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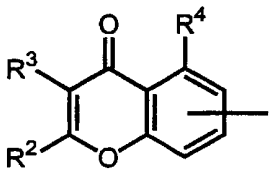
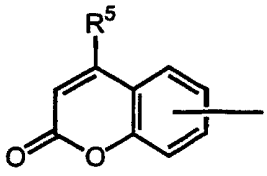
(54) Title: NOVEL DERIVATIVES OF FLAVONES, XANTHONES AND COUMARINS

$$Z\text{—}OCH_2\text{—}C{\equiv}CCH_2NRR^1$$

(I)



(IA)



(IB)

(57) Abstract: Disclosed are novel compounds having the Formula (I): Z-OCH_2-C≡CCH_2NRR^1 or a pharmaceutically acceptable salt or solvate thereof wherein Z can represent Formulae (IA) or (IB). The compounds possess antiproliferative activity, and are useful as modulators of multiple drug resistance in cancer chemotherapy. The compounds may also be useful for the manufacture of a medicament for the treatment or prevention of neoplams, menopausal disorders and osteoporosis.

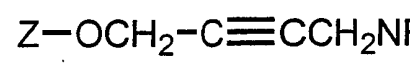
WO 01/17985 A1

NOVEL DERIVATIVES OF FLAVONES, XANTHONES AND COUMARINS

The development of multiple drug resistance represents an increasing problem in cancer treatment. Within the past decade several mechanisms of drug resistance of tumor cells have been identified. One type of multiple resistance (MDR) has been shown to be mediated by an energy dependent, membrane-bound efflux pump termed P-glycoprotein (PGP) (Biochem. Biophys. Acta, 455, 152, 1976). PGP represents a member of the ATP-binding cassette with low substrate specificity (Nature, 323, 448, 1986). A broad range of cytostatic drugs such as anthracyclines, epipodophyllotoxins, actinomycin D, vinca alkaloids, colchicines and taxol are eliminated via PGP-mediated efflux. Within the past few years a variety of substances have been shown to inhibit PGP-mediated drug efflux and thereby re-establish sensitivity toward chemotherapeutic agents (Pharmacol. Rev. 42, 155, 1990). These include ion channel blockers such as verapamil (Cancer Res 41, 1967, 1981), amiodarone (Cancer Res 46, 825, 1986), propafenone (Proc. Am. Assoc. Cancer Res. 34, 321, 1993), dihydropyridines (Cancer Res. 43, 2267, 1983) phenothiazines (Mol. Pharmacol 35, 105, 1989). Preliminary results obtained in clinical studies clearly demonstrate that modulation of MDR might be a successful approach in haematological malignancies, but serious side effects (cardiac effects, immuno-suppresion and nephrotoxicity) often preclude optimal dosage of modulators (Cancer 72, 3553, 1993). Therefore, specifically designed highly active modulators with limited side effects are urgently required.

The present invention relates to a novel class of compounds which have structures related to certain naturally occurring and synthetic flavonoids and to pharmaceutical uses thereof.

Thus according to one aspect of the present invention, there is provided a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof wherein:

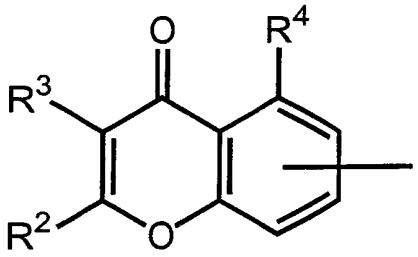
R and R^1 are the same or different and each represents

lower C_{1-6} alkyl, or a carbocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings wherein the or each ring contains 5 or 6 ring atoms, or

R and R^1 taken together with the nitrogen atom to which they are attached, form a four- to eight-membered heterocyclic ring which may contain one or more additional heteroatoms selected from N, O or S, said heterocyclic ring being optionally substituted with a lower C_{1-4} alkyl group or a benzyl group;

Z represents:

(A)



wherein

R^2 and R^3 are each independently selected from:

(i) hydrogen, (ii) a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

(a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} lower alkyl (in particular CH_3), (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8, are the same or different and each represents H or lower C_{1-4} alkyl, (k) OR^{10} wherein R^{10} represents H or lower C_{1-6} alkyl which may be saturated or unsaturated and being unsubstituted or substituted with the group NRR^1 wherein R and R^1 is as defined above, and (l) $OCOR^{11}$ wherein R^{11} represents H or lower C_{1-4} alkyl,

(iii) Cl, (iv) Br, (v) F, (vi) OH, (vii) NO_2, (viii) a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, (ix) $NHCOCH_3$, (x) $N(R^6)(R^8)$, (xi) SR^{10}, (xii) OR^{10}, and (xiii) $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined above;

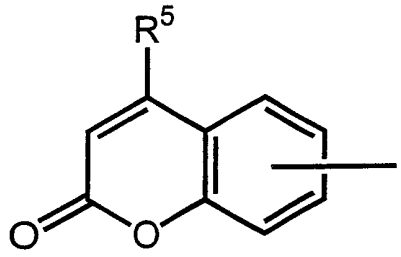
or

R_2 and R_3 taken together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic ring having 5 or 6 ring atoms, any heteroatom being selected from N, O or S, said carbocyclic or heterocyclic ring being saturated or unsaturated, and being unsubstituted or substituted with one or more substituents selected from Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl, SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined above; and

R^4 represents hydrogen, or OR^{10} wherein R^{10} is as defined above

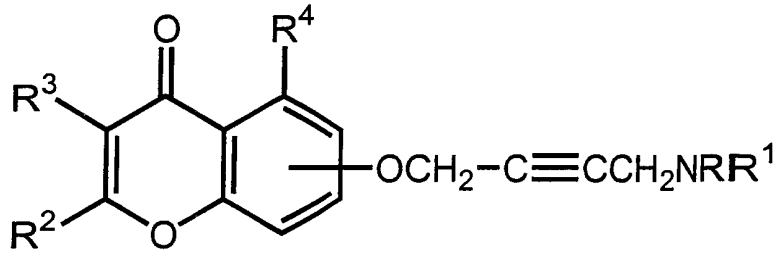
or

(B)



wherein R^5 represents hydrogen or a lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3.

Thus in one aspect the invention provides compounds having the structure (IA'):



(IA')

wherein

R^2 and R^3 are each independently selected from:

(i) hydrogen, (ii) a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are the same or different and each represents H or lower C_{1-4} alkyl,

(iii) Cl, (iv) Br, (v) F, (vi) OH, (vii) NO_2, (viii) a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, (ix) $NHCOCH_3$, (x) $N(R^6)(R^8)$, (xi) SR^{10}, (xii) OR^{10}, and (xiii) $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined above;

or

R_2 and R_3 taken together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic ring having 5 or 6 ring atoms, any heteroatom being selected from N, O or S, said carbocyclic or heterocyclic ring being saturated or unsaturated, and being unsubstituted or substituted with one or more substituents selected from Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl, SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined above; and

R^4 represents hydrogen, or OR^{10} wherein R^{10} is as defined above.

A preferred group of compounds are those wherein R, R^1 and R^4 are as defined for Formula (IA') above, and

R^2 and R^3 are each independently selected from:

(i) hydrogen, (ii) a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

(a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} lower alkyl (in particular CH_3), (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8, are the same or different and each represents H or lower C_{1-4} alkyl, (k) OR^{10} wherein R^{10} represents H or lower C_{1-6} alkyl which may be saturated or unsaturated and being unsubstituted or substituted with the group NRR^1 wherein R and R^1 is as defined above, and (l) $OCOR^{11}$ wherein R^{11} represents H or lower C_{1-4} alkyl,

(iii) Cl, (iv) Br, (v) F, (vi) OH, (vii) NO_2, (viii) a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, (ix) $NHCOCH_3$, (x) $N(R^6)(R^8)$, (xi) SR^{10}, (xii) OR^{10}, and (xiii) $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined for Formula (I).

Within this group, R^2 and R^3 can both represent hydrogen. A further preferred group of compounds are those wherein one of R^1 or R^2 is hydrogen, and the other is selected from the group consisting of: (i) a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are the same or different and each represents H or lower C_{1-4} alkyl,

(ii) Cl, (iii) Br, (iv) F, (v) OH, (vi) NO_2, (vii) a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by

1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, (viii) $NHCOCH_3$, (ix) $N(R^6)(R^8)$, (x) SR^{10}, (xi) OR^{10}, and (xii) $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined for Formula (I).

Within this preferred group of compounds, a further preferred group of compounds are those wherein R^2 hydrogen and R^3 is selected from the group consisting of: (i) a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are the same or different and each represents H or lower C_{1-4} alkyl,

(ii) Cl, (iii) Br, (iv) F, (v) OH, (vi) NO_2, (vii) a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, (viii) $NHCOCH_3$, (ix) $N(R^6)(R^8)$, (x) SR^{10}, (xi) OR^{10}, and (xii) $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined for Formula (I).

A further preferred group of compounds are those wherein R^3 is hydrogen and R^2 is selected from the group consisting of: (i) a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are the same or different and each represents H or lower C_{1-4} alkyl,

(ii) Cl, (iii) Br, (iv) F, (v) OH, (vi) NO_2, (vii) a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, (viii) $NHCOCH_3$, (ix) $N(R^6)(R^8)$, (x) SR^{10}, (xi) OR^{10}, and (xii) $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined for Formula (I).

A further preferred embodiment of the present invention are compounds wherein R^2 represents a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of: Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined as for Formula (I). For these compounds, R^3 is preferably selected from the group consisting of H, Cl, Br, F, OH, NO_2, a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from

Cl, Br, F, OMe, NO_2 and CF_3,

$NHCOCH_3$, $N(R^6)(R^8)$, SR^{10}, OR^{10}, and $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined for Formula (I).

Alternatively compound R^3 may represent a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined for Formula (I).

