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(54) Title: SELECTIVE MMP INHIBITORS HAVING REDUCED SIDE-EFFECTS

(57) Abstract

A matrix metalloproteinase (MMP) inhibitor that exhibits an IC_{50} of below 10^{-4}M against MMP and has substantially no activity against non-MMP metalloproteinase-related events has reduced side-effects, especially with respect to joint pain.

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SELECTIVE MMP INHIBITORS HAVING REDUCED SIDE-EFFECTS

Field of the Invention

This invention relates to selective MMP inhibitors having reduced side-effects.

Background of the Invention

Compounds having the ability to inhibit matrix metalloproteinases (MMPs) and optionally also TNFα release are described in WO-A-9513289, WO-A-9611209, WO-A-9635711, WO-A-9635712, WO-A-9635714, WO-A-9635687, WO-A-9712902, WO-A-9719075, WO-A-9738007, WO-A-9805635 and WO-A-9806696. All these specifications are incorporated herein by reference. By way of example, WO-A-9611209 (Examples 52 and 72) and WO-A-9712902 (Example 6) disclose (*S*)-N-[2-mercapto-5-phthalimido]pentanoyl-*L*-leucyl-(*S*)-*tert*-leucine N-methylamide, 2*S*-[4-(2,5-dioxopyrrolidin-1-yl)-2-mercaptobutyrylamino]-4-methylpentanoic acid (2,2-dimethyl-1*S*-methylcarbamoylpropyl)amide, and 2-[2-mercapto-4-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)butyrylamino]-4-methylpentanoic acid (2,2-dimethyl-1-methylcarbamoylpropyl)amide, as racemates. Other compounds of this general type are also known.

MMPs are a group of structurally related endopeptidases that degrade the proteinaceous elements of the extracellular matrix. A number of important features are shared by members of the MMP family and include a zinc atom at the catalytic active site, catalytic activity at neutral pH, initial existence as inactive proenzymes, activation involving removal of an N-terminal domain, structural stabilisation by calcium, and inhibition of the catalytically active forms by a family of specific protein inhibitors called Tissue Inhibitor of Metalloproteinases (TIMPs). The MMP family currently consists of twenty members including MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-18, MMP-19 and MMP-20 ("classical MMPs").

The MMPs are a sub-family of a much larger group of zinc-containing proteinases which include the Reprolysins and Serralysins, and the Astacin family. Of particular interest are the Adamalysins, members of the Reprolysin family, which include the metalloproteinase involved in the release of TNFα and which is presumably inhibited by compounds such as those described in the patent publications/applications identified above.

It has been demonstrated that compounds which inhibit MMPs also have the capability to inhibit a number of other events that are mediated by metalloproteinases and that include the release of TNFα, CSF-1, TGFα, L-selectin, CD30 and Fas Ligand and the shedding of the IL-6, TNF-RI and TNF-RII receptors. See Hooper *et al* (1997), Biochem. J., 321:265-279.

MMP inhibitors have been proposed for use in patients with arthritis conditions especially where degradation of cartilage occurs, a process known to involve MMPs. In addition, the use of these compounds in the treatment of various cancers has been advocated. Inhibition of the MMPs, which have been associated with certain disease modalities, offers potential therapeutic benefit. However, the inhibition of other non-MMP metalloproteinases may offer no therapeutic benefit and indeed could be deleterious. For example, it has been suggested that MMP inhibitors which also inhibit the release of TNFα may have a role in exacerbating liver injury; see Solorzano *et al* (1997), J. Immunol., 158:414-419.

Similarly, early clinical evidence from the use of MMP inhibitors suggests that their use is associated, in many patients, with joint pain. See Wojtowicz-Praga *et al*, Lombardi Cancer Center, Georgetown University Hospital, Washington DC & BBL Anapolis MD, Am. Soc. Clin. Oncol. (May 1996) "The Pharmacokinetics (PK) of Marimastat (BB-2516), A Novel Matrix Metalloproteinase Inhibitor (MMPI) administered orally to patients with metastatic lung cancer". The problem may require treatment "holidays", for up to 50% of the course of treatment, or the administration of non-steroidal anti-inflammatory agents (NSAIDs).

