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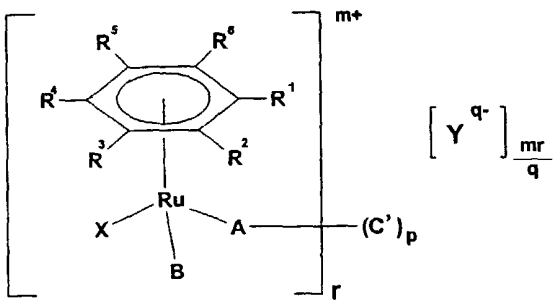
(54) Title: HALF-SANDWICH RUTHENIUM (II) COMPOUNDS COMPRISING NITROGEN CONTAINING LIGANDS FOR TREATMENT OF CANCER



(I)

(57) Abstract: Compounds which may be used in the treatment and/or prevention of cancer have the formula (I) wherein: R^1, R^2, R^3, R^4, R^5 and R^6 independently represents H, alkyl, $-CO_2R'$, aryl or akylaryl, which latter two groups are optionally substituted on the aromatic ring; R' represent alkyl, aryl or alkaryl; X is halo, H_2O, (R')(R'')SO, $R'CO_2^-$ or (R')(R'')C=O, where R'' represents alkyl, aryl or alkaryl; Y is a counterion; m is 0 or 1; q is 1, 2 or 3; C' is C_1 to C_{12} alkylene, optionally substituted in or on the alkylene chain, bound to two A groups; p is 0 or 1 and r is 1 when p is 0 and r is 2 when p is 1; and A and B are: each independently N-donor nitrile ligands; or B is halo and A is an N-donor pyridine ligand, optionally substituted at one or more of the carbon atoms of the pyridine ring; or p is 0, A is NR^7R^8 and B is NR^9R^{10}, wherein R^7, R^8, R^9 and R^{10} independently represent H or alkyl, and A and B are linked by an alkylene chain, optionally substituted in or on the alkylene chain; or p is 1, A is NR^7 and B is NR^9R^{10}, wherein R^7, R^9 and R^{10} are as previously defined, and A and B are linked by an alkylene chain, optionally substituted.

HALF-SANDWICH RUTHENIUM (II) COMPOUNDS COMPRISING NITROGEN CONTAINING LIGANDS LIGANDS FOR TREATMENT OF CANCER

This invention relates to ruthenium (II) compounds, to their use in medicine, particularly for the treatment and/or prevention of cancer, and to a process for their preparation.

Certain ruthenium (II) complexes have been proposed for use in treating cancer. For example, US 4980473 discloses 1,10-phenanthroline complexes of ruthenium (II) and cobalt (III) which are said to be useful for the treatment of tumour cells in a subject.

Some other ruthenium (II) and ruthenium (III) complexes which have been shown to exhibit antitumour activity are mentioned in Guo *et al*, Inorganica Chimica Acta, 273 (1998), 1-7, specifically *trans*-$[RuCl_2(DMSO)_4]$, *trans*-$[RuCl_2(imidazole)_2]$- and *trans*-$[RuCl_4(indazole)_2]^-$. Guo *et al* discloses that the most interesting feature of these complexes is their anti-metastatic activity. Clarke *et al* have reviewed the anticancer and in particular the antimetastatic activity of ruthenium complexes: Chem. Rev. 1999, **99**, 2511-2533. Also, Sava has reveiwed the antimetastatic activity in "Metal Compounds in Cancer Therapy" Ed by S P Fricker, Chapman and Hall, London 1994, p. 65-91.

Dale *et al,* Anti-Cancer Drug Design (1992), 7, 3-14, describes a metronidazole complex of ruthenium (II) ie, $[(\eta^6\text{-}C_6H_6)RuCl_2(metronidazole)]$ and its effect on DNA and on *E. coli* growth rates. Metronidazole sensitises hypoxic tumour cells to radiation and appears to be an essential element of the complexes of Dale *et al*. There

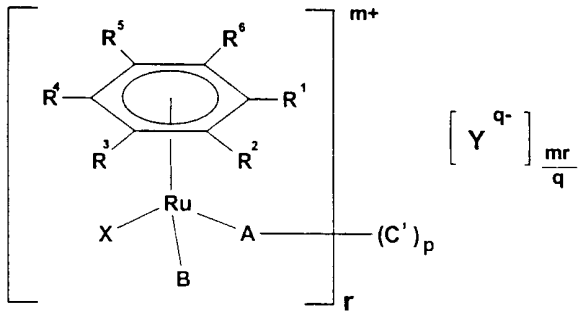
is no indication in Dale *et al* that the complexes would be at all effective in the absence of the metronidazole ligand.

Krämer *et al, Chem Eur J.*, **1996**, 2, No. 12, p. 1518-1526 discloses half sandwich complexes of ruthenium with amino esters.

There exists a need for novel anti-cancer compounds which can be used as alternatives to the compounds which are currently available.

The present invention provides a novel class of ruthenium (II) complexes having anti-tumour activity.

According to the present invention there is provided a ruthenium (II) compound of formula (I):



(I)

wherein: R^1, R^2, R^3, R^4, R^5 and R^6 independently represent H, alkyl, $-CO_2R'$, aryl or alkylaryl, which latter two groups are optionally substituted on the aromatic ring;

R' represents alkyl, aryl or alkaryl;

X is halo, H_2O, (R')(R'')SO, $R'CO_2^-$ or (R')(R'')C=O, where R'' represents alkyl, aryl or alkaryl;

Y is a counterion;

m is 0 or 1;

q is 1, 2 or 3;

C' is C_1 to C_{12} alkylene, optionally substituted in or on the alkylene chain, bound to two A groups;

p is 0 or 1 and r is 1 when p is 0 and r is 2 when p is 1; and

A and B are: each independently N-donor nitrile ligands; or B is halo and A is an N-donor pyridine ligand, optionally substituted at one or more of the carbon atoms of the pyridine ring; or p is 0, A is NR^7R^8 and B is NR^9R^{10}, wherein R^7, R^8, R^9 and R^{10} independently represent H or alkyl, and A and B are linked by an alkylene chain, optionally substituted in or on the alkylene chain; or p is 1, A is NR^7 and B is NR^9R^{10}, wherein R^7, R^9 and R^{10} are as previously defined, and A and B are linked by an alkylene chain, optionally substituted.