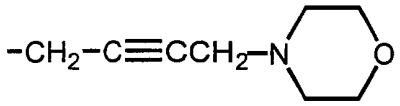
For these compounds, R^2 is preferably selected from the group consisting of H, Cl, Br, F, OH, NO_2, a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from

Cl, Br, F, OMe, NO_2 and CF_3,

$NHCOCH_3$, $N(R^6)(R^8)$, SR^{10}, OR^{10}, and $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined for Formula (I).

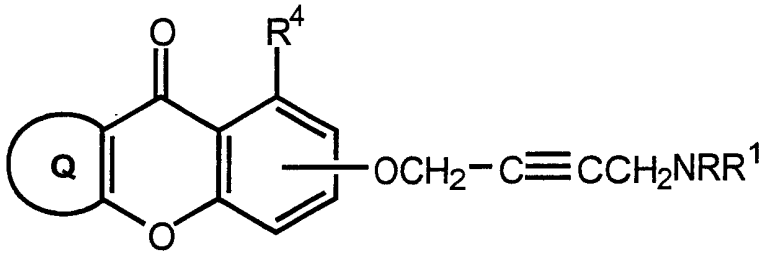
Where R^2 and/or R^3 represents a substituted carbocyclic or heterocyclic group, the substituents on the carbocyclic or heterocyclic group are preferably selected from OH or OR^{10} wherein R^{10} is as defined for Formula (I).

A particularly preferred carbocyclic group is phenyl or phenyl substituted with 1 to 3 OH or OR^{10} groups. For these compounds, R^{10} preferably represents methyl or



Also preferred are compounds wherein one of R^2 or R^3 represents H or a lower C_{1-6} straight or branched hydrocarbyl group, with methyl being especially preferred.

The invention also provides a compound of Formula (I) having the structure (IA"):



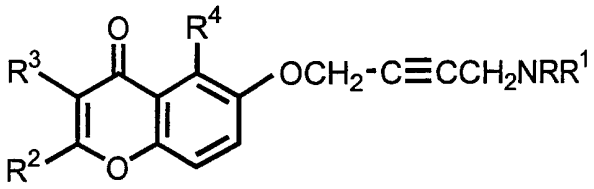
(IA")

wherein R, R^1 and R^4 are as defined as for Formula (I), and R^2 and R^3 taken together represent Ring Q, said Ring Q being a carbocyclic or heterocyclic ring having 5 or 6 ring atoms, any heteroatom being selected from N, O or S, said carbocyclic or heterocyclic ring being saturated or unsaturated and being unsubstituted or substituted with one or more substituents selected from Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl, SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined as for Formula (I).

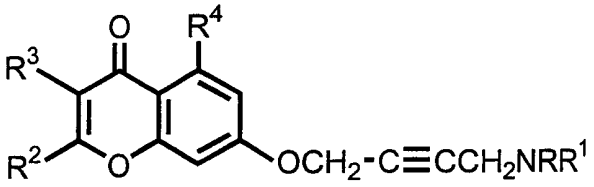
For these compounds Ring Q preferably represents a carbocyclic or heterocyclic aromatic ring, any heteroatom being selected from N, O or S, said ring being unsubstituted or substituted with one or more substituents selected from Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl, SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$,

wherein R^6, R^8, R^{10} and R^{11} are as defined as in Formula (I). Particularly preferred are those compounds wherein Ring Q represents a benzene or pyridine ring.

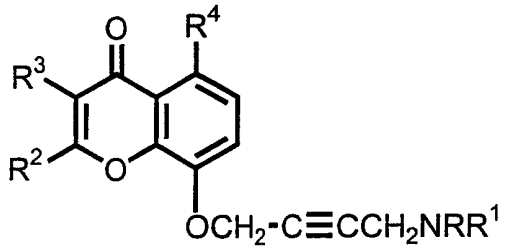
The substituent Z may be attached to any position in the aromatic ring. Thus the compounds of Formula (IA') or (IA") described above include compounds having the structures (IA)x, (IA)y and (IA)z:



(IA)x ,



(IA)y , and

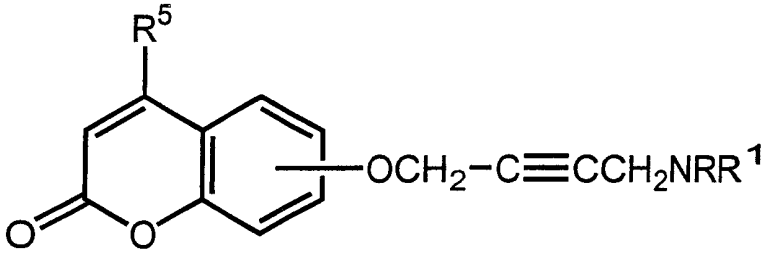


(IA)z .

wherein R, R^1, R^2, R^3 and R^4 are as defined above.

For the compounds of Formula (IA') or (IA") described above, R^4 preferably represents H, OH or OCH_3.

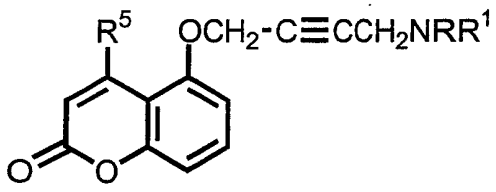
The invention further provides compounds of Formula (I) having the structure (IB):



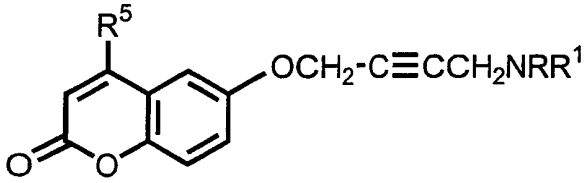
(IB)

wherein R and R^1 are as defined for Formula (I) and R^5 represents H or a lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3. In a preferred embodiment, R^5 represents H or methyl.

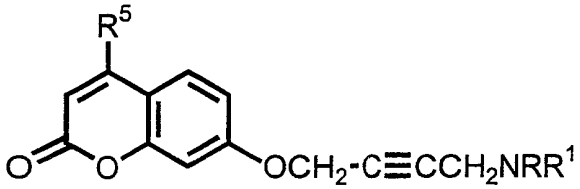
For the compounds of Formula (IB) described above, the substituent Z may be attached to any position in the aromatic ring. Thus the compounds of Formula (IB) described above include compounds having the structures (IB)w, (IB)x, (IB)y and (IB)z:



(IB)w ,

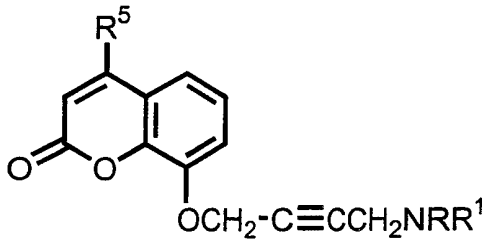


(IB)x ,



(IB)y , and

44



(IB)z .

wherein R, R^1 and R^5 are as defined for Formula (I).

For the compounds of Formulae (I), (IA'), (IA") or (IB), the substituent R and R^1 are the same or different and preferably each represents a C_{1-4} alkyl group or a C_{5-8} cycloalkyl group. Within this group of compounds, R and R^1 are preferably independently selected from methyl, ethyl, propyl, cyclopropyl or a cyclohexyl group.

In a preferred group of compounds, the R and R^1 groups taken together with the nitrogen atom to which they are attached, form a four- to eight-membered heterocyclic ring. Of these, it is preferred that R and R^1 taken together with the nitrogen atom to which they are attached, form a pyrrolidine, piperidine, piperazine, N-methylpiperazine, N-benzylpiperazine or a morpholine group.

It will be appreciated that the compounds of Formula (I) contain a basic amino function and thus may be converted to acid addition salts, with pharmacologically acceptable acids, e.g. hydrochloric acid and phosphoric acid. Such salts are also included in the present invention.

The compounds of Formula (I) may be conveniently prepared by a process comprising the steps of:

(i) reacting a hydroxy derivative, Z-OH, with propargyl bromide to form an alkyne, $Z\text{-}OCH_2C{\equiv}H$; and

(ii) reacting the alkyne $Z\text{-}OCH_2C{\equiv}H$ with an amine $HNRR^1$. Such a process forms a further aspect of the present invention.

The invention further provides a compound of Formula (I) as defined above for use as a modulator of multiple drug resistance in cancer chemotherapy or an

antiproliferative medicament. In particular, the compounds of Formula (I) are especially useful for the modulation of multiple drug resistance mediated by P-glycoprotein.

The compounds of Formula (I) as defined above may also be useful for the manufacture of a medicament for the treatment or prevention of neoplasms, particularly those located in the uterus, ovary or breast. Further the compounds Formula (I) may be especially useful for the manufacture of a medicament for the treatment of paclitaxel- and docetaxel-resistant cancer cells.

The compounds of Formula (I) may also advantageously be used as an antiproliferative medicament in combination therapies involving the combined use of a compound of Formula (I) with one or more anti-neoplastic or cytostatic agents, such as paclitaxel or docetaxel. The combination therapy may involve simultaneous or successive administration of a compound of Formula (I) with one or more antineoplastic or cytostatic agents, including anthracyclines, epipodophyllotoxins, actinomycin D, vinca alkaloids, colchicines, paclitaxel or docetaxel. Such combination therapy forms a further aspect of the invention.

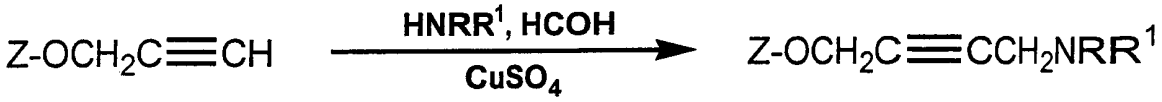
The compounds of the invention may also be useful in the manufacture of a medicament for the treatment or prevention of menopausal disorders and osteoporosis.

The invention further provides a pharmaceutical composition comprising one of more of the compounds of Formula (I) in combination with one or more pharmaceutically acceptable excipients. Such a composition may also comprise one or more antineoplastic or cytostatic agents, such as paclitaxel or docetaxel.

The invention will now be described by way of illustrative examples and with reference to the accompanying formulae drawings.

