(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 July 2004 (15.07.2004)

PCT

(10) International Publication Number
WO 2004/058751 A1

(51) International Patent Classification[7]: C07D 417/04, 417/14, A61K 31/427, A61P 35/00

(21) International Application Number: PCT/GB2003/005654

(22) International Filing Date: 24 December 2003 (24.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0230162.0 24 December 2002 (24.12.2002) GB

(71) Applicant *(for all designated States except US)*: **METRIS THERAPEUTICS LIMITED** [GB/GB]; 400 Thames Valley Park Drive, Reading RG6 1PT (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KNOX, Peter** [GB/GB]; 400 Thames Valley Park Drive, Reading RG6 1PT (GB). **PAPPA, Helen** [GB/GB]; 400 Thames Valley Park Drive, Reading RG6 1PT (GB). **LAM, Winnie** [GB/GB]; 400 Thames Valley Park Drive, Reading RG6 1PT (GB).

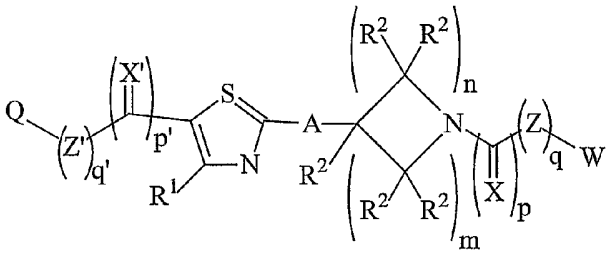
(74) Agents: **GOODFELLOW, Hugh, Robin** et al.; Carpmaels & Ransford, 43-45 Bloomsbury Square, London WC1A 2RA (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

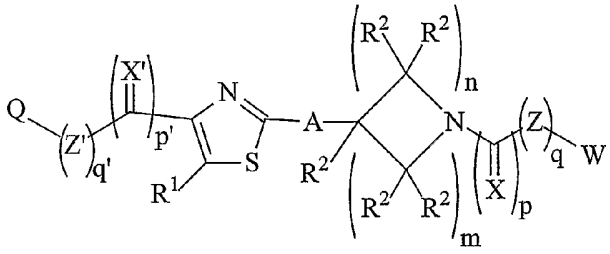
(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,

[Continued on next page]

(54) Title: PIPERIDINYL-THIAZOLE CARBOXAMIDE DERIVATIVES FOR ALTERING VASCULAR TONE



(I)



(II)

(57) Abstract: This invention relates to compounds of formulae (I) and (II) that are specific to the EP3 receptor and useful in altering vascular tone, in particularly uterine vascular tone (including myometrial and endometrial vascular tone). The invention further provides a method for the alteration of uterine vascular tone comprising administering to a patient a compound that binds specifically to the EP3 receptor. The invention is particularly useful in the treatment of menstrual disorders, cardiovascular conditions and hypertension.

WO 2004/058751 A1

SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PIPERIDINYL-THIAZOLE CARBOXAMIDE DERIVATIVES FOR ALTERING VASCULAR TONE

Technical Field

The present invention relates to novel methods for the treatment of diseases in which the alteration of vascular tone plays a role. These methods involve specific targeting of a receptor known as the EP3 receptor, which is implicated herein in diseases of this nature. In particular, this invention relates to targeting EP3 receptor for alteration of vascular tone in myometrium and endometrium. The invention also relates to the use of compounds that bind to EP3 receptor in a highly specific manner useful in treating conditions in which EP3 receptor plays a role. The invention also relates to the use of these compounds and to pharmaceutical compositions comprising these compounds.

Technical Background

Vascular tone, in particular vasoconstriction and vasodilation plays a key role in human physiology. The walls of arteries, arterioles, venules and veins contain smooth muscle whose contractile state is controlled by mediators released locally from sympathetic nerve terminals and endothelial cells, and by circulating hormones. Arterioles and small muscular arteries are the main resistance vessels in circulation, while veins are capacity vessels. Like other muscle cells, vascular smooth muscle contracts when the intracellular Ca2+ concentration rises. Vasoconstrictors and vasodilators act by increasing or reducing intracellular Ca2+, and/or by altering the sensitivity of the contractile machinery to Ca2+ (Rang H.P., Dale M.M., Ritter J.M., 1999 Pharmacology 4th Edition, Churchill Livingstone).

Agents causing vasoconstriction act by either releasing intracellular Ca2+, in response to receptor-mediated IP3 formation or by allowing Ca2+ entry through voltage-gated Ca2+ channels or by allowing Ca2+ entry through receptor-operated Ca2+ channels. Agents causing vasodilation act by either direct or indirect inhibition of Ca2+ entry through voltage-gated Ca2+ channels or increase of intracellular cAMP or cGMP concentration. A family of compounds that alter cAMP and intracellular Ca2+ levels and that has been implicated in affecting muscular tone consists of the molecules known as prostanoids.

Prostanoids are particularly unstable molecules and they are therefore considered to act in a paracrine fashion through a number of seven transmembrane receptors (7-TM) G-protein coupled receptors, namely EP, FP, IP, DP and TP. The known EP family of receptors consists of four members EP1, EP2, EP3 and EP4, all cloned and sequenced in the early 90s (Funk C.D. et al., 1993 J. Biol. Chem. 268 No.35 26767-26772; Regan J.W. et al., 1994 Mol. Pharmacology 46 213-220; Kotani M et al., 1995 Mol. Pharmacology 48 869-879; Regan J.W. et al., 1994 Br. J. Pharmacol. 112 377-385; Bastien L. et al., 1994 J. Biol. Chem. 269, No.16, 11873-11877). The EP3 receptor is unique among the class of EP receptors in that it exists as multiple isoforms generated by alternative mRNA splicing of the EP3 receptor gene (Kotani M et al., 1995 Mol. Pharmacology 48 869-879; Regan J.W. et al., 1994 Br. J. Pharmacol. 112 377-385). These isoforms differ only at the C-terminal end and although they display very similar binding affinities for PGE2 (Regan J.W. et al., 1994 Br. J. Pharmacol. 112 377-385) they mediate different intracellular signalling pathways (Asboth G et al., 1998 Acta Phys. Hung. 85 (1) 39-50; Asboth G et al., 1995 Endocrinology 137 (6) 2572-2579).

Prostanoids affect most tissues by acting on their respective receptors as follows. The action of PGD2 and PGI2 on DP and IP-receptors respectively causes vasodilation and inhibition of platelet aggregation. On the other hand, the action of PGF2a and TXA2 on FP and TP-receptors results to intense muscle contractions. The actions of PGE2 are more variable, complicated by the fact that PGE2 bind to four different receptors. It is suggested in literature that PGE2 causes muscle contraction by acting on EP1 and EP3 receptors but relaxation when it binds on EP2 and EP4 receptors (Coleman, R. A. et al (1994) Pharmacol. Rev., 46, 205-229).

However, the exact mechanism of PGE2 and other prostanoid action in each tissue remains elusive as pharmacological attempts to determine receptor distribution and function have been complicated by the lack of selectivity of the existing receptor agonists and antagonists (Coleman, R. A. et al (1994) Pharmacol. Rev., 46, 205-229; Abramovitz et al., 2000 Biochimica et Biophysica Acta 1483 285-293). The limited knowledge of the target receptor distribution together with the lack of availability of highly selective receptor agonists and antagonists for some of these receptors has hindered the discovery and development of effective treatments. In many systems, the efficacy of EP receptor

agonists and antagonists is diminished due to the opposite effects exerted on the target receptor and other EP and prostanoid receptors. Moreover, the lack of specificity of these compounds creates a number of undesirable side effects that limit the tolerability of these treatments. For these reasons, the discovery of new receptor binding molecules capable of effectively blocking receptor subtypes while minimizing side effects is desirable in the art for use in treating diseases where prostanoids play a vital role.

The present invention relates to the discovery that a particular receptor, known as the EP3 receptor, is expressed in vascular smooth muscle of uterine myometrium and endometrium. The present invention implicates the EP3 receptor in altering uterine vascular tone in particular of myometrium and endometrium and playing a role in menstrual disorders such as menorrhagia, dysmenorrhea, endometriosis and menstrual-migraines. The present invention relates to compounds specific for EP3 receptor that could provide new highly effective treatments with minimum side effects for conditions where EP3 receptor plays a role. In addition to the menstrual disorders mentioned above, these conditions include indications in which the prostaglandin PGE2 is implicated, such as pre-eclampsia, uterine contractions, cardiovascular conditions, hypertension, shock, hypotensive states, ulcer, asthma, allergic inflammation, fever, pain, PGE2-induced immunosuppression and renal failure. Although various treatments for these diseases do exist, there is a continuing need for new and improved treatments for these conditions.

Summary of the Invention

According to the present invention there is provided a method for the alteration of uterine vascular tone in a patient comprising administering to the patient a therapeutically-effective amount of a compound that binds specifically to the EP3 receptor.

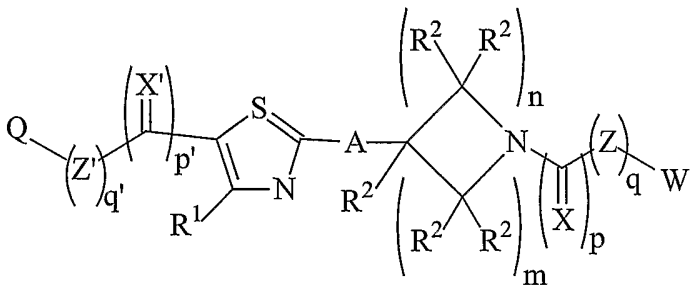
The present invention also provides the use of a compound that binds specifically to the EP3 receptor for the manufacture of a medicament for altering uterine vascular tone.

Uterine vascular tone includes myometrial and endometrial vascular tone.

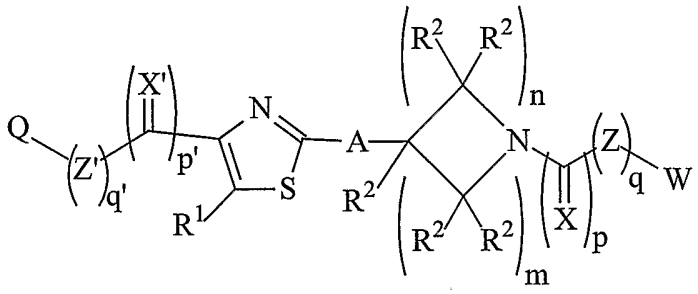
By "binding specifically to the EP3 receptor" is meant that the compound binds to the EP3 receptor with an EC50 of less than 25μM, preferably less than 10μM, more preferably less than 7μM, more preferably less than 5μM, even more preferably less than 1μM. EC50 values may be determined by a number of methods, as the skilled reader will appreciate, and an illustration is presented in the specific examples included herein. Preferably, a compound that binds specifically to the EP3 receptor does not bind to any of the FP, TP, IP and EP2 receptors to any significant degree. This means that the compounds have substantially greater affinity for the EP3 receptor than their affinity for other related receptors. By "substantially greater affinity" we mean that there is a measurable increase in the affinity of a compound of the invention that binds specifically to the EP3 receptor as compared with the affinity of the same compound for other known cell-surface receptors, including the FP, TP, IP and EP2 receptors. Preferably, the affinity of the compound is at least 1.5-fold, 2-fold, 5-fold 10-fold, 100-fold, 10^3-fold, 10^4-fold, 10^5-fold, 10^6-fold or greater for the EP3 receptor than for related receptors such as any of the FP, EP2, TP and IP receptors.

Compounds particularly useful in the present invention include those of formulae (I), (II) and (III).

The present invention further provides a compound of formula (I) or formula (II):



(I)



(II)

wherein:

Q is an optionally substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, alkylthio, aralkylthio, amino, alkylamino, dialkylamino, carboxyl, carboxylalkyl, esterified carboxyl, alkylsulfoxyl, alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy, or heterocyclic group;

A is a single bond or alkylene;

X is O or S;

X' is O or S;

Z is O, S or NR^3;

Z' is O, S or NR^3;

p is 0 or 1;

p' is 0 or 1;

q is 0 or 1;

q' is 0 or 1;

n is an integer from 0 to 10;

m is an integer from 0 to 10;

W is an optionally substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, alkylthio, aralkylthio, amino, alkylamino, dialkylamino, carboxyl, carboxylalkyl, esterified carboxyl, alkylsulfoxyl, alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy, or heterocyclic group;

R^1 is H or alkyl;

R^2 is independently H or alkyl; and

R^3 is independently H or alkyl;

or a pharmaceutically acceptable derivative thereof.

The term "pharmaceutically acceptable derivative" as used herein, means any pharmaceutically acceptable salt, addition compound, or any other compound which upon administration to a recipient is capable of providing, whether directly or indirectly, a compound of the invention or a pharmaceutically acceptable metabolite.

The term "pharmaceutically acceptable metabolite" as used herein, means a metabolite or residue of a compound of the invention which gives rise to a biological activity exhibited by the compounds of the invention.

The term "pharmaceutically acceptable salt", as used herein, refers to a salt prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic or organic acids and bases.

Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, sulfuric, and phosphoric acids. Appropriate organic acids may be selected, for example, from aliphatic, aromatic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, benzenesulfonic, stearic, sulfanilic, algenic, and galacturonic. Examples of such inorganic bases include metallic salts made from aluminium, calcium, lithium, magnesium, potassium, sodium, and zinc. Appropriate organic bases may be selected, for example, from N,N-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumaine (N-methylglucamine), and procaine.

As used herein, the term "alkyl" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the alkyl group is preferably C_3 to C_{12}, more preferably C_5 to C_{10}, more preferably C_5, C_6 or C_7. Where acyclic, the alkyl group is preferably C_1 to C_{10}, more preferably C_1 to C_6, more preferably methyl, ethyl, propyl (n-propyl or isopropyl), butyl (n-butyl, isobutyl or tertiary-butyl) or pentyl (including n-pentyl and iso-pentyl), more preferably methyl. It will be appreciated therefore that the term "alkyl" as used herein includes alkyl (branched or unbranched), alkenyl (branched or unbranched), alkynyl (branched or unbranched), cycloalkyl, cycloalkenyl and cycloalkynyl.

Saturated hydrocarbyl radicals are generally preferred.

As used herein, the term "lower alkyl" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical, wherein a cyclic lower alkyl group is C_5, C_6 or C_7, and wherein an acyclic lower alkyl group is C_1 to C_6, that is, methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl), more preferably methyl.