The compounds of the invention may be in the form of solvates and/or prodrugs. Prodrugs are variants of the compounds of the invention which can be converted to compounds of formula (I) *in vivo*.

The compounds of formula (I) may have one or more chiral centres. When the compounds of formula (I) have one or more chiral centres, they may be in the form of one enantiomer, may be enriched in one enantiomer or may be a racemic mixture.

The term "alkyl" as used herein includes C_1 to C_6 alkyl groups which may be branched or unbranched and may be open chain or, when they are C_3 to C_6 groups, cyclic. Unbranched open chain alkyl groups include, for

example, methyl, ethyl, propyl, butyl, pentyl and hexyl. Branched open chain alkyl groups include, for example, 2-propyl, 2-butyl and 2-(2-methyl)propyl. Cyclic groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The alkyl groups in the compounds of the invention may optionally be substituted. Substituents include one or more further alkyl groups and/or one or more further substituents, such as, for example, cyano, nitro, hydroxyl, haloalkyl, $-CO_2$alkyl, halo, thiol (SH), thioether (eg, S-alkyl) and sulfonate. The term "alkylene" is defined similarly to the definition of the term "alkyl" but includes C_2 to C_{12} groups and is a divalent species with radicals separated by two or more (eg, from two to twelve) carbon atoms linked in a chain. Preferably, the alkylene groups are straight chain groups. Alkylene groups are optionally substituted in the alkylene chain, preferably with one or more phenylene (eg, 1,4-phenylene) and/or $-CONR^{1a}-$ groups and/or $-NR^{2a}-$ groups, where R^{1a} and R^{2a} independently represent H, alkyl, aryl or alkaryl. Preferably, R^{1a} and R^{2a} are H or C_1 to C_3 alkyl.

The term "aryl" as used herein includes aromatic carbocyclic rings such as phenyl and naphthyl and heterocyclic rings such as pyridyl, imidazolyl, pyrrolyl and furanyl. Aryl groups may optionally be substituted with one or more substituents including, for example, alkyl, cyano, nitro, hydroxyl, haloalkyl, $-CO_2$alkyl, halo, thiol (SH), thioether (eg, S-alkyl) and sulfonate.

The term "alkaryl" means alkyl substituted with aryl eg, benzyl.

The term "halo" means a halogen radical selected from fluoro, chloro, bromo and iodo.

The term "haloalkyl" means alkyl substituted with one or more halo groups eg, trifluoromethyl.

In the compounds of formula (I), R^1, R^2, R^3, R^4, R^5 and R^6 may represent H. Alternatively, R^1 may be 2-propyl and R^4 may be methyl, with R^2, R^3, R^5 and R^6 all representing hydrogen. As a further alternative, R^1 may be phenyl, with R^2, R^3, R^4, R^5 and R^6 all representing hydrogen. In a yet further alternative, R^1 may be $-CO_2R'$, such as $-CO_2CH_3$ for example, with R^2, R^3, R^4, R^5 and R^6 all representing hydrogen.

In one aspect, A and B in the compounds of formula (I) both represent R^{11}-CN. R^{11} is alkyl, preferably C_1 to C_3 alkyl, more preferably methyl.

In another aspect, one of A and B in the compounds of formula (I) represents a 4-substituted pyridine and the other represents halo. The pyridine may be substituted at the 4- position by, for example, groups including nitro, cyano and $C(O)NR^{12}R^{13}$ wherein R^{12} and R^{13} are independently selected from H and alkyl (eg, C_1 to C_6 alkyl). The group at the 4- position of the pyridine ring is preferably an electron withdrawing group.

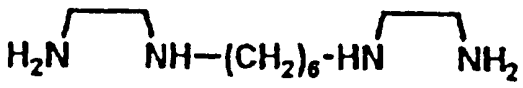
In a further aspect, A and B may together represent NR^7R^8-$(CR^{12}R^{13})_n$-NR^9R^{10}, wherein R^{12} and R^{13} are independently H or alkyl or R^{12} and R^{13} groups, on the same carbon atom or on neighbouring carbon atoms, are

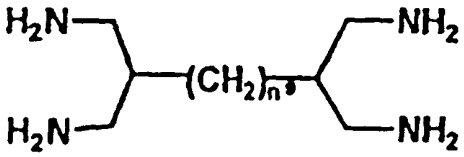
linked to form a carbocylic ring and n is an integer from 1 to 4. Preferably, R^{12} and R^{13} are both hydrogen and n is 2 or 3, more preferably 2. R^7, R^8, R^9 and R^{10} are preferably H or methyl and, more preferably, all of R^7, R^8, R^9 and R^{10} are H.

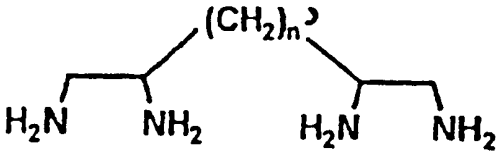
When R^8 is present in A, then p is 0. When R^8 is absent, then p is 1.

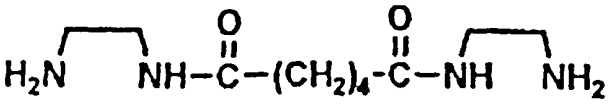
In a further aspect of the invention, R^8 is absent from A, p is 1 and C' is C_4 to C_{10} straight chain alkylene (eg, hexylene). Compounds according to this aspect of the invention are so-called dinuclear complexes comprising two ruthenium atoms per complex.

