper and evaporated. The residue was purified by flash chromatography on silica gel, eluting with methanol/dichloromethane/0.89 S. G. ammonium hydroxide v:v:v 7.5/92.5/0.75 to give RS methyl 4-[4-[4-(4-pyridyl)piperazin-1-yl]-phenoxy]-3-vinylbutyrate (0.29g); NMR($CDCl_3$) δ 8.3(2H,d), 6.88(4H,m), 6.70(2H,d), 5.85(1H,m), 5.20(2H,m), 3.90(2H,m), 3.67(3H,s), 3.48(2H,m), 3.18(2H,m), 3.06(1H,m), 2.68(1H,m), 2.47(1H,m), 1.80(1H,br); m/e 382 $(M+H)^+$.

EXAMPLE 205: Ethyl 4-[2-allyl-4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]butyrate

In a similar manner to Example 50 but starting from 2-allyl-4-[4-(4-pyridyl)piperazin-1-yl]phenol, the title compound was prepared in 50% yield as a solid, m.p. 53-55°C NMR($CDCl_3$) δ 8.3(2H,d), 6.83(1H,m), 6.79(2H,d), 6.71(2H,d.d), 6.0(1H,m), 5.1(2H,m), 4.15(2H,q), 3.98(2H,t), 3.49(4H,m), 3.39(2H,d), 3.19(4H,m), 2.53(2H,t), 2.11(2H,q), 1.76(3H,t), m/e 410$(M+H)^+$; calculated for $C_{24}H_{31}N_3O_3.0.5\ H_2O$: C, 68.9; H, 7.7; N, 10.0. Found: C, 68.8; H, 7.7; N, 9.9%.

The necessary starting material was prepared as follows:-

(i) Sodium hydride (60% dispersion in mineral oil, 0.4g) was added to a stirred suspension of 4-[4-(4-pyridyl)piperazin-1-yl]phenol (2.55g) in DMF (25ml) and the mixture stirred for 20 minutes at room temperature. Allyl chloride (0.756g) was added dropwise and stirring continued for 20 hours. Ice-water (75ml) was added and the mixture extracted three times with ethyl acetate. The combined extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was triturated with hexane and filtered to give 4-[4-(4-pyridyl)piperazin-1-yl]phenol allyl ether (2.5g) as a solid; NMR(d_6DMSO) δ 8.18(2H,dd), 6.8-7.0(6H,m), 5.92-6.13(1H,m), 5.2-5.45(2H,m), 4.5(2H,m), 3.45(4H,m), 3.11(4H,m).

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(ii) The product from step (i) (5g) was heated under argon in gently refluxing diphenyl ether (15g) for 2 1/2 hours. The mixture was cooled to room temperature and ether (70ml) was added. The solid material was filtered and purified by flash chromatography on silica gel, eluting with methanol/dichloromethane (1/4 v/v) to give 2-allyl-4-[4-(4-pyridyl)piperazin-1-yl]phenol (0.88g) as a solid, m.p. 180 - 182°C; NMR (d_6-DMSO) δ 8.88(1H,s), 8.19(2H,dd), 6.87(2H,dd), 6.7(3H,m), 5.88-6.03(1H,m), 5.0(2H,m), 3.44(4H,t), 3.28(2H,d), 3.05(4H,t); m/e 296 $(M+H)^+$.

EXAMPLE 206: 4-[2-allyl-4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]butyric acid

In a similar manner to Example 51, but starting from the product of Example 205, the title compound was prepared as solid in 61% yield; m.p. 209-210°C (dec); NMR (d_6DMSO) δ 8.19(2H,d), 6.84(5H,m), 5.82-6.08(1H,m), 4.92-5.12(2H,m), 3.91(2H,t), 3.44(4H,t), 3.3(2H,d), 3.1(4H,t), 2.4(2H,t), 1.93(2H,t); m/e 382$(M+H)^+$; calculated for $C_{22}H_{27}N_3O_3$: C, 69.3; H, 7.13; N, 11.0. Found: C, 69.2; H, 7.3; N, 11.2%.

EXAMPLE 207: Ethyl 4-[2-n-propyl-4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]butyrate

In a similar manner to Example 50, but starting from 2-n-propyl-4-[4-(4-pyridyl)piperazin-1-yl]phenol, the title compound was prepared in 24% yield as a solid, m.p. 65-67°C; NMR($CDCl_3$) δ 8.29(1H,d), 6.8(1H,d), 6.73(2H,d), 6.7(2H,d), 4.13(2H,q), 3.94(2H,t), 3.46(4H,t), 3.18(4H,t), 2.52(4H,m), 2.09(2H,m), 1.54(2H,m), 1.24(3H,t), 0.94(3H,t); m/e 412$(M+H)^+$.

The necessary starting material was prepared as follows:-

The product from Example 205, step (ii) (0.74g) in ethanol (25ml) and 1N hydrochloric acid (2.5ml) was hydrogenated at room temperature and atmospheric pressure over 10% palladium charcoal (0.15g) until uptake of hydrogen was complete. Catalyst was removed by filtration through diatomaceous earth and the filtrate evaporated.

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The residue was triturated with a mixture of ethyl acetate (25ml) and saturated sodium bicarbonate solution (25ml) and the insoluble solid was filtered and washed with water and ethyl acetate. The aqueous layer of the filtrate was extracted twice with dichloromethane and the combined organic extracts evaporated. The residue was combined with the ethyl acetate-insoluble material and treated with boiling ethanol (40ml), unsoluble material being removed by filtration. Evaportion of the filtrate gave 2-n-propyl-4-[4-(4-pyridyl)piperazin-1-yl]phenol (0.7g) as a solid NMR (d_6DMSO) δ 8.84-8.68(1H,m), 8.18(2H,d), 6.82(2H,m), 6.7(3H,m), 4.1(1H,m), 3.42(4H,t), 3.17(3H,s), 3.05(4H,t), 2.48(DMSO), 1.55(2H,m), 0.89(3H,t).

EXAMPLE 208: 4-[2-n-propyl-4-[4-(4-pyridyl)piperazin-1-yl]-phenoxy]butyric acid

In a similar manner to Example 51, but starting from the product of Example 207 was prepared the title compound in 64% yield; m.p. 207-209°C (from isopropanol); NMR(d_6DMSO) δ 8.18(2H,d), 6.7-6.92(5H,m), 3.91(2H,t), 3.45(4H,t), 3.10(4H,t), 2.5(DMSO), 2.4(2H,t), 1.91(2H,?), 1.54(2H,m), 0.9(3H,t) + isopropanol (0.69 mole %) at 3.79 and 1.04; m/e 384$(M+H)^+$. Calculated for $C_{22}H_{29}N_3O_3 \cdot 0.7C_3H_7O$: C, 68.0; H, 8.2; N, 9.9. Found C, 68.1; H, 8.2; N, 9.9%.

EXAMPLE 209: Ethyl 4-[2-methyl-4-[4-(4-pyridyl)piperazin-1-yl]-phenoxy]butyrate

In a similar manner to Example 50, but starting from 2-methyl-4-[4-(4-pyridyl)piperazin-1-yl]phenol dihydrochloride was prepared the title compound in 29% yield as a gum; NMR($CDCl_3$ δ 8.3(2H,m), 6.45-6.35(5H,m), 4.14(2H,q), 3.87(2H,t), 3.14(4H,m), 2.53(2H,t), 2.21(3H,s), 2.11(2H,m), 1.24(3H,t); m/e 384$(M+H)^+$.

The necessary starting material was made as follows:-

i) Carbonyl diimidazole (5g) was added portionwise to a stirred suspension of N-benzyliminodiacetic acid (3.14g) in dry THF (50ml) at room temperature under argon. After 5 minutes, the mixture was heated at gentle reflux for 15 minutes and (4-amino-2-methyl)-

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phenylbenzylether (3.0g) added and the mixture stirred at reflux for 17 hours. Solvent was evaporated and the residue was stirred with ethyl acetate (100ml) and water (150ml) for 1 1/2 hours. The solid was filtered, washed with water and dried to give (4-[4-benzyl-2,6-diketopiperazin-1-yl]-2-methyl)phenylbenzylether (4.7g); m.p. 118-126°C (dec); NMR ($CDCl_3$) δ 7.1-7.32(10H,m), 6.78(3H,s), 4.93(2H,s), 3.56(2H,s), 3.4(4H,s), 2.12(3H,s); m/e $373(M+H)^+$.

(ii) To a solution of the product of step i) (2.9g) in dry THF (50ml) was added lithium aluminium hydride (0.6g) and the mixture heated at reflux for 1 1/2 hours. The mixture was allowed to cool and more (0.3g) lithium aluminium hydride added and reflux continued for a further 1 1/2 hours. The mixture was cooled and water (0.9ml) added followed by sodium hydroxide solution (1N, 3.6ml) and the mixture refluxed for 10 minutes. The solid was filtered and washed with THF. The filtrate and washings were evaporated and the residue purified by flash chromatography on silica gel, eluting with 5% ethyl acetate in dichloromethane increasing to 25% ethyl acetate. Thus was obtained [2-methyl-4-{4-benzylpiperazin-1-yl}]phenylbenzyl ether as a solid (1g); m.p. 118-120°C; NMR($CDCl_3$) δ 7.2-7.5(10H,m), 6.82(1H,d), 6.80(1H,d), 6.7(1H,m), 5.01(2H,s), 3.1(4H,m), 2.53(3H,s); m/e $373(M+H)^+$.

(iii) A suspension of the product of step ii) (1g) in 1,2-dichloroethane (25ml) was cooled in ice-water and treated with 1-chloroethylchloroformate (0.77g). The mixture was allowed to warm to room temperature, stirred for 30 minutes and heated at reflux for 30 minutes. Methanol (20ml) was added and the mixture refluxed again for 30 minutes and evaporated. The residue was triturated with ether and filtered. The solid was washed with ether and dried to give [2-methyl-[4-piperazin-1-yl]]phenylbenzylether hydrochloride (0.95g); m.p. 195-198°C; NMR(d_6DMSO) δ9.44(2H,bs), 7.3-7.5(6H,m), 6.98(2H,m), 5.08(?,s), 4.98(4H,bs), 3.38(4H,d), 2.2(3H,s); m/e $281(M+H)^+$.

(iv) A mixture of the product of step iii) (0.95g), 4-chloropyridine hydrochloride (0.46g) and triethylamine (0.615g) in water (10ml) was heated at 100°C for 3 hours. More 4-chloropyridine (0.34g) and triethylamine (0.3ml) was added and reflux continued for a

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further 3 hours. The solution was cooled and extracted with dichloromethane (2 x 15ml). The organic layer was evaporated and the residue was purified by flash chromatography on silica gel, eluting with 5% methanol in dichloromethane, containing 0.4% concentrated ammonia, to give [2-methyl-4-[4-(4-pyridyl)piperazin-1-yl]]phenylbenzyl ether (0.26g); as a solid; NMR(d_6-DMSO) δ 8.19(2H,d), 7.25-7.5(5H,m), 6.88(4H,m), 6.74(1H,m), 5.03(2H,s), 3.44(4H,bt), 3.1(4H,bt), 2.18(3H,s); m/e 360$(M+H)^+$.

(v) A solution of the product of step (iv) (0.52g) in ethanol (20ml) containing 2N hydrochloric acid (2ml) was stirred with 10% palladium/carbon (0.16g) under an atmosphere of hydrogen until hydrogen uptake was complete. The mixture was filtered and the filtrate evaporated. The residue was triturated with hot ethyl acetate and filtered to give, as a solid, 2-methyl-4-[4-(4-pyridyl)-piperazin-1-yl]phenol dihydrochloride (0.55g); NMR(d_6-DMSO) δ 8.25(2H,d), 7.24(2H,d), 7.12(2H,bd), 6.8(1H,d), 4.02(4H,m), 3.46(4H,m), 2.1(3H,s); m/e 270$(M+H)^+$.

EXAMPLE 210: 4-[2-methyl-4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]-butyric acid

In a similar manner to Example 51, but starting from the product of Example 209, the title compound was obtained in 80% yield as a solid, m.p. 261-262°C; NMR(d_6DMSO) δ 8.18(2H,d), 6.7-6.9(2H,m), 3.9(2H,t), 3.43(4H,bt), 3.1(4H,bt), 2.39(2H,t), 2.13(3H,s),1.72(2H,m); m/e 356$(M+H)^+$. Calculated for $C_{20}H_{25}N_3O_3$: C, 67.6; H, 7.1; N, 11.8. Found: C, 67.4; H, 6.9; N, 12.2%.

EXAMPLE 211: RS Methyl-2-t-butoxycarbonylamino-4-[4-[4-(4-pyridyl)-piperazin-1-yl]phenoxy]butyrate

In a similar manner to Example 50, but starting from RS methyl 4-bromo-2-t-butoxycarbonylaminobutyrate, the title compound was prepared in 65% yield as an oil; NMR($CDCl_3$) δ 8.31(2H,d), 6.9(4H,m), 6.71(2H,m), 5.3(1H,br), 4.5(1H,br.d), 4.01(2H,t), 3.77(3H,s),

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3.5(4H,m), 3.21(4H,m), 2.3(2H,m), 1.46(9H,s); also signals at 6.03, 2.97 and 2.9(DMF) and 1.8(H_2O); m/e 471 $(M+H)^+$. Calculated for $C_{25}H_{34}N_4O_5$. 0.5DMF. 0.5H_2O: C, 61.7; H, 7.5; N, 12.2. Found: C, 61.8; H, 7.2; N, 11.9%.

The necessary starting material was made as follows:-

A solution of RS-methyl-N-butoxycarbonyl homoserinate (1.7g) and carbon tetrabromide (3.6g) in dichloromethane (20ml) was stirred at 5°C. Triphenylphosphine (3.77g) was added portionwise over 5 minutes. After 2 hours at room temperature the dark solution was evaporated and the residue triturated with ether/hexane (1/1, 30ml) until a solid was obtained. The solid was filtered and the filtrate evaporated. The residue was purified by flash chromatography, the product being eluted with 25% ethyl acetate/hexane to give RS methyl 4-bromo-2-butyloxycarbonylaminobutyrate (0.41g) as an oil; NMR($CDCl_3$) δ 5.16(1H,br), 4.45(1H,m), 3.8(3H,s), 3.45(2H,t), 2.52-2.11(2H,m), 1.48(9H,s); m/e 296 $(M+H)^+$.

EXAMPLE 212: RS 2-t-butoxycarbonylamino-4-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]butyric acid

In a similar manner to Example 51, but starting from the compound of Example 211, there was obtained in 58% yield, the title compound as a solid; m.p. 198-207°C; NMR(d_6DMSO) δ 8.2(2H,d), 6.91(6H,m), 4.06(1H,m), 3.92(2H,t), 3.48(4H,t), 3.12(4H,t), 2.2-1.84(2H,m), 1.37(9H,s); m/e 457 $(M+H)^+$. Calculated for $C_{24}H_{32}N_4O_5$. H_2O: C, 60.7; H, 7.2; N, 11.8. Found: C, 60.7; H, 7.2; N, 11.7%.