An alkyl group may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 or 2 substituents. Substituents may include halogen atoms and halomethyl groups such as CF_3 and CCl_3; oxygen containing groups such as oxo, hydroxy, carboxy, carboxyalkyl, alkoxy, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, amido, alkylamino, dialkylamino, cyano, azide, nitrato, nitro, $-C(O)-NH_2$, $-C(O)-NHR^4$ and $-C(O)-NR^4_2$ (where R^4 is independently optionally substituted alkyl or aryl (preferably alkyl)); sulphur containing groups such as thiol, alkylthiol, sulphonyl, sulphoxide, $-S(O)_2-H$, $-S(O)_2-R^4$, -S(O)-H and $-S(O)-R^4$ (where R^4 is optionally substituted alkyl or aryl (preferably alkyl)); heterocyclic groups containing one or more, heteroatom, such as thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl, carbolinyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl and pyrimidinyl; alkyl groups, which may themselves be substituted; and aryl groups, which may themselves be substituted, such as phenyl and substituted phenyl.

As used herein, the term "alkylene" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenylene or alkynylene) hydrocarbylene radical. Where cyclic, the alkylene group is preferably C_3 to C_{12}, more preferably C_5 to C_{10}, more preferably C_5 to C_7. Where acyclic, the alkylene group is preferably C_1 to C_{16}, more preferably C_1 to C_4, more preferably methylene.

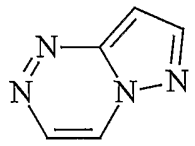
An alkylene group may be substituted or unsubstituted, preferably unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include halogen atoms and halomethyl groups such as CF_3 and CCl_3; oxygen containing groups such as oxo, hydroxy, carboxy, carboxyalkyl, alkoxy, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, amido, alkylamino, dialkylamino, cyano, azide, nitrato, nitro, -C(O)-NH_2, -C(O)-NHR^4 and -C(O)-NR^4_2 (where R^4 is independently optionally substituted alkyl or aryl (preferably alkyl)); sulphur containing groups such as thiol, alkylthiol, sulphonyl, sulphoxide, -$S(O)_2$-H, -$S(O)_2$-R^4, -S(O)-H and -S(O)-R^4 (where R^4 is optionally substituted alkyl or aryl (preferably alkyl)); heterocyclic groups containing one or more, heteroatom, such as thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl, carbolinyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl and pyrimidinyl; alkyl groups, which may themselves be substituted; and aryl groups, which may themselves be substituted, such as phenyl and substituted phenyl.

As used herein, the term "aryl" means a cyclic or bicyclic aromatic group, such as phenyl or naphthyl. C_{6-12} (e.g. C_{6-10}) aryl groups are preferred. An aryl group may be substituted or unsubstituted, preferably unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include halogen atoms and halomethyl groups such as CF_3 and CCl_3; oxygen containing groups such as oxo, hydroxy, carboxy, carboxyalkyl, alkoxy, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, amido, alkylamino, dialkylamino, cyano, azide, nitrato, nitro, -C(O)-NH_2, -C(O)-NHR^4 and -C(O)-NR^4_2 (where R^4 is independently optionally substituted alkyl or aryl (preferably alkyl)); sulphur containing groups such as thiol, alkylthiol, sulphonyl, sulphoxide, -$S(O)_2$-H, -$S(O)_2$-R^4, -S(O)-H and -S(O)-R^4 (where R^4 is optionally substituted alkyl or aryl (preferably alkyl)); heterocyclic groups containing one or more, heteroatom, such as thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl,

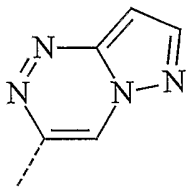
tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl, carbolinyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl and pyrimidinyl; alkyl groups, which may themselves be substituted; and aryl groups, which may themselves be substituted, such as phenyl and substituted phenyl.

As used herein, the term "heterocyclic" means a saturated or unsaturated cyclic or bicyclic group containing one or more heteroatoms, such as thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isoxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl, carbolinyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl and pyrimidinyl.

The term “heterocyclic group” also includes groups derived from:



preferably



Heterocyclic groups containing from 5 to 12 (e.g. 5 to 10) atoms are preferred. Heterocyclic groups preferably contain 1, 2, 3 or 4 heteroatoms. Preferred heteroatoms are N, O and S.

A heterocyclic group may be substituted or unsubstituted, preferably unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include halogen atoms and halomethyl groups such as CF_3 and CCl_3; oxygen containing groups such as oxo, hydroxy, carboxy, carboxyalkyl, alkoxy, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, amido, alkylamino, dialkylamino, cyano, azide, nitrato, nitro, $-C(O)-NH_2$, $-C(O)-NHR^4$ and $-C(O)-NR^4{}_2$ (where R^4 is independently optionally substituted alkyl or aryl (preferably alkyl)); sulphur containing groups such as thiol, alkylthiol, sulphonyl, sulphoxide, $-S(O)_2-H$, $-S(O)_2-R^4$, -S(O)-H and $-S(O)-R^4$ (where R^4 is optionally substituted alkyl or aryl (preferably alkyl)); heterocyclic groups containing one or more, heteroatom, such as thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl, carbolinyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl and pyrimidinyl; alkyl groups, which may themselves be substituted; and aryl groups, which may themselves be substituted, such as phenyl and substituted phenyl.

As used herein, the term "aralkyl" means aryl-alkyl- (e.g. benzyl).

As used herein, the term "alkoxy" means alkyl-O-. As used herein, the term "lower alkoxy" means loweralkyl-O-. As used herein, the term "aryloxy" means aryl-O-. As used herein, the term "aralkoxy" means aralkyl-O-,

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine or chlorine radical.

Compounds of the invention of formula (II) are preferred.

Preferably, A is a single bond.

Preferably, X is O. Alternatively, it is preferred that X is S and Z is NR^3.

Preferably, X' is O. Preferably, Z' is NR^3.

Preferably, R^3 is H.

Preferably, p = 1.

Preferably, q = 0.

Preferably, p' = 0 and q' = 0, or p' = 1 and q' = 1.

Optionally, the compounds disclosed in the co-pending PCT application of the same filing date entitled "Compounds useful in inhibiting angiogenesis" and claiming priority from GB application no. 0230162.0 filed on 24.12.2002 are disclaimed and are thus excluded from the subject matter of the present invention. Optionally, compounds of formula (I), (II) and (III) wherein p' = 1, q' = 1, X' = O and Z' = NH are disclaimed.

Preferably, the sum n +m is an integer from 2 to 10, more preferably 2 to 6, more preferably 2 to 4, more preferably 3 or 4, most preferably 4.

Preferably, n is from 0 to 3, preferably 2.

Preferably, m is from 0 to 3, preferably 2.

Preferably, n = 2 and m = 2.

Preferably, R^1 is H.

Preferably, each R^2 is H.

The substituents Q and W may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 or 2 substituents. Substituents may include halogen atoms and halomethyl groups such as CF_3 and CCl_3; oxygen containing

groups such as oxo, hydroxy, carboxy, carboxyalkyl, alkoxy, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, amido, alkylamino, dialkylamino, cyano, azide, nitrato, nitro, $-C(O)-NH_2$, $-C(O)-NHR^4$ and $-C(O)-NR^4_2$ (where R^4 is independently optionally substituted alkyl or aryl (preferably alkyl)); sulphur containing groups such as thiol, alkylthiol, sulphonyl, sulphoxide, $-S(O)_2-H$, $-S(O)_2-R^4$, -S(O)-H and $-S(O)-R^4$ (where R^4 is optionally substituted alkyl or aryl (preferably alkyl)); heterocyclic groups containing one or more, heteroatom, such as thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl, carbolinyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl and pyrimidinyl; alkyl groups, which may themselves be substituted; and aryl groups, which may themselves be substituted, such as phenyl and substituted phenyl.

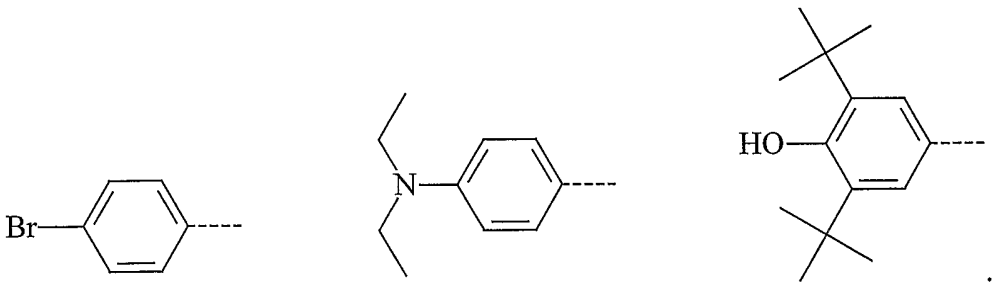
Preferably, Q comprises an optionally substituted aryl or heterocyclic group. More preferably, Q is an optionally substituted aryl or heterocyclic group. A preferred aryl group is phenyl. A preferred heterocyclic group is an unsaturated heterocyclic group, more preferably a monocyclic unsaturated heterocyclic group.

When substituted, Q is preferably independently substituted by one or more (e.g. 1, 2 or 3) of: halogen; trihalomethyl; $-NO_2$; -CN; $-Y-C(=Y)-R^5$; $-C(=Y)-R^5$; $-C(=Y)-Y-R^5$; $-Y-C(=Y)-Y-R^5$; $-SOR^5$; $-S(=O)_2R^5$; $-Y-S(=O)OR^5$; $-Y-S(=O)_2R^5$; $-S(=O)_2-YR^5$; $-Y-S(=O)_2-YR^5$; $-R^5$; $-YR^5$; or alkyl (preferably methyl) substituted with one or more (e.g. 1, 2 or 3, preferably 1) of halogen, trihalomethyl, $-NO_2$, -CN, $-Y-C(=Y)-R^5$, $-C(=Y)-R^5$, $-C(=Y)-Y-R^5$, $-Y-C(=Y)-Y-R^5$, $-SOR^5$, $-S(=O)_2R^5$, $-Y-S(=O)OR^5$, $-Y-S(=O)_2R^5$, $-S(=O)_2-YR^5$, $-Y-S(=O)_2-YR^5$ or $-YR^5$. Y is independently O, S or NR^5, and R^5 is independently H or an optionally substituted alkyl, aryl or heterocyclic group (preferably H or alkyl). More preferred substituents are: halogen; trihalomethyl; $-NO_2$; -CN; $-CO_2H$; $-CO_2R^5$; -C(=O)H; $-C(=O)R^5$; $-OC(=O)R^5$; $-OC(=O)OR^5$; $-C(=O)NH_2$; $-C(=O)NR^5_2$; $-N(R^5)C(=O)R^5$; $-N(R^5)C(=O)OR^5$; $-OC(=O)NR^5_2$; $-N(R^5)C(=O)NR^5_2$; $-C(=S)NH_2$; $-C(=S)NR^5_2$; $-N(R^5)C(=S)R^5$; $-N(R^5)C(=S)NR^5_2$; $-C(=NH)NH_2$; $-C(=NR^5)NR^5_2$;

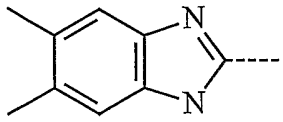
$-N(R^5)C(=NR^5)R^5$; $-N(R^5)C(=NR^5)NR^5{}_2$; $-SOR^5$; $-S(=O)_2R^5$; $-S(=O)_2OH$; $-S(=O)_2OR^5$; $-S(=O)_2NR^5{}_2$; $-N(R^5)SO_2R^5$; $-N(R^5)SO_2NR^5{}_2$; $-NR^5{}_2$; $-R^5$; $-YR^5$; or alkyl (preferably methyl) substituted with one or more (e.g. 1, 2 or 3, preferably 1) of halogen, trihalomethyl, $-NO_2$, -CN, $-CO_2H$, $-CO_2R^5$, -C(=O)H, $-C(=O)R^5$, $-OC(=O)R^5$, $-OC(=O)OR^5$, $-C(=O)NH_2$, $-C(=O)NR^5{}_2$, $-N(R^5)C(=O)R^5$, $-N(R^5)C(=O)OR^5$, $-OC(=O)NR^5{}_2$, $-N(R^5)C(=O)NR^5{}_2$, $-C(=S)NH_2$, $-C(=S)NR^5{}_2$, $-N(R^5)C(=S)R^5$, $-N(R^5)C(=S)NR^5{}_2$, $-C(=NH)NH_2$, $-C(=NR^5)NR^5{}_2$, $-N(R^5)C(=NR^5)R^5$, $-N(R^5)C(=NR^5)NR^5{}_2$, $-SOR^5$, $-S(=O)_2R^5$, $-S(=O)_2OH$, $-S(=O)_2OR^5$, $-S(=O)_2NR^5{}_2$, $-N(R^5)SO_2R^5$, $-N(R^5)SO_2NR^5{}_2$, $-NR^5{}_2$ or $-YR^5$. Still more preferred substituents are: halogen; -CN; $-CO_2H$; $-CO_2R^5$; $-C(=O)R^5$; $-C(=O)NH_2$; $-C(=O)NR^5{}_2$; $-N(R^5)C(=O)R^5$; $-C(=S)NH_2$; $-C(=S)NR^5{}_2$; $-C(=NH)NH_2$; $-C(=NR^5)NR^5{}_2$; $-S(=O)_2R^5$; $-NR^5{}_2$; $-R^5$; $-YR^5$ or alkyl (preferably methyl) substituted with $-C(=O)NR^5{}_2$. Still more preferred substituents are halogen (e.g. Br), $-YR^5$ (e.g. $-N(CH_2CH_3)_2$ or OH) or $-R^5$ (e.g. $-C(CH_3)_3$).

When Q is substituted by $-R^5$, it is preferred that R^5 is an alkyl group, preferably $-C(CH_3)_3$.

In one embodiment, especially when p' = 0 and q' = 0, Q is a phenyl group optionally substituted with 1 or more (e.g. 1, 2 or 3) substituents. Preferably Q is a phenyl group having at least one substituent selected from halogen, alkyl, dialkylamine and hydroxy. More preferably, Q is a radical selected from:



In another embodiment, especially when p' = 1 and q' = 1, Q is a heterocyclic group optionally substituted with 1 or more (e.g. 1, 2 or 3) substituents. Preferably Q is an optionally substituted unsaturated heterocyclic group, preferably an optionally substituted unsaturated bicyclic heterocyclic group (e.g. benzimidazolyl). More preferably, Q is an unsaturated bicyclic heterocyclic group having at least one alkyl substituent (e.g. methyl). More preferably Q is:



Preferably, W is an optionally substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, alkylthio, aralkylthio, carboxyl, carboxylalkyl, esterified carboxyl, alkylsulfonyl, carbo-alkoxy, carbo-aryloxy or heterocyclic group.