EXAMPLES

Example 1. General conditions to obtain the propynyloxy derivatives



(I)

A mixture of hydroxy derivative (0.01 mol), K_2CO_3 (0.02 mol), KI (0.01 mol), propargyl bromide (0.015 mol) and acetone (100 mL) was refluxed 10 h and hot filtered. The solvent was evaporated and the residue was crystallized with a suitable solvent.

Example 2. Preparation of 7-propynyloxy-4'-methoxyisoflavone

A mixture of 7-hydroxy-4'-methoxyisoflavone (2.68 g, 0.01 mol), K_2CO_3 (2.8 g, 0.02 mol), KI (0.166 g, 0.001 mol), propargyl bromide (1.78 g, 0.015 mol) and acetone (100 mL) was refluxed 10 h and hot filtered. The solvent was evaporated and the residue was crystallized by toluene. This yields 2.75 g of a product with the following characteristics: m.p.145-146°C; ^{1}H NMR ($CDCl_3$) δ: 2.6 (m, 1H), 3.83 (s, 3H), 4.8 (s, 2H), 6.93-8.27 (m, 8H).

Example 3. Preparation of 7-propynyloxyisoflavone

A mixture of 7-hydroxyisoflavone (2.38 g, 0.01 mol), K_2CO_3 (2.8 g, 0.02 mol), KI (0.166 g, 0.001 mol), propargyl bromide (1.78 g, 0.015 mol) and acetone (100 mL was refluxed 10 h and hot filtered. The solvent was evaporated and the residue was crystallized by toluene. This yields 2.1 g of a product with the following characteristics: m.p. 130-131°C; ^{1}H NMR ($CDCl_3$) δ: 2.6 (m, 1H), 4.8 (s, 2H), 6.99-8.28 (m, 7H).

Example 4. Preparation of 7-propynyloxy-2-methyl-4'-methoxyisoflavone

A mixture of 7-hydroxy-2-methyl-4'-methoxyisoflavone (2.82 g, 0.01 mol), K_2CO_3 (2.8 g, 0.02 mol), KI (0.166 g, 0.001 mol), propargyl bromide (1.78 g, 0.015 mol) and acetone (100 mL) was refluxed 10 h and hot filtered. The solvent was evaporated and the residue was crystallized by toluene. This yields 2.24 g of a product with the

following characteristics: m.p. 139-140°C; ^{1}H NMR ($CDCl_3$) δ: 2.29 (s, 3H), 2.6 (m, 1H), 3.85 (s, 3H), 4.75 (s, 2H), 6.93-8.17 (m, 7H).

Example 5. Preparation of 7-propynyloxy-5-hydroxy-4'-methoxyisoflavone

A mixture of 5,7-dihydroxy-4'-methoxyisoflavone (2.84 g, 0.01 mol), K_2CO_3 (2.8 g, 0.02 mol), KI (0.166 g, 0.001 mol), propargyl bromide (1.78 g, 0.015 mol) and acetone (100 mL) was refluxed 10 h and hot filtered. The solvent was evaporated and the residue was crystallized by toluene. This yields 2.25 g of a product with the following characteristics: m.p. 174-176°C; ^{1}H NMR ($CDCl_3$) δ: 2.6 (m, 1H), 3.86 (s, 3H), 4.8 (s, 2H), 6.47-7.91 (m, 7H), 12.90 (s, 1H).

Example 6. Preparation of 7,4'-dipropynyloxyisoflavone

A mixture of 5,7-dihydroxy-4'-methoxyisoflavone (2.54 g, 0.01 mol), K_2CO_3 (2.8 g, 0.02 mol), KI (0.166 g, 0.001 mol), propargyl bromide (1.72 g, 0.015 mol) and acetone (100 mL) was refluxed 10 h and hot filtered. The solvent was evaporated and the residue was crystallized by toluene. This yields 2.31 g of a product with the following characteristics: m.p. 162-163°C; ^{1}H NMR ($CDCl_3$) δ: 2.44 (m, 1H, CH), 2.57 (m, 1H), 4.54 (s, 2H), 4.56 (s, 2H), 6.85-8.08 (m, 8H).

Example 7. Preparation of 1-propynyloxyxanthen-9-one

A mixture of 3-hydroxyxanthen-9-one (2.12 g, 0.01 mol), K_2CO_3 (2.8 g, 0.02 mol), KI (0.166 g, 0.001 mol), propargyl bromide (1.78 g, 0.015 mol) and acetone (100 mL) was refluxed 10 h and hot filtered. The solvent was evaporated and the residue was crystallized by toluene. This yields 2.0 g of a product with the following characteristics: m.p. 168-169°C; ^{1}H NMR ($CDCl_3$) δ: 2.56 (m, 1H), 4.94 (s, 2H), 6.95-8.33 (m, 7H).

Example 8. Preparation of 2-propynyloxyxanthen-9-one

A mixture of 2-hydroxyxanthen-9-one (2.12 g, 0.01 mol), K_2CO_3 (2.8 g, 0.02 mol), KI (0.166 g, 0.001 mol), propargyl bromide (1.78 g, 0.015 mol) and acetone (100 mL) was refluxed 10 h and hot filtered. The solvent was evaporated and the residue was crystallized by toluene. This yields 2.25 g of a product with the following

characteristics: m.p.153-154°C; ^{1}H NMR ($CDCl_3$) δ: 2.58 (m, 1H), 4.8 (s, 2H), 7.35-8.38 (m, 7H).

Example 9. Preparation of 3-propynyloxyxanthen-9-one

A mixture of 3-hydroxyxanthen-9-one (2.12 g, 0.01 mol), K_2CO_3 (2.8 g, 0.02 mol), KI (0.166 g, 0.001 mol), propargyl bromide (1.78 g, 0.015 mol) and acetone (100 mL) was refluxed 10 h and hot filtered. The solvent was evaporated and the residue was crystallized by toluene. This yields 2.25 g of a product with the following characteristics: m.p.142-144°C; ^{1}H NMR ($CDCl_3$) δ: 2.61 (m, 1H), 4.84 (s, 2H), 6.98-8.38 (m, 7H).

Example 10. Preparation of 7-propynyloxyflavone

A mixture of 7-hydroxyflavone (2.38 g, 0.01 mol), K_2CO_3 (2.8 g, 0.02 mol), KI (0.166 g, 0.001 mol), propargyl bromide (1.78 g, 0.015 mol) and acetone (100 mL) was refluxed 10 h and hot filtered. The solvent was evaporated and the residue was crystallized by toluene. This yields 2.58 g of a product with the following characteristics: m.p. 199-200°C; ^{1}H NMR ($CDC1_3$) δ: 2.6 (m, 1H), 4.8 (s, 2H), 6.75-8.18 (m, 9H).

Example 11. Preparation of 7-propynyloxy-3-methylflavone

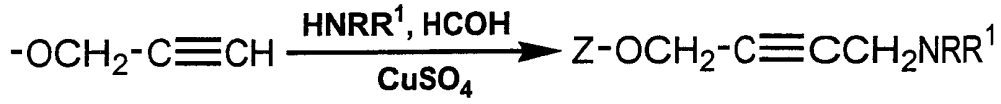
A mixture of 7-hydroxy-3-methylflavone (2.52 g, 0.01 mol), K_2CO_3 (2.8 g, 0.02 mol), KI (0.166 g, 0.001 mol), propargyl bromide (1.78 g, 0.015 mol) and acetone (100 mL) was refluxed 10 h and hot filtered. The solvent was evaporated and the residue was crystallized by toluene. This yields 2.32 g of a product with the following characteristics: m.p. 179-180°C; ^{1}H NMR ($CDCl_3$) δ: 2.15 (s, 3H), 2.69 (m, 1H), 4.8 (s, 2H), 6.95-8.25 (m, 8H).

Example 12. Preparation of 7-propynyloxy-4-methylcoumarin

A mixture of 7-hydroxy-4-methylcoumarin (1.76 g, 0.01 mol), K_2CO_3 (2.8 g, 0.02 mol), KI (0.166 g, 0.001 mol), propargyl bromide (1.78 g, 0.015 mol) and acetone (100 mL) was refluxed 10 h and hot filtered. The solvent was evaporated and the residue was crystallized by toluene. This yields 1.93 g of a product with the following

characteristics: m.p.140-141°C; ^{1}H NMR ($CDCl_3$) δ: 2.4 (s), 2.69 (m), 4.8 (s, 2H), 6.15-7.58 (m, 4H).

Example 13. General conditions to obtain the aminopropynyloxy derivatives



(I)

A solution of formaldehyde (0.5 ml), selected amine (6 mmol) and $CuSO_4$ (0.1 g) in EtOH/H_2O (20 mL) was added to a solution of propynyloxy derivative (4.6 mmol) in EtOH/H_2O (20 mL). H_2SO_4 was added until pH 8 and the mixture was refluxed 24 h. NH_3 (30 mL) was added and the mixture was extracted with ether. After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by suitable solvent.

Example 14. 7-(4-Piperidinobut-2-yn)-oxy-4'-methoxyisoflavone (see accompanying formula drawing VIB 15)

A solution of formaldehyde (1 ml), piperidine (0.85 g, 0.01 mol) and $CuSO_4$ (0.2 g) in EtOH/H_2O (40 mL) was added to a solution of propynyloxy derivative (3.08 g, 0.01 mol) in EtOH/H_2O (40mL). H_2SO_4 was added until pH 8 and the mixture was refluxed 24 h. NH_3 (60 mL) was added and the mixture was extracted with ether. After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by ligroin. This yields 1.63 g of a product with the following characteristics: m.p. 95-97°C; ^{1}H NMR δ: 1.73-1.98 (m, 2H), 1.52-1.68, (q, 4H), 2.4-2.55 (t, 4H), 3.3 (s, 2H), 3.85 (s, 3H), 4.85 (s, 2H), 6.9-8.25 (m, 8H).