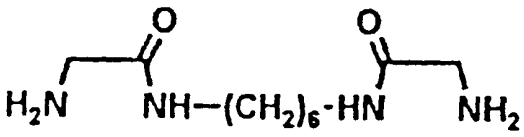
Other examples of dinuclear complexes of the invention are those in which A and B together represent:

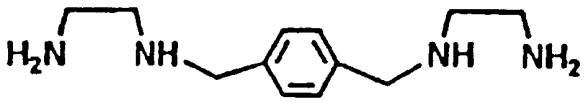


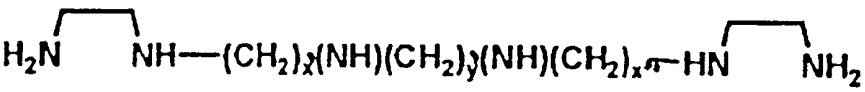


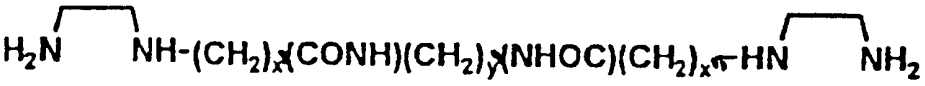


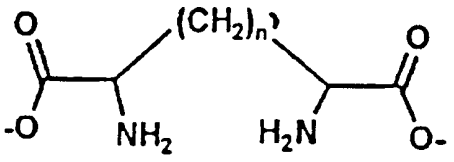


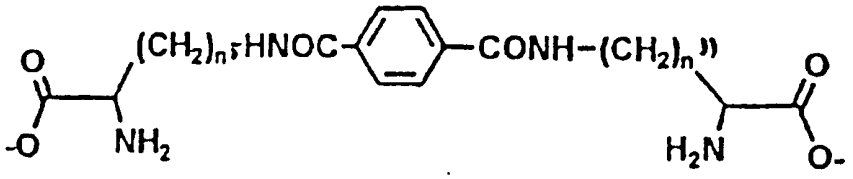












wherein each n', n'', x', x'' and y' independently represents an integer from 1 to 12, preferably 1 to 6.

Y^{q-} in compounds of formula (I) is a counterion and is only present in the compound when the complex containing the metal ion is charged. Y^{q-} is preferably a non-nucleophilic anion such as PF_6^-, for example.

R' and R'' are preferably alkyl. Most preferably, both R' and R'' are methyl.

Compounds of formula (I) may be used in medicine. In particular, compounds of formula (I) may be used to treat and/or prevent cancer.

Therefore, the present invention also provides the use of a compound of the invention (ie, a compound of formula (I)) in the manufacture of a medicament for the treatment and/or prevention of cancer.

Further provided by the invention is a method of treating and/or preventing cancer which comprises administering to a subject a therapeutically effective amount of a compound of the invention.

The compounds of the invention may be used directly against a tumour. Alternatively or additionally, the compounds may be used to prevent or inhibit metastasis and/or to kill secondary tumours. It will be understood that the prevention or inhibition of metastasis is encompassed by the term "preventing cancer", as used herein.

The invention also provides a pharmaceutical composition comprising one or more compounds of the invention together with one or more

pharmaceutically acceptable excipients. Suitable excipients include diluents and/or carriers.

The compounds of the invention may be administered by a number of routes including, for example, orally, parenterally (eg, intramuscularly, intravenously or subcutaneously), topically, nasally or via slow releasing microcarriers. Thus, suitable excipients for use in the pharmaceutical compositions of the invention include saline, sterile water, creams, ointments, solutions, gels, pastes, emulsions, lotions, oils, solid carriers and aerosols.

The compositions of the invention may be formulated in unit or sub-unit dosage form including, for example, tablets, capsules and lozenges and containers containing the composition in a form suitable for parenteral administration.

The specific dosage level of the compounds and compositions of the invention will depend upon a number of factors, including the biological activity of the specific compound used and the age, body weight and sex of the subject. It will be appreciated that the subject may be a human or a mammalian animal.

The compounds and compositions of the invention can be administered alone or in combination with other compounds. The other compounds may have a biological activity which complements the activity of the compounds of the invention eg, by enhancing its effect in killing tumours

or by reducing any side-effects associated with the compounds of the invention.

The present invention also provides a process for preparing the compounds of the invention which comprises the reaction of a compound of formula $[(\eta^6\text{-}C_6(R^1)(R^2)(R^3)(R^4)(R^5)(R^6))RuX_2]$, which may be in the form of a monomer or a dimer, with A and B, optionally in the presence of Y^{q-}, in a suitable solvent for the reaction, wherein R^1, R^2, R^3, R^4, R^5, R^6, X, A, B and Y are as defined above for the compounds of the invention.

Suitable compounds of formula $[(\eta^6\text{-}C_6(R^1)(R^2)(R^3)(R^4)(R^5)(R^6))RuX_2]$ for use as starting materials (starting ruthenium complexes) in the process of the invention include $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$, $[(\eta^6\text{-}C_6H_6)RuBr_2]_2$, $[(\eta^6\text{-}C_6H_6)RuI_2]_2$, $[(\eta^6\text{-}$*p*$\text{-cymene})RuCl_2]_2$, $[(\eta^6\text{-}$*p*$\text{-cymene})RuBr_2]_2$ and $[(\eta^6\text{-}$*p*$\text{-cymene})RuI_2]_2$ which can be prepared by known methods eg Bennett *et al, J.Chem. Soc. Dalton Trans.*, **1974**, 233.

When A and B in the compounds of the invention are R^{11}-CN, the solvent for the reaction may be R^{11}-CN itself. Preferred reaction conditions include stirring the starting ruthenium complex, as described above, in R^{11}-CN as solvent at room temperature until a sufficient amount of product is formed. The reaction mixture comprises a source of Y^{q-}, such as a compound of formula $(NH_4^+)Y^{q-}$ eg, NH_4PF_6.

