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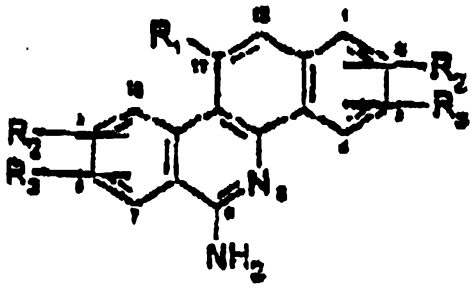
(54) Title: PHENANTHRIDINE DERIVATIVES, METHODS OF PRODUCING THEM AND MEDICAMENTS CONTAINING PHENANTHRIDINE DERIVATIVES

(54) Bezeichnung: PHENANTHRIDINDERIVATE, VERFAHREN ZU IHRER HERSTELLUNG UND ARZNEIMITTEL, ENTHALTEND PHENANTHRIDINDERIVATE

(57) Abstract

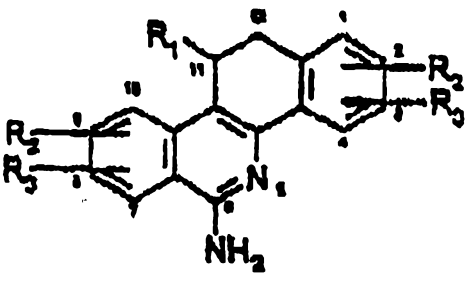
Disclosed are novel phenanthridine derivatives of general formulæ (I) and (II) and the salts thereof. In the formulæ, R_1 is a hydrogen atom or aromatic carbocyclic or heterocyclic group, and R_2 and R_3 can be either identical or different and stand for a hydrogen atom, an alkyloxy group, an alkylene-oxy group, a halogen atom or a nitro group. The derivatives in question have anti-tumoral, anti-microbial, fungicidal, anti-viral and anti-inflammatory properties.



(I)

(57) Zusammenfassung

Neue Phenanthridinderivate der allgemeinen Formel (I) und (II) sowie deren Salze, worin R_1 ein Wasserstoffatom, einen aromatischen carbocyclischen oder heterocyclischen Rest, und R_2 und R_3, die gleich oder verschieden sein können, ein Wasserstoffatom, einen Alkyloxyrest, einen Alkylenoxyrest, ein Halogenatom oder eine Nitrogruppe bedeuten, besitzen antitumorale, antimikrobielle, antifungizide, antivirale und antiinflammatorische Eigenschaften.



(II)

**Phenanthridine Derivatives,
Method for producing the Above and Medicines containing
Phenanthridine Derivatives**

The invention relates to new phenanthridine derivatives, which have an amino-group in position 6, a method for their production and for producing medicines containing phenanthridine derivatives.

Presently known syntheses of benzo(c)phenanthridine, its 11,12 dihydro-derivatives and similar compounds are very complex. The methods of Robinson et al. concerning the Bischler-Napieralski cyclisation and also of Ninomiya et al. using photocyclisation by Enamiden or by Shamma et al. and Cushman et al. concerning the Dickman-Thorpe-cyclisation should be mentioned here, said methods all extending over a great number of reaction steps (see I. Ninomya and T. Naito: Synthesis of the benzo(c)phenanthridine alkaloids. Recent. Dev. Nat. Carbon compd. 10,

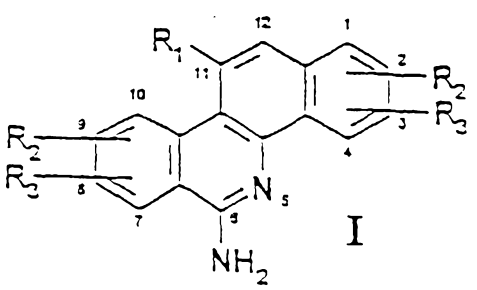
11-90 (1984) and the literature mentioned there).

Furthermore, benzo(c)phenanthridine derivatives and their anti-tumour effect are known from Pharmacy 44 pp. 593-597 (1989). Further phenanthridine derivatives are described in Tetrahedron 49 pp. 10305-10316 (1993) and in J. Chem. Soc. Perkin Trans. I, pp. 1137-1140 (1983) and in J. Me. Chem. 36, pp. 3686-3692 (1993). In the publications in J. Med. Chem. and Tetrahedron, derivatives with an amino-group in position 6 were also indeed described, said amino-group being substituted however in every case. Other derivatives have up till now not become known. This can be attributed mainly to the fact that the presently known derivatives are based on synthesis methods which are costly and complex. Therefore production of other phenanthridine derivatives was up till now not possible.

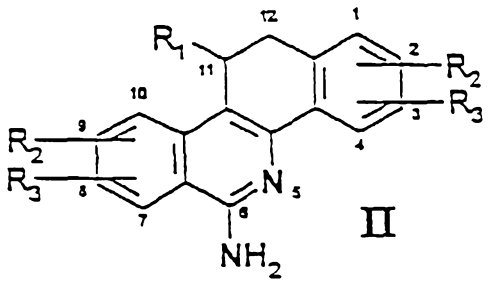
This assumed, it is the object of the present invention to make known new phenanthridine derivatives, a method for their production and their application.

The object is achieved, with respect to the phenanthridine derivatives, by the characterising features of Claim 1 and, with respect to the production method, by the features of Claim 5. The application according to the invention of these phenanthridine derivatives is mentioned in Claim 10. The subclaims demonstrate advantageous further developments.

According to Claim 1, the new phenanthridine derivatives are defined by the general formulae I and II,



I



II

in which R_1 means a hydrogen atom, an aromatic or heterocyclic residue, and R_2 and R_3, which can be the same or different, mean hydrogen atoms an alkyl-oxy residue, an alkylene-oxy residue, a halogen atom or a nitro group.

By an aromatic carbocylic residue R_1 can be understood particularly such residues as are derived from benzene, naphthalene, anthracine, phenanthrene and pyrene. By an aromatic heterocyclic residue R_1 can be understood particularly residues, which are derived from furane, thiophene, pyridine, 1,2,4-oxdiazole, 1,2,3-triazole, benzofurane, benzoxazole, benzimidazole, benzthiazole, also the corresponding naphtho-analogues of the type named benzo-five ring heterocyclenes and from indole, quinolene and isoquinolene. The aromatic carbocyclic or heterocyclic residues can be substituted once or several times.

For this purpose, as substitutes under the reaction conditions, inert groups and/or atoms may be considered such as mono-amino groups, alkyl amino groups, dialkyl amino groups, alkyl groups, alkoxyl groups, alkylene oxy groups and halogens.