More preferably, W is an optionally substituted alkyl, alkenyl, alkynyl, aryl or heterocyclic group. A preferred alkyl group is methyl. A preferred alkenyl group is vinyl. A preferred alkynyl group is ethenyl. A preferred aryl group is phenyl. A preferred heterocyclic group is an unsaturated heterocyclic group, more preferably a monocyclic unsaturated heterocyclic group.

Alternatively, where W is a substituted alkyl, alkenyl or alkynyl group, it may be substituted with -(O-alkylene)$_a$-O-alkyl (preferably -(O-ethylene)$_a$-O-alkyl or -(O-propylene)$_a$-O-alkyl), where a is from 1 to 20 (preferably 1 to 10, preferably 1 to 5, more preferably 2).

Where substituted, W is preferably independently substituted by one or more (e.g. 1, 2 or 3) of: halogen; trihalomethyl; -NO_2; -CN; -Y-C(=Y)-R^5; -C(=Y)-R^5; -C(=Y)-Y-R^5; -Y-C(=Y)-Y-R^5; -SOR^5; -S(=O)$_2R^5$; -Y-S(=O)OR^5; -Y-S(=O)$_2R^5$; -S(=O)$_2$-YR^5; -Y-S(=O)$_2$-YR^5; -R^5; -YR^5; or alkyl (preferably methyl) substituted with one or more (e.g. 1, 2 or 3, preferably 1) of halogen, trihalomethyl, -NO_2, -CN, -Y-C(=Y)-R^5, -C(=Y)-R^5, -C(=Y)-Y-R^5, -Y-C(=Y)-Y-R^5, -SOR^5, -S(=O)$_2R^5$, -Y-S(=O)OR^5, -Y-S(=O)$_2R^5$, -S(=O)$_2$-YR^5, -Y-S(=O)$_2$-YR^5 or -YR^5. Y is independently O, S or NR^5, and R^5 is independently H or an optionally substituted alkyl, aryl or heterocyclic group (preferably H or alkyl). More preferred substituents are halogen, trihalomethyl, -NO_2, -CN, -CO_2H, -CO_2R^5, -C(=O)H, -C(=O)R^5, -OC(=O)R^5, -OC(=O)OR^5, -C(=O)NH_2, -C(=O)$NR^5{}_2$, -N(R^5)C(=O)R^5, -N(R^5)C(=O)OR^5, -OC(=O)$NR^5{}_2$, -N(R^5)C(=O)$NR^5{}_2$, -C(=S)NH_2, -C(=S)$NR^5{}_2$, -N(R^5)C(=S)R^5, -N(R^5)C(=S)$NR^5{}_2$, -C(=NH)NH_2, -C(=NR^5)$NR^5{}_2$, -N(R^5)C(=NR^5)R^5, -N(R^5)C(=NR^5)$NR^5{}_2$, -SOR^5, -S(=O)$_2R^5$, -S(=O)$_2$OH, -S(=O)$_2OR^5$,

$-S(=O)_2NR^5{}_2$, $-N(R^5)SO_2R^5$, $-N(R^5)SO_2NR^5{}_2$, $-NR^5{}_2$, $-R^5$ or $-YR^5$. Still more preferred substituents are halogen, -CN, $-CO_2H$, $-CO_2R^5$, $-C(=O)R^5$, $-C(=O)NH_2$, $-C(=O)NR^5{}_2$, $-N(R^5)C(=O)R^5$, $-C(=S)NH_2$, $-C(=S)NR^5{}_2$, $-C(=NH)NH_2$, $-C(=NR^5)NR^5{}_2$, $-S(=O)_2R^5$, $-NR^5{}_2$, $-R^5$ or $-YR^5$.

Where W is a substituted alkyl, alkenyl or alkynyl group, it is preferably substituted with $-C(=O)NR^5{}_2$ (preferably $-C(=O)NHR^5$, preferably R^5 is an optionally substituted aryl or heterocyclic group) or an optionally substituted alkyl (preferably cycloalkyl), aryl or heterocyclic group. Where W is a substituted alkyl, alkenyl or alkynyl group substituted with $-C(=O)NR^5{}_2$ and R^5 is an optionally substituted aryl or heterocyclic group, the aryl or heterocyclic group may optionally be substituted by one or more (e.g. 1, 2 or 3) of halogen, trihalomethyl, $-NO_2$, -CN, $-Y-C(=Y)-R^5$, $-C(=Y)-R^5$, $-C(=Y)-Y-R^5$, $-Y-C(=Y)-Y-R^5$, $-SOR^5$, $-S(=O)_2R^5$, $-Y-S(=O)OR^5$, $-Y-S(=O)_2R^5$, $-S(=O)_2-YR^5$, $-Y-S(=O)_2-YR^5$, $-R^5$ or $-YR^5$. Y is independently O, S or NR^5, and R^5 is independently H or an optionally substituted alkyl, aryl or heterocyclic group (preferably H or alkyl). More preferred substituents on the aryl or heterocyclic group R^5 are halogen, trihalomethyl, $-NO_2$, -CN, $-CO_2H$, $-CO_2R^5$, $-C(=O)H$, $-C(=O)R^5$, $-OC(=O)R^5$, $-OC(=O)OR^5$, $-C(=O)NH_2$, $-C(=O)NR^5{}_2$, $-N(R^5)C(=O)R^5$, $-N(R^5)C(=O)OR^5$, $-OC(=O)NR^5{}_2$, $-N(R^5)C(=O)NR^5{}_2$, $-C(=S)NH_2$, $-C(=S)NR^5{}_2$, $-N(R^5)C(=S)R^5$, $-N(R^5)C(=S)NR^5{}_2$, $-C(=NH)NH_2$, $-C(=NR^5)NR^5{}_2$, $-N(R^5)C(=NR^5)R^5$, $-N(R^5)C(=NR^5)NR^5{}_2$, $-SOR^5$, $-S(=O)_2R^5$, $-S(=O)_2OH$, $-S(=O)_2OR^5$, $-S(=O)_2NR^5{}_2$, $-N(R^5)SO_2R^5$, $-N(R^5)SO_2NR^5{}_2$, $-NR^5{}_2$, $-R^5$ or $-YR^5$. Still more preferred substituents are $-NO_2$, $-R^5$ (e.g. $-CH_3$) or $-YR^5$ (e.g. OH).

Where W is a substituted alkyl, alkenyl or alkynyl group substituted with an optionally substituted alkyl, aryl or heterocyclic group, the alkyl, aryl or heterocyclic substituent group may optionally be substituted by one or more (e.g. 1, 2 or 3) of: halogen; trihalomethyl; $-NO_2$; -CN; $-Y-C(=Y)-R^5$; $-C(=Y)-R^5$; $-C(=Y)-Y-R^5$; $-Y-C(=Y)-Y-R^5$; $-SOR^5$; $-S(=O)_2R^5$; $-Y-S(=O)OR^5$; $-Y-S(=O)_2R^5$; $-S(=O)_2-YR^5$; $-Y-S(=O)_2-YR^5$; $-R^5$; $-YR^5$; or alkyl (preferably methyl) substituted with one or more (e.g. 1, 2 or 3, preferably 1) of halogen, trihalomethyl, $-NO_2$, -CN, $-Y-C(=Y)-R^5$, $-C(=Y)-R^5$, $-C(=Y)-Y-R^5$, $-Y-C(=Y)-Y-R^5$, $-SOR^5$, $-S(=O)_2R^5$, $-Y-S(=O)OR^5$, $-Y-S(=O)_2R^5$, $-S(=O)_2-YR^5$, $-Y-S(=O)_2-YR^5$ or $-YR^5$. Y is independently O, S or NR^5, and R^5 is independently H or an optionally substituted alkyl, aryl or heterocyclic group (preferably H or alkyl). More

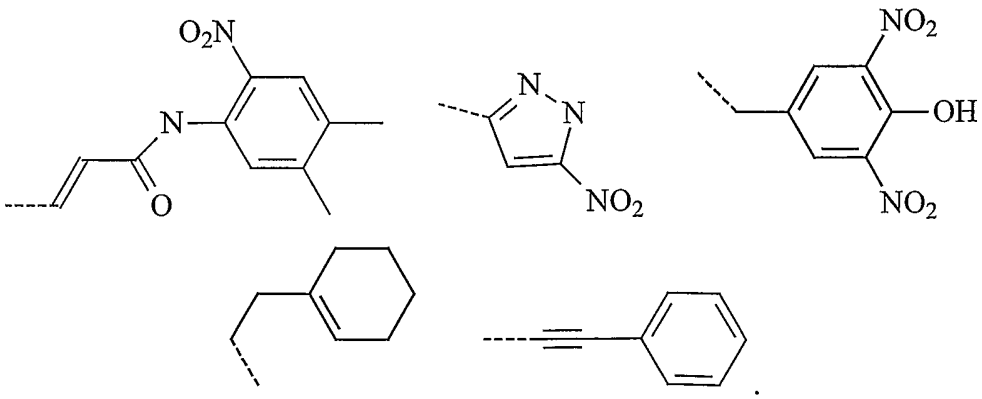
preferred substituents on the alkyl, aryl or heterocyclic substituent group are halogen, trihalomethyl, $-NO_2$, -CN, $-CO_2H$, $-CO_2R^5$, $-C(=O)H$, $-C(=O)R^5$, $-OC(=O)R^5$, $-OC(=O)OR^5$, $-C(=O)NH_2$, $-C(=O)NR^5{}_2$, $-N(R^5)C(=O)R^5$, $-N(R^5)C(=O)OR^5$, $-OC(=O)NR^5{}_2$, $-N(R^5)C(=O)NR^5{}_2$, $-C(=S)NH_2$, $-C(=S)NR^5{}_2$, $-N(R^5)C(=S)R^5$, $-N(R^5)C(=S)NR^5{}_2$, $-C(=NH)NH_2$, $-C(=NR^5)NR^5{}_2$, $-N(R^5)C(=NR^5)R^5$, $-N(R^5)C(=NR^5)NR^5{}_2$, $-SOR^5$, $-S(=O)_2R^5$, $-S(=O)_2OH$, $-S(=O)_2OR^5$, $-S(=O)_2NR^5{}_2$, $-N(R^5)SO_2R^5$, $-N(R^5)SO_2NR^5{}_2$, $-NR^5{}_2$, $-R^5$ or $-YR^5$. Still more preferred substituents are halogen, -CN, $-CO_2H$, $-CO_2R^5$, $-C(=O)R^5$, $-C(=O)NH_2$, $-C(=O)NR^5{}_2$, $-N(R^5)C(=O)R^5$, $-C(=S)NH_2$, $-C(=S)NR^5{}_2$, $-C(=NH)NH_2$, $-C(=NR^5)NR^5{}_2$, $-S(=O)_2R^5$, $-NR^5{}_2$, $-R^5$ or $-YR^5$.

In one embodiment, W comprises an optionally substituted aryl or heterocyclic group. Preferably, W is an optionally substituted aryl or heterocyclic group. A preferred aryl group is phenyl. A preferred heterocyclic group is an unsaturated heterocyclic group, more preferably a monocyclic unsaturated heterocyclic group.

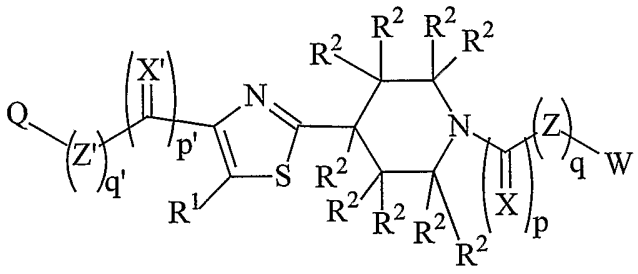
In a second embodiment, W is a heterocyclic group optionally substituted with 1 or more (e.g. 1, 2 or 3) substituents. Preferably W is an optionally substituted pyrazolyl. Preferably, the substituents are nitro.

In a third embodiment, W is an alkyl group substituted with an optionally substituted cycloalkyl (e.g. cycloalkenyl) or aryl (e.g. phenyl) group.

Preferably, W is a radical selected from:



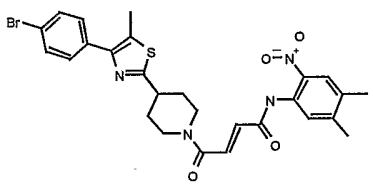
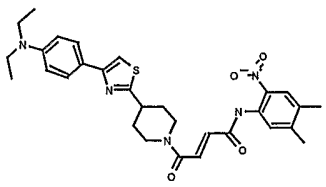
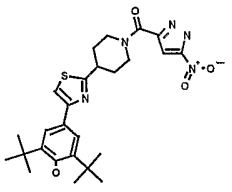
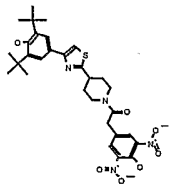
Preferably, the compound of the invention has the formula (III):

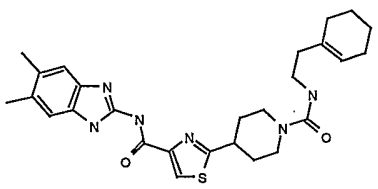
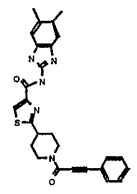


formula (III)

wherein Q, R^1, R^2, X, X', Z, Z', W, p, p', q and q' are as defined above.

Particularly preferred compounds of the invention are:

Compound RR-code	Structural Formula	Name
1507-03555		(E)-4-{4-[4-(4-Bromo-phenyl)-5-methyl-thiazol-2-yl]-piperidin-1-yl}-4-oxo-but-2-enoic acid (4,5-dimethyl-2-nitro-phenyl)-amide
1507-02199		(E)-4-{4-[4-(4-Diethylamino-phenyl)-thiazol-2-yl]-piperidin-1-yl}-4-oxo-but-2-enoic acid (4,5-dimethyl-2-nitro-phenyl)-amide
1507-02705		{4-[4-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-thiazol-2-yl]-piperidin-1-yl}-(5-nitro-1H-pyrazol-3-yl)-methanone
1507-02567		1-{4-[4-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-thiazol-2-yl]-piperidin-1-yl}-2-(4-hydroxy-3,5-dinitro-phenyl)-ethanone

1506-07479		4-[4-(5,6-Dimethyl-1H-benzoimidazol-2-ylcarbamoyl)-thiazol-2-yl]-piperidine-1-carboxylic acid (2-cyclohex-1-enyl-ethyl)-amide
1506-01386		2-[1-(3-Phenyl-propynoyl)-piperidin-4-yl]-thiazole-4-carboxylic acid (5,6-dimethyl-1H-benzoimidazol-2-yl)-amide

According to a further aspect of the present invention there is provided a compound of formula (I), (II) or (III) for use in a method of treatment of disease.