EXAMPLE 213: RS Methyl 2-amino-4-[4-[4-(4-pyridyl)piperazin-1-yl]-phenoxy]butyrate

The compound of Example 211 (0.96g) in TFA (10ml) was kept at room temperature for 2 hours. The solution was evaporated and the residue dissolved in water (15ml) and the solution basified with sodium carbonate. The mixture was extracted three times with dichloromethane. Evaporation of the combined extracts gave the title compound (0.56g); m.p. 125-127°C; NMR(d_6DMSO) δ 8.2(2H,d), 6.92(6H,m),

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4.0(2H,m), 3.64(3H,s), 3.46(4H,t), 3.15(4H,t), 2.04(2H,m), 1.84(1H,m); m/e 371$(M+H)^+$. Calculated for $C_{20}H_{26}N_4O_3$. 0.75 H_2O: C, 62.5; H, 7.17; N, 14.6. Found: C, 62.8; H, 6.8; N, 14.3%.

EXAMPLE 214: 4-[2-[4-(4-pyridyl)piperazin-2-one-1-yl]acetyl]-phenoxyacetic acid, sodium salt

The title compound of Example 61 (0.25g) in methanol (5ml) was treated with aqueous sodium hydroxide (1N, 0.65ml) and the mixture kept at room temperature for 6 hours. The solid thus formed was filtered and washed with methanol to give the title compound (0.18g); m.p. 317-318°C; NMR(d_6DMSO) δ 8.2(2H,d), 7.89(2H,d), 6.91(2H,d), 6.83(2H,d), 4.89(2H,s), 4.21(2H,s), 4.01(2H,s), 3.68(2H,m), 3.51(2H,m); m/e 392$(M+H)^+$; calculated for $C_{19}H_{18}N_3O_5Na$. 0.25H_2O: C, 57.6; H, 4.6; N,10. Found: C, 57.2; H, 4.6; N, 10.4%.

EXAMPLE 215: Ethyl 4-[2-[4-(4-pyridyl)piperazin-2-one-1-yl]acetyl]-phenoxyacetate

A crude sample of the product of Example 62 (3.4g) was treated with a solution, at 0°C, made by adding thionyl chloride (2.25g) dropwise to ethanol (45ml) with stirring at below 0°C. The mixture was stirred at room temperature for 2 hours, heated at gentle reflux for 2 1/2 hours, and evaporated. The residue was treated with water and adjusted to pH6 with aqueous sodium bicarbonate solution. The gum which precipitated was separated and the aqueous solution was adjusted to pH8 and extracted with dichloromethane (2 x 50ml). The combined extracts were washed with brine, dried and evaporated. The residue was purified by chromatography using a 10g. Mega Bond Elut silica gel column, eluting with 5% methanol/dichloromethane/0.5% triethylamine to give the title product as a solid (0.2g); m.p. 163-165°C; NMR($CDCl_3$) δ 8.34(2H,m), 7.97(2H,m), 6.98(2H,m), 6.63(2H,m), 4.89(2H,s), 4.7(2H,s), 4.29(2H,q), 4.1(2H,s), 3.7(2H,m), 3.6(2H,m), 1.31(3H,t); m/e 398$(M+H)^+$; calculated for $C_{21}H_{23}N_3O_5$: C, 63.5; H, 5.83; N, 10.6. Found: C, 61.5; H, 5.9; N, 10.5%.

EXAMPLE 216: Ethyl N 4-[2-(4-(4-pyridyl)piperazin-2-one-1-yl)acetyl]-phenoxyacetylglycinate

The compound of Example 62 (0.37g) was stirred in DMF (10ml) with hydroxybenzotriazole (0.17g) and the mixture cooled in ice-water. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.14g) was added, followed by triethylamine (0.14ml) and the mixture stirred for 30 minutes. Glycine ethyl ester hydrochloride (0.15g) was now added, followed by triethylamine (0.28ml). After ten minutes stirring in the cold, the mixture was allowed to warm to room temperature, stirred for two days and evaporated. Water (10ml) was added to the residue and sodium bicarbonate added to pH6-7. The mixture was evaporated and the residue purified by chromatography on a Mega Bond Elut silica gel column (10g), eluting with 2% - 20% methanol/dichloromethane. The product was recrystallised from ethanol to give the title compound as a solid (36mg); m.p. 209-211°C; NMR(d_6DMSO) δ 8.55(1H,t), 8.2(2H,brd), 7.99(2H,m), 7.12(2H,m), 6.86(2H,d), 4.92(2H,s), 4.11(2H,q), 4.02(2H,s), 3.9(2H,d), 3.2(2H,m), 3.52(2H,m), 1.2(3H,t); m/e 455(M+H); calculated for $C_{23}H_{26}N_4O_6$: C, 60.8; H, 5.77; N, 12.3. Found: C, 60.6; H, 5.7; N, 12.5%.

EXAMPLE 217: Ethyl 4-[2-nitro-4-[4-(4-pyridyl)piperazin-1-yl]-phenoxy]butyrate

Sulphuric acid (98%, 2.5ml) was added slowly to the compound of Example 50 (1g) with stirring at room temperature. The solution was cooled to below 5°C and a mixture of nitric acid (0.18ml) and sulphuric acid (0.18ml) was added dropwise. The solution was stirred at below 10°C for 1 1/2 hours, poured onto ice and basified with ammonia solution to pH10. The mixture was extracted with ethyl acetate (2 x 50ml) and the extract washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel, the product being eluted with 5% - 10% methanol/-dichloromethane to give the title product as an oil (0.18g); NMR($CDCl_3$) δ 8.32(2H,d), 7.41(1H,d), 7.14(1H,m), 7.04(1H,d), 6.77(2H,m), 4.17-4.14(4H,m), 3.51-3.28(8H,m), 2.57(2H,t), 2.14(2H,m),

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1.28(3H,t), plus H_2O (1.87); m/e 415$(M+H)^+$; calculated for $C_{21}H_{26}N_4O_5 . 0.25H_2O$: C, 60.1; H,6.3; N, 13.1. Found: C, 60.2; H, 6.3; N 13.2%.

EXAMPLE 218: RS Methyl 2-n-butanesulphonylamino-4-[4-[4-(4-pyridyl)-piperazin-1-yl]phenoxy]butyrate

n-Butanesulphonylchloride (0.233g) was added to a stirred solution of the compound of Example 213 (0.5g) and triethylamine (0.15g) in dichloromethane (15ml) at room temperature. The solution was kept for 2 days and subjected to flash column chromatography on silica gel. The product was eluted with methanol/-dichloromethane/0.88SG ammonia (7/93/0.7) v:v:v to give, after trituration with ether, the title compound in 58% yield as a solid; m.p. 124-125°c; NMR($CDCl_3$) δ 8.3(2H,d), 6.88(4H,q), 6.72(2H,m), 5.18(1H,br.d), 4.16(1H,br,q), 4.08(2H,t), 3.8(3H,s), 3.47(4H,m), 3.18(4H,m), 2.98(2H,m), 2.28(2H,m), 1.73(2H,m), 1.45-1.27(2H,m), 0.9(3H,t); m/e491$(M+H)^+$; calculated for $C_{24}H_{34}N_4O_5S$: C, 58.8; H, 7.0; N, 11.4. Found: C, 58.4; H, 7.0; N, 11.1%.

EXAMPLE 219: RS 2-n-butanesulphonylamino-4-[4-[4-(4-pyridyl)-piperazin-1-yl]phenoxy]butyric acid

In a similar manner to Example 51, but starting from the compound of Example 218, was prepared the title compound in 58% yield as a solid; m.p. 251-252°C; NMR(d_6DMSO) δ 8.18(2H,d), 7.3(1H,vbr), 6.9(6H,m), 3.97(2H,t), 3.9(1H,m), 3.45(4H,t), 3.11(4H,t), 2.9(2H,t), 2.12(1H,m), 1.92(1H,m), 1.58(2H,m), 0.81(3H,t); m/e 477$(M+H)^+$; calculated for $C_{23}H_{32}N_4O_5S . 0.5\ H_2O$: C, 56.9; H, 6.8; N, 11.5. Found: C,57.0; H, 6.8; N, 11.3%.

EXAMPLE 220: RS 3-Benzyl-4-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]-butyric acid

In a similar manner to Example 51, but starting from RS ethyl 3-benzyl-4-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]butyrate, was prepared the title compound in 65% yield as a solid; m.p. 205-206°C;

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NMR (d_6DMSO) δ 8.2(2H,d), 7.22(5H,m), 6.9(6H,m), 3.8(2H,d), 3.45(4H,m), 3.15(4H,m), 2.72(2H,m), 2.5-2.18(Me_2SO + 3H,m); m/e 432 $(M+H)^+$; calculated for $C_{26}H_{29}N_3O_3$. $0.25H_2O$: C, 71.6; H, 6.8; N, 9.7. Found: C, 71.9; H, 6.8; N, 9.5%.

The necessary starting material was made as follows:-

(i) A solution of RS 3-benzylbutyrolactone (1.14g) in ethanol (20ml) was stirred at 5°C and gassed for 4 hours with a slow stream of hydrogen bromide. The solution was kept at 5°C for 20 hours and water (70ml) added followed by sodium carbonate to neutralise the acid. The mixture was extracted with ethyl acetate and the organic layer filterd through phase separating paper and evaporated to give ethyl 4-benzyl-3-bromobutyrate as an oil; NMR($CDCl_3$) δ 7.24(5H,m), 4.13(2H,q); 3.45(2H,m), 2.62(2H,d), 2.44(3H,m), 1.25(3H,t); m/e 285$(M+H)^+$.

(ii) In a similar manner to Example 50, but starting from the product of step (i) was prepared RS ethyl 3-benzyl-4-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]butyrate in 40% yield as an oil; NMR ($CDCl_3$) δ 8.34(2H,d), 7.29(5H,m), 6.9(4H,m), 6.72(2H,m), 5.13(2H,q), 3.85(2H,m), 3.5(4H,m), 3.3(4H,m), 2.9-2.38(5H,m), 1.26(3H,t); m/e 460$(M+H)^+$.

EXAMPLE 221: RS 3-phenyl-4-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]-butyric acid

In a similar manner to Example 51, but starting from RS methyl 3-phenyl-4-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]butyrate, was prepared the title compound in 39% yield as a solid; m.p. 120-125°C; NMR(d_6DMSO) δ 8.18(2H,d), 7.32(5H,m), 7.25(2H,d), 6.87(6H,m), 4.04(2H,q), 3.45(5H,m), 3.11(4H,t), 2.7(2H,m); m/e 418$(M+H)^+$; calculated for $C_{25}H_{27}N_3O_3$. $0.25H_2O$: C, 7.1; H,6.5; N,9.9. Found: C, 7.2; H, 6.5; N,9.8%.

The necessary starting material was made as follows:-

In a similar manner to Example 204 step (ii), but starting from RS ethyl 4-hydroxy-3-phenylbutyrate was made RS methyl-3-phenyl-4-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]butyrate in 10% yield as an oil; NMR(d_6DMSO +CD_3COOD) δ 8.23(2H,d), 7.3(5H,m), 7.17(2H,d),

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6.95(2H,d), 6.83(2H,d), 4.06(2H,m), 3.77(4H,t), 3.55(3H,s), 3.51(1H,m), 3.17(4H,t), 2.83(2H,m); m/e 432$(M+H)^+$.

EXAMPLE 222: N-[1-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-piperidin-4-ylmethyl]-4-methylphenylsulphonamide

A solution of N-(1-bromoacetylpiperidin-4-ylmethyl)-4-methylphenylsulphonamide (1.0g), 1-(4-pyridyl)piperazine (600mg) and triethylamine (0.5ml) in acetonitrile (20ml) was stirred for 1 hr and then left to stand overnight. The solvent was evaporated in vacuo and the residue purified by chromatography on silica, eluting with 5% v/v methanol/dichloromethane. Evaporation of the eluant fractions gave a colourless solid (280mg). The title compound was obtained as colourless prisms (150mg), m.p. 156-158°C (from ethyl acetate); NMR (d_6 DMSO) : δ 0.8-1.2 (2H,m); 1.5-1.8 (3H,m); 2.35 (3H,s); 2.4 (6H,m), 2.6 (2H,t); 2.8-3.0 (1H,t); 3.2 (1H,d); 3.2-3.5 (4H,m); 4.0 (1H,d); 4.3 (1H,d); 6.8 (2H,d); 7.4 (2H,d); 7.55 (1H,t); 7.7 (2H,d); 8.2 (2H,d); m/e 472 $(M+H)^+$; calculated for $C_{24}H_{33}N_5O_3S$: C,61.1; H,7.1; N,14.8; found : C,60.9; H,7.1; N,14.5%.

The starting material was prepared as follows:-

(i) Sodium hydride (300mg of a 60% suspension) was added to a stirred solution of 4-methylphenylsulphonamide and the mixture stirred at room temperature until effervescence had ceased. N-benzyloxy-carbonylpiperidine-4-methanol mesylate (1.09g) was added and the mixture heated at 100°C for 7 hours. After cooling to room temperature it was diluted with water (200ml) and extracted with ether (4 x 40ml); the extracts were combined, washed with water (2x) and brine, dried ($MgSO_4$) and evaporated to yield N-(1-benzyloxy-carbonylpiperidin-4-ylmethyl)-4-methylphenylsulphonamide
NMR (d_6 DMSO) : δ 0.8-1.1 (2H,m); 1.5-1.7 (3H,m); 2.35 (3H,s); 2.6 (2H,t); 2.7-2.9 (2H,m); 4.0 (2H,d); 5.0 (2H,s); 7.2-7.5 (7H,m); 7.55 (1H,t); 7.7 (2H,d); m/e 403 $(M+H)^+$.

(ii) To a solution of the product of step (i) (1.2g) in absolute ethanol (30ml), was added 10% palladium-on-charcoal catalyst (200mg) and the mixture stirred in an atmosphere of hydrogen until all the

starting material had reacted (Tlc). After removal of the catalyst by filtration, the solvent was evaporated in vacuo and the residue dried under high vacuum to yield the free amine as a colourless gum (800mg). This was dissolved in dichloromethane, the solution stirred with ice-cooling and treated sequentially with triethylamine (0.45ml) and bromoacetyl bromide (0.3ml). The mixture was stirred for 1 hr and then washed with water (25ml) and brine (25ml), dried (PS paper) and evaporated in vacuo to yield crude N-(1-bromoacetylpiperidin-4-ylmethyl)-4-methylphenylsulphonamide as a colourless gum (1.0g) which was used without further purification or characterisation.