On the basis of the found pharmacological characteristics, the derivatives which are of particular importance are those in which R_2 and R_3 hydrogen, and R_1 hydrogen are an unsubstituted phenyl residue, a phenyl residue with one or several methoxyl groups or a *N,N*-dimethyl amino

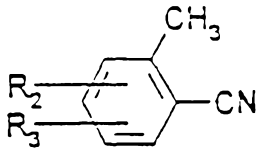
function. For this purpose, those derivatives in which R_1 is a substituted or unsubstituted phenyl residue, in particular 2,4-dimethoxyphenyl or 3,4-dimethoxyphenyl, may be emphasized. The 2,4-dimethoxyphenyl derivative is particularly preferred here. The phenanthridine derivatives according to the invention readily form physiologically acceptable salts. Such salts are e.g. salts with inorganic and organic acids, e.g. dihydrochloride, hydrobromide and sulphates. Particularly well suited salts of organic acids are formed with aliphatic mono- and di- carbon acids. Examples of such salts are acetates, maleates and fumarates.

The compounds were able to be confirmed by IR- and HNMR-analysis.

The invention relates furthermore to a method for producing phenanthridine derivatives. The applicant was able to show surprisingly that it is possible to obtain the phenanthridine derivatives according to the invention by smean replacing appropriately substituted aldehydes with appropriately substituted methobenzonitrile. Carrying on in detail at this stage with transformation of an aldehyde of Formula III

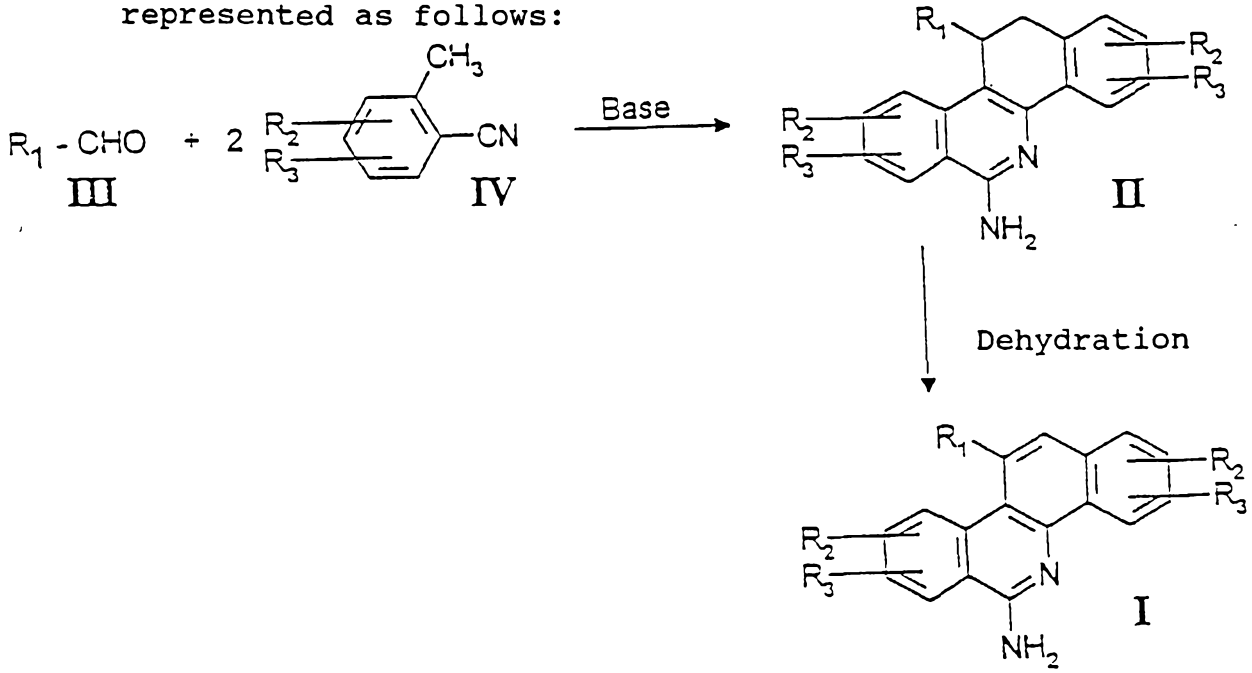
$$R_1\text{-CHO} \qquad \text{III}$$

R_1 having the previously mentioned meaning and with 2 mol of a 2-methylbenzonitrile of Formula IV



IV

and R_2 and R_3, having the previously mentioned meaning, are introduced in the presence of a base and an aprotic dipolar solvent and after isolation in a further step according to generally valid methods, dehydration results with an appropriate dehydration medium in the presence or absence of solvent. The reaction process can be represented as follows:



Preferably, amides such as dimethylformamide, dimethyl-acetamide, diethylacetamide, hexamethyl-phosphoric acid-trisamide and carbamides such as tetramethyl carbamide, 1,3-dimethyltetrahydro-2-pyrimidinon and 1,3-dimethylimidazolidinon or dimethylsulphoxide may be used as aprotic dipolar solvent for the reaction according to the invention.

Alkali hydrides or alkaline earth hydrides such as sodium hydride, alkali amides such as sodium amide, sodium methyl acetamide, alkali alcoholate, alkaline earth alcoholates or aluminum alcoholates such as potassium-*tert*-butylate, sodium methylate, sodium ethylate or aluminium ethylate can for example be used as a base.

The reaction can be conducted as follows: on to a solution of a base in an appropriate dipolar aprotic solvent, a solution of the compounds III and IV in the same solvent is dropped slowly in an inert gas atmosphere. After agitating for several hours at 35° C to 50° C in an inert gas atmosphere the product is poured on to ice-cold water and shaken out with an appropriate organic solvent. The organic phase is reduced and, separated from the residue by introducing a halogen hydrogen acid or by shaking with an appropriate inorganic or organic acid, the 6-amino-11,12-dihydrobenzo(c)phenanthridine II is precipitated or is isolated, by using an aqueous acid solution, from the aqueous phase after neutralisation and removal of the base. The 6-amino-11,12-dihydrobenzo(c)phenanthridine II can then be dehydrated to the 6-aminobenzo(c)phenanthridine I, according to generally accepted methods, with an appropriate dehydration medium in the presence or absence of an inert solvent.

It should be emphasized especially, in the method according to the invention, that phenanthridine derivatives, which have a substituted or an unsubstituted phenyl residue in position-11, are hereby synthesized. It is surprising that the synthesis is possible by means of the simple reaction which is described here, in which a great variation in range exists on the basis of the original substances which are put in with respect to the educts which can be obtained.