Example 15. 7-(4-Morpholinobut-2-yn)-oxy-4'-methoxyisoflavone (see accompanying formula drawing VIB 17)

A solution of formaldehyde (1 ml), morpholine (0.87 g, 0.01 mol) and $CuSO_4$ (0.2 g) in EtOH/H_2O (40 mL) was added to a solution of propynyloxy derivative (3.08 g, 0.01 mol) in EtOH/H_2O (40 mL). H_2SO_4 was added until pH 8 and the mixture was refluxed 24 h. NH_3 (60 mL) was added and the mixture was extracted with ether.

After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by ligroin. This yields 1.62 g of a product with the following characteristics: m.p. 98-100°C; ^{1}H NMR δ: 2.43-2.61 (m, 4H), 3.3 (s, 2H), 3.6-3.78 (m, 4H), 3.78 (s, 3H), 4.75 (s, 2H), 6.9-8.3 (m, 8H).

Example 16. 7-[4-(4-Benzyl-piperazin-1-yl)-but-2-yn]-oxy-4'-methoxyisoflavone (see accompanying formula drawing VIB 16)

A solution of formaldehyde (1 ml), benzylpiperazine (1.76 g, 0.01 mol) and $CuSO_4$ (0.2 g) in EtOH/$H_2$0 (40 ml) was added to a solution of propynyloxy derivative (3.08 g, 0.01 mol) in EtOH/H_2O (40 mL). H_2SO_4 was added until pH 8 and the mixture was refluxed 24 h. NH_3 (60 mL) was added and the mixture was extracted with ether. After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by ligroin. This yields 1.1 g of a product with the following characteristics: m.p. 98-100°C; ^{1}H NMR δ: 2.45-2.65 (m, 8H), 3.35 (s, 2H), 3.52 (s, 2H), 3.85 (s, 3H), 4.85 (s, 2H), 6.95-8.27 (m, 13 H).

Example 17. 7-(4-Pyrrolidinobut-2-yn)-oxy-4'-methoxyisoflavone (see accompanying formula drawing VIB 91)

A solution of formaldehyde (1 ml), pyrrolidine (0.71 g, 0.01 mol) and $CuSO_4$ (0.2 g) in EtOH/$H_2$0 (40 mL) was added to a solution of propynyloxy derivative (3.08 g, 0.01 mol) in EtOH/H_2O (40 mL). H_2SO_4 was added until pH 8 and the mixture was refluxed 24 h. NH_3 (60 mL) was added and the mixture was extracted with ether. After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by ligroin. This yields 0.8 g of a product with the following characteristics: m.p. 111-112°C; ^{1}H NMR δ: 1.68-1.83 (m, 4H), 2.6-2.65 (m, 4H), 3.5 (m, 2H), 3.85 (s, 3H), 4.83 (m, 2H), 6.96-8.26 (m, 8H).

Example 18. 7-(4-Diethylaminobut-2-yn)-oxy-4'-methoxyisoflavone (see accompanying formula drawing VIB 90)

A solution of formaldehyde (1 ml), diethylamine (0.73 g, 0.01 mol) and $CuSO_4$ (0.2 g) in EtOH/H_2O (40 mL) was added to a solution of propynyloxy derivative (3.08 g, 0.01 mol) in EtOH/$H_2$0 (40 mL). H_2SO_4 was added until pH 8 and the mixture was refluxed

24 h. NH_3 (60 mL) was added and the mixture was extracted with ether. After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by ligroin. This yields 1.2 g of a product with the following characteristics: m.p. 73-75°C; ^{1}H NMR δ: 1 (t, 6H), 2.5 (q, 4H), 3.49 (s, 2H), 3.85 (s, 3H), 4.85 (s, 2H), 6.95-8.28 (m, 8H)

Example 19. 7-(4-Diethylaminobut-2-yn)-oxyisoflavone (see accompanying formula drawing VIB 92)

A solution of formaldehyde (1 ml), diethylamine (0.73 g, 0.01 mol) and $CuSO_4$ (0.2 g) in EtOH/H_2O (40 mL) was added to a solution of propynyloxy derivative (2.94 g, 0.01 mol) in EtOH/$H_2$0 (40mL). H_2SO_4 was added until pH 8 and the mixture was refluxed 24 h. NH_3 (60 mL) was added and the mixture was extracted with ether. After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by ligroin. This yields 0.62 g of a product with the following characteristics: m.p. 79-80°C; ^{1}H NMR δ: 1.03 (t, 6H), 2.5 (q, 4H), 3.49 (s, 2H), 4.84 (s, 2H), 7.0-8.26 (m, 9H).

Example 20. 7-(4-Morpholinobut-2-yn)-oxyisoflavone (see accompanying formula drawing VIB 93)

A solution of formaldehyde (1 ml), morpholine (0.87 g, 0.01 mol) and $CuSO_4$ (0.2 g) in EtOH/H_2O (40 mL) was added to a solution of propynyloxy derivative (2.94 g, 0.01 mol) in EtOH/$H_2$0 (40mL). H_2SO_4 was added until pH 8 and the mixture was refluxed 24 h. NH_3 (60 mL) was added and the mixture was extracted with ether. After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by ligroin. This yields 1.5 g of a product with the following characteristics: m.p. 104-105°C; ^{1}H NMR δ: 2.5-2.6 (m, 4H), 3.35 (s, 2H), 3.75 (m, 4H), 4.85 (m, 2H), 6.95-8.22 (m, 9H).

Example 21. 7-(4-Morpholinobut-2-yn)-oxy-2-methyl-4'-methoxyisoflavone (see accompanying formula drawing VIB 105)

A solution of formaldehyde (1 ml), morpholine (0.87 g, 0.01 mol) and $CuSO_4$ (0.2 g) in EtOH/H_2O (40 mL) was added to a solution of propynyloxy derivative (3.2 g, 0.01 mol) in EtOH/H_2O (40 mL). H_2SO_4 was added until pH 8 and the mixture was

refluxed 24 h. NH_3 (60 mL) was added and the mixture was extracted with ether. After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by ligroin. This yields 1.2 g of a product with the following characteristics: m.p. 136-139°C; ^{1}H NMR δ: 2.15 (s, 3H), 2.5-2.6 (m, 4H), 3.35 (s, 2H), 3.7 (m, 4H), 4.7 (m, 2H), 6.95-8.25 (m, 8H).

Example 22. 7-(4-Morpholinobut-2-yn)-oxy-5-hydroxy-4'-methoxyisoflavone (see accompanying formula drawing VIB 102)

A solution of formaldehyde (1 ml), morpholine (0.87 g, 0.01 mol) and $CuSO_4$ (0.2 g) in EtOH/H_2O (40 mL) was added to a solution of propynyloxy derivative (3.2 g, 0.01 mol) in EtOH/H_2O (40 mL). H_2SO_4 was added until pH 8 and the mixture was refluxed 24 h. NH_3 (60 mL) was added and the mixture was extracted with ether. After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by ligroin. This yields 0.84 g of a product with the following characteristics: oil, hydrochloric salt m.p. 120-123°C (methanol-ether); ^{1}H NMR δ: 2.3 (m, 4H), 3.3 (s, 2H), 3.7 (m, 4H), 3.85 (s, 3H), 4.85 (m, 2H), 6.48-7.90 (m, 7H), 12.85 (s, 1H).

Example 23. 7-(4-Bis-4-Morpholinobut-2-yn)-oxyisoflavone (see accompanying formula drawing VIB 97)

A solution of formaldehyde (1 ml), morpholine (0.87 g, 0.01 mol) and $CuSO_4$ (0.2 g) in EtOH/H_2O (40 mL) was added to a solution of propynyloxy derivative (3.2 g, 0.01 mol) in EtOH/H_2O (40 mL). H_2SO_4 was added until pH 8 and the mixture was refluxed 24 h. NH_3 (60 mL) was added and the mixture was extracted with ether. After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by ligroin. This yields 1.06 g of a product with the following characteristics: m.p. 158-159°C; ^{1}H NMR δ: 2.55 (m, 8H), 3.34 (s, 4H), 3.74 (m, 8H), 4.7 (s, 2H), 4.85 (s, 2H), 6.98-8.26(m, 8H).

Example 24. 7-(4-Morpholinobut-2-yn)-oxyflavone (see accompanying formula drawing VIB 103)

A solution of formaldehyde (1 ml), morpholine (0.87 g, 0.01 mol) and $CuSO_4$ (0.2 g) in EtOH/H_2O (40 mL) was added to a solution of propynyloxy derivative (2.94 g, 0.01

mol) in EtOH/H_2O (40 mL). H_2SO_4 was added until pH 8 and the mixture was refluxed 24 h. NH_3 (60 mL) was added and the mixture was extracted with ether. After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by ligroin. This yields 0.75 g of a product with the following characteristics: m.p. 126-127°C; ^{1}H NMR δ: 2.56 (m, 4H), 3.35 (s, 2H), 3.7 (m, 4H), 4.86 (m, 2H), 6.79-8.2 (m, 9H). Mass: m/z 374 (M+, 14.38), 238 (100), 137 (82.79).

Example 25. 7-(4-Morpholinobut-2-yn)-oxy-3-methylflavone (see accompanying formula drawing VIB 104)

A solution of formaldehyde (1 ml), morpholine (0.87 g, 0.01 mol) and $CuSO_4$ (0.2 g) in EtOH/H_2O (40 mL) was added to a solution of propynyloxy derivative (3.09 g, 0.01 mol) in EtOH/H_2O (40 mL). H_2SO_4 was added until pH 8 and the mixture was refluxed 24 h. NH_3 (60 mL) was added and the mixture was extracted with ether. After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by ligroin. This yields 0.78 g of a product with the following characteristics: m.p.139-140°C; ^{1}H NMR δ: 2.13 (s, 3H), 2.6 (m, 4H), 3.35 (m, 2H), 3.8 (m, 4H), 4.03 (s, 2H), 6.85-8.10(m, 8H).