Compounds of formula (I) in which A and B represent, together, $NR^7R^8\text{-}(CR^{12}R^{13})_n\text{-}NR^9R^{10}$ or $NR^9R^{10}\text{-}(CR^{12}R^{13})_n\text{-}NR^7\text{-}C'\text{-}NR^7\text{-}(CR^{12}R^{13})_n\text{-}NR^9R^{10}$

can be produced, according to the process of the invention, by stirring the starting ruthenium complex in the presence of a slight excess of NR^7R^8-$(CR^{12}R^{13})_n$-NR^9NR^{10} or an equimolar amount of NR^9R^{10}-$(CR^{12}R^{13})_n$-NR^7-C'-NR^7-$(CR^{12}R^{13})_n$-NR^9R^{10}, respectively, in a suitable solvent, preferably an alcoholic solvent such as methanol. The reaction may be carried out at room temperature or at elevated temperature (eg, 30°C to 90°C) until a sufficient amount of product is formed; optionally after cooling the reaction mixture. The reaction mixture comprises a source of Y^{q-}, such as a compound of formula $(NH_4^+)Y^{q-}$ eg, NH_4PF_6.

Compounds of formula (I) in which A or B is an N-donor pyridine ligand may be obtained, according to the process of the invention, by heating a mixture of the starting ruthenium complex and excess pyridine compound (such as a 1.5- to 3- fold molar excess) in a suitable solvent such as benzene until a sufficient amount of product is formed. The reaction may be carried out under reflux conditions.

The precipitate which is formed in the process of the invention comprises or consists of the compound of the invention. The compound of the invention may be isolated from the reaction mixture by separating the precipitate from the liquid phase (eg, by filtration) and then removing the solvent from the precipitate (eg, under reduced pressure). The solid thus formed, which comprises or consists of the compound of the invention may, optionally, be purified eg, by recrystallisation from a suitable solvent (including, for certain compounds of the invention, acetonitrile or acetonitrile/ether (where A and B are R^{11}-CN and R^{11} is methyl) and methanol/ether).

The following non-limiting examples illustrate the present invention.

Examples

A. Synthesis

General

The starting materials, $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$, $[(\eta^6\text{-}C_6H_6)RuBr_2]_2$, $[(\eta^6\text{-}C_6H_6)RuI_2]_2$, $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$, $[(\eta^6\text{-}p\text{-cymene})RuBr_2]_2$, $[(\eta^6\text{-}p\text{-cymene})RuI_2]_2$ were prepared as previously reported[i]. Acetonitrile was dried over CaH_2 and ethylenediamine distilled over Na metal prior to use.

The preparations of Examples 1 and 2 were based on a published synthesis[ii] and followed the same general procedure.

Example 1

Preparation of $[(\eta^6\text{-}p\text{-cymene})RuCl(CH_3CN)_2]^+[PF_6]^-$

$[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ (0.31 g, 0.51 mmol) was stirred in 20 ml reagent grade acetonitrile. NH_4PF_6 (0.18 g, 1.10 mmol) in 5 ml acetonitrile was added in one portion, the flask sealed without specific precautions to exclude air and the reaction stirred at room temperature. After 14 h the pale precipitate was filtered off and the orange filtrate evaporated to leave an orange solid. This was dissolved in the minimum hot acetonitrile, filtered and allowed to cool. Ether was added until precipitation was obvious and the mixture placed in the freezer for 2 d. The precipitate was filtered, washed with ether and dried *in vacuo*.

Yield: 0.28 g, 0.56 mmol, 54.9 %

$C_{14}H_{20}ClF_6N_2PRu$ (497.82) Calc. %C = 33.78 %H = 4.05 %N = 5.62

Found %C = 33.80 %H = 3.91 %N = 5.53

Example 2

Preparation of $[(\eta^6\text{-}p\text{-cymene})RuBr(CH_3CN)_2]^+[PF_6]^-$

Procedure as in Example 1. $[(\eta^6\text{-}p\text{-cymene})RuBr_2]$ (0.24 g, 0.3 mmol), NH_4PF_6 (0.12 g, 0.74 mmol), dry acetonitrile (12 ml). Final product recrystallised from acetonitrile/ether as deep red crystals.

Yield: 0.28 g, 0.52 mmol, 86.67 %

$C_{14}H_{20}BrF_6N_2PRu$ (542.27) Calc. %C = 31.01 %H = 3.72 %N = 5.16

Found %C = 31.22 %H = 3.75 %N = 5.09

The ethylenediamine complexes of Examples 3 to 6 were prepared in the following manner[i]:

Example 3

Preparation of $[(\eta^6\text{-}C_6H_6)RuCl(H_2NCH_2CH_2NH_2\text{-}N, N)]^+[PF_6]^-$

$[(\eta^6\text{-}C_6H_6)RuCl_2]_2$ (0.167 g, 0.33 mmol) was suspended in dry methanol (50 ml) and ethylenediamine (0.06 g, 1 mmol) added in one portion. This was stirred for 3 h, filtered and NH_4PF_6 (0.5 g, 3.07 mmol) added. The volume was slowly reduced to approx. 15 ml on the rotary evaporator. The product formed as a microcrystalline solid on leaving to stand at 4 ^oC. This was collected, washed with ether and recrystallised from methanol/ether.

Yield: 0.128 g, 0.31 mmol, 46.96 %

$C_8H_{14}ClF_6N_2PRu$ (419.69) Calc. %C = 22.89 %H = 3.36 %N = 6.67

Found %C = 22.81 %H = 3.24 %N = 6.51

Example 4

Preparation of $[(\eta^6\text{-}C_6H_6)RuI(H_2NCH_2CH_2NH_2\text{-}N, N)]^+[PF_6]^-$

Procedure as in Example 3. $[(\eta^6\text{-}C_6H_6)RuI_2]_2$ (0.48 g, 0.55 mmol), dry methanol (80 ml), ethylenediamine (0.12 g, 2 mmol), NH_4PF_6 (0.5 g, 3.07 mmol).