It was then found that the previously described phenanthridine derivatives possessed excellent anti-tumour, anti-microbial, anti-fungicidal, anti-viral and anti-inflammatory properties. In order to examine the

pharmacological properties, the compounds of the general Formula I and II were examined in an "*in-vitro*-Antitumor-Screening" of the National Cancer Institute (NCI), Bethesdal, Maryland, USA. About 58 different human pathogenic tumour cell series, which stemmed from nine types of cancer (leukaemia, non-small cell lung carcinoma, large intestine cancer, central nervous system cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer). In order to determine the level of efficacity, tumour cells were subjected to the compounds over two days and subsequently the inhibition of growth was determined indirectly via the calculation of the protein biomass with sulphorhodomine B. Untreated cultures served as a reference.

In these experiments, 6-amino-11-(2,4-dimethoxy-phenyl)benzo(c)phenanthridiniumperchlorate for example showed inhibitions of growth. Surprisingly, the compound indicates activities which lie outwith the category of anti-tumour compounds studied in a similar manner, with the result that a completely new spectrum of effect is achieved.

From the present data, dosage-effect curves are depicted in Figures 1 to 9 for this compound for example. The nine different figures contain the various forms of cancer. The percentage growth respectively is plotted with respect to the concentration of compound (as $\log_{10}$ of the molar concentrations). The individual curves of each type of cancer are different cell strains of this form of cancer, which appear as keys in their normal abbreviations. Horizontal lines in the Figures indicate percentage growth of +100, +50, 0, -50 and -100. 100% growth indicates for example no change in growth after

two days without supplement of substance. It can be seen in the individual curves that with increasing concentrations of the substance the percentage growth declines.

The invention also relates therefore to medicines containing phenanthridine derivatives which are described here. The medicine contains, for this purpose, at least one phenanthridine derative, in the manner described here, together with at least one inert pharmaceutically acceptable carrier or dilution medium. A derivative of the general Formula 1 is preferred as a phenanthridine derivative in which R_1 is a 2,4-methoxyphenyl residue and R_2 and R_3 are hydrogen. The compound, according to the invention, can be administered orally, topically or parenterally, or in the form of suppositories. The preferred mode of administration is oral administration. This can be administered in the form of the base or as a physiologically acceptable salt. It is generally mixed with a pharmaceutically acceptable carrier or dilution medium, in order to create a medicine. For oral administration the medicine can be made available most usefully in the form of capsules or tablets or possibly even slow-release tablets. They can also be available in the form of dragees or in syrup form. Suitable topic preparations are e.g. salts, lotions, creams, powders and sprays.

In the following, the invention is described in greater detail with the help of several embodiment examples.

Embodiments:

Production of the 6-amino-11,12-dihydrobenzo(c)phenanthridine II:

Example 1:

6-amino-11,12-dihydrobenzo(c)phenanthridiniumchloride

A solution of 2.47g (22mmol) $KOBu^t$ in 20ml DMPU in a nitrogen atmosphere is prepared and a solution of 300mg (10mmol) paraformaldehyde and 2.34g (20mmol) 2-methylbenzonitrile in 12ml DMPU is dropped slowly into the preparation in portions of 2ml at a spacing of 15 minutes in a contra-flow of nitrogen. After six hours' agitation at 35°C in a nitrogen atmosphere the product is poured on to a solution of 2.2g (40mmol) ammonium chloride in 100ml ice water and shaken out three times with 100ml dichloromethane. The combined organic phases are filtered through wadding, rotated to approx. 100ml and shaken vigorously with 3 N hydrochloric acid. The detached organic phase is further rotated until there is heavy precipitation, then being placed in the fridge overnight. The precipitation is stopped, washed with a little dichloromethane, dried and recrystallised out of methanol/dichloromethane. 6-amino-11,12-dihydrobenzo(c)phenanthridiniumchloride is obtained. Pale yellow platelets, yield: 16 % of theoretical yield, melting point 350 °C - IR (KBr): ν = 3244 cm^{-1}, 3102, 2946, 1654, 1630, 1616. - ^1H NMR (360 MHz, $[D_6]$DMSO): δ = 3.0 (mc, 2H, $-CH_2-$) , 3.08 (mc, 2 H, $-CH_2,-$) , 7.43 (mc, 3H, Ar-H), 7.77 (t, 1H, Ar-H), 8.02 (t, 1H, Ar-H), 8.16 (d, 1H, Ar-H), 8.27 (mc, 1H, Ar-H), 8.60 (d, 1H, Ar-H), 9.49 (br, 2H, $-NH_2$) , 13.78 (br, 1H, $\equiv N^+-H$).

$C_{17}H_{15}N_2Cl$(292.77) Ber. C 72.21 H 5.35 N 9.91
Gef. C 72.13 H 5.35 N 9.99

Example 2:

6-amino-11,12-dihydro-11-phenylbenzo(c)phenanthridiniumchloride

A solution of 1.06g (10mmol) benzaldehyde and 2.34g (20mmol) 2-methylbenzonitrile in 5ml DMPU is dropped slowly into a solution of 2.47mg (22mmol) KOBu^t in 20ml DMPU in a nitrogen gas atmosphere. After five hours' agitation at 35° C in a nitrogen gas atmosphere the product is poured on to a solution of 2.2g (40mmol) ammonium chloride in 100ml ice water, and shaken out three times with 100ml dichloromethane. The organic phase is filtered through wadding and rotated roughly to 100 ml and shaken vigorously with 3 N hydrochloric acid. The resulting precipitation is suctioned off, washed with dichloromethane and dried. After recrystallisation from methanol/dichloromethane 6-amino-11,12-dihydro-11-phenylbenzo(c)-phenanthridiniumchloride is obtained.
Bright yellow platelets, yield: 52 % of theoretical yield, melting point 355 °C. - IR (KBr): ν = 3446 cm^{-1}, 3076, 1662, 1620, 1570. - ^1H NMR (400 MHz, [D_6] DMSO) : δ = 3.18 (mc, 1H, 12-H), 3.56 (mc, 1H, 12-H), 4.95 (mc, 1H, 11-H), 7.09 (mc, 5H, C6H5-), 7.24 (d, 1H, Ar-H), 7.35 (t, 1H, Ar-H), 7.44 (t, 1H, Ar-H), 7.74 (mc, 1H, Ar-H), 7.91 (mc, 2H, Ar-H), 8.3 (d, 1H, Ar-H), 8.61 (d, 1H, Ar-H), 9.3 (br, 2H, $-NH_2$,), 13.7 (br, 1H, $\equiv N^+-H$) .