EXAMPLE 223: N-[2-[1-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-piperidin-4-ylethyl]-4-methylphenylsulphonamide, dihydrochloride

In a similar manner to Example 222, but starting from N-[2-(1-bromoacetylpiperidin-4-ylethyl]-4-methylphenylsulphonamide, the title compound was obtained as a dihydrochloride salt (160 mg colourless prisms) containing 1/3 mole ethanol of crystallisation, m.p. 258-260°C (from ethanol); NMR (d_6 DMSO+CD_3COOD) : δ 0.8-1.2 (2H,m); 1.5-1.8 (3H,m); 2.4 (3H,s); 2.6 (2H,m); 2.8 (2H,t); 3.0 (1H,t); 3.4-3.7 (5H,m); 3.9-4.2 (4H,m); 4.3-4.5 (3H,m); 7.25 (2H,d); 7.4 (2H,d); 7.7 (2H,d); 8.35 (2H,d); m/e 486 (M+H)+; calculated for $C_{25}H_{35}N_5O_3S.2HCl.0.33$ EtOH : C,53.7; H,6.9; N,12.1; found : C,53.5; H,7.0;N, %.

The necessary starting material was prepared as follows:-

(i) 4-Piperidine ethanol was reacted with benzyloxycarbonyl chloride in triethylamine to yield (after chromatography) 1-benzyloxycarbonylpiperidin-4-ylethanol as a colourless oil, (2.0g) NMR (d_6 DMSO) : δ 0.9-1.2 (2H,m); 1.2-1.4 (2H,q); 1.5-1.8 (3H,m); 2.6-2.9 (2H,t); 3.45 (2H,q); 4.0 (2H,d);4.35 (1H,t); 5.1 (2H,s); 7.35 (5H,m); m/e 264 $(M+H)^+$.

(ii) A solution of methanesulphonyl chloride (0.85ml) in dichloromethane (20ml) was added dropwise to a stirred, ice-cooled solution of triethylamine (1.55ml) and the product of step (i) (2.64g) in dichloromethane (50ml). After stirring for 3 hours the reaction

mixture was washed with water (3x) and brine, dried (PS paper) and evaporated in vacuo to yield N-benzyloxycarbonylpiperidin-4-ylethanol mesylate as a colourless paste (3.4g) NMR (d_6 DMSO) : δ 0.9-1.2 (2H,m); 1.5-1.8 (5H,m);2.6-2.9 (2H,m); 4.0 (2H,d);4.25 (2H,t);4.4 (2H,s); 5.1 (2H,s); 7.35 (5H,m); m/e 342 $(M+H)^+$.

(iii) Following a method similar to that described in Example 222 step (i), but starting from the product of step (ii) there was obtained N-(1-benzyloxycarbonylpiperidin-4-ylethanol)-4-methylphenylsulphonamide as a colourless gum (900mg) after chromatography on alumina, NMR (d_6 DMSO) : δ 0.8-1.0 (2H,m); 1.3 (2H,q); 1.4-1.6 (3H,m); 2.4 (3H,s); 2.6-2.8 (4H,m); 4.0 (2H,d); 5.1 (2H,s); 7.2-7.5 (7H,m); 7.5 (1H,t); 7.7 (2H,d); m/e 417 $(M+H)^+$.

(iv) In a similar manner to Example 222, step (ii) but starting from the product of step (iii) there was obtained N-(1-bromoacetylpiperidin-4-ylmethyl)-4-methylphenylsulphonamide as a pale yellow gum (800mg), NMR ($CDCl_3$) : δ 1.0-1.4 (3H,m); 1.45 (2H,q); 1.5-1.8 (3H,m); 2.45 (3H,s); 2.5-2.7 (1H,m); 3.0 (2H,m); 3.8 (2H,m); 4.4-4.7 (2H,m); 7.3 (2H,d); 7.75 (2H,d); m/e 403/405 $(M+H)^+$.

EXAMPLE 224: 4-[4-[3-(4-dimethylaminopyrid-3-yl)propyloxy]phenoxy)-butyric acid

To a solution of ethyl 4-[4-[3-(4-dimethylaminopyrid-3-yl)-propyloxy]phenoxy]butyrate (160mg) in methanol (10ml) was added sodium hydroxide solution (2.0ml of 1.0M) and the solution left until all starting ester had disappeared (Tlc). The reaction mixture was neutralised with hydrochloric acid (2.0ml of 1.0M) and evaporated in vacuo. A small amount (5ml) water was added and the resulting solution extracted with dichloromethane (3 x 15ml). The organic extracts were combined, dried (PS paper) and evaporated to yield the title compound as colourless prisms, (90mg) m.p. 106-108°C (from ethyl acetate); NMR (d_6DMSO) : δ 1.8-2.1 (2H,q;2H,q); 2.4 (2H,t); 2.8

(2H,t;6H,s); 3.9 (2H,t;2H,t); 6.8(5H,m); 8.2 (2H,d); m/e 359 $(M+H)^+$; calculated for $C_{20}H_{26}N_2O_4$: C,67.0; H,7.3; N,7.8; found : C,67.1; H,7.6;N,7.7%.

The necessary starting material was prepared as follows:-

(i) A solution of 4-benzyloxyphenol (4.2g) in dimethyl formamide (50ml) was treated with sodium hydride (840mg of a 60% dispersion), and the mixture stirred until evolution of gas ceased. There was then added ethyl 3-bromobutyrate (2.9ml), and the solution stirred overnight. It was then poured into water (300ml) and the mixture extracted with ether (3 x 50ml). The combined extracts were washed with water (3x) and brine, dried ($MgSO_4$) and evaporated to give a crude product as a brown oil (6g). This was purified by chromatography on silica, eluting with hexane containing increasing amounts of ethyl acetate to give ethyl 3-(4-benzyloxyphenoxy)butyrate as a colourless crystalline solid (4.5g) NMR (d_6 DMSO) : δ 1.25 (3H,t);1.8-2.0 (2H,m); 2.45 (2H,t); 3.9 (2H,t); 4.1 (2H,q); 5.0 (2H,s); 6.8-7.0 (4H,m); 7.4 (5H,m); m/e 314 $(M+H)^+$.

(ii) To a solution of the product of step (i) (4.5g) in absolute ethanol (200ml) was added 10% palladium-on-charcoal catalyst (1.2g) and the resulting suspension hydrogenated at ambient temperature and pressure until uptake of hydrogen ceased. The catalyst was removed by filtration through celite and the filtrate was concentrated <u>in vacuo</u> to give ethyl 3-(4-hydroxyphenoxy)butyrate as a low-melting crystalline solid (3.0g) NMR (d_6 DMSO) : δ 1.25 (3H,t); 1.8-2.0 (2H,m); 2.5 (2H,t); 3.9 (2H,t); 4.1 (2H,q); 6.7 (4H,m); 8.8 (1H,br.s); m/e 224 $(M)^+$.

(iii) A solution of 4-dimethylaminopyridine-3-aldehyde prepared according to J. Het. Chem. <u>25</u> p81 (1988).(1.5g) and ethyl triphenylphosphoranylidene acetate (3.85g) in acetonitrile (25ml) was refluxed for seven hours. The solvent was removed <u>in vacuo</u> and the residue dissolved in dilute hydrochloric acid (30ml of 1M); the solution was washed with ethyl acetate (2 x 20ml) and then basified with solid sodium hydrogen carbonate. The resulting solution was

extracted with dichloromethane (3 x 20ml) and the combined extracts washed with brine, dried (PS paper) and evaporated to yield the crude product as a brown oil (2.0g). This was purified by chromatography on silica, eluting with ethyl acetate, to give ethyl 2-(4-dimethylamino-3-pyridyl)propenoate as a pale yellow oil (1.5g) NMR (d_6 DMSO) : δ 1.25 (3H,t); 2.85 (6H,s); 4.2 (2H,q); 6.5 (1H,d); 6.9 (1H,d);7.5 (1H,d); 8.25 (1H,d); 8.5 (1H,s); m/e 221 $(M+H)^+$.

(iv) To a solution of the product of step (iii) (3.6g) in absolute ethanol (100ml) was added 5% palladium/charcoal catalyst, and the mixture hydrogenated at ambient temperature and pressure until the theoretical volume of hydrogen had been consumed. The catalyst was removed by filtration through celite and the filtrate evaporated to yield ethyl 2-(4-dimethylamino-3-pyridyl)propanoate as a pale yellow oil (3.1g) NMR (d_6 DMSO) : δ 1.15 (3H,t); 2.65 (2H,t); 2.8 (6H,s); 2.9 (2H,t); 4.05 (2H,q); 6.8 (2H,d); 8.2 (2H,d); m/e 223 $(M+H)^+$.

(v) To a stirred solution of the product of step (iv) (2.6g) in tetrahydrofuran (100ml) was added lithium aluminium hydride (1.2g) and the resulting suspension stirred for 4 hours at ambient temperature. Excess reducing agent was destroyed by the sequential addition of ethyl acetate, water, and conc. HCl. The mixture was then basified and extracted sequentially with ethyl acetate and dichloromethane. The organic extracts were combined, dried (PS paper and $MgSO_4$) and evaporated to yield 4-dimethylamino-3-(3-hydroxypropyl)pyridine as a pale yellow oil (2.2g), essentially pure by Tlc NMR (d_6 DMSO) : δ 1.6-1.8 (2H,m); 2.65 (2H,t); 2.8 (6H,s); 3.5 (2H,t); 4.5 (1H,br.s); 6.7 (2H,d); 8.2 (2H,d); m/e 181 $(M+H)^+$.

(vi) A solution of the product of step (v) (600mg), the product of step (ii) (750ml) and triphenylphosphine (920mg) in tetrahydrofuran (20ml) was stirred at ambient temperature for 0.5hr. To this was added diethylazodicarboxylate (0.61ml) and the resulting solution stirred for 1 hr. The solvent was evaporated and the residue purified by chromatography on silica eluting with 2% v/v ethanol/dichloromethane. Evaporation of the eluant fractions gave

ethyl 4-[4-[3-(4-dimethylaminopyrid-3-yl)propyloxy]phenoxy]butyrate as an orange oil (450mg); NMR (d_6 DMSO +CD_3COOD) : δ 1.1 (3H,t); 1.8-2.0 (2H,q;2H,q); 2.35 (2H,t); 2.85 (2H,t); 3.1 (6H,s); 3.8 (2H,t;2H,t); 4.0 (2H,q); 6.7 (4H,s); 6.9 (1H,d); 8.0 (2H,d); m/e 387 $(M+H)^+$.

EXAMPLE 225: 2-S-(benzyloxycarbonylamino-3-[4-[3-[4-dimethylamino-pyrid-3-yl]propoxy]phenyl]propionic acid

In a similar manner to Example 224 but starting from methyl 2-S-(benzyloxycarbonylamino)-3-[4-[3-[4-dimethylaminopyrid-3-yl]-propoxyphenyl]propionate the crude title compound was prepared as a colourless foam (200mg). This was dissolved in distilled water (25ml) containing dilute hydrochloric acid (1.0ml of 1M), the solution washed with ether (2 x 10ml), filtered and lyophilised to give the title compound as a colourless solid (180mg); NMR (d_6 DMSO+CD$_3$OD) : δ 2.05 (2H,m); 2.7-3.2 (5H,m);3.2 (6H,s); 4.0 (2H,t); 4.3 (1H,q); 5.0 (2H,s); 6.8 (2H,d);7.0 (1H,d); 7.2 (2H,d); 7.3 (5H,m); 8.1 (2H,d); m/e 478 (M+H)+; calculated for $C_{27}H_{31}N_3O_5.HCl.0.75\ H_2O$: C,61.5; H,6.4; N,8.0; H_2O 2.5; found : C,61.6; H,6.6; N,7.8; H_2O 2.1%.

The necessary starting material was prepared in a similar manner to Example 224 step (vi), but starting from methyl 2-S-benzyloxycarbonylamino-3-(4-hydroxyphenyl)propionate, yielding a colourless gum (1.0g); NMR (d_6 DMSO+CD_3COOD) : δ 2.05 (2H,m); 2.7-3.2 (4H,m);3.2 (6H,s);3.7 (3H,s); 4.0 (2H,t); 4.3 (1H,q); 5.0 (2H,s); 6.8 (2H,d);7.0 (1H,d); 7.2 (2H,d); 7.3 (5H,m); 8.1 (2H,d); m/e 492 $(M+H)^+$.

EXAMPLE 226: Ethyl 4-[3-[4-(4-pyridyl)piperazin-1-yl]phenoxy]-butyrate

In a similar manner to that described in Example 50, but starting from 3-[4-(4-pyridyl)piperazin-1-yl]phenol, the title compound was prepared as colourless prisms, 560mg m.p. 160-162°C (from ethanol); NMR (d_6 DMSO) : δ 1.2 (3H,t); 1.85-2.05 (2H,q); 2.45 (2H,t); 3.4 (4H,m); 3.85 (4H,m); 4.0 (2H,t); 4.1 (2H,q); 6.45 (1H,m); 6.65 (2H,m); 7.15 (1H,t); 7.25 (2H,d); 8.2 (2H,t); m/e 370

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$(M+H)^+$; calculated for $C_{21}H_{27}N_3O_3.2HCl.\ 0.6\ H_2O$: C,55.7; H,6.7; N,9.3; H_2O,2.8; found : C,56.0; H,6.8; N,9.2; H_2O,3.0%.

The necessary starting material was prepared as follows:

(i) 3-[4-(3-pyridyl)piperazin-1-yl)]anisole was prepared in a manner similar to that described in Example 50, but starting from 3-(1-piperazinyl)anisole, giving yellow prisms (from carbon tetrachloride), 4.8g. NMR (d_6 DMSO) : δ 3.25 (4H,m); 3.45 (4H,m); 3.75 (3H,s); 6.4 (1H,m); 6.5 (1H,m); 6.55 (1H,m); 6.85 (2H,d); 7.15 (1H,t); 8.2 (2H,d); m/e 270 $(M+H)^+$.

(ii) 3-[4-(4-pyridyl)piperazin-1-yl]phenol was prepared in a similar manner to that described in Example 50, but starting from 3-[4-(4-pyridyl)piperazin-1-yl]anisole to give the phenol as a pale brown solid, (3.5g) NMR (d_6 DMSO) : δ 3.3 (4H,m); 3.6 (4H,m); 6.35 (1H,m); 6.5 (2H,m); 7.0 (2H,d); 7.15 (1H,t); 8.3 (2H,d); 9.0-9.5 (1H,br.s); m/e 256 $(M+H)^+$.