Yield: 0.412 g, 0.81 mmol, 73.27 %

$C_8H_{14}IF_6N_2PRu$ (511.14) Calc. %C = 18.80 %H = 2.76 %N = 5.48

Found %C = 18.52 %H = 2.43 %N = 5.14

Example 5

Preparation of $[(\eta^6\text{-}p\text{-cymene})RuCl(H_2NCH_2CH_2NH_2\text{-}N, N)]^+[PF_6]^-$

Procedure as in Example 3. $[(\eta^6\text{-}p\text{-cymene})RuCl_2]$ (0.39 g, 0.64 mmol), methanol (60 ml), ethylenediamine (0.12 g, 2.00 mmol). The reaction was stirred for 1.5 h and the green liquid filtered. NH_4PF_6 (0.52 g, 3.2 mmol) was added to the yellow filtrate and the volume reduced to 15 ml. This was left to stand at 4 ^{0}C for 6 h during which time orange crystals formed.

Yield 0.23 g, 0.48 mmol, 37.73 %

$C_{12}H_{22}ClF_6N_2PRu$ (475.81) Calc. %C = 30.29 %H = 4.66 %N = 5.88

Found %C = 30.05 %H = 4.41 %N = 5.98

Example 6

Preparation of [(η^6-*p*-cymene)RuI($H_2NCH_2CH_2NH_2$-*N, N*)]$^+$[PF_6]$^-$

Procedure as in Example 3.[(η^6-*p*-cymene)RuI_2] (0.34 g, 0.348 mmol), ethylenediamine (0.06 g, 1mmol), NH_4PF_6 (0.52 g, 3.2 mmol). The volume was reduced to 15 ml and left stand at 4 ^{0}C overnight during which red crystals formed.

Yield: 0.235 g, 0.41 mmol, 59.48%

$C_{12}H_{22}IF_6N_2PRu$ (567.26) Calc. %C = 25.41 %H = 3.91 %N = 4.94

Found %C = 25.64 %H = 3.72 %N = 5.24

Example 7

Preparation of [(η^6-*p*-cymene)$RuCl_2$(isonicotinamide)]

[(η^6-*p*-cymene)$RuCl_2$] (0.129 g, 0.21 mmol) was set stirring in benzene (50 ml) and isonicotinamide (0.052 g, 0.43 mmol) added in one portion. The mixture was heated to reflux under argon for 4 h during which time a mustard coloured precipitate had formed. This was collected, washed with a little benzene and recrystallised from methanol/ether to give a red crystalline material.

Yield: 0.061 g, 0.142 mmol, 33.81 %

$C_{16}H_{20}Cl_2N_2ORu$ (428.30) Calc. %C = 44.87 %H = 4.71 %N = 6.54

Found %C = 44.65 %H = 4.54 %N = 6.23

Example 8

Preparation of [η^6-$C_6H_5CO_2CH_3$)RuCl($H_2NCH_2CH_2NH_2$-*N, N*)]$^+$[PF_6]$^-$

(a) Preparation of 1, 4-dihydrobenzoic acid[iv]

Benzoic acid (15.5 g, 0.13 mmol) was added to dry ethanol (100 ml) in a 1 l flask equipped with a mechanical stirrer, Dewar condenser and cooling bath (dry ice/acetone). NH_3 (600 ml) was condensed into the flask and Na

metal (8.3 g, 0.36 mmol) added in small pieces over a period of 30 min. When the final blue colour was discharged the mixture was left to stir for 20 min after which time solid NH_4Cl (20 g, 0.22 mol) was carefully added. The cooling bath was removed and the NH_3 allowed to evaporate with stirring, leaving a white residue. The residue was taken up in chilled H_2O (500 ml) and acidified to about pH3 by addition of 10% HCl. This was extracted with ether (4 x 200 ml) and the combined ether layers washed with saturated NaCl solution (1 x 100 ml) and dried over $MgSO_4$. The ether was removed on the rotary evaporator leaving a crude oil which was distilled under reduced pressure giving a clear oil.

Yield: 13.56 g, 109 mmol, 90.8 %

(b) Preparation of 3-methoxycarbonylcyclohexa-1, 4-diene

Concentrated H_2SO_4 (1 ml) was added to a solution of 1,4-dihydrobenzoic acid (3g, 23.97 mmol) in freshly dried methanol (10 ml). The reaction was heated to reflux in air for 1 h, cooled, poured into H_2O (25 ml) and extracted with ether (3 x 50 ml). The combined ether layers were washed with 5 % $Na[HCO_3]$ solution (50 ml) and saturated NaCl solution (50 ml) and dried over $MgSO_4$. The ether was removed on the rotary evaporator to leave a colourless oil which was used without further purification.

Yield: 2.60 g, 18.80 mmol, 42.8 %

(c) Preparation of $[(\eta^6\text{-}C_6H_5CO_2CH_3)RuCl_2]_2$

3-methoxycarbonylcyclohexa-1,4-diene (2.6 g, 18.80 mmol) was added to a filtered solution of $RuCl_3.3H_2O$ (1 g, 3.80 mmol) in methanol (50 ml). The reaction was heated to reflux for 8 h under argon. The reaction was cooled, filtered and the volume reduced to 20 ml. After standing for 12 h

at 4^{0}C the precipitate was collected, washed with a little methanol followed by ether and dried *in vacuo*.

Yield = 1.08 g, 1.75 mmol, 93.1 %

$C_{16}H_{16}Cl_4O_4Ru_2$ (616.24) Calc. %C = 31.18 %H = 2.62

Found %C = 31.05 %H = 2.39

(d) Preparation of $[(\eta^6\text{-}C_6H_5CO_2CH_3)RuCl(H_2NCH_2CH_2NH_2\text{-}N, N)]^+[PF_6]^-$

Ethylenediamine (0.09 g, 1.5 mmol) was added to a stirring suspension of $[(\eta^6\text{-}C_6H_5CO_2CH_3)RuCl_2]_2$ (0.355 g, 0.576 mmol) in methanol (200 ml). After 4 h the orange solution was filtered and the volume reduced to 20 ml. NH_4PF_6 (0.49 g, 2.3 mmol) was added and the mixture stirred for a further minute. The sealed flask was left to stand overnight at 4 ^{0}C. The precipitated yellow microcrystalline solid was collected, washed with a little methanol followed by ether and dried *in vacuo*.