$C_{23}H_{19}N_2Cl$(358.87) Ber. C 76.98 H 5.34 N 7.81
Gef. C 76.52 H 5.37 N 7.75

Example 3

6-amino-11,12-dihydro-11-(3,4-dimethoxyphenyl)benzo-[c]phenanthridiniumchloride

Similar to Example 1. Light-yellow needles. Yield: 53 % of theoretical yield, melting point 205° C (methanol/water). - IR (KBr): ν = 3438 cm-, 3268, 3106, 2938, 1648, 1616, 1584.-^{1}H NMR (400 MHz, [D6] DMSO) :δ = 3.08 (mc, 1H, 12-H), 3.42 (mc, 1H, 12-H), 3.61 (s, 3H, -OCH_3), 3.99 (s, 3H, -OCH_3) , 5.02 (mc, 1H, 11-H), 6.04 (mc, 1H, Ar-H), 6.21 (mc, 1H, Ar-H), 6.61 (mc, 1H, Ar-H), 7.20 (d, 1H, Ar-H), 7.34 (t, 1H, Ar-H), 7.43 (t, 1H, Ar-H), 7.63 (d, 1H, Ar-H), 7.73 (t, 1H, Ar-H), 7.91 (t, 1H, Ar-H), 8.36 (d, 1H, Ar-H), 8.61 (d, 1H, Ar-H), 9.56 (br, 2H, -NH_2), 13.85 (br, 1H, $\equiv N^+$-H) .

$C_{25}H_{23}N_2O_2Cl$ (418. 92) Ber. C 71.68 H 5.53 N 6.69
Gef. C 70.95 H 5.37 N 6.80

Production of 6-aminobenzo(c)phenanthridine I:

Example 1

6-aminobenzo(c)phenanthridiniumperchlorate

A solution of 404 mg (1.7mmol) DDQ in 35 ml dioxan is added to a solution of 250mg (1.02 mmol) 6-amino-11,12-dihydrobenzo(c)phenanthridine in 15ml dioxan and heated for four hours in a contra-flow situation. The cooled solution is subsequently poured on to a sodium hydrogen carbonate solution and shaken out with diethyl ether. The diethyl ether phase is washed once with diluted sodium hydrogen carbonate solution and three times with water. After addition of 70% perchloric acid, precipitation is

obtained. After drying out and recrystallising from methanol, brown needles, yield: 44 % of theoretical yield, melting point 325 °C. - IR (Kbr):ν = 3404 cm^{-1}, 3348, 3298, 3276, 3234, 1666, 1616.- ^1H NMR (300 MHz, [D_6] DMSO) : δ = 7.82 (mc,3H, Ar-H, 8.0 (d, 1H, Ar-H), 8.13 (mc, 2H, Ar-H), 8.56 (mc, 2H, Ar-H), 8.69 (d, 1H, Ar-H), 8.83 (d, 1H, Ar-H), 9.73 (br, 2H, $-NH_2$), 12.84 (br, 1H, $\equiv N^+-H$).

$C_{17}H_{13}N_2O_4Cl$ (344.06) Ber. C 59.29 H 3.81 N 8.14
Gef. C 59.23 H 3.83 N 8.24

Example 2

6-amino-11-phenylbenzo[c]phenanthridiniumperchlorate

similar to Example 1. Grey-brown needles, yield: 50 % of theoretical yield, melting point 345 °C. - IR (KBr) ν = 3412 cm^{-1}, 3358, 3310, 3226, 1668, 1642, 1612. - ^1H NMR (300 MHz, [D6]DMSO) : δ = 7.51 (mc, 7H, Ar-H), 7.80 (mc, 4H, Ar-H), 8.15 (d, 1H, Ar-H), 8.66 (mc, 2H, Ar-H), 9.88 (br, 2H, $-NH_2$) , 12.8 (br, 1H, $\equiv N^+-H$).

$C_{23}H_{17}N_2O_4Cl$(420.09) Ber. C 65.70 H 4.08 N 6.67
Gef. C 65.67 H 4.03 N 6.67

Example 3

6-amino-11-(2,4dimethoxyphenyl)benzo[c]phenanthridiniumperchlorate

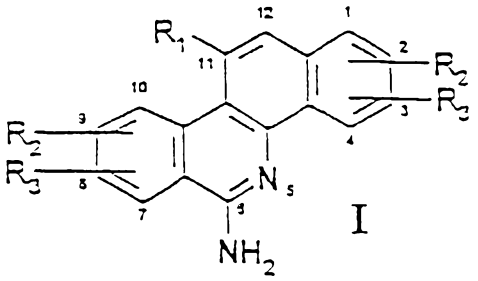
Similar to Example 1. Dark brown needles, yield: 45% of theoretically yield, melting point 336 °C. - IR (KBr) : ν = 3418 cm^{-1}, 3352, 3302, 3270, 1660, 1608. - ^1H NMR (300 MHz, [D6] DMSO) : δ = 3.38 (s, 3H, $-OCH_3$), 3.87 (s, 3H, -

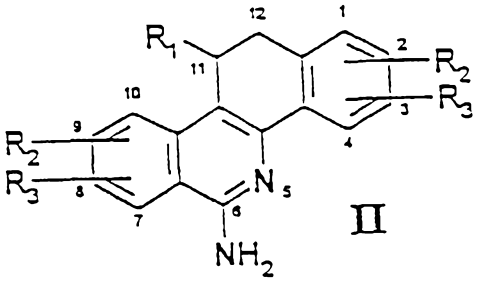
OCH_3), 6.69 (mc, 1H, Ar-H), 6.77 (mc, 1H, Ar-H), 7.34 (mc, 1H, Ar-H), 7.77 (mc, 6H, Ar-H), 8.11 (mc, 1H, Ar-H), 8.77 (mc, 2H, Ar-H), 9.72 (br, 2H, $-NH_2$); 12.58 (br, 1H, $\equiv N^+-H$).

$C_{25}H_{21}N_2O_6Cl$ (480.19) Ber. C 62.49 H 4.41 N 5.83
Gef. C 62.56 H 4.30 N 5.87

New Patent Claims (as amended)

1. Phenanthridine derivatives of the general Formula I and II





and also its salts, in which R_1 means an aromatic carbocylic or heterocyclic residue and R_2 and R_3, which can be the same or different, mean a hydrogen atom, an alkyloxy residue, an alkylene oxy residue, a halogen atom or a nitro group.

2. Phenanthridine derivatives according to Claim 1, characterized in that
R_1 is a hydrogen or an unsubstituted phenyl residue or a phenyl residue with one or several methoxy groups or a residue with a *N,N*-dimethylamine function, R_2 and R_3 equalling H.