EXAMPLE : 4-[3-[4-(4-pyridyl)piperazin-1-yl]phenoxy]butyric acid

In a manner similar to that described in Example 51, but starting from the product of Example 226, the title compound (180mg) was obtained as pale yellow prisms, m.p. 196-198°C (from water); NMR (d_6 DMSO) : δ 1.8-2.0 (2H,q); 2.4 (2H,t); 3.25 (4H,m); 3.45 (4H,m); 4.0 (2H,t); 6.4 (1H,m); 6.5 (2H,m); 6.85 (2H,m); 7.15 (1H,t); 8.2 (2H,d); m/e 342 $(M+H)^+$; calculated for $C_{19}H_{23}N_3O_3.\ 0.2\ H_2O$: C,66.1; H,6.8; N,12.2; H_2O,1.0; found : C,65.8; H,6.7; N,12.1; H_2O,0.8%.

EXAMPLE 228: Ethyl 5-[3-[4-(4-pyridyl)piperazin-1-yl]phenoxy]-pentanoate

Following the method of Example 226, the title compound (340mg) was obtained as a colourless prisms, m.p. 62-64°C (from ethanol); NMR (d_6 DMSO) : δ 1.2 (3H,t); 1.6-1.8 (4H,m); 2.35 (2H,t); 3.25 (4H,m); 3.45 (4H,m); 3.95 (2H,t); 4.05 (2H,q); 6.4 (1H,m); 6.5 (1H,m); 6.55 (1H,m); 6.85 (2H,m); 7.15 (1H,t); 8.2 (2H,d); m/e 384

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$(M+H)^+$; calculated for $C_{22}H_{29}N_3O_3$: C,68.9; H,7.6; N,11.0; found : C,68.7; H,7.8; N,11.0%.

EXAMPLE 229: 5-[3-[4-(4-pyridyl)piperazin-1-yl]phenoxy]pentanoic acid

Following the method of Example 227, the title compound (150mg) was obtained as a pale yellow prisms, m.p. 235-237°C (from water); NMR (d_6 DMSO) : δ 1.55-1.85 (4H,m); 2.3 (2H,t); 3.35 (4H,m); 3.75 (4H,m); 4.0 (2H,t); 6.4 (1H,m); 6.5 (1H,m); 6.55 (1H,m); 7.15 (3H,m); 8.2 (2H,d); m/e 356 $(M+H)^+$; calculated for $C_{20}H_{25}N_3O_3$: C,67.6; H,7.1; N,11.8; found : C,67; H,7.2; N,11.8%.

EXAMPLE 230: trans-methyl-4-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]-cyclohexyl carboxylate

To a mixture of 4-((4-pyridyl)piperazin-1-yl)phenol (860mg), methyl 4-hydroxycyclohexane carboxylate (533mg) and triphenylphosphine (884mg) in dry THF (50ml), cooled to 5°C, was added dropwise diethyl azodicarboxylate (0.53ml). The resulting mixture was stirred at room temperature for 18 hours. The mixture was concentrated and purified by flash column chromatography on silica, eluting with methanol/dichloromethane (5:95 v/v) to give the title compound (178 mg) as a solid; NMR ($CDCl_3$) δ 1.4-1.65 (4H,m), 2.05-2.1 (2H,m), 2.15-2.2 (2H,m), 2.3-2.4 (1H,m), 3.15-3.2 (4H,m), 3.45-3.5 (4H,m), 3.7 (3H,s), 4.05-4.15 (1H,m), 6.7 (2H,d), 6.85-6.95 (4H,dd), 8.3 (2H,d); m/e 396 $(M+H)^+$; calculated for $C_{23}H_{29}N_3O_3.0.5H_2O$: C,68.3; H,7.4; N,10.4. Found: C,68.3; N,7.4; N,10.5%.

EXAMPLE 231: trans-4-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]-cyclohexane carboxylic acid

In a similar manner to Example 57 was prepared the title compound in 98% yield as a solid; NMR (d_6-DMSO+CF_3COOD) δ 1.35-1.65 (4H,m), 1.95-2.15 (4H,m), 2.2-2.35 (1H,m), 3.6-3.75 (4H,m), 4.05-4.2

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(4H,m), 4.25-4.4 (1H,m), 7.05 (2H,d), 7.35 (2H,d), 7.45 (2H,d), 8.35 (2H,d); m/e 380 $(M-H)^+$; calculated for $C_{22}H_{27}N_3O_3.0.5H_2O$: C,67.7; H,7.2; N,10.8. Found: C,67.6; H,7.1; N,10.7%.

EXAMPLE 232: Methyl 6-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]-pyridine-3-carbxylate

To a suspension of 4-((4-pyridyl)piperazin-1-yl)phenol (1.13g) in DMF (10ml) was added a 60% dispersion of sodium hydride in oil (195mg) and the resulting mixture was stirred for 20 minutes. A solution of methyl 6-chloronicotinate (758mg) in DMF (2ml) was added and the mixture was heated at 60°C for 2 hours. The mixture was partitioned between ethyl acetate(100ml) and water(20ml). The organic layer was dried ($MgSO_4$) and evaporated to give an oil which was purified by flash column chromatography on silica, eluting with methanol/dichloromethane (5:95 v/v) to give the title compound as a solid (815mg): mp 143-144°C; NMR (d_6DMSO) δ 3.2-3.35 (4H,m), 3.45-3.55 (4H,m), 3.85 (3H,s), 6.9 (2H,dd), 7.05-7.1 (4H,m), 8.15-8.3 (3H,m), 8.7 (2H,d); m/e 391 $(M+H)^+$; calculated for $C_{22}H_{22}N_4O_3.0.25H_2O$: C,66.9; H,5.7; N,14.2. Found: C,66.9; H,5.7; N,14.1%.

EXAMPLE 233: 6-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]-pyridine-3-carboxylic acid

In a similar manner to Example 57, but using the product of Example 232, was prepared the title compound in 95% yield as a solid: mp 335-340°C (dec); NMR (d_6DMSO+ CF_3COOD) δ 3.4-3.5 (4H,m), 3.9-4.0 (4H,m), 7.05 (1H,d), 7.2 (4H,s), 7.3 (2H,d), 8.25-8.35 (3H,m), 8.7 (1H,d); m/e 376 $(M+H)^+$; calculated for $C_{21}H_{20}N_4O_3.0.25H_2O$: C,66.2; H,5.4; N,14.7. Found; C,66.1; H,5.4; N,14.9%.

EXAMPLE 234: 4-[(4-pyridyl)piperazin-1-yl]benzoylisonipecotic acid

In a similar manner to Example 57, but starting from ethyl 4-[(4-pyridyl)piperazin-1-yl]benzoylisonipecotate, the title compound was prepared in 26% yield as a solid; NMR (d_6DMSO+CF_3COOD) δ 1.4-1.65

(2H,m), 1.8-1.95 (2H,m), 2.95-3.15 (3H,m), 3.4-3.55 (4H,m)3.8-3.9 (4H,m), 3.9-4.1 (2H,m), 6.95 (2H,d), 7.2 (2H,d), 7.3 (2H,d), 8.25 (2H,d); m/e 395 $(M+H)^+$; calculated for $C_{22}H_{26}N_4O_3.1.6CF_3CO_2H$: C, 52.5; H, 4.8; N, 9.7. Found: C, 52.4; H, 5.1; N, 9.8%.

The necessary starting material was prepared as follows:

(i) In a similar manner to Example 56 but using ethyl isonipecotate, ethyl 4-[(4-pyridylpiperazin-1-yl]benzoylisonipecotate was prepared in 32% yield as a solid; NMR(d_6DMSO) δ 1.2 (3H,t), 1.4-1.6 (2H,m), 1.8-1.9 (2H,m), 2.55-2.7 (1H,m), 2.95-3.1 (2H,m), 3.2-3.5 (10H,m), 4.1 (2H,q), 6.85 (2H,d), 7.0 (2H,d), 7.3 (2H,d), 8.2 (2H,d); m/e 423 $(M+H)^+$; calculated for $C_{24}H_{30}N_4O_3.1.6H_2O$: C,63.9; H, 7.4; N, 12.4. Found: C, 64.1; H, 7.4; N, 11.9%.

EXAMPLE 235: 4-[(4-pyridyl)piperazin-1-yl]benzoylnipecotic acid

In a similar manner to Example 57, but starting from ethyl 4-[(4-pyridyl)piperazin-1-yl]benzoylnipecotate was prepared the title compound in 35% yield as a solid; NMR (d_6DMSO) δ 1.4-1.75 (3H,m), 1.9-2.1 (1H,m), 2.3-2.5 (1H,m), 2.85-3.15 (2H,m), 3.4-3.5 (4H,m), 3.8-3.9 (4H,m), 4.0-4.3 (2H,bm), 6.95 (2H,d), 7.25 (2H,d), 7.3 (2H,d), 8.25 (2H,d); m/e 395 $(M+H)^+$; calculated for $C_{22}H_{26}N_4O_3.1.6CF_3COOH$: C, 52.5; H, 4.8; N, 9.7. Found: C, 52.4; H, 4.5; N, 9.3%.

The necessary starting material was prepared as follows:-

(i) In a similar manner to Example 56 but using ethyl nipecotate, was prepared ethyl 4-[(4-pyridyl)piperazin-1-yl]-benzoylnipecotate in 35% yield as a solid; NMR (d_6DMSO) δ 1.15 (3H,t), 1.35-1.75 (3H,m), 1.9-2.05 (1H,m), 2.3-2.5(1H,m), 3.0-3.3 (4H,m), 3.3-3.4 (4H,m), 3.4-3.5 (4H,m), 4.05 (2H,q), 6.85 (2H,d), 6.95 (2H,d), 7.25 (2H,d), 8.15 (2H,d); m/e 423 $(M+H)^+$; calculated for $C_{24}H_{30}N_4O_3.0.5H_2O$: C, 66.8; H, 7.2; N, 13.0. Found C, 66.4; H, 7.3; N, 13.1%.

EXAMPLE 236: 3-[4-[4-(4-pyridyl)piperazin-1-yl]]-N-benzylbenzamidopropionic acid

In a similar manner to Example 57, but starting from methyl 3-[4-[4-(4-pyridyl)piperazin-1-yl]]-N-benzylbenzamido propionate was prepared the title compound in 72% yield as a solid; NMR (d_6DMSO) δ 2.5-2.6 (2H,m), 3.4-3.55 (6H,m), 3.75-3.85 (4H,m), 4.65 (2H,s), 6.95 (2H,d), 7.15 (2H,d), 7.2-7.45 (7H,m), 8.25 (2H,d); m/e 445 $(M+H)^+$; calculated for $C_{26}H_{28}N_4O_3.0.5H_2O$: C, 68.8; H, 6.3; N, 12.3. Found: C, 69.2; H, 5.8; N, 12.4%.

The necessary starting material was prepared as follows:-

(i) In a similar manner to Example 56, but using N-benzyl β-alanine methyl ester, was prepared methyl 3-[4-[4-(4-pyridyl)-piperazin-1-yl]]-N-benzylbenzamido propionate in 34% yield as a solid; NMR ($CDCl_3$) δ 2.0-2.1 (2H,m), 2.6-2.7 (2H,t), 3.35-3.4 (4H,m), 3.45-3.55 (4H,m), 3.65 (3H,s), 4.65 (2H,s), 6.7 (2H,d), 6.85 (2H,d), 7.2-7.45 (7H,m), 8.2-8.35 (2H,m); m/e 459 $(M+H)^+$.

EXAMPLE 237: 3-[4-[4-(pyridyl)piperazin-1-yl]phenoxy]cyclohexane carboxylic acid

In a similar manner to Example 57, but starting from methyl 3-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]cyclohexylcarboxylate, was prepared the title compound in 60% yield as a solid; NMR (d_6DMSO) δ 1.2-1.5 (4H,m), 1.5-1.9 (2H,m), 2.0-2.1 (1H,m), 2.25-2.3 (2H,m), 2.35-2.45 (1H,m), 3.2-3.25 (4H,m), 3.3-3.35 (4H,m), 6.85-7.0 (4H,m), 7.2 (2H,d), 8.2 (2H,d); m/e 396 $(M+H)^+$; calculated for $C_{22}H_{27}N_3O_3.0.5H_2O$: C,67.6; H, 7.2; N, 10.7. Found: C, 67.9; H, 7.2; N, 10.9%.

The necessary starting material was prepared as follows:-

(i) In a similar manner to Example 230, but using methyl 3-hydroxy cyclohexane carboxylate, was prepared methyl 3-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]cyclohexyl carboxylate in 8% yield as a solid; NMR (d_6DMSO) δ 1.25-1.6 (4H,m), 1.85-2.0 (2H,m), 2.05-2.2 (1H,m), 2.3-2.45 (2H,m), 3.15-3.25 (4H,m), 3.45-3.55 (4H,m), 3.65 (3H,s), 4.05-4.15 (1H,m), 6.7 (2H,d), 6.8-7.0 (4H,m), 8.3 (2H,d); m/e 396 $(M+H)^+$.

EXAMPLE 238: 4-[4-[4-(pyridyl)piperazin-1-yl]phenoxy]piperidineacetic acid

In a similar manner to Example 18, but starting from tert-butyl 4-[4-[4-(pyridyl)piperazin-1-yl]phenoxypiperidinyl acetate, was prepared the title compound in 77% yield as a solid; NMR (d_6DMSO) δ 1.85-2.2 (4H,m), 3.15-3.25 (4H,m), 3.25-3.45 (4H,m), 3.8-3.9 (4H,m), 4.15 (2H,s), 4.45-4.55 (1H,m), 6.95 (4H,s), 7.25 (2H,d), 8.25 (2H,d); m/e 397 $(M+H)^+$; calculated for $C_{22}H_{28}N_4O_3.2.CF_3COOH.2.H_2O$: C, 47.3; H, 5.1; N, 8.45. Found: C, 47.3; H, 4.8; N, 8.0%.

The necessary starting material was prepared as follows:-

(i) In a similar manner to Example 230, but using tert-butyl 4-hydroxypiperidinyl acetate, was prepared tert-butyl 4-[4-[4-(pyridyl)piperazin-1-yl]phenoxypiperidinyl acetate in 35% yield as a solid; NMR (d_6DMSO+CD_3COOD) δ 1.4 (9H,s), 1.6-1.75 (2H,m), 1.8-2.0 (2H,m), 2.4-2.65 (2H,m), 2.8-2.9 (2H,m), 3.15-3.25 (4H,m), 3.25 (2H,s), 3.75-3.8 (4H,m), 4.2-4.3 (1H,m), 6.85-7.0 (4H,m), 7.15 (2H,d), 8.2 (2H,d); m/e 453 $(M+H)^+$; calculated for $C_{26}H_{36}N_4O_3.0.5H_2O$: C,67.7; H, 8.0; N, 12.1. Found: C, 67.9; H, 8.3; N, 12.1%.