Summary of the Invention

This invention is based on the appreciation that compounds having particularly valuable properties are of the type which have activity against the classical MMPs, but lack or have little activity against non-MMP metalloproteinase (MP)-related events. This particular profile of activity may confer a therapeutic benefit, particularly regarding the joint pain and tendonitis seen with less selective compounds. Treatment "holidays" may be avoided, e.g. allowing continued treatment. The use of NSAIDs can also be avoided.

This selectivity may be defined in terms of a specific range of activity in defined models of MMP and MP effects. In particular, compounds to which this invention relates have characteristics x and y wherein:

x = MMP inhibition, in terms of IC_{50} measured as described in Example A below; and

y = Inhibition of MP-related effects, in terms of IC_{50} as described in Examples B-F below;

x is below 10^{-4} M, preferably below 10^{-6} M, more preferably 10^{-6} M to 10^{-9} M or 10^{-10} M; and

y is greater than 10^{-7} M, preferably greater than 10^{-6} M, more preferably 10^{-6} M to 10^{-4} M.

An important characteristic related to y is that y is greater or equal to 2×10^{-5} for at least 4 out of 5 MP-related effects defined by Examples B-F; this is distinct from most prior art compounds having characteristic x.

Description of the Invention

It has become clear that MMP inhibitors that are very effective in certain areas, e.g. as anti-cancer agents, may have undesirable side-effects. In particular, it appears that, by attaining the selectivity described above, compounds of this invention may overcome the known problems of joint pain experienced by a proportion, albeit significant (c. 30%), of patients treated with MMP inhibitors. The selectivity may be determined by the use of an appropriate assay, for example as described in Examples A-F.

Specific examples of compounds showing the desired profile are those of Examples 1 and 2 and cpd. 3 (see below). These three compounds have been tested in the marmoset tendonitis study. This procedure for this study has been defined by Wojtowicz-Praga *et al*, *supra*. The study was performed with oral dosing at 30 and 100 mg/kg for 3 months. Repeated plasma sampling showed sustained levels in excess of the enzymes' IC_{50}, up to 9 h post-dose. Continuous clinical observation revealed no adverse effects. Histological observation revealed no adverse effects on joints and tendons. This is not necessarily seen with all MMP inhibitors. See Hooper *et al*, *supra*. It indicates that such compounds are suitable for continued administration.

A compound of the invention may be given in a composition, by a route and/or in an amount that is already known for that compound or for analogues thereof, e.g. as described in the patent specifications identified above. It may be given to patients who have already experienced joint pain (under any circumstances) and to those who are

susceptible to joint pain, e.g. those having injured joints. It is within the ability of one skilled in the art to determine which patients are at risk from this complication.

The compound may be used in the treatment or prophylaxis of cancer, inflammation or any condition associated with MMP activity. Many examples are given in the patent publications/applications identified above.

The duration of administration may be conducted on a regular basis, without interruption. This may involve periods of at least 1, 2 , 3, 6 or more months

Example A MMP Inhibition Activity-Fluorimetric Assay

The potency of inhibitors of collagenase-1(MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), gelatinase-A (MMP-2), gelatinase-B (MMP-9) and stromelysin-1 (MMP-3) is determined using the following procedure:

Inhibitors are dissolved in dimethyl sulphoxide containing 0.02% β-mercaptoethanol, and serial dilutions are prepared. Activated enzyme is incubated in assay buffer containing 50mM Tris, pH 7.4, 5mM $CaCl_2$, 0.002% NaN_3 and Brij 35 in the presence and absence of inhibitor. Samples are preincubated at 37°C for 15 minutes before the addition of the fluorimetric substrate (Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2) to a final concentration of 10 μM. The assay is incubated for 20-30 min at 37°C and then read in a Fluoroscan II at λ_{ex} (340nm) and λ_{em} (405nm).

The enzyme activity is compared to activity in a control devoid of inhibitor. Results are reported as that inhibitor concentration effecting 50% inhibition of the enzyme (IC_{50}).