3. Phenanthridine derivatives according to Claim 2, characterized in that
R_1 is a phenyl residue, a 2,4-methoxyphenyl residue or a 3,4-methoxyphenyl residue.

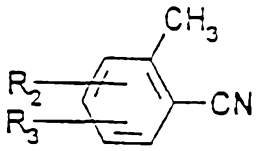
4. Phenanthridine derivative according to Claim 3, characterized in that
in the general Formula I, R_1 is a 2,4-methoxyphenyl

residue.

5. Method for producing phenanthridine derivatives of the general Formula II according to one of the Claims 1 to 4,
characterized in that
an aldehyde of the Formula III

$$R_1\text{-CHO}$$

is caused to react with a 2-methylbenzonitrile of Formula IV



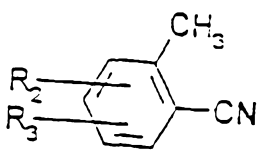
IV

in the presence of bases in an aprotic, dipolar solvent, the residues R_1, R_2 and R_3 possessing the meanings mentioned in Claims 1 to 4 and with the proviso that R_1 can also be H.

6. Method for producing phenanthridine derivatives of the general Formula I according to one of the Claims 1 to 4,
characterized in that
an aldehyde of the Formula III

$$R_1\text{-CHO}$$

is caused to react with a 2-methylbenzonitrile of Formula IV



IV

in the presence of a base in an aprotic, dipolar solvent, the residues R_1, R_2 and R_3 possessing the meanings mentioned in Claims 1 to 4 and with the proviso that R_1 can also be H and in that, in a further step, dehydration then results with an appropriate dehydration medium in the absence or presence of solvents.

7. Method for producing phenanthridine derivatives according to Claims 5 or 6, characterized in that an aldehyde of the general Formula III is introduced, in which R_1 is a phenyl residue, a 2,4- or 3,4 methoxyphenyl residue or hydrogen.

8. Method according to Claim 7, characterized in that R_1 is a 2,4- or 3,4-methoxyphenyl residue.

9. Method according to at least one of the Claims 5 to 8, characterized in that a 2-methylbenzonitrile of the general Formula IV is introduced, in which R_2 and R_3 are hydrogen.

10. Medicament, characterized in that it contains at least one of the phenanthridine derivatives of Claims 1 to 4 together with at least one inert, pharmaceutically acceptable carrier or dilution medium.

11. Medicament according to Claim 10, characterized in that it contains a phenanthridine derivative of the general Formula I, in which R_1 is a 2,4-methoxyphenyl residue and R_2 and R_3 are hydrogen.

FIG.1

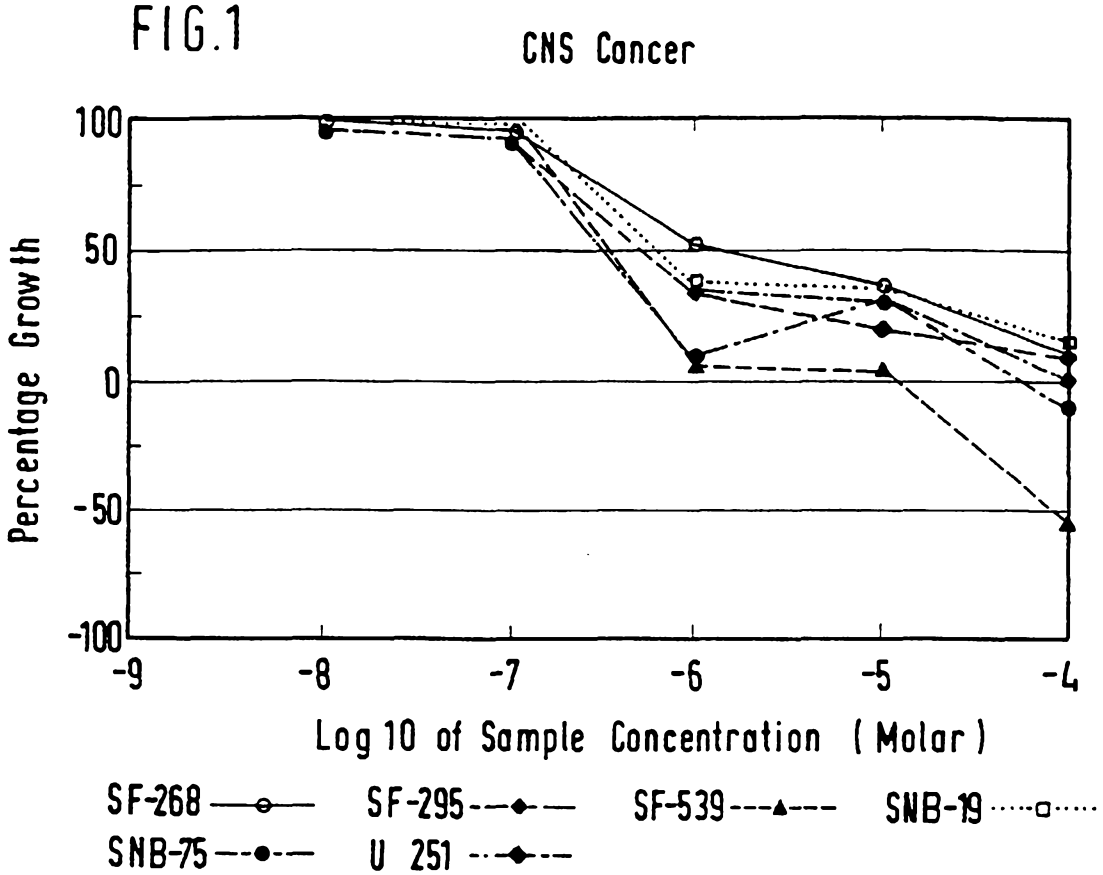

CNS Cancer
Percentage Growth
100
50
0
-50
-100
-9
-8
-7
-6
-5
-4
Log 10 of Sample Concentration (Molar)
SF-268
SF-295
SF-539
SNB-19
SNB-75
U 251