According to a further aspect of the present invention there is provided a compound of formula (I), (II) or (III) for use in therapy or diagnosis.

According to a further aspect of the present invention there is provided the use of a compound of formula (I), (II) or (III) for the manufacture of a medicament for the treatment of a disease, e.g. a disease in which alteration of vascular tone is implicated.

According to a further aspect of the present invention there is provided a method of treating a disease, e.g. a disease in which alteration of vascular tone is implicated, comprising administering to a patient in need of such treatment an effective dose of a compound of formula (I), (II) or (III).

The present invention is useful in the treatment of diseases in which alteration of vascular tone is implicated (in particular uterine vascular tone, including myometrial and endometrial vascular tone), such as menstrual disorders (e.g. menorrhagia, dysmenorrhea, endometriosis and menstrual migraines), renal and cardiovascular conditions and hypertension (including pre-eclampsia).

Additional preferred diseases which may be treated are those in which the EP3 is implicated, such as fever, ulcers and gastric acid secretion; those in which the interaction of prostaglandins with the EP3 receptor is implicated, such as renal failure; and those in

which the interaction of PGE2 with the EP3 receptor is implicated, such as pre-eclampsia, uterine contractions, cardiovascular conditions, hypertension, shock, hypotensive states, ulcer, asthma, allergic inflammation, fever, pain, PGE2-induced immunosuppression and renal failure.

In the methods of treatment and the uses for the manufacture of a medicament of the present invention, compounds having either: (i) p' = 0 and q' = 0 or (ii) p' = 1, q' = 1, X' = O, and Z' = NH are preferred.

According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of the present invention in combination with a pharmaceutically acceptable excipient.

The agents described could be used alone or conjointly with treatments such as anti-hormone therapy, surgery, radiotherapy or chemotherapy.

Compounds of the present invention may be administered in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use including transmucosal and transdermal use, for example a cream, ointment, gel, aqueous or oil solution or suspension, salve, patch, plaster or as a component of a lubricant for a condom; for nasal use, for an example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example a finely divided powder or a liquid aerosol; for intra-ocular, sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oil solution or suspension, or incorporated in a biodegradable polymer. In general the above compositions may be prepared in a conventional manner using convention excipients, using standard techniques well known to those skilled in the art of pharmacy. The preferred modes of administration of the compound are oral or intravaginal. Oral administration is particularly preferred.

For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate. The compounds of the invention may also be provided in a biodegradable polymer, for example for use in conjunction with stents in surgery (e.g. adsorbed on a stent or applied directly to the site of the procedure for slow release of the active agent).

Intravaginal administration is particularly useful for the delivery of pharmaceuticals selectively to the female reproductive tract and is thus a preferred route of administration. When drug substances come into contact with the surface of vaginal mucosa, the tissue lining the vagina, the pharmaceutical diffuses across the mucosa and into the copious blood and lymphatic vessels that are to be found at the base of the mucosa.

The anatomical arrangement of blood and lymphatic vessels in this anatomical region is such that a large proportion of the drug that enters these vessels immediately finds its way into the organs of the reproductive tract including the uterus. Only a smaller proportion

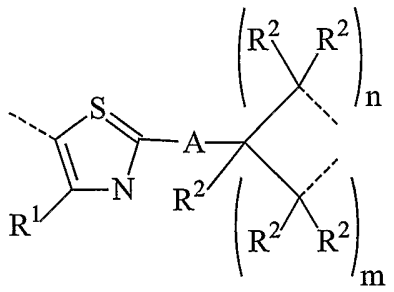
enters the systemic circulation and is rapidly diluted as a result of a large total body blood and lymph volume. The term 'first pass uterine effect' has been used to describe the result of intravaginal delivery (Cicinelli & de Ziegler, D. (1999) Human Reproduct. Update, 5, 365-372). The term describes the phenomenon that pharmaceuticals will be transported directly from vagina to uterus without entering whole body blood circulation.

Furthermore intravaginal delivery is advantageous with respect to oral delivery, since any drug administered orally will have to pass through the liver before it reaches the target organ. Most drugs are significantly metabolised by the liver thus rapidly reducing the available drug pool. The 'first pass uterine effect' avoids transport through the liver.

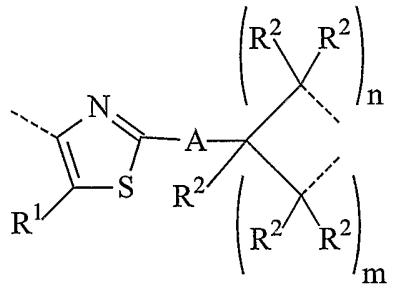
Intravaginal delivery results in high local concentrations of pharmaceutical and low peripheral levels; this is turn leads to a requirement for lower total administered dose. The significant advantage of intravaginal delivery for the present invention described here is that prostaglandin receptors are ubiquitous and found in various tissues. Parenteral administration of ligands might result in peripheral levels that have a pharmacological consequence. However, local delivery via the vagina will ensure that while pharmacologically active levels are reached in the uterus, organs outside the reproductive tract are unlikely to be affected.

It will be appreciated that the dosage levels used may vary over quite a wide range depending upon the compound used, the severity of the symptoms exhibited by the patient and the patient's body weight. Without limitation to the present invention, typical dosages for treatment of endometriosis may be, for example, of the order of 1 microgram/kg/day to 1 milligram/kg/day, more preferably 10 microgram/kg/day to 0.25 milligram/kg/day orally. For intra-ocular administration, typical dosages would be of the order of 10 nanogram/kg/day to 1 microgram/kg/day. For treatment of tumours up to 5 milligrams/kg/day would be preferable. For intra-vaginal administration typical dosages would be 10 micrograms/kg/day to 0.25 milligrams/kg/day.

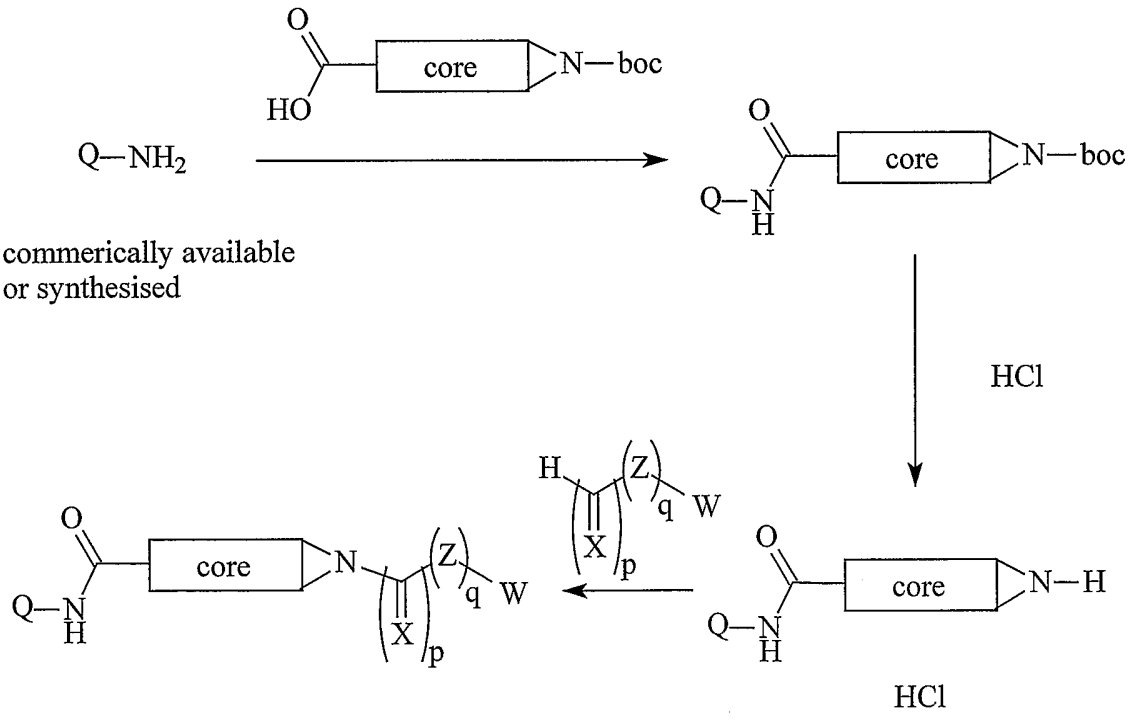
Compounds of the invention may be prepared by the general reaction scheme below, Reaction Scheme 1, wherein by "core" is meant the radical:



or



Reaction Scheme 1



Brief Description of the Figures

Figure 1 shows that EP3 antibody stained positive for endometrial glands, endothelium and vascular smooth muscle in human endomyometrium.

Figure 1(a) shows staining by EP3 antibody in myometrial vessels.

Figure 1(b) shows staining by EP3 antibody in endometrial vessels.

Figure 1(c) shows staining by EP3 antibody in myometrial vessels at secretory day 27.

Figure 1(d) shows staining by EP3 antibody in endometrial vessels at secretory day 27.

The invention is now further illustrated by means of the following Examples.

Examples

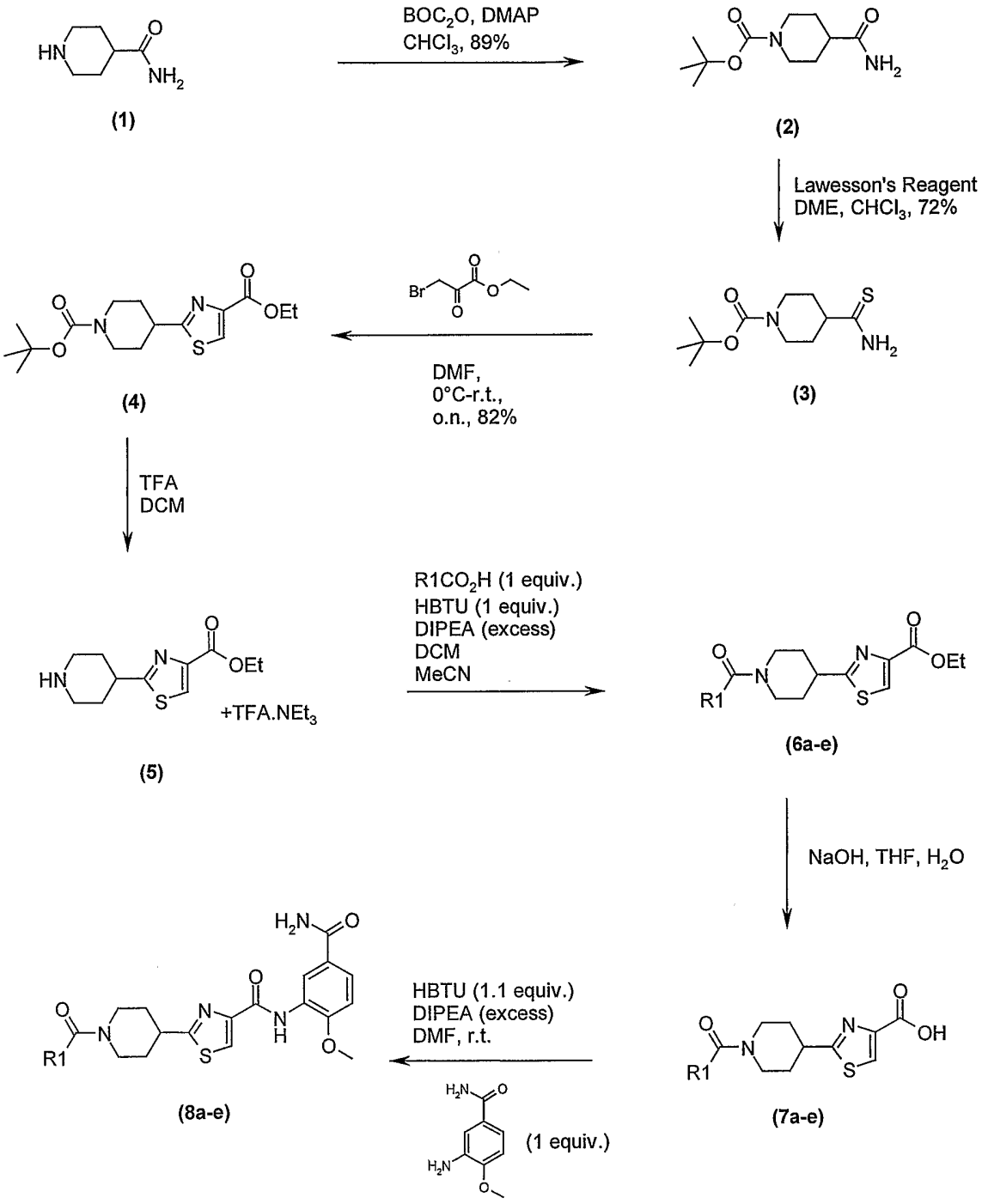
Synthesis of Specific Compounds of the Invention

Examples 1-6

Preparation of *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(4,7-dimethylpyrazolo[5,1-*c*][1,2,4]triazin-3-yl)carbonyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide; *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-(1-benzofuran-2-ylcarbonyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide; *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-(3-phenyl-2-propynoyl)-4-piperidinyl] -1,3-thiazole-4-carboxamide; 2-(1-{[2-(allylsulfanyl)-3-pyridinyl]carbonyl}-4-piperidinyl)-*N*-[5-(aminocarbonyl)-2-methoxyphenyl]-1,3-thiazole-4-carboxamide; *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(2-chlorophenyl)acetyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide; and *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(3,4-dimethylphenoxy)acetyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide.

The above-mentioned compounds were synthesised by Reaction Scheme 2 below:

Reaction Scheme 2



4-Carbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester (2)

Isonipecotamide **(1)** (28.8 g, 0.22 mol) was suspended in chloroform (288 mL). To this was added 4-(dimethylamino)pyridine (DMAP) (23 mg, catalytic) followed by dropwise addition of a solution of BOC-anhydride (56 g, 0.26 mol, 1.14 equiv.) in chloroform (57 mL). The solution was stirred at room temperature for 1 h and then partitioned between chloroform and 10% citric acid solution. The organic phase was washed with citric acid solution and back extracted with chloroform. The combined organic extracts were washed with water, 10% brine and dried ($MgSO_4$). Filtration followed by evaporation of the filtrate gave the crude product as a pink solid. Crystallisation from ethyl acetate/hexane gave the title compound **(2)** as a colourless solid in 4 crops (45.5 g, 0.20 mol, 89%), m.p. 159-161°C (lit. 154-156°C).