Example B Inhibition of TNFα production

The potency of inhibitors of the production of TNFα is determined using the following procedure:

A 100 μM solution of the inhibitor being tested or dilutions thereof is incubated at 37° C in an atmosphere of 5% CO_2 with peripheral blood mononuclear cells (PBMC). PBMC are isolated from buffy coats by standard procedures using Ficoll. The PBMC are suspended in RPMI 1640 medium with 2% fetal calf serum at a cell density of 2 x 10^6/ml and stimulated with LPS. After 18 hours the supernatant is assayed for the levels of TNFα using a commercially available ELISA kit.

The activity in the presence of 100 μM inhibitor or dilutions thereof is compared to activity in a control devoid of inhibitor. Results are reported as that inhibitor concentration effecting 50% inhibition of the production of TNFα.

Example C Inhibition of L-selectin shedding

An assay of L-selectin shedding by peripheral blood mononuclear cells (PBMC) is conducted as follows:

PBMC are isolated from buffy coats by standard procedures using Ficoll. A 100 μM solution of the inhibitor being tested or dilutions thereof is incubated for 20 min at 37°C in an atmosphere of 5% CO_2 with 4 x 10^6/ml PBMC stimulated with PMA. The cells are centrifuged down and the supernatants tested for sL-selectin using a commercially available ELISA kit.

The activity in the presence of 100 μM inhibitor or dilutions thereof is compared to activity in a control devoid of inhibitor. Results are reported as that inhibitor concentration effecting 50% inhibition of the shedding of L-selectin.

Example D Inhibition of sIL-1RII shedding

An assay of sIL-1RII shedding by PBMC is conducted as follows:

PBMC are isolated from buffy coats by standard procedures using Ficoll. A 100 μM solution of the inhibitor being tested or dilutions thereof are incubated for 18h at 37° C in an atmosphere of 5% CO_2 with 2 x 10^6/ml PBMC stimulated with IL-13. The cells are centrifuged down and the supernatants tested for sIL-1RII using a commercially available ELISA kit.

The activity in the presence of 100 μM inhibitor or dilutions thereof is compared to activity in a control devoid of inhibitor. Results are reported as that inhibitor concentration effecting 50% inhibition of the shedding of sIL-1RII.

Example E Inhibition of IL-6R shedding

An assay of sIL-6R shedding by HL-60 cells is conducted as follows:

PBMC are isolated from buffy coats by standard procedures using Ficoll. A 100μM solution of the inhibitor being tested or dilutions thereof is incubated for 24h at 37° C in an atmosphere of 5% CO_2 with 2 x 10^6/ml HL-60 cells stimulated with PMA. The cells are centrifuged down and the supernatants tested for sIl-6R using a commercially available ELISA kit.

The activity in the presence of 100μM inhibitor or dilutions thereof is compared to activity in a control devoid of inhibitor. Results are reported as that inhibitor concentration effecting 50% inhibition of the shedding of IL-6R.

Example F Inhibition of TNF RII shedding

The potency of inhibitors of the shedding of TNF RII is determined using the following procedure:

A 100 μM solution of the inhibitor being tested or dilutions thereof is incubated at 37° C in an atmosphere of 5% CO_2 with THP-1 cells (human monocytes) suspended in RPM1 1640 medium and 20μM ß-mercaptoethanol at a cell density of 1 x 10^6/ml and stimulated with LPS (lipopolysaccharide). After 18 hours the supernatant is assayed for the levels of sTNF RII using a commercially available ELISA kit.

The activity in the presence of 0.1 mM inhibitor or dilutions thereof is compared to activity in a control devoid of inhibitor. Results are reported as that inhibitor concentration effecting 50% inhibition of the shedding of TNF RIL

The following Intermediates illustrate stages in the synthesis of the compound of Example 1.

Intermediate 1 (*S*)-(2,2-Dimethyl-5-oxo[1,3]dioxolan-4-yl)acetic Acid

(L)-Malic acid (200 g) was added to a mixture of acetone (800 mL) and 2,2-dimethoxypropane (342 mL) with stirring under nitrogen. Montmorillonite K-10 clay (5 g) was added to the solution and stirred for 17 hours, then the solution was filtered and reduced in volume to approximately 450 mL. The solution was cooled to 5°C, and the resultant crystals of the title compound filtered off (108 g, 42%).