FIG.2

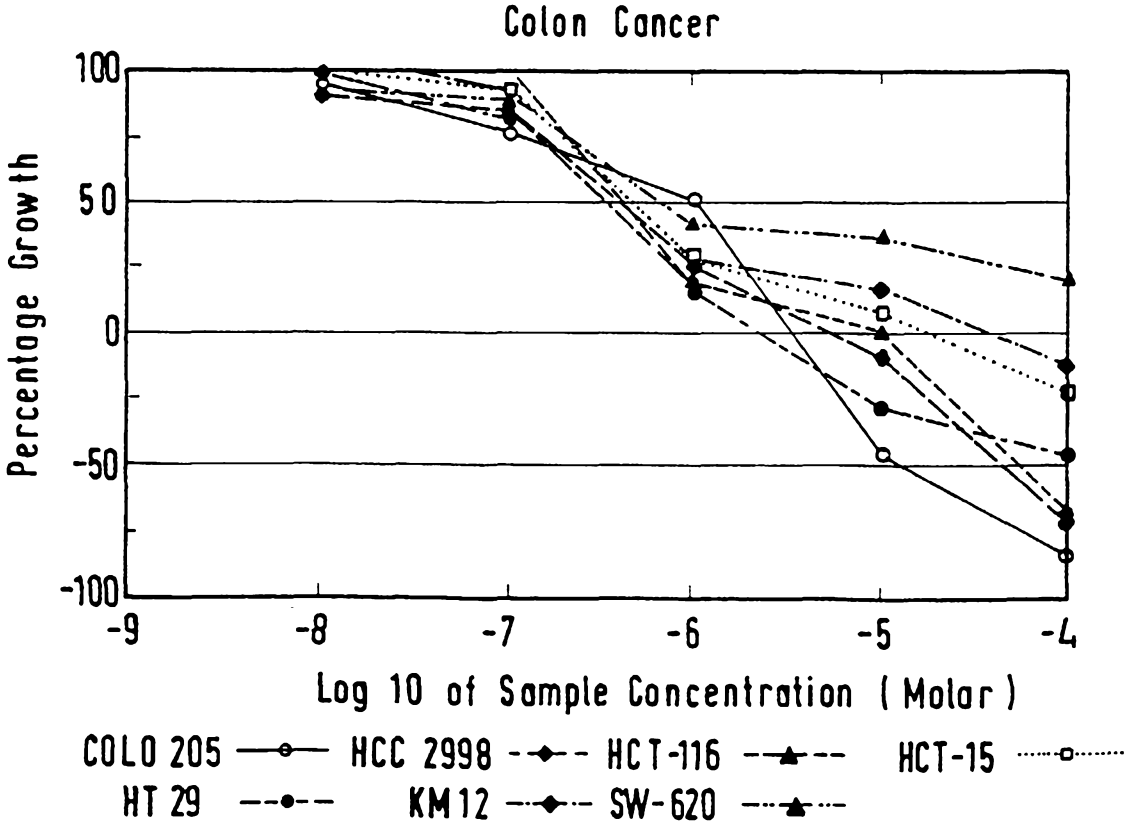

Colon Cancer
Percentage Growth
100
50
0
-50
-100
-9
-8
-7
-6
-5
-4
Log 10 of Sample Concentration (Molar)
COLO 205
HCC 2998
HCT-116
HCT-15
HT 29
KM12
SW-620

FIG. 3

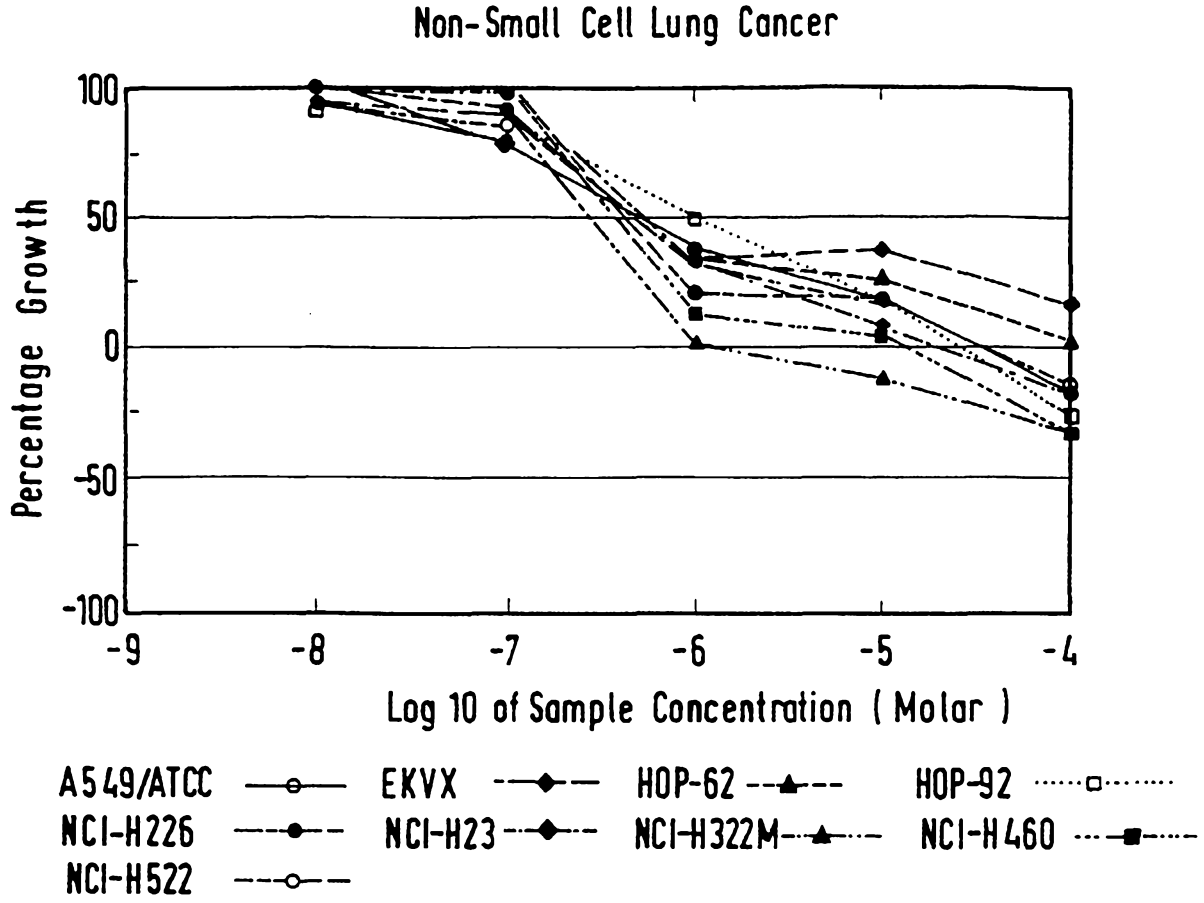

Non-Small Cell Lung Cancer
Percentage Growth
100
50
0
-50
-100
-9
-8
-7
-6
-5
-4
Log 10 of Sample Concentration (Molar)
A549/ATCC
EKVX
HOP-62
HOP-92
NCI-H226
NCI-H23
NCI-H322M
NCI-H460
NCI-H522