Example 26. 7-(4-Morpholinobut-2-yn)-oxy-4-methylcoumarin (see accompanying formula drawing VIB 95)

A solution of formaldehyde (1 ml), morpholine (0.87 g, 0.01 mol) and $CuSO_4$ (0.2 g) in EtOH/H_2O (40 mL) was added to a solution of propynyloxy derivative (2.14 g, 0.01 mol) in EtOH/H_2O (40 mL). H_2SO_4 was added until pH 8 and the mixture was refluxed 24 h. NH_3 (60 mL) was added and the mixture was extracted with ether. After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by ligroin. This yields 1.9 g of a product with the following characteristics: m.p.125-126°C; ^{1}H NMR δ: 2.4 (s, 3H), 2.52 (m, 4H), 3.3 (m, 2H), 3.7 (m, 4H), 4.78 (m, 2H), 6.16-7.54(m, 4H).

Example 27. 7-(4-Diethylaminobut-2-yn)-oxy-4-methylcoumarin (see accompanying formula drawing VIB 94)

A solution of formaldehyde (1 ml), morpholine (0.73 g, 0.01 mol) and $CuSO_4$ (0.2 g) in $EtOH/H_2O$ (40 mL) was added to a solution of propynyloxy derivative (2.14 g, 0.01 mol) in $EtOH/H_2O$ (40 mL). H_2SO_4 was added until pH 8 and the mixture was refluxed 24 h. NH_3 (60 mL) was added and the mixture was extracted with ether. After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by ligroin. This yields 1.9 g of a product with the following characteristics: m.p. 108-110°C; ^1H NMR δ: 1.04 (t, 6H), 2.42 (s, 2H), 2.5 (q, 4H), 3.7 (m, 2H), 4.8 (m, 2H), 6.18-7.57(m, 4H).

Example 28. 1-(4-Morpholinobut-2-yn)-oxyxanthone (see accompanying formula drawing VIB 99)

A solution of formaldehyde (1 ml), morpholine (0.87 g, 0.01 mol) and $CuSO_4$ (0.2 g) in $EtOH/H_2O$ (40 mL) was added to a solution of propynyloxy derivative (2.5 g, 0.01 mol) in $EtOH/H_2O$ (40 mL). H_2SO_4 was added until pH 8 and the mixture was refluxed 24 h. NH_3 (60 mL) was added and the mixture was extracted with ether. After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by ligroin. This yields 1.8 g of a product with the following characteristics: m.p. 98-101°C; ^1H NMR δ: 2.53 (m, 4H), 3.34 (m, 2H), 3.73 (m, 4H), 4.98 (m, 2H), 6.98-8.33 (m, 7H).

Example 29. 1-(4-Diethylaminobut-2-yn)-oxyxanthone (see accompanying formula drawing VIB 98)

A solution of formaldehyde (1 ml), diethylamine (0.73 g, 0.01 mol) and $CuSO_4$ (0.2 g) in $EtOH/H_2O$ (40 mL) was added to a solution of propynyloxy derivative (2.5 g, 0.01 mol) in $EtOH/H_2O$ (40 mL). H_2SO_4 was added until pH 8 and the mixture was refluxed 24 h. NH_3 (60 mL) was added and the mixture was extracted with ether. After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by ligroin. This yields 0.64 g of a product with the following characteristics: m.p. 70-72°C; ^1H NMR δ:1.02 (t, 6H), 2.5 (q, 4H), 3.45 (m, 2H), 4.96 (m, 2H), 6.98-8.33 (m, 7H).

Example 23. 2-(4-Morpholinobut-2-yn)-oxyxanthone (see accompanying formula drawing VIB 101)

A solution of formaldehyde (1 ml), morpholine (0.87 g, 0.01 mol) and $CuSO_4$ (0.2 g) in EtOH/H_2O (40 mL) was added to a solution of propynyloxy derivative (2.5 g, 0.01 mol) in EtOH/H_2O (40mL). H_2SO_4 was added until pH 8 and the mixture was refluxed 24 h. NH_3 (60 mL) was added and the mixture was extracted with ether. After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by ligroin. This yields 1.8 g of a product with the following characteristics: m.p. 105-106°C; ^{1}H NMR δ: 2.53 (m, 4H), 3.33 (m, 2H), 3.7 (m, 4H), 4.84 (m, 2H), 7.39-7.83 (m, 7H).

Example 31. 2-(4-Diethylaminobut-2-yn)-oxyxanthone (see accompanying formula drawing VIB 100)

A solution of formaldehyde (1 ml), diethylamine (0.73 g, 0.01 mol) and $CuSO_4$ (0.2 g) in EtOH/H_2O (40 mL) was added to a solution of propynyloxy derivative (2.5 g, 0.01 mol) in EtOH/H_2O (40 mL). H_2SO_4 was added until pH 8 and the mixture was refluxed 24 h. NH_3 (60 mL) was added and the mixture was extracted with ether. After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by ligroin. This yields 0.64 g of a product with the following characteristics: m.p. 66-68°C; ^{1}H NMR δ: 1.08 (t, 6H), 2.54 (q, 4H), 3.5 (m, 2H), 4.86 (m, 2H), 7.35-8.38 (m, 7H).

Example 32. 2-(4-Morpholinobut-2-yn)-oxyxanthone (see accompanying formula drawing VIB 96)

A solution of formaldehyde (1 ml), morpholine (0.87 g, 0.01 mol) and $CuSO_4$ (0.2 g) in EtOH/H_2O (40 mL) was added to a solution of propynyloxy derivative (2.5 g, 0.01 mol) in EtOH/H_2O (40 mL). H_2SO_4 was added until pH 8 and the mixture was refluxed 24 h. NH_3 (60 mL) was added and the mixture was extracted with ether. After evaporation of the solvent the residue was purified by flash-chromatography (eluent: toluene/acetone 4/1) and crystallized by ligroin. This yields 1.5 g of a product with the following characteristics: m.p. 126-128°C; ^{1}H NMR δ: 2.56 (m, 4H), 3.4 (m, 2H), 3.7 (m, 4H), 4.86 (m, 2H), 6.97-8.37 (m, 7H).

BIOLOGICAL EVALUATION

Compounds VIB 16, VIB 94, VIB 99 and VIB 100 were tested for their cytotoxicity against drug-resistant cancer cells, both alone, and in combination with paclitaxel. The results of these studies are shown below.

When tested alone these compounds were found to possess relatively low cytotoxicity (IC_{50} > 30 μM) against drug-resistant cancer cells.

The compounds were then evaluated in combination with paclitaxel for their cytostatic activity against the drug-resistant breast cancer cells MDA-435/LCC6-MDR. In the experiments, the compounds were used in combination with paclitaxel, the paclitaxel being at a concentration of 1 μM. The IC_{50} of paclitaxel decreases by 2-4 fold when used in combination with each of compounds, i.e. from 426 nM to 210-110 nM compared with paclitaxel alone. Consequently, in the presence of these compounds, paclitaxel can recover its excellent inhibitory activity against the drug-resistant cancer cells.

Compound	IC_{50}/nM	% Reduction in IC_{50} of paclitaxel
Paclitaxel	426	-
VIB 16 + Paclitaxel	136	67
VIB 94 + Paclitaxel	210	50
VIB 99 + Paclitaxel	200	53
VIB 100 + Paclitaxel	110	70

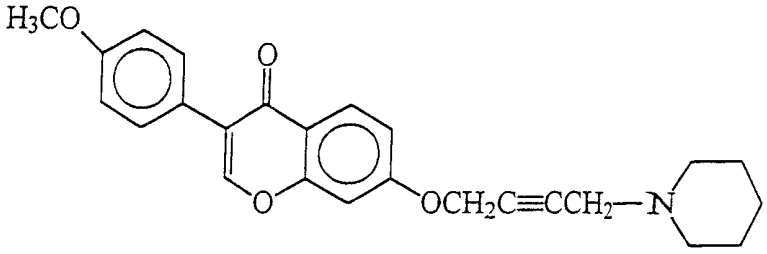
Table 1

Experimental

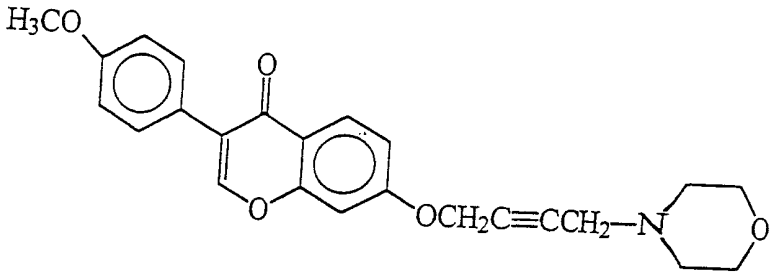
The treatment consisted of concurrent exposure of MDA-435/LCC-MDR cells to paclitaxel in the presence or absence of the compounds reversing agent (1 μM) for

72 h *in vitro*. Assessment of cytotoxicity, i.e. cell growth inhibition, was determined according to the methods of Skehan, et al. as discussed in J. Nat. Cancer Inst., 82, 1107, 1990.

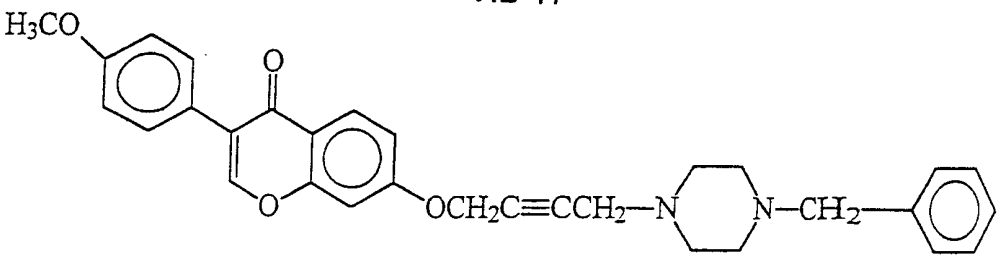
Briefly, cells were plated between 400 and 1200 cells/well in 96 well plates and incubated at 37°C for 15-18 h prior to drug addiction to allow attachment of cells. Compounds were solubilized in 100% DMSO and further diluted in RPMI-1640 containing 10 mM HEPES. After a 72 h incubation, 100 ml of ice-cold 50% TCA was added to each well and incubated for 1 h at 4°C. Plates were then washed 5 times with tap water to remove TCA, low-molecular weight metabolites and serum proteins. Sulforhodamine B (SRB) (0.4%, 50 ml) was added to each well. Following a five minute incubation at room temperature, plates were rinsed 5 times with 0.1% acetic acid and air dried. Bound dye was solubilized with 10 mM Tris Base (pH 10.5) for 5 min on a gyratory shaker. Optical density was measured at 570 nm.