EXAMPLE 239: 3-[4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]-piperidineacetic acid

(i) In a similar manner to Example 18, but starting from tert-butyl 3-[4-[4-(pyridyl)piperazin-1-yl]phenoxy]piperidinyl acetate was prepared the title compound in 75% yield as a solid; NMR (d_6DMSO)

δ 1.7-2.3 (4H,m), 3.2-3.4 (4H,m), 3.9-4.05 (4H,m), 4.1 (2H,s), 4.1-4.45 (4H,m), 4.75-4.85 (1H,m), 7.0 (2H,d), 7.25-7.4 (4H,m), 8.3 (2H,d); m/e 397 $(M+H)^+$

(i) In a similar manner to Example 230, but using tert-butyl 3-hydroxypiperidinyl acetate, was prepared tert-butyl 3-[4-[4-(pyridyl)piperazin-1-yl]phenoxy]piperidinyl acetate in 17% yield as an oil; NMR (d_6DMSO) δ 1.4 (9H,d), 1.6-1.8 (2H,m), 1.85-2.0 (1H,m), 2.2-2.3 (1H,m), 2.5-2.7 (2H,m), 2.95-3.05 (2H,m), 3.05-3.15 (4H,m), 3.4-3.5 (4H,m), 3.65-3.9 (2H,m), 4.1-4.25 (1H,m), 6.8-6.95 (6H,m), 8.2 (2H,d); m/e 453 $(M+H)^+$.

EXAMPLE 240: [2-propyl-4-[2-[4-(4-pyridyl)piperazin-2-one-1-yl]acetyl]]phenoxyacetic acid

Using the method of Example 202 but starting from methyl 2-^{n}propyl-phenoxyacetate, was prepared the title compound: NMR (d_6DMSO) δ 0.9 (3H,t), 1.55-1.7 (2H,m), 2.65 (2H,t), 3.45-3.55 (2H,m), 3.65-3.75 (2H,m), 4.05 (2H,s), 4.8 (2H,s), 4.9 (2H,s), 6.85 (2H,d), 6.9 (1H,d), 7.75-7.85 (2H,m), 8.2 (2H,d); m/e 412 $(M+H)^+$; calculated for $C_{22}H_{25}N_3O_5.0.25H_2O$: C, 63.5; H, 6.1; N, 10.1. Found: C, 63.5; H, 6.2; N, 9.9%.

The starting material was prepared as follows:-

(i) In a similar manner to Example 3 step (i), but starting from 2-allyl phenol, was prepared methyl 2-allyl-phenoxyacetate as an oil in 97% yield; NMR (d_6DMSO) δ 3.45 (2H,d), 3.7 (3H,s), 4.8 (2H,s), 5.0-5.1 (2H,m), 5.9-6.1 (1H,m), 6.85-6.95 (2H,m), 7.1-7.2 (2H,m); m/e 207 $(M+H)^+$.

(ii) The product of step (i)(5.86g) was dissolved in methanol (100ml) and a catalytic amount of 10% palladium on carbon was added. The mixture was hydrogenated at atmospheric pressure for 18 hours. The mixture was filtered and concentrated to an oil which was purified by flash column chromatography, eluting with ethyl acetate/hexane (10:90 v/v) to give methyl 2-^{n}propyl-phenoxyacetate (4.82g) as an oil; NMR

(d_6DMSO) δ 1.4 (3H,t), 1.5-1.7 (2H,m), 2.6 (2H,t), 3.7 (3H,s), 4.8 (2H,s), 6.8-6.95 (2H,m), 7.1-7.2 (2H,m); m/e 208 $(M)^+$.

EXAMPLE 241: [2-methyl-4-[2-[4-(4-pyridyl)piperazin-2-one-1-yl]-acetyl]]phenoxyacetic acid

In a similar manner to Example 202, but starting from methyl 2-methylphenoxyacetate , was prepared the title compound as a solid; NMR (d_6DMSO+CD_3COOD) δ 2.3 (3H,s), 3.6-3.7 (2H,m), 3.9-4.0 (2H,m), 4.35 (2H,s), 4.8 (2H,s), 4.95 (2H,s), 6.95 (1H,d), 7.15 (2H,d), 7.8-7.9 (2H,m), 8.25 (2H,d); m/e 384 $(M+H)^+$; calculated for $C_{20}H_{21}N_3O_5.1H_2O$: C, 59.8; H, 5.8; N, 10.0. Found: C, 59.3; H, 5.8: N, 10.1%.

EXAMPLE 242: Ethyl 4-[4-[4-(4-pyridyl)piperazin-2-one-1-yl] phenoxy]butyrate.

In a similar manner to that described in Example 50, but starting from 4-[4-(4-pyridyl)piperazin-2-one-1-yl] phenol, the title compound was prepared as a colourless solid (100 mg); NMR (d6 DMSO) : δ 1.2 (3H,t); 1.9-2.05 (2H,q); 2.45 (2H,t); 3.85 (2H,m); 3.95 (2H,m and 2H,t); 4.05 (2H,q); 4.4 (2H,s); 6.9 (2H,d); 7.15 (2H,d); 7.25 (2H,d); 8.25 (2H,d); m/e 384 (M+H)+.

The necessary starting material was prepared as follows:

(i) To a stirred suspension of 4-(4-pyridyl) piperazin-2-one (880 mg) in dimethyl formamide (20 ml) was added potassium hydride (1.0 ml of a 20% dispersion) and the mixture stirred for 0.5 hr, after which time was added copper (I) iodide (1.0 g). After 0.25 hr there was added 4-benzyloxybromobenzene (1.2 g) and the mixture stirred at 140°C in an argon atmosphere for 2 hr. The reaction mixture was diluted with water and brine and extracted with dichloromethane (3x40 ml); the combined extracts were washed with water and brine, dried (PS paper) and evaporated to give crude product as a pasty solid (2.0 g). This was purified by flash chromatography on silica, eluting with

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dichloromethane/methanol/conc. ammonia (97:2.5:0.5 v/v) to give 4-benzyloxy [4-(4-pyridyl)piperazin-2-one-1-yl]benzene as a colourless solid (1.1 g) NMR δ (d6 DMSO) :3.7-3.9 (4H,m); 4.1 (2H,s); 5.1 (2H,s); 6.85 (2H,d); 7.05 (2H,d); 7.25 (2H,d); 7.3-7.6 (5H,m); 8.2 (2H,d); m/e 360 (M+H)+.

(ii) To a solution of the product of step (i) (1.1 g) in a mixture of methanol (500 ml) and tetrahydrofuran (100 ml) was added 30% palladium-on-charcoal catalyst (300 mg) and the mixture stirred in an atmosphere of hydrogen at ambient temperature and pressure until all the starting material had been consumed. After removal of the catalyst by filtration, the solvent was evaporated in vacuo to give 4-[4-(4-pyridyl)piperazin-2-one-1-yl] phenol as a colourless solid, essentially one spot by tlc, which was used without further purification or characterisation.

EXAMPLE 243: 4-[4-[4-(4-pyridyl)piperazin-2-one-1-yl] phenoxy]butyric acid.

In a manner similar to that described in Example 51, but starting from the product of Example 242, the title compound was prepared as a colourless solid (95 mg); NMR (d6 DMSO) : δ 1.8-2.0 (2H,q); 2.35 (2H,t); 3.7-4.0 (4H,m + 2H,t); 4.3 (2H,s); 6.85 (2H,d); 7.05 (2H,d); 7.2 (2H,d); 8.15 (2H,d); m/e 356 (M+H)+.

EXAMPLE 244: 4-[2-Nitro-4-[4-(4-pyridyl)piperazin-1-yl]phenoxy]-butyric acid

In a similar manner to Example 51, but starting from the compound of Example 217, the title compound was obtained in 68% yield as a solid; m.p. 219-220°C; NMR(d_6DMSO) δ 8.2(2H,d), 7.4(1H,d), 7.27(2H,m), 6.98(2H,d), 4.08(2H,t), 3.23(4H,br.t), 2.36(2H,t), 1.69(2H,m); m/e 387$(M+H)^+$. Calculated for $C_{19}H_{22}N_4O_5 . H_2O$: C, 56.4; H, 5.98; N, 13.9. Found: C, 56.7; H, 5.7; N, 13.9%.

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EXAMPLE 245 (S)-3-[1-[1-(4-pyridyl)piperidin-4-yl]hexahydro-2-oxodiazepin-4-carboxamido]propionic acid, trifluoroacetate

In a similar manner to Example 189, methyl (S)-3-[1-[1-(4-pyridyl)piperidin-4-yl]hexahydro-2-oxodiazepin-4-carboxamido]propionate (72 mg), methanol (5 ml) and sodium hydroxide solution (1N, 0.36 ml) gave, after preparative rp-hplc and lyophilisation, the title compound (81 mg) as an off-white glassy solid: NMR (d_6-DMSO) δ 1.70 (8H, m), 2.40 (2H, t), 3.20 (6H, m), 3.65 (1H, m), 4.12 (1H, m), 4.29 (2H, m), 5.58 (1H, d), 7.20 (2H, d), 8.00 (1H, t), 8.19 (2H, d), 13.25 (1H, br, s); m/Z 390 $(M + H)^+$; calculated for $C_{19}H_{27}N_5O_4 \cdot 1.5\ CF_3CO_2H \cdot 1.0\ H_2O$: C, 45.7%; H, 5.3%; N, 12.1%; found: C, 45.8%; H, 5.2%; N, 12.0%.

The necessary starting material was prepared as follows:-

(i) A mixture of 1,4-dioxa-8-azaspiro[4,5]decane (51.2 ml), 4-chloropyridine hydrochloride (20 g) and potassium carbonate (18.4 g) in isoamyl alcohol (400 ml) was gently refluxed for 18 hr. The reaction mixture was cooled and filtered. The filtrate was evaporated to give a waxy solid which was triturated with hexane to give 8-(4-pyridyl)-1,4-dioxa-8-azaspiro[4,5]decane (24.16 g) as a colourless solid; NMR (d_6-DMSO) δ 1.65-1.70 (4H, m), 3.45-3.55 (4H, m), 3.9 (4H, s), 6.90 (2H, m), 8.15 (2H, m); m/Z 221 $(M + H)^+$.

(ii) A solution of 8-(4-pyridyl)-1,4-dioxa-8-azaspiro[4,5]decane (10 g) in 2N sulphuric acid (140 ml) and tetrahydrofuran (70 ml) was stirred for 72 hr. The reaction was quenched with water (700 ml) and extracted with dichloromethane (400 ml). The organic extracts were dried ($MgSO_4$) and evaporated to give a yellow solid which was purified by flash chromatography on silica, eluting with methanol/dichloromethane (10:90 v/v) to give 1-(4-pyridyl)-4-oxopiperidine as a solid (3.97 g); m.p. 101-104°C; NMR (d6-DMSO) δ 2.45 (4H, t), 3.75 (4H, t), 6.65 (2H, m), 8.20 (2H, m); m/e 177 $(M + H)^+$.

(iii) To a stirred solution of N^{α}-Z-L-ornithine, tert.-butyl ester (preparation described in Milewska, M. J. et al (1990), Synthesis, 233-4) (1.56 g) and 1-(4-pyridyl)-4-oxopiperidine (0.94 g) in methanol (50 ml) at room temperature was added sodium cyanoborohydride (0.30 g). Acetic acid was added dropwise with stirring until the pH of the reaction mixture was 5. The reaction mixture was stirred for 2 hr at room temperature then evaporated to near dryness. The residue was partitioned between saturated aqueous sodium carbonate solution (50 ml) and ethyl acetate (100 ml). The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica, eluting with methanol/dichloromethane/concentrated ammonia, 10:90:0.1 to 10:90:0.2, to give tert. butyl (S)-2-(benzyloxycarbonyl)amino-5-[1-(4-pyridyl)piperidin-4-yl]aminopentanoate (1.35 g) as a yellow gum: NMR (d6-DMSO) δ 1.22 (9H, s), 1.70 (6H, m), 1.97 (2H, m), 2.85 (4H, m), 3.22 (1H, m), 3.75 (1H, m), 4.06 (2H, m), 4.90 (2H, d), 6.93 (2H, d), 7.20 (5H, m), 8.06 (2H, d); m/Z 483 $(M + H)^+$.

(iv) To a solution of the product of step (iii) (1.34 g) and acetic acid (0.48 ml) in methanol under argon was added 10% Pd on C (100 mg). The mixture was covered with a blanket of hydrogen and stirred at room temperature for 4 hr. The catalyst was then removed by filtration through a pad of kieselguhr and the pH of the filtrate was adjusted to 4 by addition of acetic acid. To this mixture, under argon, was then added a further quantity of 10% Pd on C (100 mg), it was covered again with hydrogen and stirred at room temperature for 3 days. The catalyst was filtered off through a pad of kieselguhr and the filtrate was evaporated to dryness. Toluene (100 ml) was then added to the residue and the solvents were again removed in vacuo to give tert. butyl (S)-2-amino-5-[1-(4-pyridyl)piperidin-4-yl]aminopentanoate, triacetate salt (1.68 g) as a yellow gum: NMR (d6-DMSO + CD_3CO_2D) δ 1.49 (9H, s), 1.70 (6H, m), 2.23 (2H, m), 3.03 (2H, m), 3.25 (2H, m), 3.50 (1H, m), 3.96 (1H, m), 4.30 (2H, m), 7.18 (2H, d), 8.20 (2H, d); m/Z 349 $(M + H)^+$.

(v) To a mixture of the product of step (iv) (1.65 g) triethylamine (1.2 ml) and tetrahydrofuran (15 ml) was added with stirring carbonyl diimidazole (0.5 g). The resultant reaction mixture was stirred at room temperature for 20 hr then at reflux for 4 hr. The solvents were then removed in vacuo and the residue was dissolved in dichloromethane, washed with water and brine, dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography on silica, by elution with methanol/dichloromethane (15% v/v to 25% v/v) to give a yellow gum, which, on trituration with ether gave tert. butyl (S)-1-[1-(4-pyridyl)piperidin-4-yl]-hexahydro-2-oxodiazepin-4-carboxylate (257 mg) as a white solid: NMR (d6-DMSO + CD_3CO_2D) δ 1.37 (9H, s), 1.70 (8H, m), 3.10 (4H, m), 3.78 (1H, m), 4.11 (1H, m), 4.21 (2H, m), 7.06 (2H, d), 8.08 (2H, d); m/Z 375 $(M + H)^+$.

(vi) A solution of the product of step (v) (219 mg) in trifluoroacetic acid (5 ml) was stirred at room temperature for 90 min then evaporated to dryness. The residue was triturated with ether and the resultant solid was collected to give (S)-1-[1-(4-pyridyl)-piperidin-4-yl]hexahydro-2-oxodiazepin-4-carboxylic acid, trifluoroacetate salt (124 mg) as a cream-coloured solid: NMR (d6-DMSO) δ 1.70 (8H, m), 3.05 (2H, m), 3.20 (2H, m), 3.81 (1H, m), 4.12 (1H, m), 4.30 (2H, m), 5.59 (1H, d), 7.20 (2H, d), 8.18 (2H, d), 13.35 (1H, br, s); m/Z 319 $(M + H)^+$.