FIG. 4

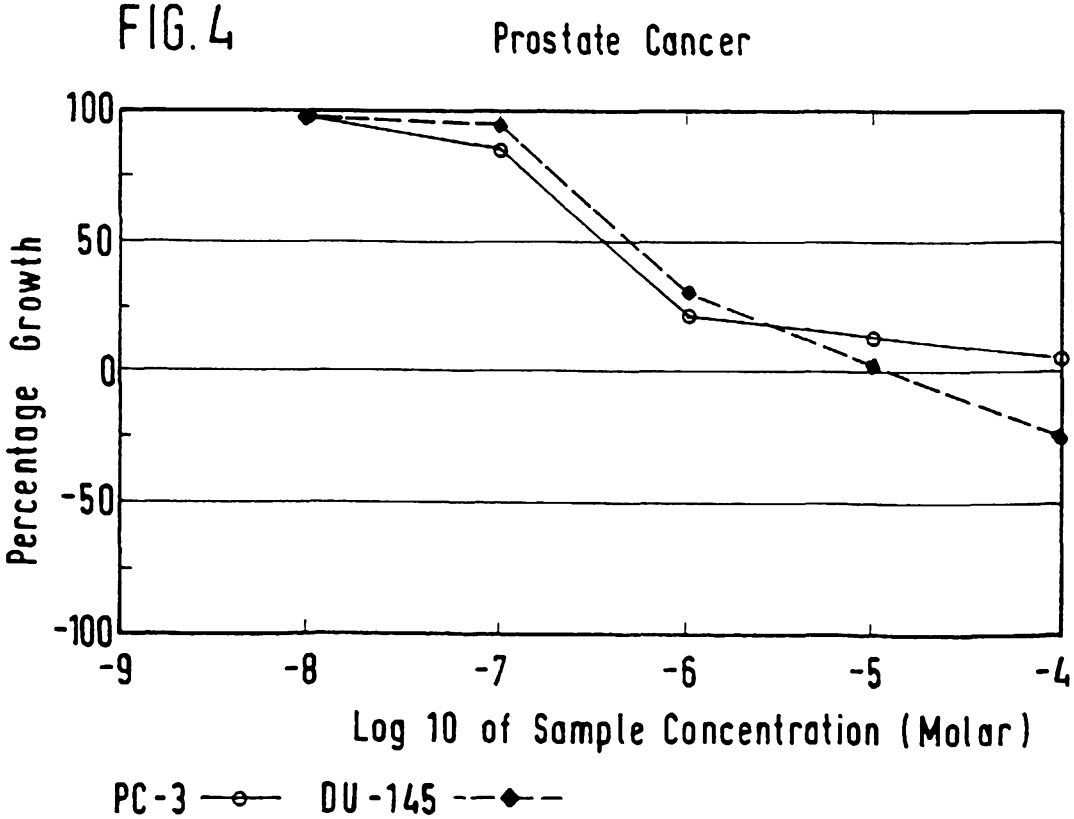

Prostate Cancer
Percentage Growth
100
50
0
-50
-100
-9
-8
-7
-6
-5
-4
Log 10 of Sample Concentration (Molar)
PC-3
DU-145

FIG.5

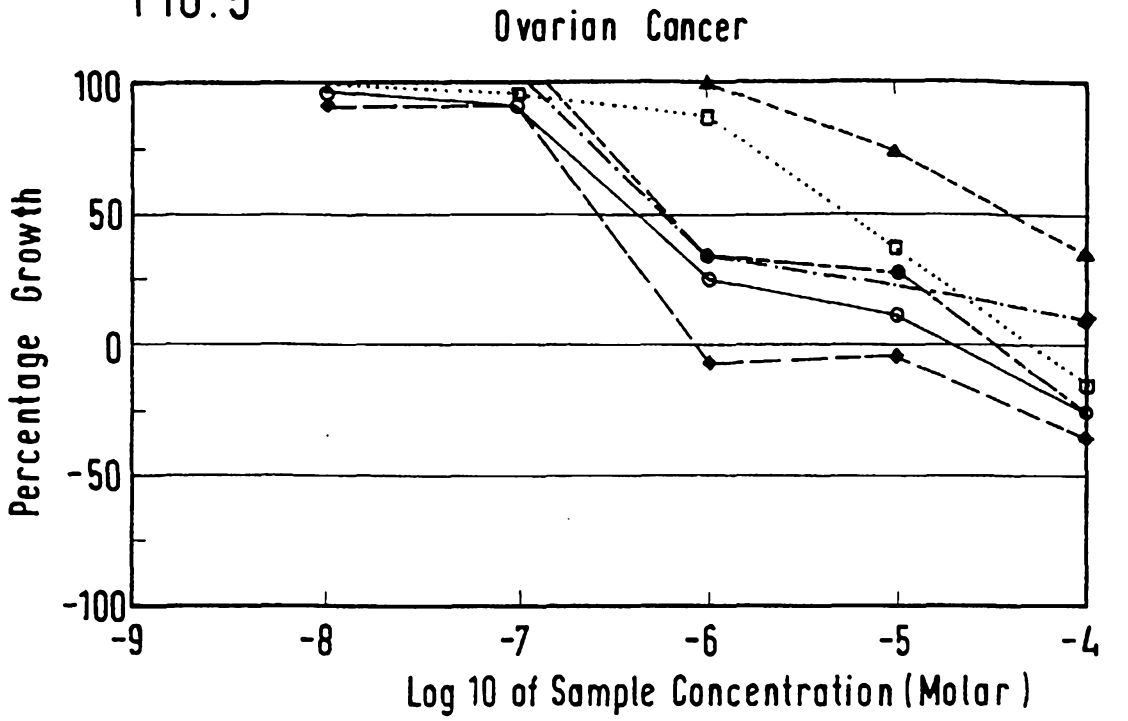

Ovarian Cancer
Percentage Growth
100
50
0
-50
-100
-9
-8
-7
-6
-5
-4
Log 10 of Sample Concentration (Molar)
IGROV1
OVCAR-3
OVCAR-4
OVCAR-5
OVCAR-8
SK-OV-3