4-Thiocarbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester (3)

4-Carbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester **(2)** (45.4 g, 0.199 mol), Lawesson's reagent (40.2 g, 0.099 mol, 0.5 equiv), 1,2-dimethoxyethane (DME) (500 mL) and chloroform (200 mL) were combined and stirred at room temperature. The course of the reaction was followed by tlc analysis (30% ethyl acetate/hexane) and on completion the reaction mixture was evaporated to dryness (glassy solid). The solid was dissolved in ethyl acetate and washed with half saturated potassium carbonate solution, dried ($MgSO_4$), filtered and concentrated to yield the title compound as a colourless solid. The crude product was crystallised from ethyl acetate and hexane to give the title compound **(3)** (35 g, 0.14 mol, 72%).

4-(4-Ethoxycarbonyl-thiazol-2-yl)-piperidine-carboxylic acid *tert*-butyl ester (4)

4-Thiocarbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester **(3)** (25 g, 102 mmol) was dissolved in anhydrous *N,N*-dimethylformamide (DMF) (125 mL) and cooled to 0°C in an ice-bath. A solution of ethyl bromopyruvate (22.2 g, 14.3 mL, 114 mmol, 1.1 equiv) in anhydrous DMF (125 mL) was added dropwise with stirring. The reaction mixture was allowed to warm slowly to room temperature and stirred overnight. Triethylamine (25 mL) was added dropwise with stirring at the rate of 1 mL/g of thioamide used. The DMF was

removed *in vacuo* keeping the temperature below 60°C. The resulting residue was partitioned between ethyl acetate (75 mL) and brine (100 mL). Sufficient water was added to ensure complete dissolution of the precipitated salts in the aqueous phase. The aqueous phase was extracted twice with ethyl acetate and the combined organic extracts washed successively with brine (x2), water (x2) and brine (x2). The organic phase was simultaneously dried with $MgSO_4$ and decolourised with finely divided charcoal. The mixture was filtered through Celite and concentrated *in vacuo* to give a yellow oil. Trituration with hexane yielded a yellow solid. This was diluted with an excess of hexane and cooled overnight to allow complete crystallisation of product. The product was collected by filtration, washed with hexane and dried *in vacuo* at room temperature. Recrystallisation from IPA/water gave the title compound **(4)** (28.33 g, 83 mmol, 82%).

2-Piperidine-4-yl-thiazole-4-carboxylic acid ethyl ester (5)

To a solution of 4-(4-ethoxycarbonyl-thiazol-2-yl)-piperidine-carboxylic acid *tert*-butyl ester **(4)** (5 g, 14.7 mmol) in dichloromethane (20 mL) at 0°C was added neat trifluoroacetic acid (TFA) (17 mL, 221 mmol, 15 equivalents) dropwise with stirring, under an inert atmosphere. On completion of addition the reaction mixture was allowed to warm to room temperature and stirring continued until deprotection complete (typically 3 hours, monitored by tlc, 1:1 hexane/ethyl acetate). On completion of reaction the mixture was concentrated *in vacuo* to remove TFA. Toluene (dioxan for **(6f)**) was then added and re-concentrated to further remove TFA - this was repeated 2-3 times to ensure maximum removal of TFA. The product was further dried *in vacuo* overnight to remove the last traces of TFA. The TFA salt of the free amine was dissolved in dichloromethane (10 mL), cooled to 0°C in an ice bath and treated with triethylamine (6.15 mL, 3 equiv). It was assumed a quantitative conversion of BOC-protected **(4)** to free amine **(5)**.

Compounds (6a-e)

To a solution of 2-piperidine-4-yl-thiazole-4-carboxylic acid ethyl ester **(5)** (14.7 mmol) in dichloromethane (10 mL) at 0°C was added acetonitrile (40 mL). To this solution was sequentially added the acid to be reacted (R1COOH – see Table 2) (14.7mmol, 1 equiv.), *N,N,N',N'*-tetramethyl-O-(*1H*-benzotriazole-1-yl) uronium hexafluorophosphate (HBTU)

(14.7mmol, 5.57g, 1 equiv.), and *N,N*-diisopropylethylamine (DIPEA) (7.7 mL, 3 equiv.). The reaction mixture was stirred at room temperature for 48 h to allow for completion of reaction. After this time the reaction mixture was concentrated *in vacuo* to remove the solvent and the residue was suspended in dichloromethane (80 mL) and washed with brine (2 x 50 mL), water (50 mL), 10% citric acid (50 mL), brine, saturated sodium bicarbonate solution (50 mL) and finally brine. The organic layer was dried over $MgSO_4$ and treated with decolourising charcoal, filtered and concentrated *in vacuo*.

Table 2

id	$R1CO_2H$	yield
6a	2-chlorophenylacetic acid	not purified
6b	3,4-dimethylphenoxyacetic acid	not purified
6c	1-benzofuran-2-carboxylic acid	65% (after chromatography)
6d	3-phenylpropynic acid	not purified
6e	2-(allylthio)nicotinic acid	not purified
6f	4,7-dimethylpyrazolo[5,1-c][1,2,4]triazine-3-carboxylic acid	not purified

Compounds (7a-e)

Compound **(6a-e)** (13mmol) was dissolved in THF (35 mL) and water (23 mL) and cooled to 0°C. A solution of sodium hydroxide (1.04g, 26mmol, 2 equiv.) in water (20 mL) was added dropwise with stirring. The reaction was monitored by tlc analysis and when complete (typically 2 h) the reaction mixture was diluted with brine (30 mL) and washed with ether (100 mL). The reaction mixture was acidified using 20% citric acid solution. The acidic mixture was then extracted with a suitable organic solvent (dichloromethane or ethyl acetate) and when fully extracted the organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield essentially pure product.

Table 3

id	extraction solvent	yield
7a	ethyl acetate	58% (over two steps)
7b	ethyl acetate	61% (over two steps)
7c	ethyl acetate	80%
7d	dichloromethane	41% (over two steps)
7e	ethyl acetate	54% (over two steps)
7f	ethyl acetate	53% (over two steps)*

*product was isolated by repeated crystallisation from ethyl acetate

Compounds (8a-e)

Compound **(7a-e)** was dissolved in anhydrous DMF (0.58 M solution). 3-Amino-4-methoxybenzamide was dissolved in 10% DIPEA and anhydrous DMF (0.58 M solution). HBTU was dissolved in anhydrous DMF (0.64 M solution). The amine solution (0.3 ml, 0.175 mmol) was dispensed into an individual well in a 2.2 mL deep well plate using a Packard MPII robot. An Eppendorf multi-dispenser was used to dispense the acid solution (0.3 mL, 0.175 mmol, 1 equiv) and then to dispense the HBTU solution (0.3 mL, 0.19 mmol, 1.1 equiv). A further portion of DIPEA (0.05 mL) was added to the well, which was capped and shaken on an orbital shaker overnight. The reaction mixture was concentrated *in vacuo* (Genevac). The residue was dissolved in dichloromethane (1 mL) and given a sequence of aqueous washes using the MPII robot: 0.5 N HCl (0.7 mL), 10% potassium carbonate solution (0.7 mL) then water (0.7 mL). Finally the dichloromethane extract (0.7 mL) containing the product was concentrated and dried (Genevac) to constant mass.

Table 4

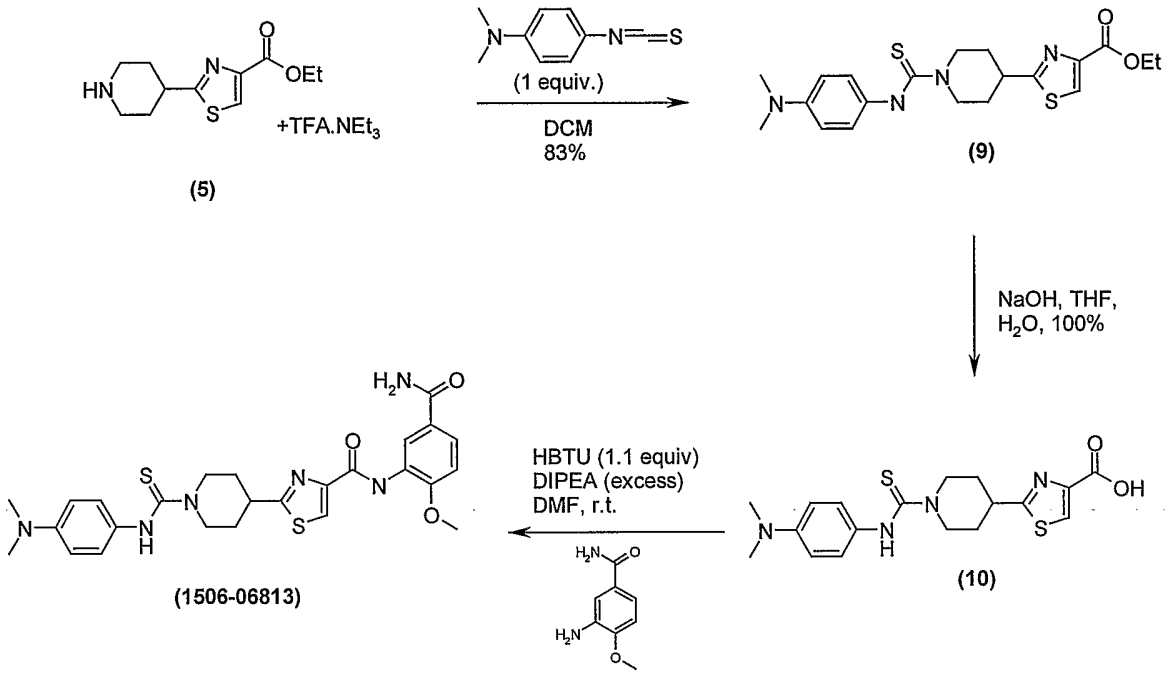
id	RRcode	DAD (254 nm)	ES+
8a	**1506-03737**	100%	513
8b	**1506-03914**	97%	523
8c	**1506-01284**	88%	505
8d	**1506-01461**	90%	489
8e	**1506-02331**	89%	538
8f	**1506-00581**	86%	535

Example 7

Preparation of *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-({[4-(dimethylamino)phenyl]amino}carbonothioyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide;

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-({[4-(dimethylamino)phenyl]amino}carbonothioyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide was prepared by the synthetic route set out in Reaction Scheme 3 below.

Reaction Scheme 3



2-[1-(4-Dimethylamino-phenylthiocarbamoyl)-piperidine-4-yl]-thiazole-4-carboxylic acid ethyl ester (9)

To a solution of 2-piperidine-4-yl-thiazole-4-carboxylic acid ethyl ester **(5)** (14.7 mmol) in dichloromethane (10 mL) at 0°C was added dichloromethane (80 mL). To this was added 4-(dimethylamino)phenylisothiocyanate (14.7mmol, 1 equiv.). The reaction mixture was stirred at room temperature for 48 h to allow for completion of reaction. After this time the reaction mixture was diluted with dichloromethane (100 mL) and washed with water (2 x 100 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the thiourea in 83% yield following chromatography.

2-[1-(4-Dimethylamino-phenylthiocarbamoyl)-piperidine-4-yl]-thiazole-4-carboxylic acid (10)

2-[1-(4-Dimethylamino-phenylthiocarbamoyl)-piperidine-4-yl]-thiazole-4-carboxylic acid ethyl ester **(9)** (13 mmol) was dissolved in THF (35 mL) and water (23 mL) and cooled to 0°C. A solution of sodium hydroxide (1.04g, 26 mmol, 2 equiv.) in water (20 mL) was added dropwise with stirring. The mixture was stirred for 2 h at r.t. The mixture was diluted with brine (30 mL) and washed with ether (100 mL). The reaction mixture was acidified using 20% citric acid solution. The acidic mixture was extracted with ethyl acetate and when fully extracted the organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the title compound **(10)** in quantitative yield.

***N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-({[4-(dimethylamino)phenyl]amino}carbonothioyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide**

2-[1-(4-Dimethylamino-phenylthiocarbamoyl)-piperidine-4-yl]-thiazole-4-carboxylic acid **(10)** was dissolved in anhydrous DMF (0.58 M solution). 3-Amino-4-methoxybenzamide was dissolved in 10% DIPEA and anhydrous DMF (0.58 M solution). HBTU was dissolved in anhydrous DMF (0.64 M solution). The amine solution (0.3 ml, 0.175 mmol) was dispensed into an individual well in a 2.2 mL deep well plate using a Packard MPII robot. An Eppendorf multi-dispenser was used to dispense the acid solution (0.3 mL,