MP 108 - 109.5°C

Intermediate 2 (*S*)-5-(2-Hydroxyethyl)-2,2-dimethyl[1,3]dioxolan-4-one

Intermediate 1 (50 g) was dissolved in tetrahydrofuran (400 mL) and cooled to 2°C. To this solution was carefully added borane-methyl sulfide complex (45.5 mL) and the mixture was stirred for 63 hours. The mixture was evaporated to a clear oil, dissolved in ethyl acetate (600 mL), washed with saturated aqueous sodium bicarbonate (100 mL) and water (100 mL) and dried over magnesium sulfate. Filtration and evaporation *in vacuo* afforded the title compound as a clear oil (36 g, 79%).

TLC R_f 0.41 (Ethyl acetate : Hexane, 1 : 1)

Intermediate 3 **(*S*)-5-(2-Mesyloxyethyl)-2,2-dimethyl[1,3]dioxolan-4-one**

Intermediate 2 (24 g) was dissolved in dichloromethane (480 mL) and cooled to 2°C. To this solution was added mesyl chloride (14.5 mL) followed by dropwise addition of triethylamine (25 mL). The solution was then warmed to room temperature and stirred for 40 minutes, washed with water (2 x 120 mL), brine (60 mL) and dried over magnesium sulfate. Filtration and evaporation *in vacuo* afforded the title compound as a clear oil (37.4 g, 100 %).

TLC R_f 0.48 (Ethyl acetate : Hexane, 1 : 1)

Intermediate 4 **(*S*)-1-[2-(2,2-Dimethyl-5-oxo[1,3]dioxolan-4-yl)-ethyl]-pyrrolidine-2,5-dione**

Intermediate 3 (5 g) was dissolved in N,N-dimethylformamide (50 mL) and potassium succinimide (3.7 g) and sodium iodide (0.6 g) added. The mixture was then heated to 70°C for 15 hours after which time the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (100 mL) and filtered through a plug of silica. The plug of silica was washed with further ethyl acetate (300 mL) and the combined organic solutions evaporated to an oil, which upon trituration with diethyl ether (5 mL) and cooling to 2°C provided crystals which were filtered to give the title compound (2.4 g, 47%).

TLC: R_f 0.88 (Ethyl acetate : Methanol, 8 : 2, one drop of acetic acid).

Intermediate 5 **(*S*)-4-(2,5-Dioxopyrrolidin-1-yl)-2-hydroxybutyric Acid**

Intermediate 4 (2.3 g) was suspended with Dowex 50WX4-400 resin (1.0 g) in methanol (23 mL) and water (4.6 mL) then stirred for 19 hours. The resin was removed by filtration and solvent removed *in vacuo* to give an oil. The oil was seeded with some crystals of the product and cooled to -25°C, upon complete crystallisation, the solid was washed on a filter bed with diethyl ether (10 mL) and ethyl acetate (1 mL) affording the title compound (1.5 g, 78%).

TLC R_f 0.20 (Ethyl acetate : Methanol, 8 : 2, one drop of acetic acid).

Intermediate 6 **(*R*)-2-Bromo-4-(2,5-dioxopyrrolidin-1-yl)butyric Acid**

Intermediate 5 (18.4 g) was dissolved in 30% hydrobromic acid / acetic acid (111 mL) under nitrogen, and the mixture stirred at ambient temperature for 35 minutes. After this time the reaction was poured into water (300 mL) and extracted with ethyl acetate (4 x 400 mL). The combined extracts were washed with brine (100 mL), dried over

magnesium sulfate, filtered and evaporated to an oil. This was then purified on silica (450 g) with an eluent of dichloromethane and ethyl acetate (3 : 1) with 2% acetic acid. The correct fractions were combined and evaporated *in vacuo* to afford an oil which was dissolved in heptane. Re-evaporation *in vacuo* afforded the title compound as a white powder (10.9 g, 45%).

TLC R_f 0.16 (99% Ethyl acetate, 1% acetic acid).