Yield 0.22 g, 0.46 mmol, 40.0 %

$C_{10}H_{16}ClN_2O_2PF_6Ru$ (477.75) Calc. %C = 25.14 %H = 3.38 %N = 5.86

Found %C = 25.18 %H = 3.12 %N = 5.50

Example 9

Preparation of $[(\eta^6\text{-}C_6H_5C_6H_5)RuCl(H_2NCH_2CH_2NH_2\text{-}N, N)]^+[PF_6]^-$

(a) Preparation of 1,4-dihydrobiphenyl[v]

A solution of biphenyl (10 g, 65 mmol) in freshly dried THF (200 ml) was added to NH_3 (400 ml) which had been condensed under argon into a 1 l flask equipped with a Dewar condenser, cooling bath (dry-ice/acetone) and mechanical stirrer. Li wire (1.125 g, 162 mmol) was added in small pieces over a period of 15 min. After a further 15 min stirring, solid NH_4Cl (15 g, 280 mmol) was added and the dark red colour discharged.

The reaction was stirred at -60 ^{0}C for 10 min, then the cooling bath removed and the NH_3 allowed to evaporate under argon flow with stirring. The remaining residue was taken up in H_2O (200 ml) and acidified to pH3 with 10 % HCl. This was extracted with ether (4 x 150 ml) and the combined ether layers washed with saturated NaCl solution (1 x 150 ml) and dried over $MgSO_4$. The ether was removed on the rotary evaporator and the remaining oil distilled under reduced pressure (46 ^{0}C, 0.2 mmHg) to give clear oil which was used without further purification.

Yield: 6.45 g, 41.26 mmol, 63.5 %

(b) Preparation of $[(\eta^6\text{-}C_6H_5C_6H_5)RuCl_2]_2$

$RuCl_3.3H_2O$ (2.28 g, 8.7 mmol) was dissolved in dry ethanol (25 ml) and filtered. 1,4-Dihydrobiphenyl (2.43 g, 15.5 mmol) was added in one portion and the solution heated to reflux under argon for 4 h. On cooling a brown solid settled out of solution. This was collected, washed with a little ethanol followed by ether and dried *in vacuo*.

Yield: 2.77 g, 8.49 mmol, 97.6 %

$C_{24}H_{24}Cl_4Ru_2$ (652.36) Calc. %C = 44.19 %H = 3.71

Found %C = 44.67 %H = 3.25

(c) Preparation of $[(\eta^6\text{-}C_6H_5C_6H_5)RuCl(H_2NCH_2CH_2NH_2\text{-}N, N)]^+[PF_6]^-$

$[(\eta^6\text{-}C_6H_5C_6H_5)RuCl_2]_2$ (0.30 g, 0.46 mmol) was refluxed in H_2O (25 ml) for 1 h. At this time ethylenediamine (0.06 g, 1 mmol) was added to the refluxing suspension. The brown suspension immediately became dark green. This was refluxed for a further 30 min and filtered while hot. NH_4PF_6 (0.5 g, 3 mmol) was added to the yellowish filtrate and the flask briefly shaken. A yellow precipitate began to form almost immediately. The flask was sealed, allowed to cool to ambient temperature and placed

in an ice-bath for 3 h. The precipitate was collected, washed with a little water, followed by ethanol, followed by ether and dried *in vacuo*. This was recrystallised from methanol/ether.

Yield: 0.11 g, 0.22 mmol, 23.9 %

$C_{14}H_{18}ClF_6N_2PRu$ (495.82) Calc. %C = 33.91 %H = 3.66 %N = 5.65

Found %C = 34.06 %H = 3.37 %N = 5.44

Example 10

Preparation of $\{(\eta^6\text{-}C_6H_5C_6H_5)RuCl[H_2N(CH_2)_2NH(CH_2CH_3)]\}^+PF_6^-$

$[(\eta^6\text{-}C_6H_5C_6H_5)RuCl_2]_2$ (0.10 g, 0.158 mmol) was refluxed in water (10 ml) for 3 h and then cooled down to 80°C To this suspension was added N-ethylethylenediamine (37 mg, 0.42 mmol) The brown suspension immediately became dark green. This was then slowly heated to reflux again for a further 1.5 h and filtered while hot. NH_4PF_6 (0.2 g, 1.23 mmol) was added to the yellowish filtrate and the flask briefly shaken. A yellow precipitate began to form almost immediately. After standing at 4°C overnight, the precipitate was collected, washed with a little methanol followed by diethyl ether and dried in *vacuo*. This was recrystallised from methanol/ether.

Yield: 0.08 g, 0.153 mmol, 48.3%

$C_{16}H_{22}ClF_6N_2PRu$ (523.85)Calc. %C=36.68 %H=4.23 %N=5.35

Found %C=36.00 %H=4.37 %N=5.24

Example 11

Preparation of

$\{[\eta^6\text{-}C_6H_5C_6H_5)RuCl]_2[H_2N(CH_2)_2NH(CH_2)_6NH(CH_2)_2NH_2\text{-}N,N',N'',N''']\}^{2+}2PF_6^-$

The starting material $[(\eta^6\text{-}C_6H_5C_6H_5)RuCl_2]_2$ was prepared as previously described. Ethylenediamine and triethylamine were freshly distilled over Na. Tetrahydrofuran (THF) was dried by distillation from Na-benzophenone. Triphenylmethyl chloride (99%) and adipoyl chloride (98%) were purchased from the Arcos Chemical Co.. All other chemicals were AR grade and were used as received.