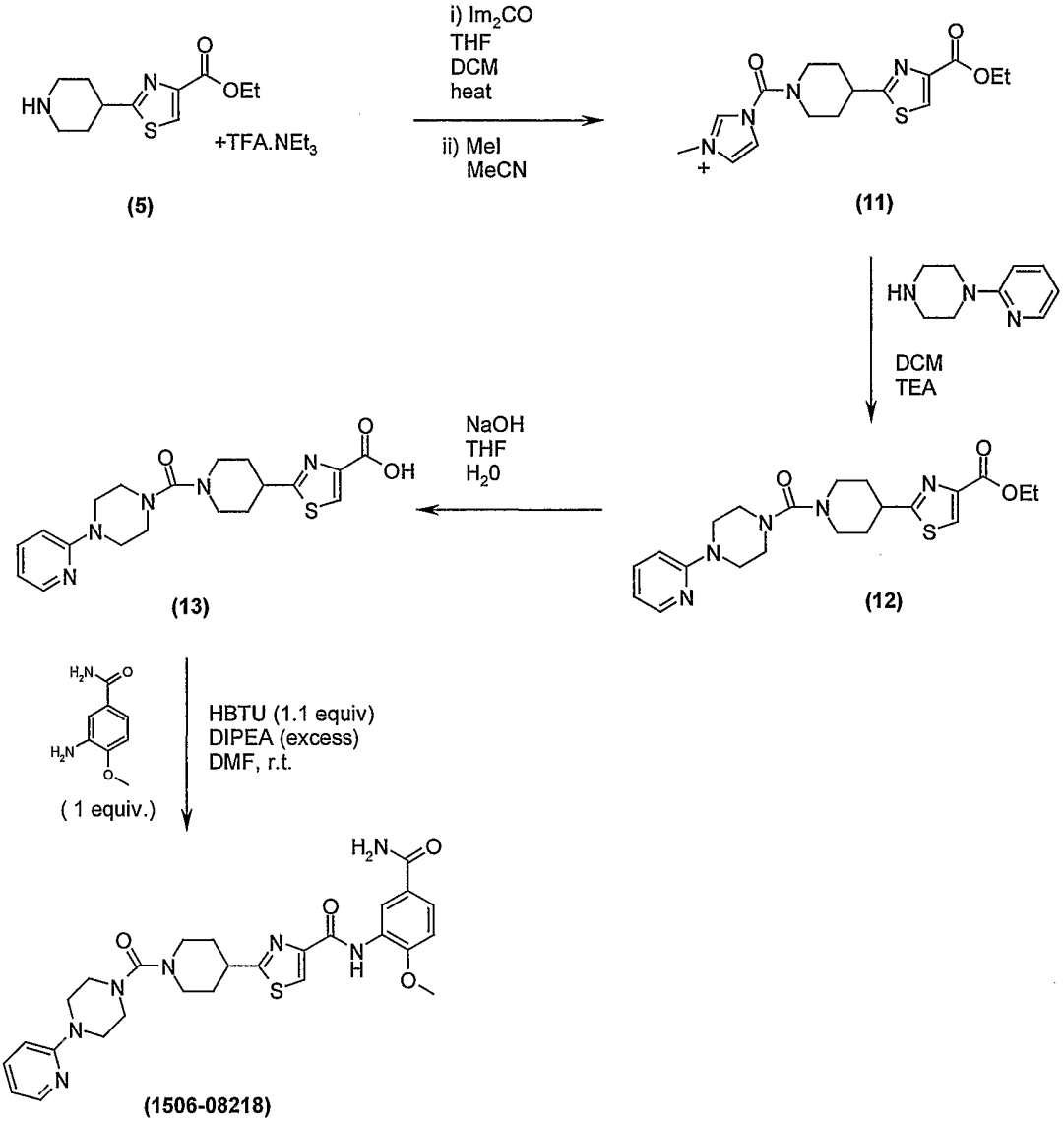
0.175 mmol, 1 equiv) and then to dispense the HBTU solution (0.3 mL, 0.19 mmol, 1.1 equiv). A further portion of DIPEA (0.05 mL) was added to the well, which was capped and shaken on an orbital shaker overnight. The reaction mixture was concentrated *in vacuo* (Genevac). The residue was dissolved in dichloromethane (1 mL) and given a sequence of aqueous washes using the MPII robot: 0.5 N HCl (0.7 mL), 10% potassium carbonate solution (0.7 mL) then water (0.7 mL). Finally the dichloromethane extract (0.7 mL) containing the product was concentrated and dried (Genevac) to constant mass to give *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-({[4-(dimethylamino)phenyl]amino}carbonothioyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide (DAD 75% (254nm), ES+ 539).

Example 8

Preparation of *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-(1-{[4-(2-pyridinyl)-1-piperazinyl]carbonyl}-4-piperidinyl)-1,3-thiazole-4-carboxamide

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-(1-{[4-(2-pyridinyl)-1-piperazinyl]carbonyl}-4-piperidinyl)-1,3-thiazole-4-carboxamide was prepared by the synthetic route set out in Reaction Scheme 4 below.

Reaction Scheme 4



3-[4-(4-Ethoxycarbonyl-thiazol-2-yl)-piperidine-1-carbonyl]-1-methyl-*3H*-imidazol-1-ium (11)

A solution of 2-piperdine-4-yl-thiazole-4-carboxylic acid ethyl ester **(5)** (14.7 mmol) in dichloromethane (15 mL) was added dropwise to a suspension of carbonyldiimidazole in tetrahydrofuran (15 mL). The mixture was heated at reflux overnight then cooled to room temperature. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (80 mL), washed with water and dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in acetontrile and methyl iodide added (59 mmol). The

mixture was stirred overnight and concentrated to give the title compound which was used without purification.

2-[1-(4-Pyridine-2-yl-piperazine-1-carbonyl)-piperidin-4-yl]-thiazole-4-carboxylic acid ethyl ester (12)

3-[4-(4-Ethoxycarbonyl-thiazol-2-yl)-piperidine-1-carbonyl]-1-methyl-*3H*-imidazol-1-ium **(11)** was taken up in dichloromethane (75 mL) and 1-(2-pyridyl)piperazine (14.7 mmol, 1 equiv.) and triethylamine (14.7 mmol, 1 equiv.) added. The mixture was stirred overnight and diluted with dichloromethane. The mixture was washed with water and brine, dried and concentrated *in vacuo* to yield the title compound which was used without purification.

2-[1-(4-Pyridine-2-yl-piperazine-1-carbonyl)-piperidin-4-yl]-thiazole-4-carboxylic acid ethyl ester (13)

The ethyl ester **(12)** was taken up in tetrahydrofuran (40 mL) / water (20 mL) and sodium hydroxide (29.4 mmol) in water (20 mL) added. The mixture was stirred for 2 h at room temperature. The mixture was then extracted with ether and the aqueous phase acidified with 10% citric acid solution. The aqueous phase was extracted with ethyl acetate and the combined extracts washed with brine, dried and concentrated *in vacuo*. Precipitated product remaining in the aqueous layer was filtered, dried and added to the residue. The title compound **(13)** was obtained as a colourless solid [total yield 59% (3 steps)].

***N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-(1-{[4-(2-pyridinyl)-1-piperazinyl]carbonyl}-4-piperidinyl)-1,3-thiazole-4-carboxamide**

2-[1-(4-Pyridine-2-yl-piperazine-1-carbonyl)-piperidin-4-yl]-thiazole-4-carboxylic acid ethyl ester **(13)** was dissolved in anhydrous DMF (0.58 M solution). 3-Amino-4-methoxybenzamide was dissolved in 10% DIPEA and anhydrous DMF (0.58 M solution). HBTU was dissolved in anhydrous DMF (0.64 M solution). The amine solution (0.3 ml, 0.175 mmol) was dispensed into an individual well in a 2.2 mL deep well plate using a Packard MPII robot. An Eppendorf multi-dispenser was used to dispense the acid solution (0.3 mL, 0.175 mmol, 1 equiv) and then to dispense the HBTU solution (0.3 mL, 0.19

mmol, 1.1 equiv). A further portion of DIPEA (0.05 mL) was added to the well, which was capped and shaken on an orbital shaker overnight. The reaction mixture was concentrated *in vacuo* (Genevac). The residue was dissolved in DCM (1 mL) and given a sequence of aqueous washes using the MPII robot: 0.5 N HCl (0.7 mL), 10% potassium carbonate solution (0.7 mL) then water (0.7 mL). Finally the DCM extract (0.7 mL) containing the product was concentrated and dried (Genevac) to constant mass to give *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-(1-{[4-(2-pyridinyl)-1-piperazinyl]carbonyl}-4-piperidinyl)-1,3-thiazole-4-carboxamide (DAD 100% (254nm), ES+ 550).

Immunohistochemical Evaluation

Example 9

Polyclonal antibodies specific for each prostaglandin receptor were used for determining the localization of each receptor on paraffin-embedded human endomyometrium at the proliferative and secretory stage of the cycle. Initially, titration experiments were conducted with each antibody to establish concentrations that would result in minimal background and maximum detection of signal.

For EP3 receptor staining, 1:100 and 1:250 dilution of a commercially available primary antibody (Cayman Chemical) was used. Antibody binding was detected by an anti-rabbit secondary antibody (Vector) and the Vector ABC-AP kit and Vector Red substrate kit. Development of a fuschia-coloured deposit indicated interaction of the antibody with the target molecule. Tissues were also stained with a positive control antibody (CD31) to ensure that the tissue antigens were preserved and accessible for immunohistochemical analysis. The negative control consisted of performing the entire immunohistochemical procedure on adjacent sections in the absence of primary antibody. Sections were imaged using a DVC 1310C digital camera coupled to a Nikon microscope. The tissues used for this study are listed below in Table 5;

Table 5

Sample	Tissue	Diagnosis	Age/Sex
1	Uterus, Endomyometrium, Proliferative	Normal	42 F
2	Uterus, Endomyometrium, Proliferative	Normal	31 F
3	Uterus, Endomyometrium, Proliferative	Normal	37 F
4	Uterus, Endomyometrium, Proliferative	Normal	36 F
5	Uterus, Endomyometrium, Proliferative	Normal	39 F
6	Uterus, Endomyometrium, Secretory – Day 25	Normal	F
7	Uterus, Endomyometrium, Secretory – Day 16	Normal	33 F
8	Uterus, Endomyometrium, Secretory – Day 27	Normal	27 F
9	Uterus, Endomyometrium, Secretory – Day26	Normal	29 F
10	Uterus, Endomyometrium, Secretory – Day 23	Normal	26 F

EP3 antibody stained positive endometrial glands, endothelium and vascular smooth muscle. Vascular smooth muscle of myometrial vessels as well as endometrial spiral arterioles stained positive in the proliferative and secretory samples and representative examples are shown in Figure 1.

For the glands, there was no appreciable difference in the level of staining in proliferative versus secretory glands, neither there was any difference in intensity of staining between glands in the functionalis layer when compared to the basalis layer. Endometrial stroma was mostly negative.

Focal positivity was present in uterine myometrial smooth muscle with staining more frequently intense in the inner aspect of the uterus near the endometrium when compared to the outer serosal aspect of the uterus.

A summary of these findings is presented in Table 6.

Table 6 – Summary of immunohistochemical findings

Receptor	Endothelium	Vascular smooth muscle	Myometrial smooth muscle	Endometrial glandular epithelium	Endometrial stroma
EP1	Positive in endometrial capillaries.	Focal faint positivity.	Focal faint positivity.	Negative.	Negative.
EP2	Negative.	Negative	Negative	Positive.	Mostly negative.
EP3	Positive.	Positive.	Focal positivity	Positive.	Negative.
EP4	Mostly negative. Rarely showed faint nuclear staining.	Mostly negative.	Mostly negative. Rarely showed faint nuclear staining.	Positive.	Faint nuclear staining.
IP	Focal faint staining.	Focal faint staining.	Focal faint staining	Positive.	Negative
TP	Strong positive staining of lymphatic channels. Negative or blush to faint staining on endothelium lining arteries and veins.	Negative or blush to faint staining.	Negative or blush to faint staining observed in myometrial stroma.	Positive.	Negative or blush to faint staining
DP	Negative.	Strongly positive.	Strongly positive.	Rare blush staining.	Negative.
FP	Faintly positive.	Faintly positive.	Faintly positive.	Faintly positive, blush staining.	Minimal blush staining.

Careful examination of the staining of vascular and smooth muscle indicates that EP3 receptor was highly expressed in myometrial as well as endometrial vascular smooth muscle but not in myometrial smooth muscle (Figure 1). Moreover, endometrial spiral arterioles stained strongly positive for EP3 (Figure 1). These findings suggested that EP3 is an excellent target for altering uterine myometrial and endometrial vascular tone without affecting contractility of the uterine muscle.

Activity Assays

Binding affinities of compounds of the invention were tested using the following assays. The results of the assays are set out in Table 7 below. For some compounds the assays were repeated to give the multiple results shown in the table.

Initially the compound was assayed for binding to EP3 receptor in a medium throughput competitive radioligand-binding assay detailed in Example 10. The cross-reactivity of the compounds against FP, TP, IP and EP2 was tested as described in Example 11.

Example 10 – EP3 receptor binding assays

EP3 receptor binding assays were performed using stable HEK293(EBNA) cell lines expressing human EP3(III) receptor. The stable cell line was prepared by transfecting HEK293(EBNA) cells with pCEP4-EP3(III) using Lipofectamine 2000 reagent (Invitrogen). Media containing hygromycin (selective media - DMEM, 10% heat inactivated FBS, 250 μg/ml G418 and 200 μg/ml hygromycin B) (GibcoBRL) were added to the transfected cells 24hr after transfection and the cells were left to grow in selective media for two weeks in a humidified incubator at 37 °C and 5% CO_2. Cells were then serially diluted and seeded in 96-well plates at a density of one cell per well, and isolated single cells were subsequently expanded into clonal cell lines under selection in complete medium. To harvest cells for use in receptor binding assays, the cells were lifted using trypsin-EDTA (GibcoBRL), centrifuged (1000 rpm for 2 min at room temperature), and the cell pellets suspended in binding buffer (10 mM MES/KOH, pH 6.0, 10 mM $MgCl_2$, 1 mM EDTA).

For the binding assay, test compounds at concentrations of 0.14 μM – 300 μM or EP3 receptor agonists (sulprostone, misoprostol free acid, PGE2 and iloprost) were added to suspensions of EP3-expressing cells (65,000 cells per well). The final DMSO concentration in the assay did not exceed 1%. All receptor-binding assays were performed in 96-well Millipore MultiScreen FB filtration plates in a final incubation volume of 0.2 ml in binding buffer.

The assay was initiated by addition of the radioligand, [^{3}H]-PGE_2 (186 Ci/mmol) at a final concentration of 1.5 nM. Total binding (TB) was determined in the absence of test compounds or ligands (i.e. 1% v/v DMSO only), whereas non-specific binding (NSB) was determined in the presence of 2 μM non-radioactive PGE_2. Incubations were conducted at room temperature with shaking for 20 hours, and terminated by filtration using a Millipore MultiScreen vacuum manifold. The plates were washed three times by adding and filtering through 200 μl per well of pre-chilled binding buffer. After drying for 2 hours at 50 °C, 50 μl of OptiPhase Supermix liquid scintillation cocktail (Wallac) were added per well and the residual radioactivity bound to each filter was measured by scintillation counting for 1 min using a MicroBeta Trilux counter (Wallac).

The % inhibition values were calculated from the equation

% Inhibition = 100-[(Sample cpm – NSB cpm)/(TB cpm – NSB cpm) x 100]

Sigmoidal one-site competition curves for each test compound and ligand were constructed by plotting % inhibition against log [concentration], and analysed using GraphPad Prism 3.0 software to determine the EC50 values.