(vii) In a similar manner to Example 189 (i), the product of step (vi), (210 mg), HBTU (203 mg), HOBt.H_2O (82 mg), DMF (5 ml), diisopropylethylamine (0.47 ml) and methyl 3-aminopropionate, hydrochloride (75 mg) gave, after purification by flash chromatography on alumina, eluting solvent dichloromethane/methanol, 20:1, methyl (S)-3-[1-[1-(4-pyridyl)piperidin-4-yl]hexahydro-2-oxodiazepin-4-carboxamido]propionate (78 mg) as a yellow gum: NMR (d6-DMSO) δ 1.70 (8H, m), 2.45 (2H, m), 2.88 (2H, m), 3.06 (2H, m), 3.32 (2H, m), 3.63 (4H, m), 4.02 (3H, m), 5.52 (1H, d), 6.81 (2H, d), 8.03 (1H, t), 8.12 (2H, d); m/Z 404 $(M + H)^+$.

EXAMPLE 246

Illustrative pharmaceutical dosage forms suitable for presenting the compounds of the invention for therapeutic or prophylactic use include the following, which may be obtained by conventional procedures well known in the art.

a)	Tablet I	mg/tablet
	Active ingredient	1.0
	Lactose Ph. Eur.	93.25
	Croscarmellose sodium	4.0
	Maize starch paste	0.75
	(5% w/v aqueous paste)	
	Magnesium stearate	1.0

b)	Tablet II	mg/tablet
	Active ingredient	50
	Lactose	223.75
	Croscarmellose sodium	6.0
	Maize starch	15.0
	Polyvinylpyrrolidone	2.25
	(5% w/v aqueous paste)	
	Magnesium stearate	3.0

c)	Tablet III	mg/tablet
	Active ingredient	100
	Lactose	182.75
	Croscarmellose sodium	12.0
	Maize starch paste	2.25
	(5% w/v aqueous paste)	
	Magnesium stearate	3.0

(d)	Capsule	mg/capsule
	Active ingredient	10
	Lactose Ph. Eur.	488.5
	Magnesium stearate	1.5

(e)	Injection	mg/ml
	Active ingredient	1.0
	(acid addition salt)	
	Sodium chloride	9.0
	Purified water to 1.0ml	

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for the prevention or treatment of a disease mediated by the binding of adhesion molecules to GPIIb/IIIa in a warm-blooded animal requiring such treatment, which comprises administering an effective amount of a compound of formula I

$$Q\text{-}M^2\text{-}L\text{-}A \qquad I$$

wherein:

Q is 4- pyridyl optionally substituted by one or more of (1-4C)alkyl, (1-4C)alkoxy, halogeno, and (3-4C)alkylene which together with the two atoms to which it is attached forms a ring; and

M^2 is $-NR^3-$ in which R^3 is hydrogen, (1-4C)alkyl or a (2-3C)alkylene bridge attached to Q; or $-NR^4\text{-}D\text{-}TR^5-$ in which

(i) T is N; D is CH_2CO; CH_2SO_2; or (2-3C)alkylene optionally substituted by carboxy, (1-4C)alkoxycarbonyl, (1-4C)alkoxymethyl or a (2-3C)alkylene bridge attached to Q; and R^4 and R^5 together represent (2-3C)alkylene or CH_2CO, or each independently represents hydrogen or (1-4C)alkyl; or R^5 represents hydrogen or (1-4C)alkyl and R^4 represents (2-3C)alkylene attached to Q; or

(ii) T is CH; D is CH_2CO, CH_2CH_2NH, (1-3C)alkylene optionally substituted by carboxy or (1-4C)alkoxycarbonyl, or (2-3C)alkyleneoxy; and R^4 and R^5 together represent (1-3C)alkylene; or

(iii) R^4 and $-D\text{-}TR^5-$ together form a (5-6C)alkenylene group;

L is (4-7C)alkylene or a group of formula $X^1\text{-}Y\text{-}X^2$ in which

X^1 is a bond or a linking group selected from (1-4C)alkylene, (2-4C)alkenylene, (2-4C)alkynylene, (1-2C)alkylenephenylene, phenyleneoxy, phenyleneoxymethylene, phenylenecarbonyl, phenyleneCONH, (1-3C)alkylenecarbonyl, (1-2C)alkylenecarbonyl substituted by benzyl or p-hydroxybenzyl, methylidenepyrrolidin-1-ylacetyl, (1-2C)alkylenecarbonyloxy, (1-2C)alkyleneCONH, (1-2C)alkyleneCONH(1-2C)alkyleneCO, (1-2C)alkyleneCONH(1-2C)alkyleneCONH, benzyl(1-2C)alkyleneCONH, (1-4C)alkyleneoxy, (1-2C)alkyleneoxy(1-2C)alkylene, (1-2C)alkyleneoxy(1-2C)alkylenecarbonyl and (1-3C)alkyleneCH(OH), and when M^2 is $-NR^4\text{-}D\text{-}TR^5-$, carbonyl, carbonyl(1-3C)alkylene, CONH, (1-2C)alkyleneNHCO and CONH(1-3C)alkylene, and when T is CH, oxy, oxy(1-3C)alkylene, oxy(1-2C)alkylenecarbonyl and oxy(1-2C)alkylenephenylene;

Y is a cyclic group of formula:-

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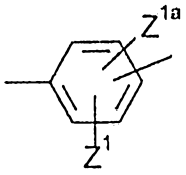

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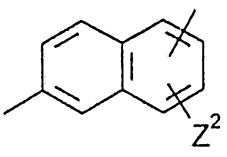

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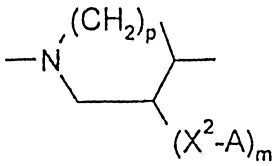

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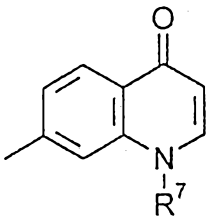

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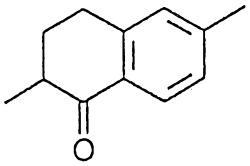

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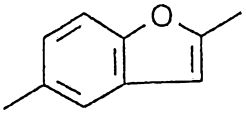

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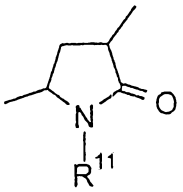

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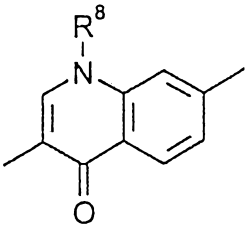

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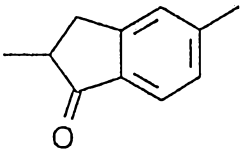

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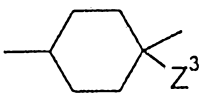

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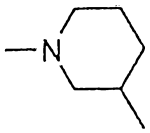

(l)

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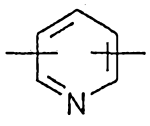

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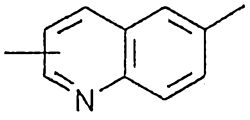

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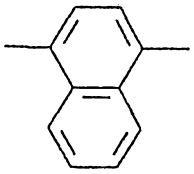

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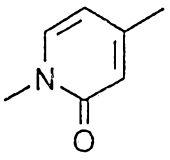

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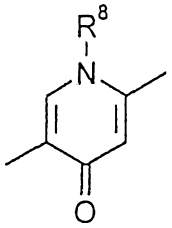

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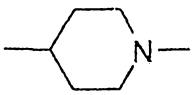

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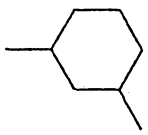

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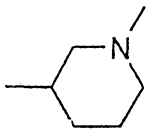

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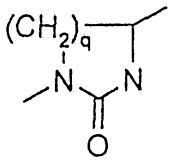

(u)

in which m is 0 or 1; p is 1 or 2; q is 0, 1, 2 or 3; Z^1, Z^{1a} and Z^2 represent hydrogen, hydroxy, halogeno, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkylnyl, (1-4C)alkoxy, (1-4C)alkylthio, (2-4C)alkenyloxy, nitro, amino, (1-4C)alkylamino, (2-4C)alkanoylamino, cyano or (1-4C)alkoxycarbonyl, or have one of the meanings given for X^2-A; Z^3 represents hydrogen or hydroxy; R^7 is hydrogen, (1-4C)alkyl or phenyl(1-4C)alkyl; R^8 is as defined for R^7; E is O, S or NH; and R^{11} is hydrogen, (1-4C)alkyl, phenyl(1-4C)alkyl or a group of formula X^2-A;

or Y is an amide-containing group selected from $CONR^{22}$, $NR^{22}CO$ and a group of formula

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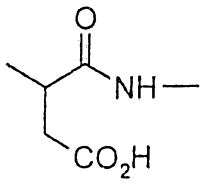

in which R^{22} represents hydrogen, (1-4C)alkyl or phenyl(1-2C)alkyl; and

X^2 is a bond or a linking group selected from (1-4C)alkylene, (2-4C)alkenylene, oxy(1-4C)alkylene, oxy(5-6C)alkylene, oxy(2-4C)alkenylene, thio(1-3C)alkylene, SO_2(1-3C)alkylene, amino(1-3C)alkylene, SO_2NH(1-3C)alkylene, $NR^{21}CO$(1-2C)alkylene and $CONR^{21}$(1-2C)alkylene (where R^{21} represents hydrogen, (1-4C)alkyl or benzyl), in any of which the alkylene group may optionally be substituted by (2-4C)alkenyl; (2-4C)alkynyl; (1-4C)alkoxy; carboxy; (1-4C)alkoxycarbonyl; phenyl(1-2C)alkylCONH; phenyl(1-4C)alkoxycarbonyl; carboxy(1-2C)alkyl; phenyl(1-2C)alkyl; phenylsulphonyl(1-2C)alkyl; pyridyl; phenyl; amino or a group of formula $NR^{12}XR^6$ in which X is SO_2, CO or CO_2; R^{12} is hydrogen or (1-4C)alkyl and R^6 is (1-6C)alkyl, (6-10C)aryl, (6-10C)aryl(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl, morpholino(1-4C)alkyl, piperidino(1-4C)alkyl or N-(1-4C)alkylpiperidino(1-4C)alkyl; and

A is an acidic group, or an ester or amide derivative thereof, or a sulphonamide group; or a pharmaceutically acceptable salt or pro-drug thereof.

2. A method as claimed in claim 1, in which the adhesion molecule is fibrinogen.

3. A method as claimed in claim 1 or 2, in which the disease involves platelet aggregation.

4. A method as claimed in any one of claims 1 to 3, for the prevention of reocclusion and restenosis following percutaneous transluminal coronary angioplasty or coronary artery bypass graft.

5. A method as claimed in any one of claims 1 to 3, for the prevention or treatment of thrombotic events accompanying unstable angina.

6. A method as claimed in any one of the preceding claims, in which M^2 is NH, methylimino, 2-oxopiperazin-1,4-diyl, 2,6-dioxopiperazin-1,4-diyl, 1,1-dioxo-1,2,5-thiadiazin-2,5-diyl, piperazin-1,4-diyl, 2-carboxypiperazin-1,4-diyl, 3-carboxypiperazin-1,4-diyl, 2-methoxycarbonylpiperazin-1,4-diyl, 3-methoxycarbonyl-piperazin-1,4-diyl, 2-methoxymethylpiperazin-1,4-diyl, 3-methoxymethyl-

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piperazin-1,4-diyl, N-[2-(N'-methylamino)ethyl]-(N-methyl)amino, pyrrolidin-3,1-diyl, 3-oxo-pyrrolidin-4,1-diyl, 2-carboxypyrrolidin-4,1-diyl, 2-methoxycarbonylpyrrolidin-4,1-diyl, 2-ethoxycarbonylpyrrolidin-4,1-diyl, piperidin-3,1-diyl, piperidin-4,1-diyl, piperazin-2,4-diyl, morpholin-2,4-diyl, 1,2,3,6-tetrahydropyrid-4,1-diyl, or together with Q is 1,2,3,4-tetrahydro-1,6-naphthyridin-1-yl, pyrrolo[3,2-c]pyridin-1-yl, 1,2,3,4-tetrahydro-1,6-naphthyridin-2-yl or pyrrolo[3,2-c]pyridin-2-ylethylamino.

7. A method as claimed in claim 6, in which M^2 is piperazin-1,4-diyl, piperidin-4,1-diyl or 2-oxopiperazin-1,4-diyl.

8. A method as claimed in claim in any one of the preceeding claims, in which Q is 4-pyridyl.

9. A method as claimed in any one of claims 1 to 7, in which Q-M^2 is 4-(4-pyridyl)-piperazin-1-yl, 4-(4-pyridyl)-2-oxopiperazin-1-yl or 1-(4-pyridyl)piperidin-4-yl.

10. A method as claimed in any one of the preceding claims, in which

X^1 is a bond, methylene, ethylene, propylene, 1-methylethylene, ethenylene, ethynylene, methylenephenylene, phenyleneoxy, phenyleneoxymethylene, phenylenecarbonyl, phenyleneCONH, methylenecarbonyl, ethylenecarbonyl, 1-methylethylenecarbonyl, ethylidenecarbonyl, 2-propylidenecarbonyl, benzylmethylene-carbonyl, p-hydroxybenzylmethylenecarbonyl, methylidenepyrrolidin-1-ylacetyl, methylenecarbonyloxy, methyleneCONH, methyleneCONHmethyleneCONH, benzyl-methyleneCONH, methyleneoxy, ethyleneoxy, propyleneoxy, butyleneoxy, methyleneoxymethylene, methyleneoxymethylenecarbonyl or methyleneCH(OH), and when M^2 is -NR^4-D-TR^5-, carbonyl, carbonylmethylene, carbonylethylene, CONH, methyleneNHCO or CONHmethylene, and when T is CH, oxy, oxymethylene, oxymethylenecarbonyl or oxymethylenephenylene;

Y is a 1,2-, 1,3- or 1,4-phenylene group of formula (a); a naphth-1,6-diyl group of formula (b); a piperidin-4,1-diyl group of formula (c); a 4-quinolon-3,7-diyl group of formula (d); a tetralon-6,2-diyl group of formula (e); a benzofuran-2,5-diyl group of formula (f); a 4-quinolon-7,3-diyl group of formula (i); a cyclohexa-4,1-diyl group of formula (k); a piperidin-3,1-diyl group of formula (l); a pyridin-2,5-diyl or pyridin-2,6-diyl group of formula (m); a quinolin-6,2-diyl or quinolin-6,4-diyl group of formula (n); a naphth-1,4-diyl group of formula (o); a 2-pyridon-4,1-diyl group of formula (p); a 4-pyridon-2,5-diyl group of formula (q); a piperidin-1,4-diyl group of formula (r); a

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cyclohexa-3,1-diyl group of formula (s); a piperidin-1,3-diyl group of formula (t), CONH, NHCO or a 2-carboxyethylideneca boxamido group; and

X^2 is a bond, methylene, ethylene, ethenylene, oxymethylene, 2-oxyethylene, 3-oxypropylene, 2-oxyprop-2-ylene, 4-oxybutylene, 5-oxypentylene, thiomethylene, aminomethylene, carboxamidomethylene, 2-carboxamidoethylene, 2-phenylethylidene, oxy(methoxycarbonyl)methylene, 1-(2-carboxyethyl)ethylene, 1-(benzyloxycarbonyl)ethylene or a group of formula $CH_2CH(NR^{12}XR^6)$.