(a) N-tritylethyldiamine

A solution of trityl chloride (5.57 g, 20 mmol) in dichloromethane (25 ml) was slowly added into a solution of ethylenediamine (8 ml, 120 mmol) in dichloromethane (75 ml) with stirring at room temperature. The addition was accomplished within 1 h and the reaction stirred overnight. The white salt was filtered off and the filtrate washed with water and dried over anhydrous sodium sulphate. Dichloromethane was removed by rotary evaporation and the residue dissolved into methanol. A white precipitate began to form after shaking for a while and the mixture was kept in the refrigerator for 5 h and then filtered off. The methanol filtrate was reduced to 10 ml and kept in the refrigerator overnight. A white solid precipitated. This was collected as the desired product and washed with diethyl ether and dried *in vacuo*.

Yield: 4.5 g, 14.88 mmol, 74.4%,

(b) N,N'-Bis(2'tritylaminoethyl)-1,6-diamidohexane

N-Tritylethyldiamine (1.5 g, 4.96 mmol) and triethylamine (1.0 g, 7.29 mmol) were dissolved in chloroform (35 ml) and cooled in an ice bath. To this solution was added adipoyl chloride (0.36 ml, 2.48 mmol) in chloroform (10 ml) slowly with stirring. After addition, the mixture was refluxed for 2 h and cooled to room temperature. This was filtered to give a clear chloroform filtrate (see below). The filtered precipitate was dissolved into dichloromethane. This was washed with water and then saturated NaCl solution and dried over anhydrous sodium sulphate. Removal of the solvent by rotary evaporation gave a white product. The chloroform filtrate was also washed with water and saturated NaCl solution and dried over anhydrous sodium sulphate. After removal of chloroform, a further crop of product was obtained.

Yield: 1.40 g, 1.91 mmol, 77%

$C_{48}H_5O_2N_4H_2O$(732.96)

Calc. % C=78.66 %H=7.15 %N=7.64

Found %C=78.81 %H=6.73 %N=7.55

(c) N,N'-Bis(2'-tritylaminoethyl)-1,6-diaminohexane

Into a solution of N,N'-bis(2'-tritylaminoethyl)-1,6-diamidohexane (1.3 g, 1.82 mmol) in dry THF was added a suspension of $LiAlH_4$ (0.69 g, 18.18 mmol) in dry THF (20 ml) under argon with vigorous stirring. After the addition, the reaction was heated to a gentle reflux with stirring for 25 h. This was cooled to 4°C. The reaction product and excess of hydride were decomposed by the dropwise addition of H_2O (0.69 ml), followed by 15% (w/v) NaOH solution (0.69 ml) and H_2O (2.07 ml) in succession. After

vigorous stirring for 30 min, the mixture was filtered by suction and the resulting cake was washed thoroughly with dichloromethane. The combined filtrate was concentrated to dryness on the rotary evaporator and the resulting residue dissolved into dichloromethane (50 ml). This was washed with water and then saturated NaCl solution and dried over anhydrous sodium sulphate. Removal of dichloromethane by rotary evaporator afforded a colourless solid.

Yield: 1.20 g, 1.75 mmol, 96%

(d) N,N'-Bis(2-aminoethyl)-1,6-diaminohexane tetrahydrochloride

A mixture of N, N'-bis(2'-tritylaminoethyl)-1,6-diaminohexane (1.0 g 1.45 mmol) and 6 M HCl (30 ml) was refluxed for 3 h. Then the mixture was filtered and the filtrate was concentrated to about 3 ml over *vacuo*. Addition of methanol into the concentrated solution afforded a white salt.

Yield: 0.46 g, 1.32 mmol, 92%

$C_{10}H_{26}N_4.4HCl(348.09)$

Calc. %C=34.48 %H=8.68 %N=16.09

Found %C=34.26 %H=8.77 %N=16.24

(e) $\{[\eta^6\text{-}C_6H_5C_6H_5)RuCl]_2[H_2N(CH_2)_2NH(CH_2)_6NH(CH_2)_2NH_2\text{-}N,N',N'',N''']\}^{2+}2PF_6^-$

$[(\eta^6\text{-}C_6H_5C_6H_5)RuCl_2]_2$ (0.106 g, 0.162 mmol) in 10 ml water was refluxed for 2.5 h and then cooled to 50°C. Into this suspension was added a solution of N,N'-bis(2-aminoethyl)-1,6-diaminohexane (0.162 mml) in methanol which was obtained by the treatment of N,N'-bis(2'-

aminoethyl)-1,6-diaminohexane tetrahydrochloride (56.39 g, 0.162 mmol) with 1.294 ml 0.5008 N KOH-MeOH solution. The mixture was then heated to reflux for 1.5 h. This was filtered while hot. NH_4PF_6 (0.175 g, 1.07 mmol) was added into the bright yellow filtrate to yield a bright yellow precipitate. This was recrystallized from methanol/ether.

Yield: 0.10 g, 0.093 mmol, 57.5%

$C_{34}H_{46}Cl_2F_{12}N_4P_2Ru_2$(1073.74)

Calc. %C=38.03 %H=4.32 %N=5.22

Found %C=37.86 %H=4.25 %N=5.20

B. Biological Data

1. Protocol for testing Ru compounds

The compounds are tested on 24-well trays. Cells growing in a flask are harvested just before they become confluent, counted using a haemocytometer and diluted down with media to a concentration of $1x10^4$ cells per ml. The cells are then seeded in the 24-well trays at a density of $1x10^4$ cells per well (i.e. 1ml of the diluted cell suspension is added to each well). The cells are then left to plate down and grow for 72 hours before adding the compounds of the invention.

The Ru complexes are weighed out and made up to a concentration of 1mg/ml with deionised water then sonicated until they go into solution. The appropriate volume of the Ru solution is added to 5ml of media to make it up to a concentration of 100μM for each drug. This 100μM

solution is then serially diluted to make up the 10μM, 1μM and 0.1μM solutions.

The media is removed from the cells and replaced with 1ml of the media dosed with drug. Each concentration is done in duplicate. A set of control wells are left on each plate, containing media without drug.