For saturation analysis, EP3(III) receptor binding assays were performed as described above using [^{3}H]-PGE_2 at the concentration range of 0.01 nM – 10.0 nM. Total binding and non-specific binding were determined for each radioligand concentration tested. Specific binding values were calculated by subtracting NSB from TB, and plotted against radioligand concentration. The resulting hyperbola curve was analysed using GraphPad Prism 3.0 software to determine the maximum number of binding sites (Bmax) and the concentration of ligand required to reach half maximal binding (Kd).

The number of receptor molecules per cell of the EP3(III) cell line was determined by saturation analysis and was found to be high, Bmax value of 554,116 binding sites per cell. Moreover, the expressed human receptor bound [^{3}H]-PGE_2 with a Kd value of 0.52 nM, which is comparable to the value of 0.33 nM previously reported (Abramovitz et al., 2000 Biochimica et Biophysica Acta 1483 285-293).

Moreover, the pharmacological rank order of the recombinant human EP3(III) receptor was tested by competition binding assays in which the binding affinities of several readily available potent agonists for EP3(III) were tested. The following rank order of potency was obtained sulprostone ≥ PGE2 > misoprostol free acid > iloprost, in this study which is consistent with the rank order of potency reported in literature (Abramovitz et al., 2000 Biochimica et Biophysica Acta 1483 285-293).

Example 11 – Cross-reactivity binding studies

The selectivity of the compounds for EP3(III) receptor was evaluated by testing their cross-reactivity of these compounds against the contractile prostanoid receptors FP, TP and relaxant receptors IP and EP2. Cross-reactivity binding studies on FP, TP, IP and EP2 receptors were performed using transient transfections for FP, TP and IP and stable HEK293(EBNA) cell lines expressing human EP2 receptor for EP2. The stable EP2 cell line was prepared by transfecting HEK293(EBNA) cells with pCEP4-EP2 using Lipofectamine 2000 reagent (Invitrogen) and selecting stable clones in a similar manner to the stable EP3 receptor cell line described above.

The transient transfections for FP, TP and IP were performed as follows; pCEP4-FP, pCEP4-TP and pCEP4-IP plasmid DNA were separately transfected into 293-EBNA (HEK) cells using Lipofectamine 2000 reagent (Invitrogen) according to the manufacturer's instructions. The transfected cells were cultured without antibiotics in high glucose DMEM supplemented with 10% heat inactivated FBS at 37 °C and 5% CO2 in a humidified incubator for 48 hours. They were then harvested and suspended in 10 mM MES/KOH, pH 6.0, 10 mM $MnCl_2$, 1 mM EDTA for FP and TP and 10 mM HEPES/KOH, pH 7.4, 10 mM $MnCl_2$, 1 mM EDTA for IP.

Competition of test compounds and ligands for binding to 293-EBNA (HEK) cells expressing these prostanoid receptors were performed as described in Example 10 with the following adaptations: i) assays were conducted in the relevant binding buffers for each receptor; ii) 100,000 cells per well were used for each receptor; iii) PGE_2, PGD_2, $PGF_{2\alpha}$ and latanoprost free acid were used for characterization of the FP cell lines; SQ29548 and U46619 for TP; iloprost, PGE_1 and carbacyclin for IP and PGE_2, butaprost free acid, misoprostol free acid and BW245C for EP2; iv) the radioligand concentrations used were 1.5 nM of [^{3}H]-$PGF_{2\alpha}$ (212 Ci/mmol) for FP, 2.0 nM of [^{3}H]-SQ29548 (38 Ci/mmol) for TP, 5.0 nM of [^{3}H]-iloprost (11 Ci/mmol) for IP and 1.5 nM of [^{3}H]-PGE2 (185 Ci/mmol) for EP2; v) non-specific binding was determined in the presence of 2 μM of the corresponding non-radioactive ligand in all cases; vi) Incubations were conducted for 1 hour at room temperature with shaking; vii) washings were performed by using the relevant pre-chilled binding buffer for each receptor.

In order to characterise the HEK cell lines expressing the FP, TP, IP and EP2 receptors and to validate the competition binding assays, we have determined the EC50 values and potency profile of some well-known agonists and antagonists for each receptor.

The following rank order of potencies was obtained in this study, which is consistent with published literature.

For FP: $PGF_{2\alpha} \geq$ latanoprost free acid > PGD_2 > PGE_2 (Abramovitz et al., 1994 J. Biol. Chem. 269 No.4 2632-263)

For TP: SQ29548 > U46619 (Abramovitz et al., 2000 Biochimica et Biophysica Acta 1483 285-293)

For IP: Iloprost > carbacyclin > PGE_1 (Katsuyama et al., 1994 FEBS Letters 344 74-78)

For EP2: PGE_2 > butaprost free acid ≥ misoprostol free acid > BW245C (Abramovitz et al., 2000 Biochimica et Biophysica Acta 1483 285-293)

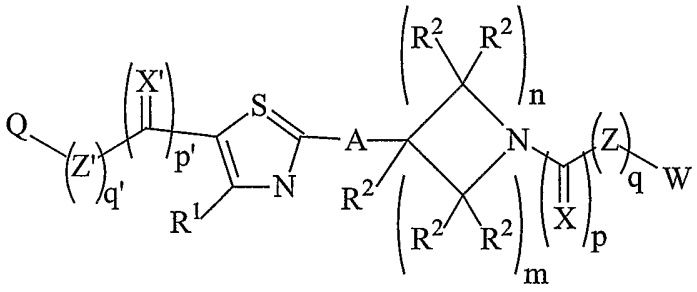
Table 7

Activities of compounds of the invention

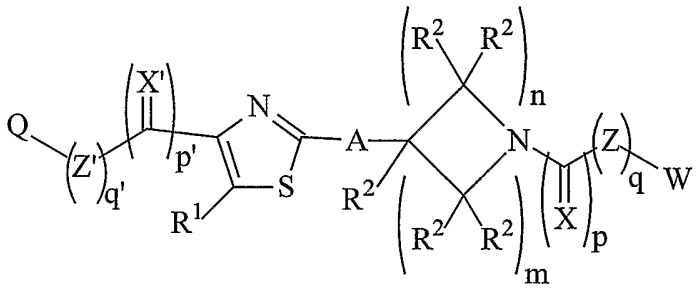
Compound RR-code	EP3 EC50 (uM)	FP EC50 (uM)	TP EC50 (uM)	IP EC50 (uM)	EP2 EC50 (uM)
1507-03555	5.7	Negative	Negative	Negative	Negative
	3.6	Negative	Negative	Negative	Negative
1507-02199	0.7	Negative	Negative	Negative	Negative
	1.8	Negative	Negative	Negative	Negative
1507-02705	17.6	6.7	2.6	Negative	not determined
	4.9				
1507-02567	9.4	1.8	3.5	6.2	not determined
	5.6				
1506-07479	2.9	Negative	Negative	Negative	28.3
	1.8	Negative	Negative	Negative	23.9
1506-01386	8.2	Negative	Negative	Negative	not determined
	12.6				

CLAIMS

1. A compound of formula (I) or formula (II):



(I)



(II)

wherein:

Q is an optionally substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, alkylthio, aralkylthio, amino, alkylamino, dialkylamino, carboxyl, carboxylalkyl, esterified carboxyl, alkylsulfoxyl, alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy, or heterocyclic group;

A is a single bond or alkylene;

X is O or S;

X' is O or S;

Z is O, S or NR^3;

Z' is O, S or NR^3;

p is 0 or 1;

p' is 0 or 1;

q is 0 or 1;

q' is 0 or 1;

n is an integer from 0 to 10;

m is an integer from 0 to 10;

W is an optionally substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, alkylthio, aralkylthio, amino, alkylamino, dialkylamino, carboxyl, carboxylalkyl, esterified carboxyl, alkylsulfoxyl, alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy, or heterocyclic group;

R^1 is H or alkyl;

R^2 is independently H or alkyl; and

R^3 is independently H or alkyl;

or a pharmaceutically acceptable derivative thereof.

2. The compound of claim 1 of formula (II).

3. The compound of claim 1 or claim 2 wherein A is a single bond.

4. The compound of any of claims 1 to 3 wherein X is O.

5. The compound of any of claims 1 to 3 wherein X is S and Z is NR^3.

6. The compound of any of claims 1 to 5 wherein X' is O.

7. The compound of any of claims 1 to 6 wherein Z' is NR^3.

8. The compound of any of claims 1 to 7 wherein R^3 is H.

9. The compound of any of claims 1 to 8 wherein p = 1.

10. The compound of any of claims 1 to 9 wherein q = 0.

11. The compound of any of claims 1 to 10 wherein p' = 0 and q' = 0.

12. The compound of any of claims 1 to 10 wherein p' = 1 and q' = 1.

13. The compound of any of claims 1 to 12 wherein the sum n + m is an integer from 2 to 10.

14. The compound of any of claims 1 to 13 wherein the sum n + m is 4.

15. The compound of any of claims 1 to 14 wherein n = 2 and m = 2.

16. The compound of any of claims 1 to 15 wherein R^1 is H.

17. The compound of any of claims 1 to 16 wherein R^2 is H.

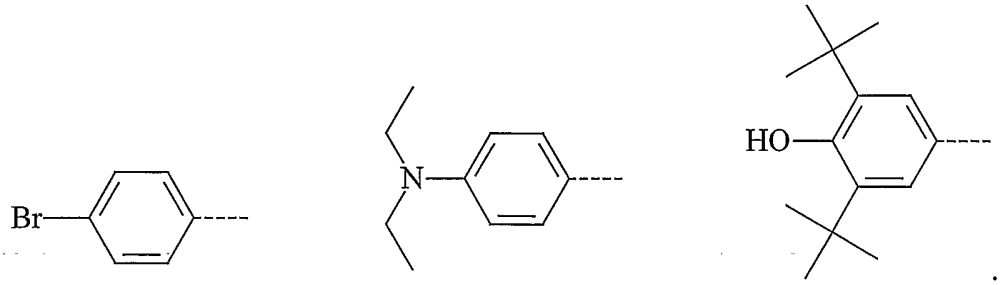
18. The compound of any of claims 1 to 17 wherein Q comprises an optionally substituted aryl or heterocyclic group.

19. The compound of any of claims 1 to 18 wherein Q is an optionally substituted aryl or heterocyclic group.

20. The compound of any of claims 1 to 18 wherein Q comprises an optionally substituted phenyl.

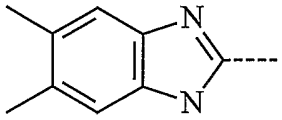
21. The compound of any of claims 1 to 20 wherein Q is an optionally substituted phenyl.

22. The compound of claim 21 wherein Q is a radical selected from:



23. The compound of any of claims 1 to 19 wherein Q is optionally substituted benzimidazolyl.

24. The compound of claim 23 wherein Q is:



25. The compound of any of claims 1 to 24 wherein W is an optionally substituted alkyl, alkenyl, alkynyl, aryl or heterocyclic group.

26. The compound of any of claims 1 to 25 wherein W comprises an optionally substituted aryl or heterocyclic group.

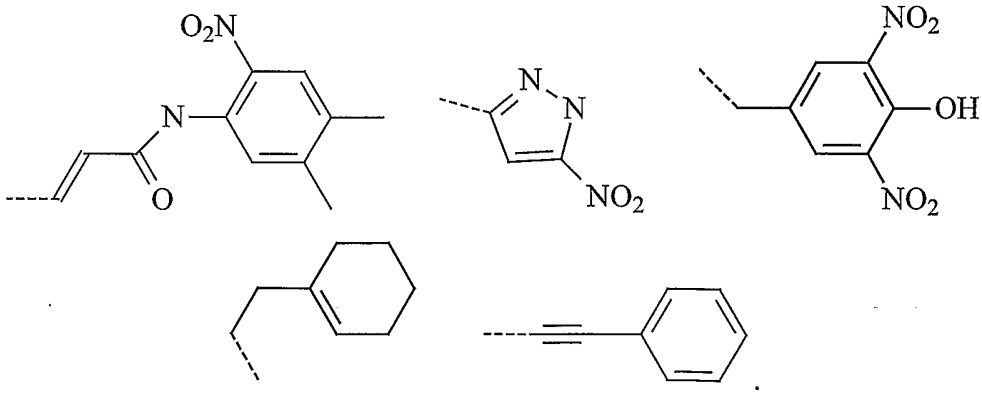
27. The compound of any of claims 1 to 26 wherein W is an optionally substituted aryl or heterocyclic group.

28. The compound of any of claims 1 to 26 wherein W comprises an optionally substituted phenyl.

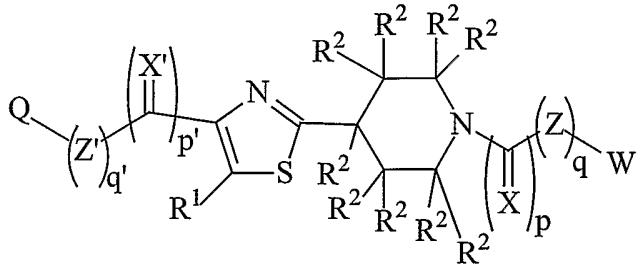
29. The compound of any of claims 1 to 28 wherein W is an optionally substituted phenyl.

30. The compound of any of claims 1 to 25 wherein W is an alkyl group substituted with an optionally substituted cycloalkyl or aryl group.