Intermediate 7 **(*S*)-2-Acetylsulfanyl-4-(2,5-dioxopyrrolidin-1-yl)butyric Acid**

Intermediate 6 (10.5 g) was dissolved in methanol (53 mL) and cooled to 0°C under nitrogen. To this solution was added potassium thioacetate (4.9 g) and the mixture warmed with stirring to ambient temperature, then stirred for 90 minutes. The solvent was then removed *in vacuo* and the residue resuspended in dichloromethane (200 mL) and water (30 mL). The aqueous layer was extracted with dichloromethane (3 x 200 mL) and the combined organic layers washed with brine (50 mL) and dried over magnesium sulfate. Filtration and evaporation afforded an oil which was mixed with diethyl ether (10 mL). After cooling to 2°C, crystals of the title compound were isolated by filtration (8.2 g, 80%).

MP 110 - 112°C.

Intermediate 8 **Thioacetic Acid 1*S*-[1*S*-(2,2-Dimethyl-1*S*-methylcarbamoyl-propylcarbamoyl)-3-methylbutylcarbamoyl]-3-(2,5-dioxo-pyrrolidin-1-yl)propyl Ester**

Intermediate 7 (1.28 g) was dissolved in dichloromethane (32 mL) and cooled to 0°C under nitrogen. To this solution was added 2-amino-4-methylpentanoic acid (2,2-dimethyl-1-methylcarbamoylpropyl)amide (1.33 g) rapidly followed by 1-hydroxybenzotriazole hydrate (0.667 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.14 g), after which the mixture was stirred at 0°C for 45 minutes, then at ambient for 3.5 hours. The reaction was then diluted with dichloromethane (35 mL), washed with saturated aqueous sodium bicarbonate (20 mL), 1 M hydrochloric acid (20 mL) and water (30 mL), and dried over magnesium sulfate. Filtration and evaporation gave the crude title compound as a glassy solid (2.5 g, 100%).

TLC: R_f 0.23 (Ethyl acetate).

Example 1 **2*S*-[4-(2,5-Dioxopyrrolidin-1-yl)-2*S*-mercaptobutyrylamino]-4-methylpentanoic Acid (2,2-Dimethyl-1*S*-methylcarbamoylpropyl)-amide**

Intermediate 8 (2.3 g) was dissolved in methanol (115 mL) and degassed. To this solution was added dithiothreitol (0.071 g). Degassing was performed again. Aqueous ammonia (3.0 mL) was added and the mixture stirred at ambient temperature for 45 minutes. The methanol was removed *in vacuo* to give an oil which was purified by column chromatography (ethyl acetate : methanol, 95 : 5). The correct fractions were combined and evaporated *in vacuo* at 40°C to provide the title compound as a glassy solid (1.8 g, 86%).

MP 81 - 84°C

TLC R_f 0.37 (Ethyl acetate : methanol, 95 : 5).

Example 2 **2*S*-[2*S*-Mercapto-4-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)butyrylamino]-4-methylpentanoic Acid (2,2-Dimethyl-1*S*-methylcarbamoylpropyl)amide**

Was prepared as described for Example 6 in WO-A-9712902, by resolution of an intermediate involved in the synthesis or by separation of the distereoisomers of Example 6 in WO-A-9712902 by hplc.

Biological Data

The following Table reports results (in μM) from the assays described above, for the compounds of Examples 1 and 2, and also for the compound (Cpd. 3) of Example 52 of WO-A-9611209, i.e. (*S*)-N-[2-mercapto-5-phthalimido]pentanoyl-*L*-leucyl-(*S*)-*tert*-leucine N-methylamide.

Assay	Cpd. 3	Ex. 1	Ex. 2
Example A			
MMP-1	0.028	0.012	0.025
MMP-8	0.009	0.010	0.010
MMP-13	0.002	0.004	0.004
MMP-2	0.015	0.130	0.041
MMP-9	0.005	0.053	0.025
MMP-3	0.179	0.381	0.157
Example B	10	IA	IA
Example C	IA	IA	IA
Example D	IA	38	IA
Example E	IA	IA	IA
Example F	IA	IA	IA

IA means no activity at the highest concentration tested, which was 50 or 100 μM.

CLAIMS

1. Use of a matrix metalloproteinase (MMP) inhibitor for the manufacture of a medicament for the treatment of a patient having a condition for which such an inhibitor is effective, wherein the inhibitor exhibits an IC_{50} of below 10^{-4} M against MMP and has substantially no activity against non-MMP metalloproteinase-related events.