11. A method as claimed in claim 10, in which Y is 1,2-phenylene; 1,3-phenylene; 5-methoxycarbonyl-1,3-phenylene; 1,4-phenylene; 2,6-dichloro-1,4-phenylene; 2-methyl-1,4-phenylene; 2-propyl-1,4-phenylene; 2-allyl-1,4-phenylene; 2,6-di-tert-butyl-1,4-phenylene; 2-methoxy-1,4-phenylene; 3-methoxy-1,4-phenylene; 2-carboxymethoxy-1,4-phenylene; 2-methoxycarbonylmethoxy-1,4-phenylene; 2-ethoxycarbonylmethoxy-1,4-phenylene; 2-tert-butyloxycarbonylmethoxy-1,4-phenylene; 3-carboxymethoxy-1,4-phenylene; 3-methoxycarbonylmethoxy-1,4-phenylene; 2-nitro-1,4-phenylene; naphth-1,6-diyl; piperidin-4,1-diyl; 3-carboxy-methoxypiperidin-4,1-diyl; 1-ethyl-4-quinolon-3,7-diyl; 1-propyl-4-quinolon-3,7-diyl; tetralon-6,2-diyl; benzofuran-2,5-diyl; 1-benzyl-4-quinolon-7,3-diyl; 1-hydroxycyclohexa-1,4-diyl; piperidin-3,1-diyl; pyridin-2,5-diyl; pyridin-2,6-diyl; quinolin-6,2-diyl; quinolin-6,4-diyl; naphth-1,4-diyl; 2-pyridon-4,1-diyl; 1-benzyl-4-pyridon-2,5-diyl; piperidin-1,4-diyl; cyclohexa-3,1-diyl; piperidin-1,3-diyl; CONH or 2-carboxyethylidenecarboxamido.

12. A method as claimed in any one of the preceding claims, in which A is carboxy or an ester or amide thereof, an acyl sulphonamide group of formula $CONHSO_2R^9$, in which R^9 is (1-4C)alkyl or optionally substituted phenyl; a 1H-tetrazol-5-yl group or a sulphonamide group of formula $NHSO_2R^{10}$ in which R^{10} is (1-6C)alkyl, fluoro(1-6C)alkyl or phenyl optionally substituted by one or two optional substituents selected from (1-4C)alkyl, (1-4C)alkoxy and halogen.

13. A method as claimed in claim 12, in which A is a carboxy group.

14. A method as claimed in claim 1, in which the compound of formula I is a compound of general formula Ia

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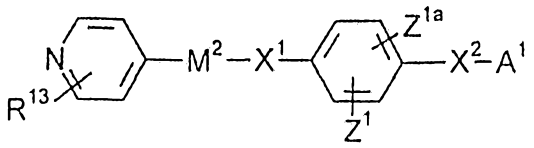
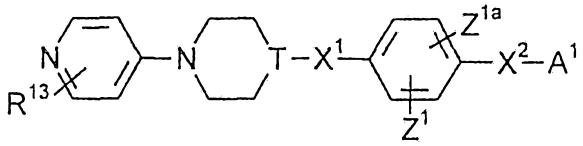


Ia

in which M^2, X^1, X^2, Z^1 and Z^{1a} are as defined in claim 1; A^1 is a carboxy group or an ester thereof; and R^{13} is hydrogen, (1-4C)alkyl, (1-4C)alkoxy or halogen.

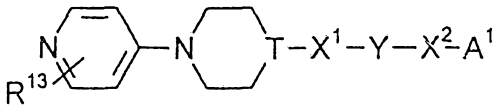
15. A method as claimed in claim 1, in which the compound of formula I is a compound of general formula Ib



Ib

in which T, X^1, X^2, Z^1 and Z^{1a} are as defined in claim 1; A^1 is a carboxy group or an ester thereof; and R^{13} is hydrogen, (1-4C)alkyl, (1-4C)alkoxy or halogen.

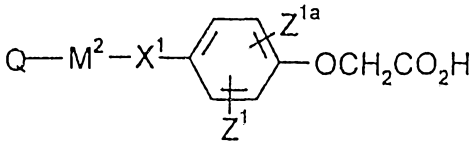
16. A method as claimed in claim 1, in which the compound of formula I is a compound of general formula Ic



Ic

in which T, X^1, Y and X^2 are as defined in claim 1; A^1 is a carboxy group or an ester thereof; and R^{13} is hydrogen, (1-4C)alkyl, (1-4C)alkoxy or halogen.

17. A method as claimed in claim 1, in which the compound of formula I is a compound of general formula Id



Id

in which Q, M^2, X^1, Z^1 and Z^{1a} are as defined in claim 1; or an ester or amide derivative thereof or a pharmaceutically acceptable salt or pro-drug thereof.

18. A method as claimed in claim 1, in which the compound of formula I is a compound of general formula Ie

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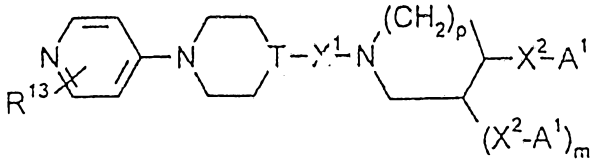
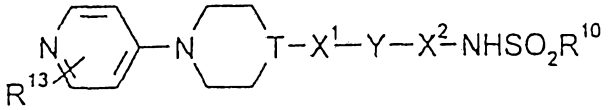


Ie

in which m,p, T, X^1 and X^2 are as defined in claim 1; A^1 is a carboxy group or an ester thereof; and R^{13} is hydrogen, (1-4C)alkyl, (1-4C)alkoxy or halogen.

19. A method as claimed in claim 1, in which the compound of formula I is a compound of general formula If



If

in which T, X^1, Y and X^2 are as defined in claim 1; R^{13} is hydrogen, (1-4C)alkyl, (1-4C)alkoxy or halogen; and R^{10} is (1-6C)alkyl or phenyl optionally substituted by one or two optional substituents selected from (1-4C)alkyl, (1-4C)alkoxy and halogen.

20. A method as claimed in claim 14, in which M^2 is piperazin-1,4-diyl, piperidin-4,1-diyl or 2-oxopiperazin-1,4-diyl.

21. A compound of the general formula

$$Q\text{-}M^2\text{-}L\text{-}A \qquad I$$

wherein:

Q is 4-pyridyl optionally substituted by one or more of (1-4C)alkyl, (1-4C)alkoxy, halogeno, and (3-4C)alkylene which together with the two atoms to which it is attached forms a ring;

M^2 is $-NR^3-$ in which R^3 is hydrogen, (1-4C)alkyl or a (2-3C)alkylene bridge attached to Q

L is (4-7C)alkylene or a group of formula X^1-Y-X^2 in which

X^1 is a bond or a linking group selected from (1-4C)alkylene, (2-4C)alkenylene, (2-4C)alkynylene, (1-2C)alkylenephenylene, phenyleneoxy, phenyleneoxymethylene, phenylenecarbonyl, phenyleneCONH, (1-3C)alkylenecarbonyl, (1-2C)alkylenecarbonyl substituted by benzyl or p-hydroxybenzyl,

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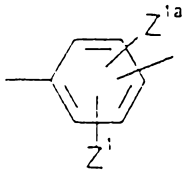
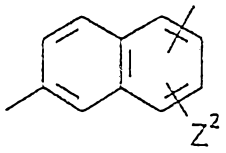
methylidenepyrrolidin-1-ylacetyl, (1-2C)alkylenecarbonyloxy, (1-2C)alkyleneCONH, (1-2C)alkyleneCONH(1-2C)alkyleneCO, (1-2C)alkyleneCONH(1-2C)alkyleneCONH, benzyl(1-2C)alkyleneCONH, (1-4C)alkyleneoxy, (1-2C)alkyleneoxy(1-2C)alkylene, (1-2C)alkyleneoxy(1-2C)alkylenecarbonyl and (1-3C)alkyleneCH(OH);

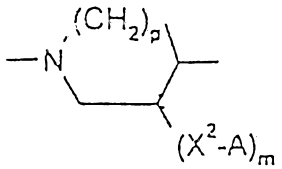
Y is a cyclic group of formula:



(a)



(b)



(c)

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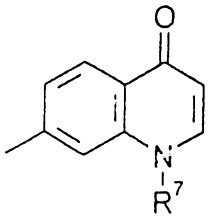
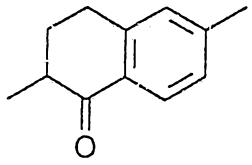


(d)



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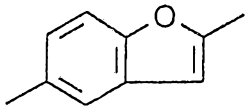
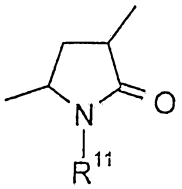


(f)



(g)



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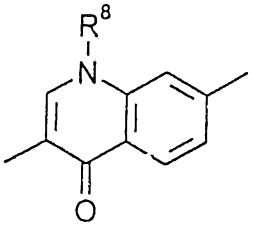
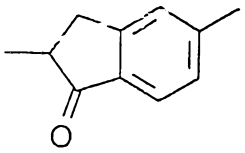
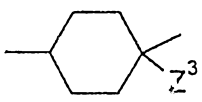


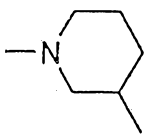
(i)



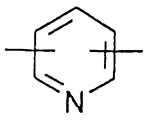
(j)



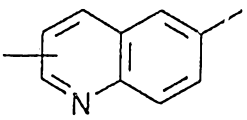
(k)



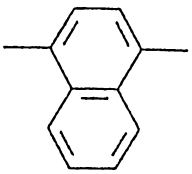
(l)



(m)



(n)



(o)

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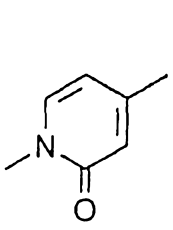
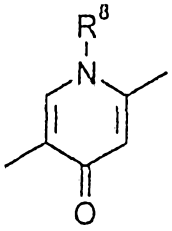
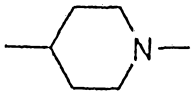


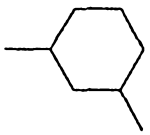
(p)



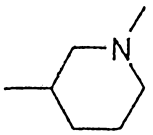
(q)



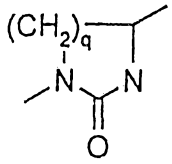
(r)



(s)



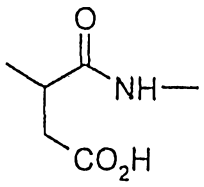
(t)



(u)

in which m is 0 or 1; p is 1 or 2; q is 0, 1, 2 or 3; Z^1, Z^{1a} and Z^2 represent hydrogen, hydroxy, halgeno, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkylthio, (2-4C)alkenyloxy, nitro, amino, (1-4C)alkylamino, (2-4C)alkanoylamino, cyano or (1-4C)alkoxycarbonyl, or have one of the meanings given for X^2-A; Z^3 represents hydrogen or hydroxy; R^7 is hydrogen, (1-4C)alkyl or phenyl(1-4C)alkyl; R^8 is as defined for R^7; E is O, S or NH; and R^{11} is hydrogen, (1-4C)alkyl, phenyl(1-4C)alkyl or a group of formula X^2-A;

c. Y is an amide-containing group selected from $CONR^{22}$, $NR^{22}CO$ and a group of formula



in which R^{22} represents hydrogen, (1-4C)alkyl or phenyl(1-2C)alkyl; and

X^2 is a bond or a linking group selected from (1-4C)alkylene, (2-4C)alkenylene, oxy(1-4C)alkylene, oxy(5-6C)alkylene, oxy(2-4C)alkenylene, thio(1-3C)alkylene, SO_2(1-3C)alkylene, amino(1-3C)alkylene, SO_2NH(1-3C)alkylene, $NR^{21}CO$(1-2C)alkylene and $CONR^{21}$(1-2C)alkylene (where R^{21} represents hydrogen,

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(1-4C)alkyl or benzyl), in any of which the alkylene group may optionally be substituted by (2-4C)alkenyl; (2-4C)alkynyl; (1-4C)alkoxy; carboxy; (1-4C)alkoxycarbonyl; phenyl(1-2C)alkylCONH; phenyl(1-4C)alkoxycarbonyl; carboxy(1-2C)alkyl; phenyl(1-2C)alkyl; phenylsulphonyl(1-2C)alkyl; pyridyl; phenyl; amino or a group of formula $NR^{12}XR^6$ in which X is SO_2, CO or CO_2; R^{12} is hydrogen or (1-4C)alkyl and R^6 is (1-6C)alkyl, (6-10C)aryl, (6-10C)aryl(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl, morpholino(1-4C)alkyl, piperidino(1-4C)alkyl or N-(1-4C)alkylpiperidino(1-4C)alkyl; and A is carboxy or an ester or amide thereof, an acyl sulphonamide group of formula $CONHSO_2R^9$, in which R^9 is (1-4C)alkyl or optionally substituted phenyl; a 1H-tetrazol-5-yl group or a sulphonamide group of formula $NHSO_2R^{10}$ in which R^{10} is (1-6C)alkyl or phenyl optionally substituted by one or two optional substituents selected from (1-4C)alkyl, (1-4C)alkoxy and halogen; or a pharmaceutically acceptable salt or pro-drug thereof, provided that Y may not represent a 1,4-phenylene group of formula (a) when A is carboxy or an amide or ester thereof, or when X^2 is a bond and A is $NHSO_2R^{10}$ in which R^{10} is (1-6C)alkyl; and provided that Y may not represent a 1,2- or 1,3-phenylene of formula (a) when X^2 is a bond or oxy(1-4C)alkylene and A is carboxy or an amide or ester thereof or A is 1H-tetrazol-5-yl.