31. The compound of any of claims 1 to 25 wherein W is a radical selected from:

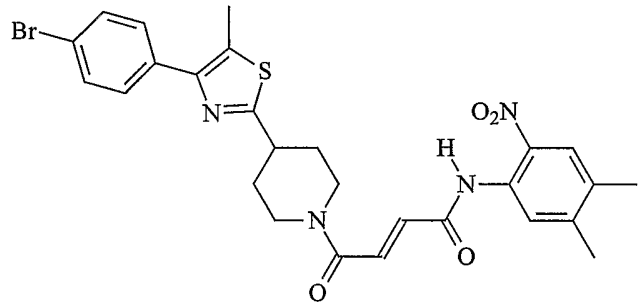


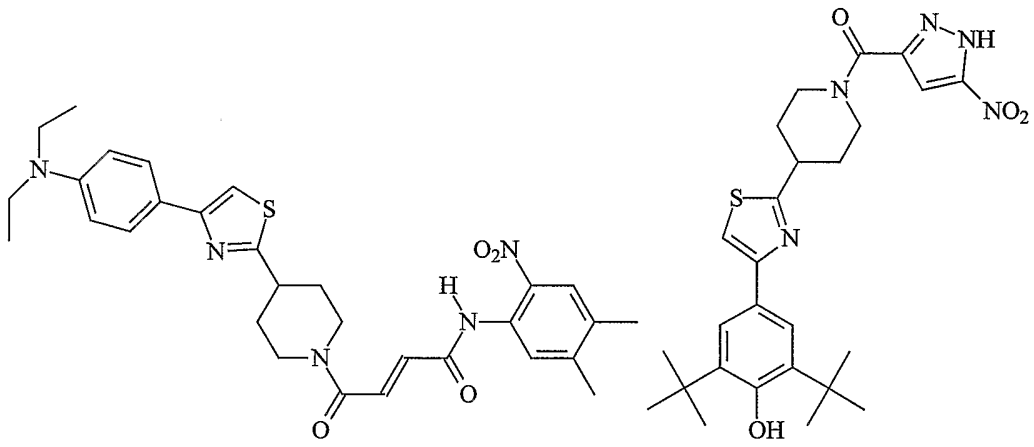
32. A compound of any of claims 1 to 31 having formula (III):

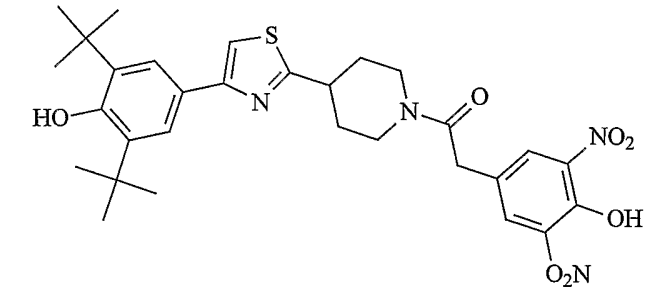


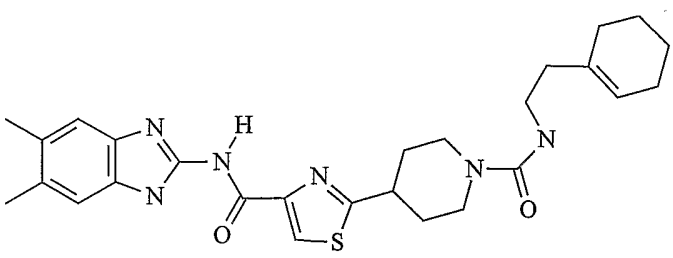
formula (III).

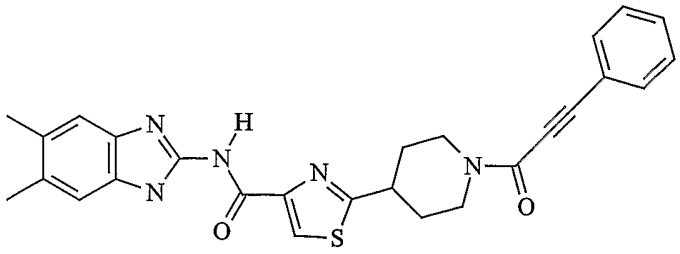
33. A compound of claim 1 selected from:











34. A method for the alteration of uterine vascular tone in a patient comprising administering to the patient a therapeutically-effective amount of a compound that binds specifically to the EP3 receptor.

35. The method of claim 34 wherein the compound is a compound of any of claims 1 to 33.

36. The use of a compound that binds specifically to the EP3 receptor for the manufacture of a medicament for altering uterine vascular tone.

37. The use of claim 36 wherein the compound is a compound of any of claims 1 to 33.

38. The compound of any of claims 1 to 33 for use in a method of treatment of disease.

39. The compound of any of claims 1 to 33 for use in therapy or diagnosis.

40. The use of a compound of any of claims 1 to 33 for the manufacture of a medicament for the treatment of a disease.

41. A method of treating a disease comprising administering to a patient in need of such treatment an effective dose of a compound of any of claims 1 to 33.

42. A pharmaceutical composition comprising a compound of any of claims 1 to 33 in combination with a pharmaceutically acceptable excipient.

FIG. 1A

Myometrial vessels - Proliferative

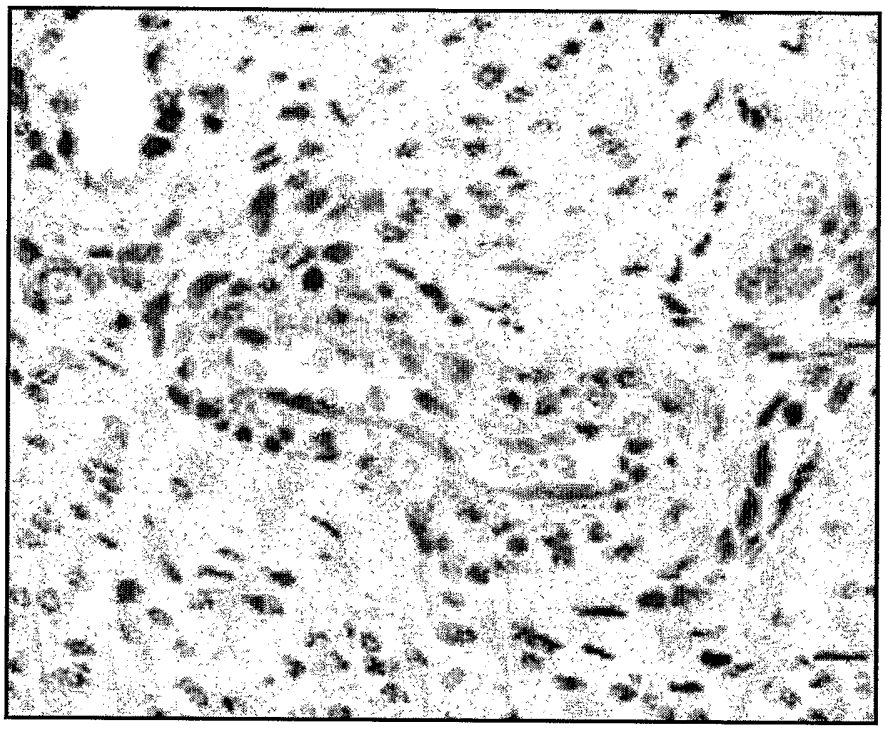


FIG. 1B

Endometrial vessels – Proliferative

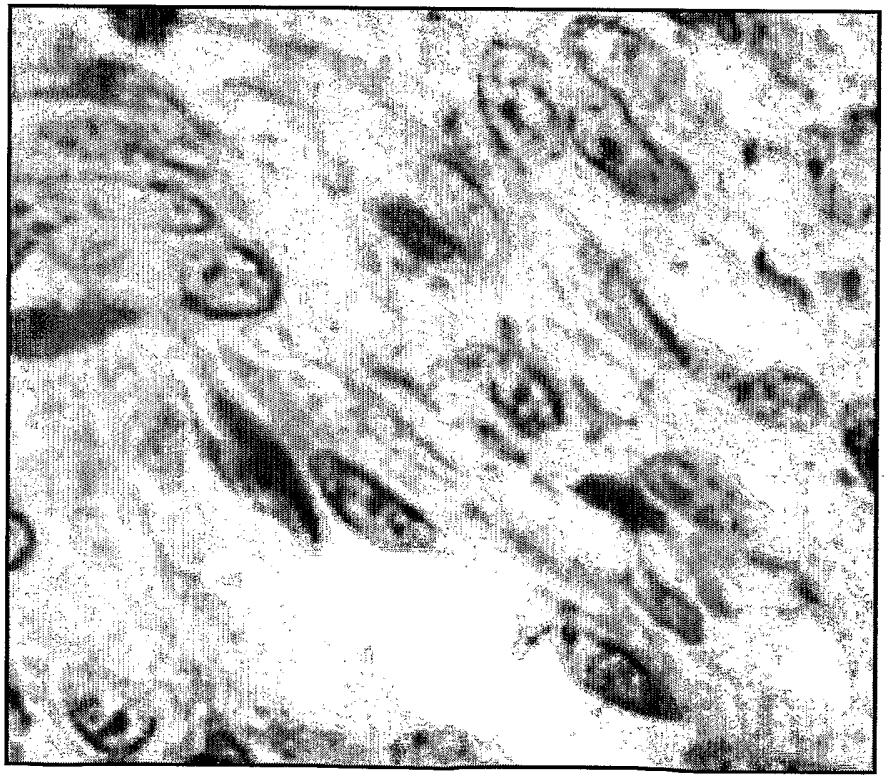


FIG. 1C

Myometrial vessels - Secretory Day 27

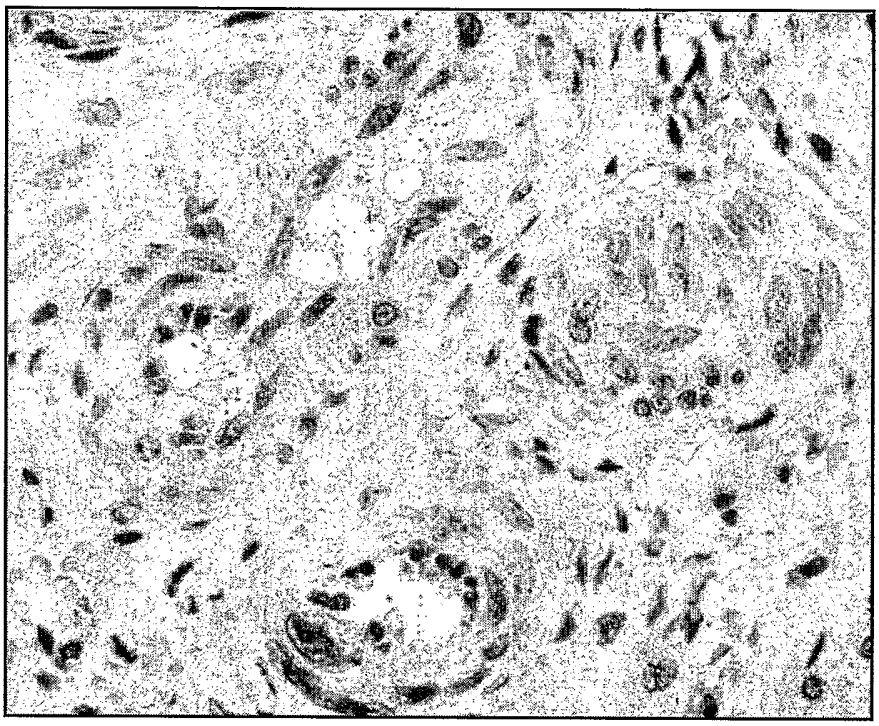
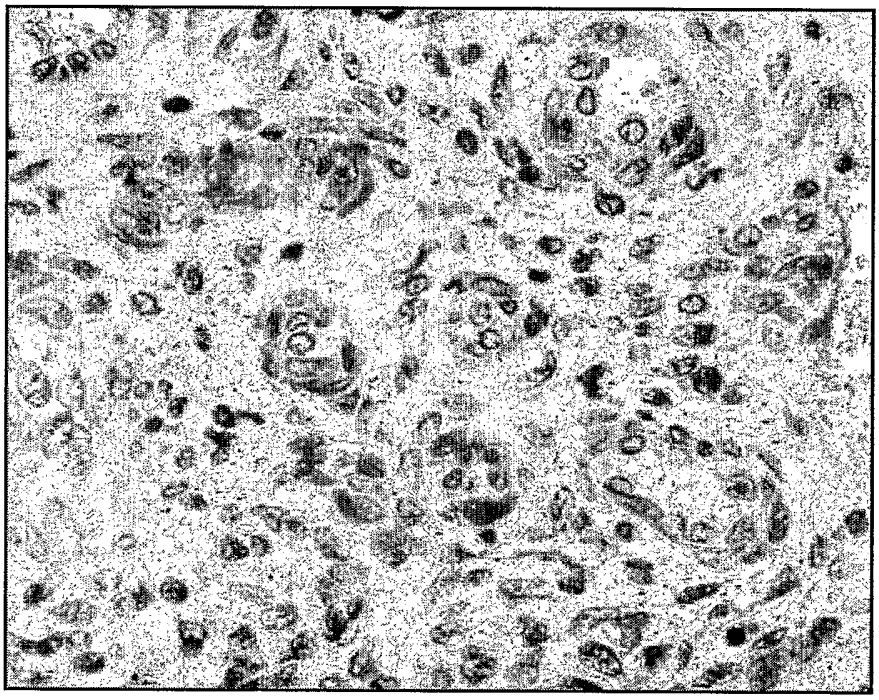


FIG. 1D

Endometrial arterioles – Secretory Day 27



INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/GB 03/05654

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/04 C07D417/14 A61K31/427 A61P35/00

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 7 C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 00356 A (GONG YONG ;KLEIN SCOTT I (US); PAULS HEINZ W (US); GUERTIN KEVIN R) 7 January 1999 (1999-01-07) claims; examples 275,290-293	1,40-42
A	WO 95 33050 A (SHARKEY ANDREW MARK ;SMITH STEPHEN KEVIN (GB); LYNXVALE LTD (GB);) 7 December 1995 (1995-12-07) claims	1,40-42
A	US 3 966 748 A (SAFIR SIDNEY ROBERT ET AL) 29 June 1976 (1976-06-29) claims; examples 4,7,12,16,21	1,40-42

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

☒ 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
22 March 2004	01/04/2004

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	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal application No.
PCT/GB 03/05654

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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 34-35, 38,41 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

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

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Internat pplication No
PCT/GB 03/05654

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9900356 A	07-01-1999	US 6080767 A	27-06-2000
		AP 1061 A	24-04-2002
		AU 741173 B2	22-11-2001
		AU 8177198 A	19-01-1999
		BG 103264 A	31-01-2000
		BR 9806060 A	31-08-1999
		CA 2264556 A1	07-01-1999
		CN 1236358 T	24-11-1999
		EA 2358 B1	25-04-2002
		EP 0931060 A1	28-07-1999
		HU 0202655 A2	28-11-2002
		JP 2001500532 T	16-01-2001
		NO 990854 A	23-04-1999
		PL 331985 A1	16-08-1999
		SK 22099 A3	09-10-2000
		WO 9900356 A1	07-01-1999
		US 6277865 B1	21-08-2001
		ZA 9805664 A	13-01-1999
WO 9533050 A	07-12-1995	AU 695393 B2	13-08-1998
		AU 2535495 A	21-12-1995
		CA 2191071 A1	07-12-1995
		CN 1159827 A	17-09-1997
		EP 0783571 A1	16-07-1997
		WO 9533050 A1	07-12-1995
		JP 10504183 T	28-04-1998
		NZ 285834 A	28-10-1998
		US 6011003 A	04-01-2000
US 3966748 A	29-06-1976	NONE	