VIB 15



VIB 17



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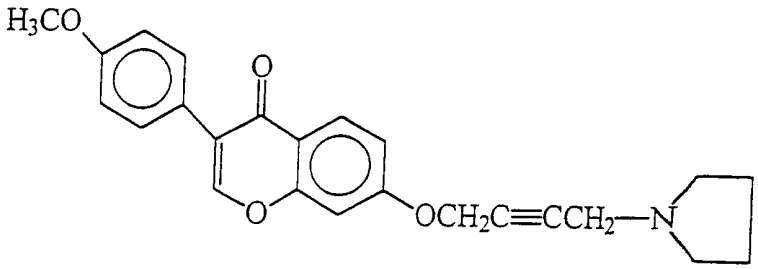

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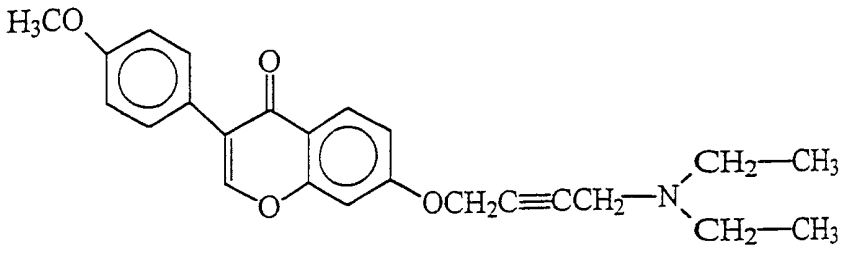

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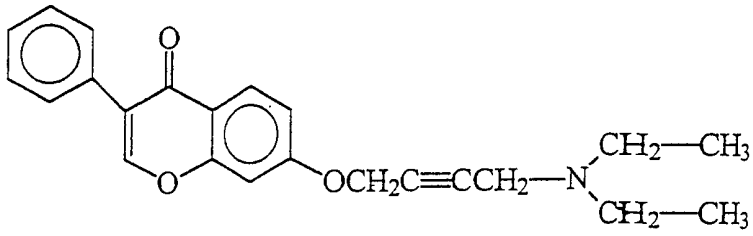

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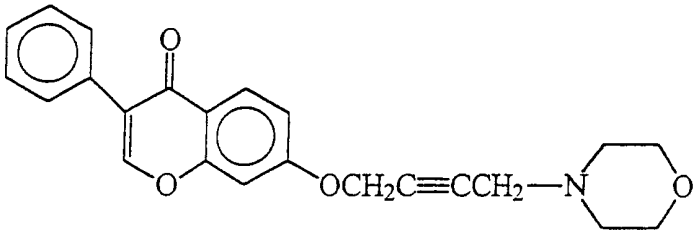

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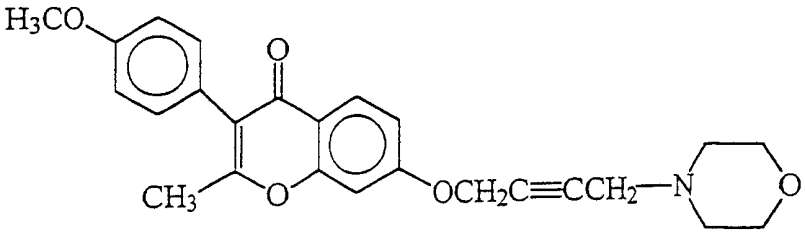

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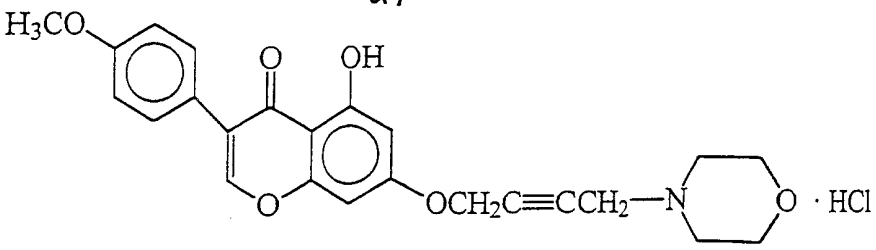

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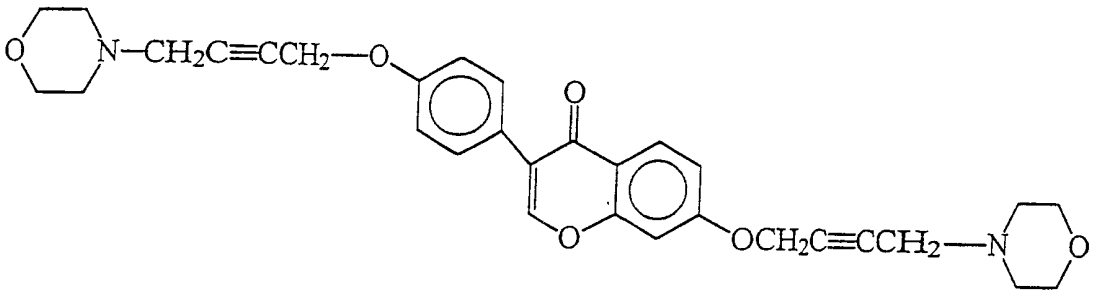

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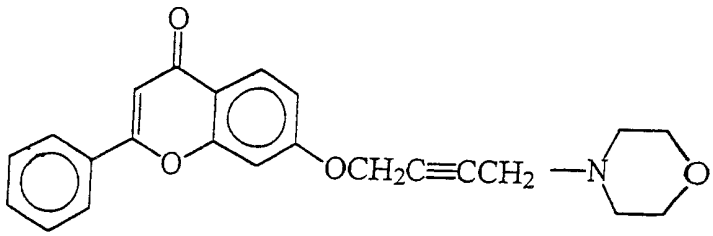

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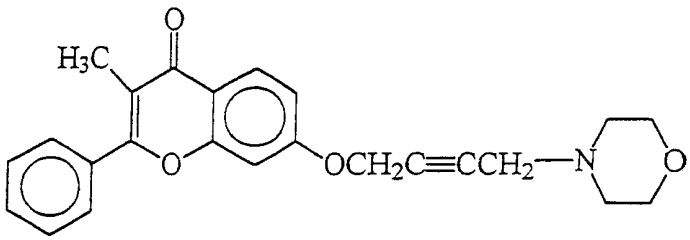

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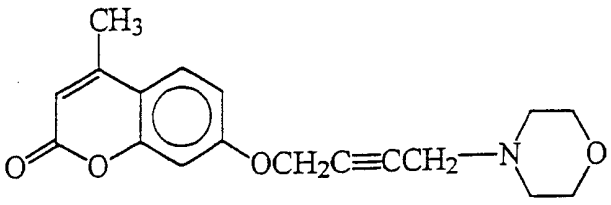

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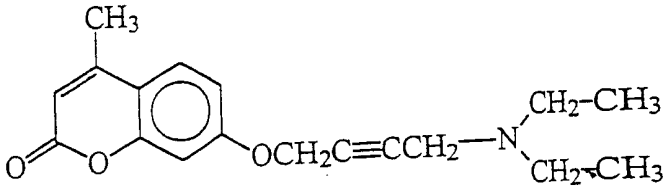

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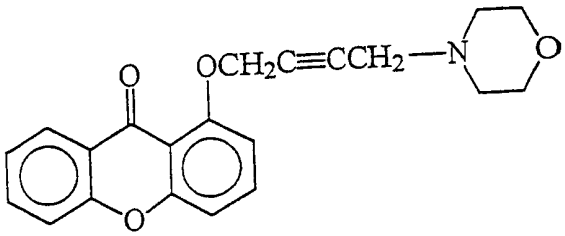

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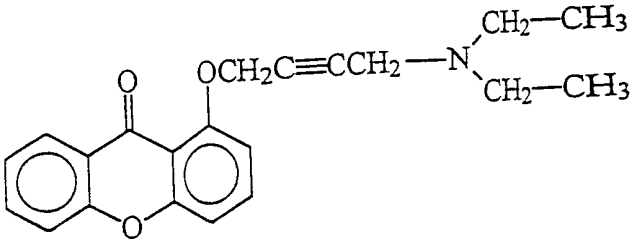

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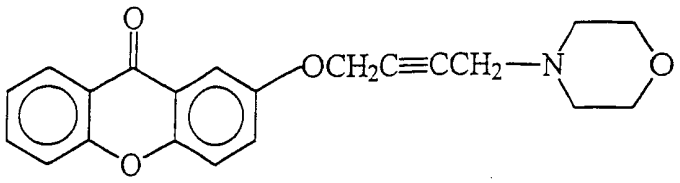

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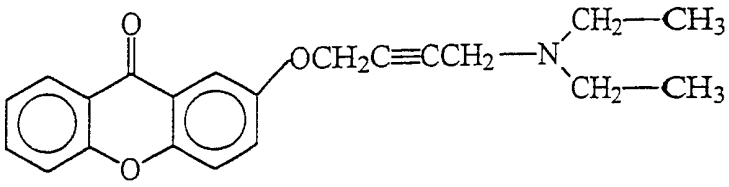

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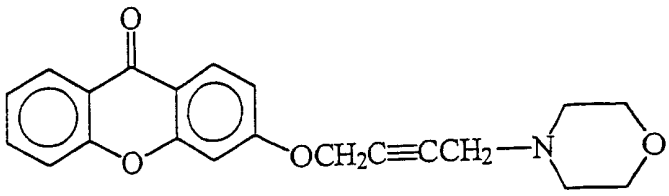