The cells are left exposed to the drugs for 24 hours and then washed with phosphate buffered saline before fresh media is added.

They are allowed to grow on for a further 3 days before being counted using a Coulter counter.

Preparing cells for counting:

Media is removed and 1ml of PBS is added to the cells.
250μl of trypsin is added and cells left in incubator for a few minutes to allow the monolayers to detach.
Once trypsinised, 250μl of media is added to each well to neutralise the trypsin. 200μl of this suspension is added to 10ml of NaCl for counting.

2. Results

Using the above protocol, a number of compounds of the invention were tested on A2780 ovarian cancer cell line. The results are as follows:

Compound (Example No.)	IC50 (μM)
1	7
2	8
7	11
5	8
4	20
3	8
6	6
9	6
8	55
10	6
11	5

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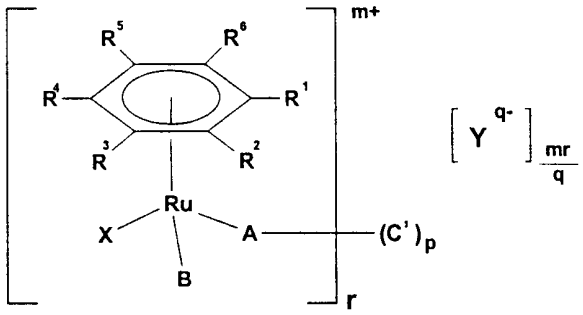
CLAIMS

1. Ruthenium (II) compound of formula (I):



(I)

wherein: R^1, R^2, R^3, R^4, R^5 and R^6 independently represent H, alkyl, $-CO_2R'$, aryl or alkylaryl, which latter two groups are optionally substituted on the aromatic ring;

R' represents alkyl, aryl or alkaryl;

X is halo, H_2O, (R')(R'')SO, $R'CO_2^-$ or (R')(R'')C=O, where R'' represents alkyl, aryl or alkaryl;

Y is a counterion;

m is 0 or 1;

q is 1, 2 or 3;

C' is C_1 to C_{12} alkylene, optionally substituted in or on the alkylene chain, bound to two A groups;

p is 0 or 1 and r is 1 when p is 0 and r is 2 when p is 1; and

A and B are: each independently N-donor nitrile ligands; or B is halo and A is an N-donor pyridine ligand, optionally substituted at one or more of the carbon atoms of the pyridine ring; or p is 0, A is NR^7R^8 and B is NR^9R^{10}, wherein R^7, R^8, R^9 and R^{10} independently represent H or alkyl, and A and B are linked by an alkylene chain, optionally substituted in or

on the alkylene chain; or p is 1, A is NR^7 and B is NR^9R^{10}, wherein R^7, R^9 and R^{10} are as previously defined, and A and B are linked by an alkylene chain, optionally substituted.

2. Compound as claimed in Claim 1, wherein R^2, R^3, R^4, R^5 and R^6 all represent H.

3. Compound as claimed in Claim 1 or Claim 2, wherein R^1 is H.

4. Compound as claimed in Claim 1, wherein R^1 is 2-propyl and R^4 is methyl.

5. Compound as claimed in Claim 1 or Claim 2, wherein R^1 is phenyl.

6. Compound as claimed in claim 1 or Claim 2, wherein R^1 is $-CO_2CH_3$.

7. Compound as claimed in any one of Claims 1 to 6, wherein A and B are both R^{11}-CN and R^{11} represents alkyl.

8. Compound as claimed in any one of Claims 1 to 6, wherein one of A and B is a 4-substituted pyridine and the other is halo.

9. Compound as claimed in any one of Claims 1 to 6, wherein A and B together represent NR^7R^8-$(CR^{12}R^{13})_n$-NR^9R^{10}, wherein R^{12} and R^{13} are hydrogen, or are linked at the same or neighbouring carbon atoms to form a carbocylic ring, and n is an integer from 1 to 4.

10. Compound as claimed in Claim 9, wherein R^7, R^8, R^9 and R^{10} all represent H.

11. Compound as claimed in Claim 9 or Claim 10, wherein R^{12} and R^{13} are both H and n is 2.

12. Compound as claimed in any one of Claims 9 to 11, wherein p is 0.

13. Compound as claimed in any one of Claims 9 to 11, wherein R^8 is absent, p is 1 and C' is C_4 to C_{10} straight chain alkylene.

14. Compound of any one of Claims 1 to 13 for use in medicine.

15. Use of a compound of any one of Claims 1 to 13 in the manufacture of a medicament for the treatment and/or prevention of cancer.

16. Pharmaceutical composition comprising a compound of any one of Claims 1 to 13 together with one or more pharmaceutically acceptable excipients.

17. A method of treating and/or preventing cancer which comprises administering to a subject a therapeutically effective amount of a compound of any one of Claims 1 to 13 or a composition of Claim 16.

18. Process for preparing the compound of any one of Claims 1 to 13 which comprises the reaction of a compound of formula [(η^6-

$C_6(R^1)(R^2)(R^3)(R^4)(R^5)(R^6))RuX_2]$, optionally in the form of a dimer, with A and B, optionally in the presence of Y^{q-}, in a suitable solvent for the reaction, wherein R^1,R^2, R^3, R^4, R^5, R^6, X, A, B, q and Y are as defined in Claim 1.

INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/GB 00/04144

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07F15/00 A61K33/24 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 C07F 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)

PAJ, CHEM ABS Data, EPO-Internal

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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X	SOLORZANO, CARMEN; DAVIS, MICHAEL A.: "Preparation of arene ruthenium(II) complexes with activated ligands" INORG. CHIM. ACTA, vol. 97, no. 2, 1985, pages 135-141, XP000980284 page 136 --- -/--	1-3,8-12

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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Date of the actual completion of the international search	Date of mailing of the international search report
29 January 2001	13/02/2001

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	Bader, K

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

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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