22. A compound as claimed in claim 21, in which X^1 is a bond, methylene, ethylene, propylene, 1-methylethylene, ethenylene, ethynylene, methylenephenylene, phenyleneoxy, phenyleneoxymethylene, phenylenecarbonyl, phenyleneCONH, methylenecarbonyl, ethylenecarbonyl, 1-methylethylenecarbonyl, ethylidenecarbonyl, 2-propylidenecarbonyl, benzylmethylenecarbonyl, p-hydroxybenzylmethylenecarbonyl, methylidenepyrrolidin-1-ylacetyl, methylenecarbonyloxy, methyleneCONH, methyleneCONHmethyleneCONH, benzylmethyleneCONH, methyleneoxy, ethyleneoxy, propyleneoxy, butyleneoxy, methyleneoxymethylene, methyleneoxymethylenecarbonyl or methyleneCH(OH);

Y is a 1,2-, 1,3- or 1,4-phenylene group of formula (a); a naphth-1,6-diyl group of formula (b); a piperidin-4,1-diyl group of formula (c); a 4-quinolon-3,7-diyl group of formula (d); a tetralon-6,2-diyl group of formula (e); a benzofuran-2,5-diyl group of

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formula (f); a 4-quinolon-7,3-diyl group of formula (i); a cyclohexa-4,1-diyl group of formula (k); a piperidin-3,1-diyl group of formula (l); a pyridin-2,5-diyl or pyridin-2,6-diyl group of formula (m); a quinolin-6,2-diyl or quinolin-6,4-diyl group of formula (n); a naphth-1,4-diyl group of formula (o); a 2-pyridon-4,1-diyl group of formula (p); a 4-pyridon-2,5-diyl group of formula (q); a piperidin-1,4-diyl group of formula (r); a cyclohexa-3,1-diyl group of formula (s); a piperidin-1,3-diyl group of formula (t), CONH, NHCO or a 2-carboxyethylidenecarboxamido group; and

X^2 is a bond, methylene, ethylene, ethenylene, oxymethylene, 2-oxyethylene, 3-oxypropylene, 2-oxyprop-2-ylene, 4-oxybutylene, 5-oxypentylene, thiomethylene, aminomethylene, carboxamidomethylene, 2-carboxamidoethylene, 2-phenylethylidene, oxy(methoxycarbonyl)methylene, 1-(2-carboxyethyl)ethylene, 1-(benzyloxycarbonyl)ethylene or a group of formula $CH_2CH(NR^{12}XR^6)$.

23. A compound as claimed in claim 22, in which Y is 1,2-phenylene; 1,3-phenylene; 5-methoxycarbonyl-1,3-phenylene; 1,4-phenylene; 2,6-dichloro-1,4-phenylene; 2-methyl-1,4-phenylene; 2-propyl-1,4-phenylene; 2-allyl-1,4-phenylene; 2,6-di-tert-butyl-1,4-phenylene; 2-methoxy-1,4-phenylene; 3-methoxy-1,4-phenylene; 2-carboxymethoxy-1,4-phenylene; 2-methoxycarbonylmethoxy-1,4-phenylene; 2-ethoxycarbonylmethoxy-1,4-phenylene; 2-tert-butyloxycarbonylmethoxy-1,4-phenylene; 3-carboxymethoxy-1,4-phenylene; 3-methoxycarbonylmethoxy-1,4-phenylene; 2-nitro-1,4-phenylene; naphth-1,6-diyl; piperidin-4,1-diyl; 3-carboxymethoxypiperidin-4,1-diyl; 1-ethyl-4-quinolon-3,7-diyl; 1-propyl-4-quinolon-3,7-diyl; tetralon-6,2-diyl; benzofuran-2,5-diyl; 1-benzyl-4-quinolon-7,3-diyl; 1-hydroxycyclohexa-1,4-diyl; piperidin-3,1-diyl; pyridin-2,5-diyl; pyridin-2,6-diyl; quinolin-6,2-diyl; quinolin-6,4-diyl; naphth-1,4-diyl; 2-pyridon-4,1-diyl; 1-benzyl-4-pyridon-2,5-diyl; piperidin-1,4-diyl; cyclohexa-3,1-diyl; piperidin-1,3-diyl; CONH or 2-carboxyethylidenecarboxamido.

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24. A compound as claimed in any one of claims 21 to 23, in which A is a carboxy group.

25. A pharmaceutical composition which comprises a compound as claimed in claim 21, together with a pharmaceutically acceptable diluent or carrier.

26. A process for preparing a compound of general formula I, or a metabolically labile ester or amide thereof, or a pharmaceutically acceptable salt thereof as defined in claim 21, which comprises

(A) For a compound of formula I in which n is 0, reacting a compound of formula

$$Q\text{-}M^2\text{-}H \qquad II$$

in which Q and M^2 are as defined in claim 1, or an acid addition salt thereof with a compound of formula

$$U^1\text{-}L\text{-}A \qquad III$$

in which U^1 is a leaving atom or group and L and A are as defined in claim 21;

(B) For a compound of formula I in which A is carboxy, decomposing an ester of formula

$$Q\text{-}M^2\text{-}L\text{-}COOR^{20} \qquad IV$$

in which R^{20} is a carboxy protecting group, and M^2, Q and L are as defined in claim 21;

(C) For a compound of formula I in which Y is a group of formula (c), reacting a compound of formula

$$Q\text{-}M^2\text{-}X^1\text{-}U^2 \qquad V$$

in which U^2 is a leaving atom or group and M^2, Q and X^1 are as defined in claim 21, or an acid addition salt thereof, with a compound of formula

$$H\text{-}Y\text{-}X^2\text{-}A \qquad VI$$

or an acid addition salt thereof, in which X^2 and A are as defined in claim 21 and Y is a group of formula (c) as defined in claim 21;

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(D) For a compound of formula I in which n is 0, reacting a compound of formula

$$Q\text{-}U^3 \qquad VII$$

in which U^3 is a leaving atom or group, and Q is as defined in claim 21, with a compound of formula

$$H\text{-}M^2\text{-}L\text{-}A \qquad VIII$$

or an acid addition salt thereof, in which M^2, L and A are as defined in claim 21;

(E) For a compound of formula I in which L is X^1-Y-X^2 and X^1 contains a CONH group, reacting the appropriate carboxylic acid of formula

$$Q\text{-}M^2\text{-}X^{1a} \qquad IX$$

in which X^{1a} is a residue of a carboxylic acid group, or a reactive derivative thereof, and M^2 and Q are as defined in claim 21 with the appropriate amine of formula

$$X^{1b}\text{-}Y\text{-}X^2\text{-}A \qquad X$$

in which X^{1b} is a residue of an amine group, and Y, X^2 and A are as defined in claim 21;

(F) For a compound of formula I in which L is X^1-Y-X^2 and X^1 is (2-4C)alkenylene, reacting a compound of formula

$$Q\text{-}M^2\text{-}X^{1c} \qquad XI$$

in which X^{1c} is an appropriate aldehyde-containing group and M^2 and Q are as defined in claim 21, with the appropriate Wittig reagent of formula

$$X^{1d}\text{-}Y\text{-}X^2\text{-}A \qquad XII$$

in which X^{1d} is a triarylphosphonylalkylene group and Y, X^2 and A are as defined in claim 21;

(G) For a compound of formula I in which L is X^1-Y-X^2 and X^1 contains an oxy (ether) link, reacting the appropriate compound of formula

$$Q\text{-}M^2\text{-}X^{1e} \qquad XIII$$

in which M^2 and Q are as defined in claim 21, with the appropriate compound of formula

$$X^{1f}\text{-}Y\text{-}X^2\text{-}A \qquad XIV$$

in which one of X^{1e} and X^{1f} is a residue of an alcohol group, and the other is a residue of an alcohol group or a group containing a leaving atom or group and Y, X^2 and A are as defined claim 21;

(H) For a compound of formula I in which X^2 is $CH_2CH(NHXR^6)$ reacting a compound of formula

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$$Q\text{-}M^2\text{-}X^1\text{-}Y\text{-}X^{2a}\text{-}A \qquad XV$$

in which X^{2a} is $CH_2CH(NH_2)$, or an acid addition salt thereof, and M^2, Q, X^1, Y, and A are as defined in claim 21, with a compound of formula

$$R^6\text{-}X\text{-}U^4 \qquad XVI$$

in which U^4 is a leaving atom or group, and R^6 and X are as defined in claim 21;

(I) For a compound of formula I in which L is X^1-Y-X^2 and X^2 represents oxyalkylene or oxyalkenylene, reacting a compound of formula

$$Q\text{-}M^2\text{-}X^1\text{-}Y\text{-}X^{2c} \qquad XVIII$$

with the appropriate compound of formula

$$X^{2d}\text{-}A \qquad XIX$$

in which X^{2c} is a hydroxy group, or a reactive derivative thereof, X^{2d} is a hydroxyalkylene or hydroxyalkenylene group, or a reactive derivative thereof and M^2, Q, X^1, Y and A are as defined in claim 21;

(J) For a compound of formula I in which L is X^1-Y-X^2 and X^2 represents CONHalkylene, reacting a compound of formula

$$Q\text{-}M^2\text{-}X^1\text{-}Y\text{-}X^{2e} \qquad XX$$

with the appropriate compound of formula

$$X^{2f}\text{-}A \qquad XXI$$

in which X^{2e} represents a carboxy group or a reactive derivative thereof and X^{2f} represents an aminoalkylene group, or an acid addition salt thereof and M^2, Q, X^1, Y and A are as defined in claim 21;

(K) For a compound of formula I in which L is X^1-Y-X^2 and X^1 represents CONH or CONHalkylene, reacting a compound of formula II with a compound of formula

$$OCN\text{-}X^{1g}\text{-}Y\text{-}X^2\text{-}A \qquad XXII$$

in which X^{1g} is a bond or an alkylene group and Y, X^2 and A are as defined in claim 21;

(L) For a compound of formula I in which L is X^1-Y-X^2 and A is $NHSO_2R^{10}$, reacting a compound of formula

$$Q\text{-}M^2\text{-}X^1\text{-}Y\text{-}X^2\text{-}NH_2 \qquad XXIV$$

in which M^2, Q, X^1 and Y are as defined in claim 21 with a compound of formula;

$$R^{10}SO_2U^5 \qquad XXV$$

in which U^5 is a leaving atom or group;

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(M) For a compound of formula I in which L is X^1-Y-X^2 and X^1 is (1-2C)alkylenecarbonyloxy, reacting a compound of formula

$$Q\text{-}M^2\text{-}X^{1k} \qquad \text{XXVI}$$

in which X^{1k} represents (1-2C)alkylenecarboxy or a reactive derivative thereof and M^2 and Q are as defined in claim 21, with a compound of formula

$$HO\text{-}Y\text{-}X^2\text{-}A \qquad \text{XXVII}$$

in which and Y, X^2 and A are as defined in claim 21;

(N) For a compound of formula I in which L is X^1-Y-X^2 and X^1 represents (1-3C)alkylenecarbonyl and Y represents a phenylene group of formula (a), reacting a compound of formula

$$Q\text{-}M^2\text{-}X^{1l} \qquad \text{XXIX}$$

in which X^{1l} represents a (1-3C)alkylenecarbonyl group, or a reactive derivative thereof and M^2 and Q are as defined in claim 21, with a compound of formula VI in the presence of a Lewis acid; or

(O) For a compound of formula I in which L is X^1-Y-X^2 and X^2 represents $NR^{21}CO$(1-2C)alkylene, reacting a compound of formula

$$Q\text{-}M^2\text{-}X^1\text{-}Y\text{-}NHR^{21} \qquad \text{XXX}$$

in which M^2, Q, X^1 and Y are as defined in claim 21, with a compound of formula

$$X^{2h}\text{-}A \qquad \text{XXXI}$$

in which X^{2h} represents a carboxy(1-2C)alkyl group, or a reactive derivative thereof and A is as defined in claim 21;

whereafter, if necessary and/or desired, a compound of formula I is converted into a pharmaceutically acceptable salt and/or metabolically labile ester or amide thereof.

27
~~29.~~ A compound of the general formula I, as defined in claim 21, or a pharmaceutically acceptable salt or prodrug thereof substantially as herein described with reference to any example thereof.

28
~~30.~~ A process, as defined in claim 28, for preparing a compound of general formula I, or a metabolically labile ester or amide thereof, or a pharmaceutically acceptable salt thereof substantially as herein described with reference to any example thereof.

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29. A method as claimed in claim 1, in which X^1 represents a bond, and X^2 represents an oxy(2-4C) alkylene group optionally substituted on the alkylene group as defined in claim 1, or X^2 represents oxymethylene and X^1 represents methylenecarbonyl.

30. A method according to claim 1 comprising administering a compound of the general formula I or a pharmaceutically acceptable salt or prodrug thereof substantially as herein described with reference to any example thereof.

31. A compound as defined in Claim 21 substantially as herein described with reference to any example thereof.

DATED: 10 September, 1997

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14 3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 94/00648

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D213/74 A61K31/44 C07D215/44 A61K31/47 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 98, no. 15, 11 April 1983, Columbus, Ohio, US; abstract no. 125889b, 'Aromatic carboxylic acid derivatives' page 621 ; see 3-(dimethylamino)propyl ester of 4-(4-pyridinylamino)-benzoic acid (Registry number=85000-31-3) & JP,A,82 183 738 (YAMANOUCHI PHARMACEUTICAL CO.) 12 November 1982 ---	1-31
X	EP,A,0 100 158 (THE UPJOHN CO.) 8 February 1984 see page 7, line 16 - page 7, line 17; examples --- -/--	1-31

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

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 September 1994	28.10.94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	De Jong, B

Form PCT ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 244 115 (PFIZER LTD) 4 November 1987 see example 15	1-31
X	US,A,3 875 165 (JOHN WYETH & BROTHER LIMITED) 1 April 1975 see the whole document	1-31
X	FR,A,2 298 330 (JOHN WYETH & BROTHER LIMITED) 20 August 1976 see the whole document	1-31
A	EP,A,0 201 988 (SMITH KLINE & FRENCH LABORATORIES LIMITED) 20 November 1986 see page 2	1,29
A	EP,A,0 477 295 (COR THERAPEUTICS) 1 April 1992	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB94/00648

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

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

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

The claims are so broad, that a complete search is not possible on economic grounds (PCT-Art. 17.2a(ii)).

Claims 1-31 searched incompletely.

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

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

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

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

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

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter national Application No
PCT/GB 94/00648

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
JP-A-82183738		NONE		
EP-A-0100158	08-02-84	JP-A-	59033263	23-02-84
EP-A-0244115	04-11-87	AU-B-	577218	15-09-88
		AU-A-	7173187	05-11-87
		JP-A-	62255480	07-11-87
		US-A-	4788196	29-11-88
US-A-3875165	01-04-75	US-A-	3971787	27-07-76
		US-A-	3971789	27-07-76
FR-A-2298330	20-08-76	GB-A-	1474296	18-05-77
		BE-A-	837698	19-07-76
		CA-A-	1067080	27-11-79
		CH-A-	586681	15-04-77
		CH-A-	586682	15-04-77
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		JP-A-	51095080	20-08-76
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		CA-A-	1252788	18-04-89
		DE-A-	3680712	12-09-91
		JP-A-	61212582	20-09-86
EP-A-0477295	01-04-92	US-A-	5318899	07-06-94
		AU-B-	636159	22-04-93
		AU-A-	6036990	08-01-91
		CA-A-	2059124	17-12-90
		JP-T-	5500750	18-02-93
		WO-A-	9015620	27-12-90