VIB 96

CLAIMS

1. A compound of Formula (I):

$$Z-OCH_2-C\equiv CCH_2NRR^1$$

(I)

or a pharmaceutically acceptable salt or solvate thereof wherein

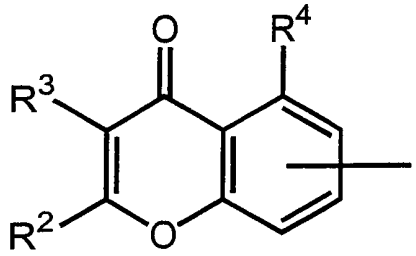
R and R^1 are the same or different and each represents

lower C_{1-6} alkyl, or a carbocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings wherein the or each ring contains 5 or 6 ring atoms, or

R and R^1 taken together with the nitrogen atom to which they are attached, form a four- to eight-membered heterocyclic ring which may contain one or more additional heteroatoms selected from N, O or S, said heterocyclic ring being optionally substituted with a lower C_{1-4} alkyl group or a benzyl group;

Z represents:

(A)



wherein

R^2 and R^3 are each independently selected from:

(i) hydrogen, (ii) a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

(a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} lower alkyl (in particular CH_3), (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8, are the same or different and each represents H or lower C_{1-4} alkyl, (k) OR^{10} wherein R^{10} represents H or lower C_{1-6} alkyl which may be saturated or unsaturated and being unsubstituted or substituted with the group NRR^1 wherein R and R^1 is as defined above, and (l) $OCOR^{11}$ wherein R^{11} represents H or lower C_{1-4} alkyl,

(iii) Cl, (iv) Br, (v) F, (vi) OH, (vii) NO_2, (viii) a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, (ix) $NHCOCH_3$, (x) $N(R^6)(R^8)$, (xi) SR^{10}, (xii) OR^{10}, and (xiii) $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined above;

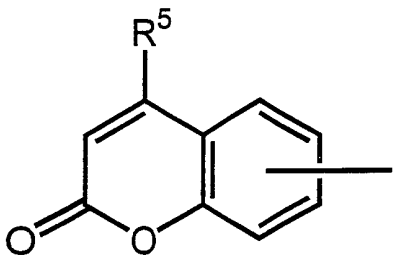
or

R_2 and R_3 taken together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic ring having 5 or 6 ring atoms, any heteroatom being selected from N, O or S, said carbocyclic or heterocyclic ring being saturated or unsaturated, and being unsubstituted or substituted with one or more substituents selected from Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl, SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined above; and

R^4 represents hydrogen, or OR^{10} wherein R^{10} is as defined above

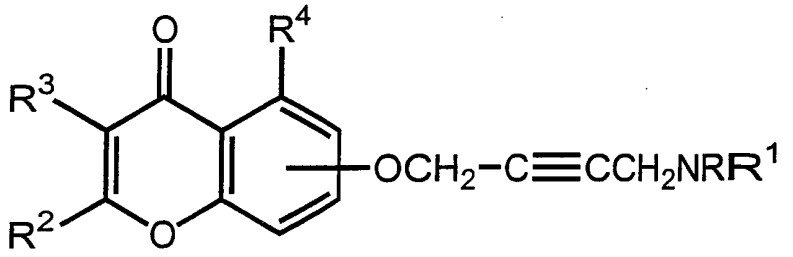
or

(B)



wherein R^5 represents hydrogen or a lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3.

2. A compound of Formula (I) according to Claim 1 having the structure (IA'):



(IA')

wherein

R^2 and R^3 are each independently selected from:

(i) hydrogen, (ii) a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are the same or different and each represents H or lower C_{1-4} alkyl,

(iii) Cl, (iv) Br, (v) F, (vi) OH, (vii) NO_2, (viii) a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, (ix) $NHCOCH_3$, (x) $N(R^6)(R^8)$, (xi) SR^{10}, (xii) OR^{10}, and (xiii) $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined above;

or

R_2 and R_3 taken together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic ring having 5 or 6 ring atoms, any heteroatom being selected from N, O or S, said carbocyclic or heterocyclic ring being saturated or unsaturated, and being unsubstituted or substituted with one or more substituents selected from Cl, Br, F, OH, NO_2, CF_3, C_{1-4}

lower alkyl, SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined above; and

R^4 represents hydrogen, or OR^{10} wherein R^{10} is as defined above.

3. A compound according to Claim 2 wherein R, R^1 and R^4 are as defined in Claim 1, and

R^2 and R^3 are each independently selected from:

(i) hydrogen, (ii) a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

(a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} lower alkyl (in particular CH_3), (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8, are the same or different and each represents H or lower C_{1-4} alkyl, (k) OR^{10} wherein R^{10} represents H or lower C_{1-6} alkyl which may be saturated or unsaturated and being unsubstituted or substituted with the group NRR^1 wherein R and R^1 is as defined above, and (l) $OCOR^{11}$ wherein R^{11} represents H or lower C_{1-4} alkyl,

(iii) Cl, (iv) Br, (v) F, (vi) OH, (vii) NO_2, (viii) a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, (ix) $NHCOCH_3$, (x) $N(R^6)(R^8)$, (xi) SR^{10}, (xii) OR^{10}, and (xiii) $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined in Claim 1.

4. A compound according to any preceding claim wherein R^2 and R^3 are hydrogen.

5. A compound according to Claim 1 or Claim 2 wherein one of R^1 or R^2 is hydrogen, and the other is selected from the group consisting of: (i) a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each

ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are the same or different and each represents H or lower C_{1-4} alkyl,

(ii) Cl, (iii) Br, (iv) F, (v) OH, (vi) NO_2, (vii) a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, (viii) $NHCOCH_3$, (ix) $N(R^6)(R^8)$, (x) SR^{10}, (xi) OR^{10}, and (xii) $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined in Claim 1.

6. A compound according to Claim 4 wherein R^2 is hydrogen and R^3 is selected from the group consisting of: (i) a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are the same or different and each represents H or lower C_{1-4} alkyl,

(ii) Cl, (iii) Br, (iv) F, (v) OH, (vi) NO_2, (vii) a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, (viii) $NHCOCH_3$, (ix) $N(R^6)(R^8)$, (x) SR^{10}, (xi) OR^{10}, and (xii) $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined in Claim 1.

7. A compound according to Claim 5 wherein R^3 is hydrogen and R^2 is selected from the group consisting of: (i) a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are the same or different and each represents H or lower C_{1-4} alkyl,

(ii) Cl, (iii) Br, (iv) F, (v) OH, (vi) NO_2, (vii) a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, (viii) $NHCOCH_3$, (ix) $N(R^6)(R^8)$, (x) SR^{10}, (xi) OR^{10}, and (xii) $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined in Claim 1.

8. A compound according to Claim 5 wherein R^2 represents a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined in Claim 1.

9. A compound according to Claim 6 wherein R^3 represents a substituted or unsubstituted, preferably aromatic, carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents being independently selected from the group consisting of:

Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined in Claim 1.

10. A compound according to Claim 3 wherein R^3 is selected from the group consisting of H, Cl, Br, F, OH, NO_2, a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from

Cl, Br, F, OMe, NO_2 and CF_3,

$NHCOCH_3$, $N(R^6)(R^8)$, SR^{10}, OR^{10}, and $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined in Claim 1.

11. A compound according to Claim 3 wherein R^2 is selected from the group consisting of H, Cl, Br, F, OH, NO_2, a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from

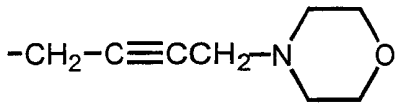
Cl, Br, F, OMe, NO_2 and CF_3,

$NHCOCH_3$, $N(R^6)(R^8)$, SR^{10}, OR^{10}, and $OCOR^{11}$ wherein R^6, R^8, R^{10} and R^{11} are as defined in Claim 1.

12. A compound according to any of Claims 1 to 9 wherein any substituents on the carbocyclic or heterocyclic group are independently selected from OH or OR^{10} wherein R^{10} is as defined in Claim 1.

13. A compound according to any of Claims 1 to 9 wherein one of R^2 or R^3 represents phenyl or phenyl substituted with 1 to 3 OH or OR^{10} groups.

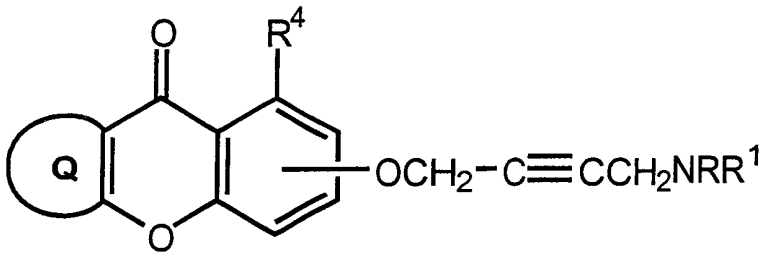
14. A compound according to Claim 12 or Claim 13 wherein R^{10} represents methyl or



15. A compound according to any of Claims 1 to 11 wherein one of R^2 or R^3 represents H or a lower C_{1-6} straight or branched hydrocarbyl group.

16. A compound according to Claim 15 wherein one of R^2 or R^3 represents methyl.

17. A compound of Formula (IA) according to Claim 2 having the structure (IA"):



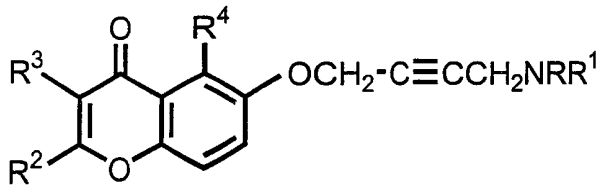
(IA")

wherein R, R^1 and R^4 are as defined in Claim 1, and R^2 and R^3 taken together represent Ring Q, said Ring Q being a carbocyclic or heterocyclic ring having 5 or 6 ring atoms, any heteroatom being selected from N, O or S, said carbocyclic or heterocyclic ring being saturated or unsaturated and being unsubstituted or substituted with one or more substituents selected from Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl, SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined as in Claim 1.