2. Use of a MMP inhibitor for the manufacture of a medicament for the treatment of a patient having a condition for which such an inhibitor is effective, wherein the inhibitor is selected following the observance of no adverse effects in the marmoset tendonitis study described herein.

3. Use according to claim 1 or claim 2, wherein the inhibitor exhibits enzyme inhibition selectivity substantially the same as that exhibited by (*S*)-N-[2-mercapto-5-phthalimido]pentanoyl-*L*-leucyl-(*S*)-*tert*-leucine N-methylamide or the compound of claim 12 or claim 13.

4. Use according to any preceding claim, wherein the inhibitor exhibits values of x below 10^{-4} and y greater than 10^{-7} M, x being the MMP inhibition, in terms of IC_{50} measured as described in Example A, and y being the inhibition of MP-related effects, in terms of IC_{50} as described in Examples B-F, provided that y is at least $2x10^{-5}$ M in 4 or 5 of these Examples.

5. Use according to claim 4, wherein x is below 10^{-6} M.

6. Use according to claim 4 or claim 5, wherein y is greater than 10^{-6} M.

7. Use according to any preceding claim, for the treatment of a patient who is susceptible to, or has experienced, joint pain.

8. Use according to any of claims 1 to 7, wherein the condition is cancer.

9. Use according to any of claims 1 to 7, wherein the condition is inflammation.

10. Use according to any preceding claim, wherein the inhibitor is administered regularly over a period of at least 3 months.

11. Use according to any preceding claim, without the concomitant use of non-steroidal anti-inflammatory agent.

12. 2*S*-[4-(2,5-Dioxopyrrolidin-1-yl)-2*S*-mercaptobutyrylamino]-4-methylpentanoic acid (2,2-dimethyl-1*S*-methylcarbamoylpropyl)amide.

13. 2*S*-[2*S*-Mercapto-4-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)butyrylamino]-4-methylpentanoic acid (2,2-dimethyl-1*S*-methylcarbamoylpropyl)amide.

14. Use according to any of claims 1 to 11, wherein the inhibitor is the compound of claim 12 or claim 13.

INTERNATIONAL SEARCH REPORT

·national Application No
PCT/GB 98/00659

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/55 C07K5/06

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 6 A61K C07K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 11209 A (CHIROSCIENCE LTD) 18 April 1996 cited in the application see page 58; example 52 see page 61; example 72 ---	1-13
X	WO 95 13289 A (CHIROSCIENCE LTD ;MONTANA JOHN (GB); DICKENS JONATHON (GB); OWEN D) 18 May 1995 see claims 1-6 ---	1-11
X	WO 96 35711 A (CHIROSCIENCE LTD ;BAXTER ANDREW DOUGLAS (GB); MONTANA JOHN (GB); O) 14 November 1996 see claims 1-33 --- -/--	1-11

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

[X] Patent family members are listed in annex.

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

INTERNATIONAL SEARCH REPORT

national Application No
PCT/GB 98/00659

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 24449 A (CELLTECH LTD ;PORTER JOHN ROBERT (GB); MORPHY JOHN RICHARD (GB); M) 9 December 1993 see page 20, paragraph 3 - page 21, paragraph 1 ---	1-11
X	WO 94 25434 A (CELLTECH LTD ;MORPHY RICHARD JOHN (GB); MILLICAN ANDREW THOMAS (GB) 10 November 1994 see page 24, line 4 - line 31 ---	1-11
P,X	WO 97 12902 A (CHIROSCIENCE LTD) 10 April 1997 cited in the application see page 30; example 6 ---	1-13
P,X	WO 97 17088 A (CHIROSCIENCE LTD ;POPE NICHOLAS ROBERT (GB); WILLS RUTH ELIZABETH) 15 May 1997 see page 2, line 20 - line 25 see page 3, line 5 - line 15 -----	1-13

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INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons.

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-11 (partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

In view of the purely functional definition of the subject-matter as defined in Claims 1 - 11 no comprehensive search covering the entire subject-matter is possible

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

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

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

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

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

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

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

Remark on Protest

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No
PCT/GB 98/00659

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