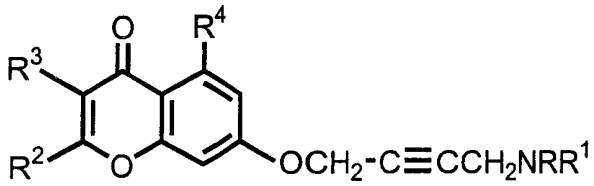
18. A compound according to Claim 17 wherein Ring Q represents a carbocyclic or heterocyclic aromatic ring any heteroatom being selected from N, O or S, said ring being unsubstituted or substituted with one or more substituents selected from Cl, Br, F, OH, NO_2, CF_3, C_{1-4} lower alkyl, SCH_3, $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined as in Claim 1.

19. A compound according to Claim 18 wherein Ring Q represents a benzene or pyridine ring.

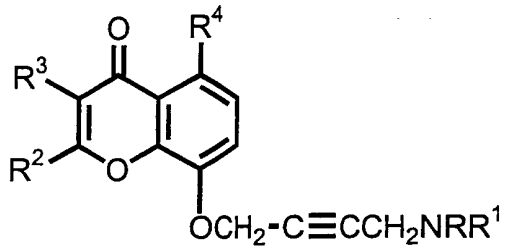
20. A compound according to any preceding claim having a structure selected from the group consisting of:



(IA)x ,



(IA)y , and



(IA)z .

wherein R, R^1, R^2, R^3 and R^4 are as defined in any preceding claim.

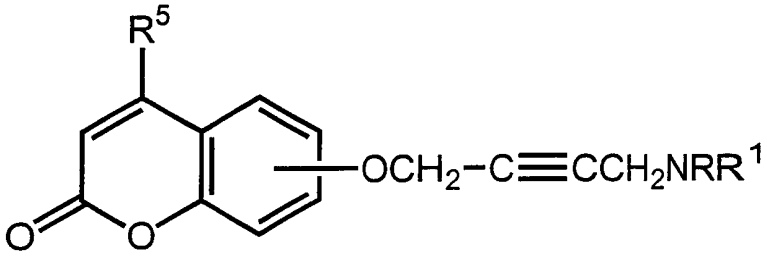
21. A compound according to Claim 20 having the structure (IA)x.

22. A compound according to Claim 20 having the structure (IA)y.

23. A compound according to Claim 20 having the structure (IA)z.

24. A compound according to any preceding claim wherein R^4 represents H, OH or OCH_3.

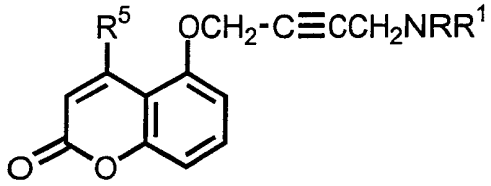
25. A compound of Formula (I) according to Claim 1 having the structure (IB):



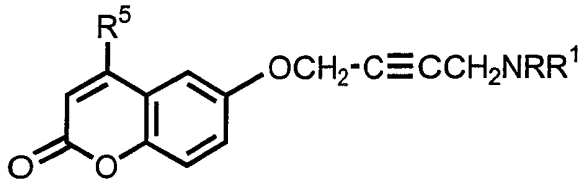
(IB)

wherein R and R^1 are as defined in Claim 1 and R^5 represents H or a lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3.

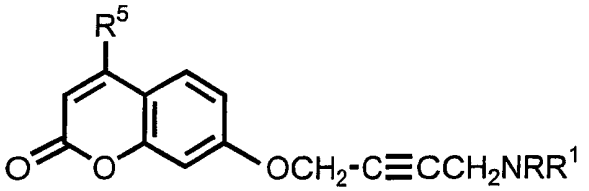
26. A compound according to Claim 25 having a structure selected from the group consisting of:



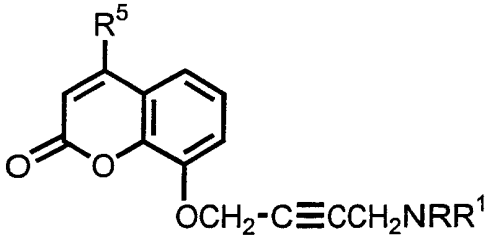
(IB)w ,



(IB)x ,



(IB)y , and



(IB)z .

wherein R, R^1 and R^5 are as defined in any preceding claim.

27. A compound according to Claim 26 having the structure (IB)w.

28. A compound according to Claim 26 having the structure (IB)x.

29. A compound according to Claim 26 having the structure (IB)y.

30. A compound according to Claim 26 having the structure (IB)z.

31. A compound according to any of Claims 25 to 30 wherein R^5 represents H or methyl.

32. A compound according to any preceding claim wherein R and R^1 are the same or different and each represents a C_{1-4} alkyl group or a C_{5-8} cycloalkyl group.

33. A compound according to any preceding claim wherein R and R^1 taken together with the nitrogen atom to which they are attached, form a four- to eight-membered heterocyclic ring.

34. A compound according to Claim 32 wherein R and R^1 are the same or different and each represents methyl, ethyl, propyl, cyclopropyl or a cyclohexyl group.

35. A compound according to Claim 33 wherein R and R^1 taken together with the nitrogen atom to which they are attached form a pyrrolidine, piperidine, N-methylpiperidine, N-benzylpiperidine or morpholine group.

36. A compound according to Claim 1 selected from:

7-(4-piperidinobut-2-yn)oxy-4'-methoxyisoflavone (VIB 15),
7-(4-morpholinobut-2-yn)oxy-4'-methoxyisoflavone (VIB 17),
7-[4-(4-benzylpiperazin-1-yl)but-2-yn]oxy-4'-methoxyisoflavone (VIB 16),
7-(4-pyrrolidinobut-2-yn)oxy-4'-methoxyisoflavone (VIB 91),
7-(4-diethylaminobut-2-yn)oxy-4'-methoxyisoflavone (VIB 90),
7-(4-diethylaminobut-2-yn)oxyisoflavone (VIB 92),
7-(4-morpholinobut-2-yn)oxyisoflavone (VIB 93),
7-(4-morpholinobut-2-yn)oxy-2-methyl-4'-methoxyisoflavone (VIB 105),
7-(4-morpholinobut-2-yn)oxy-5-hydroxy-4'-methoxyisoflavone (VIB 102),
7-(4-*bis*-4-morpholinobut-2-yn)oxyisoflavone (VIB 97),
7-(4-morpholinobut-2-yn)oxyflavone (VIB 103),
7-(4-morpholinobut-2-yn)oxy-3-methylflavone (VIB 104),
7-(4-morpholinobut-2-yn)oxy-4-methylcoumarin (VIB 95),

7-(4-diethylaminobut-2-yn)oxy-4-methylcoumarin (VIB 94),
1-(4-morpholinobut-2-yn)oxyxanthone (VIB 99),
1-(4-diethylaminobut-2-yn)oxyxanthone (VIB 98),
2-(4-morpholinobut-2-yn)oxyxanthone (VIB 101),
2-(4-diethylaminobut-2-yn)oxyxanthone (VIB 100), and
2-(4-morpholinobut-2-yn)oxyxanthone (VIB 96).

37. A compound of Formula (I) as defined in any preceding claim for use as a modulator of multiple drug resistance in cancer chemotherapy or an antiproliferative medicament.

38. A compound according to Claim 37 wherein the multiple drug resistance is mediated by P-glycoprotein.

39. Use of a compound of Formula (I) as defined in any preceding claim for the manufacture of a medicament for the treatment or prevention of neoplasms.

40. Use according to Claim 39 wherein the neoplasms are located in the uterus, ovary or breast.

41. Use according to Claim 39 or 40 of a compound of Formula (I) for the manufacture of a medicament for the treatment of paclitaxel- and docetaxel-resistant cancer cells.

42. Use according to any of Claims 39 to 41 of a compound of Formula (I) in the manufacture of an antiproliferative medicament for combination therapy.

43. Use according to Claim 42 of a compound of Formula (I) in the manufacture of an antiproliferative medicament in combination with one or more antineoplastic or cytostatic agents.

44. The use according to Claim 43 wherein the antineoplastic or cytostatic agent is selected from the group consisting of anthracyclines, epipodophyllotoxins, actinomycin D, vinca alkaloids, colchicines, paclitaxel or docetaxel.

45. The use according to Claim 39 in the manufacture of a medicament for the treatment or prevention of menopausal disorders and osteoporosis.

46. A pharmaceutical composition comprising one of more of the compounds of Formula (I) as defined in any preceding claim, in combination with one or more pharmaceutically acceptable excipients.

47. A pharmaceutical composition according to Claim 46 further comprising one or more antineoplastic or cytostatic agents.

48. A pharmaceutical composition according to Claim 47 wherein the antineoplastic agent is selected from paclitaxel or docetaxel.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/08365

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D311/30 C07D311/36 C07D311/16 C07D311/86 A61K31/37
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, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	abstract and examples 10-13 the whole document	37-48
A	EP 0 419 132 A (ALLERGAN, INC.) 27 March 1991 (1991-03-27) the whole document	1-48
A	WO 95 18803 A (ALLERGAN, INC.) 13 July 1995 (1995-07-13) the whole document	1-48
A	US 3 513 198 A (JAY PHILIP O'BRIEN) 19 May 1970 (1970-05-19) the whole document	1-48

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"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
6 February 2001	21/02/2001

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	Beslier, L

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/08365

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	PETROW V. ET AL.: "Analgesics. Part II. Some aryloxyalkyl oxaalkylamines" JOURNAL OF PHARMACY AND PHARMACOLOGY, vol. 10, 1958, pages 86-95, XP000979516 LONDON, GB ISSN: 0022-3573 particularly compound XVa in page 88 -----	1-48

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Information on patent family members

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