FIG.6

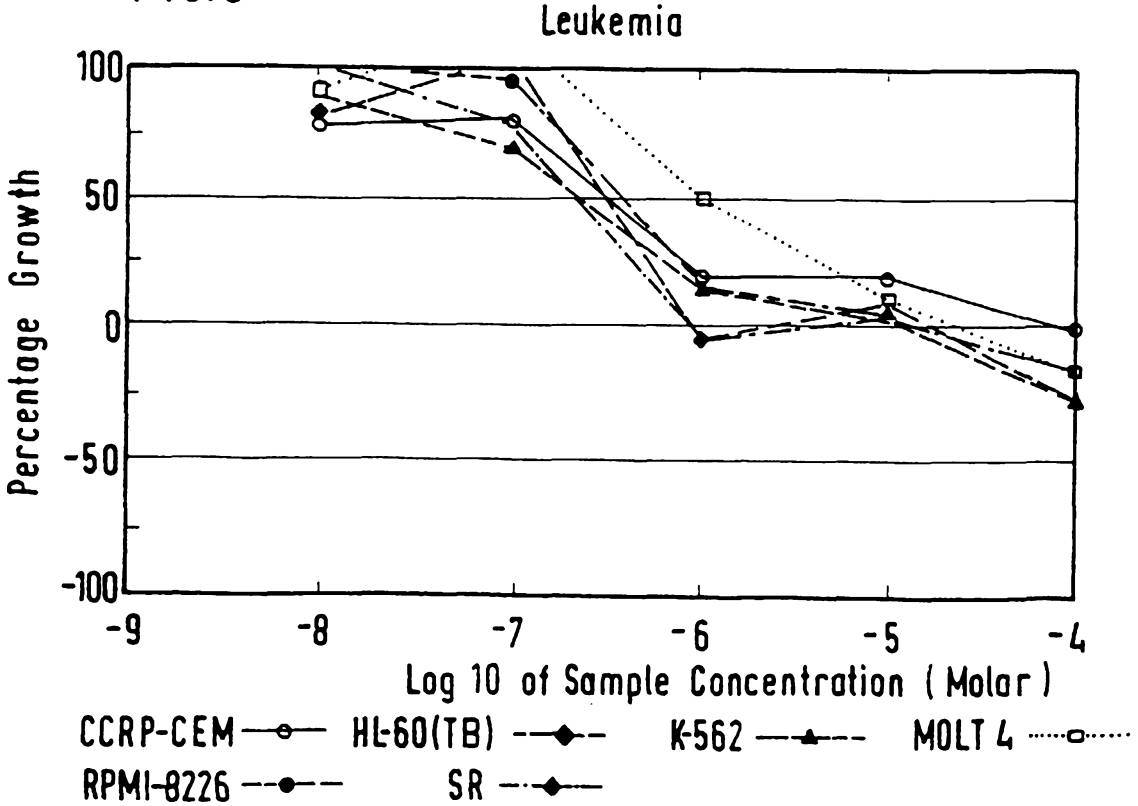

Leukemia
Percentage Growth
100
50
0
-50
-100
-9
-8
-7
-6
-5
-4
Log 10 of Sample Concentration (Molar)
CCRP-CEM
HL-60(TB)
K-562
MOLT 4
RPMI-8226
SR

FIG.7

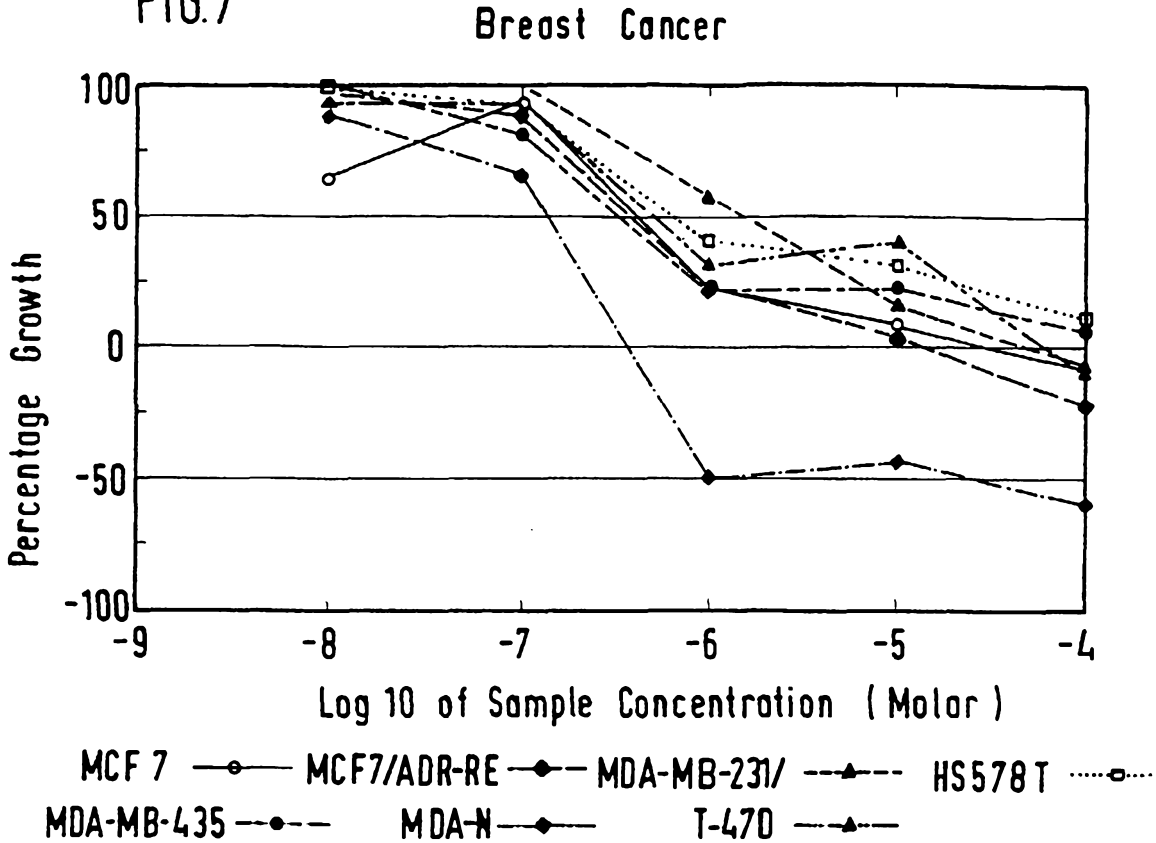

Breast Cancer
100
50
0
-50
-100
Percentage Growth
-9
-8
-7
-6
-5
-4
Log 10 of Sample Concentration (Molar)
MCF 7
MCF7/ADR-RE
MDA-MB-231/
HS578T
MDA-MB-435
MDA-N
T-470

FIG.8

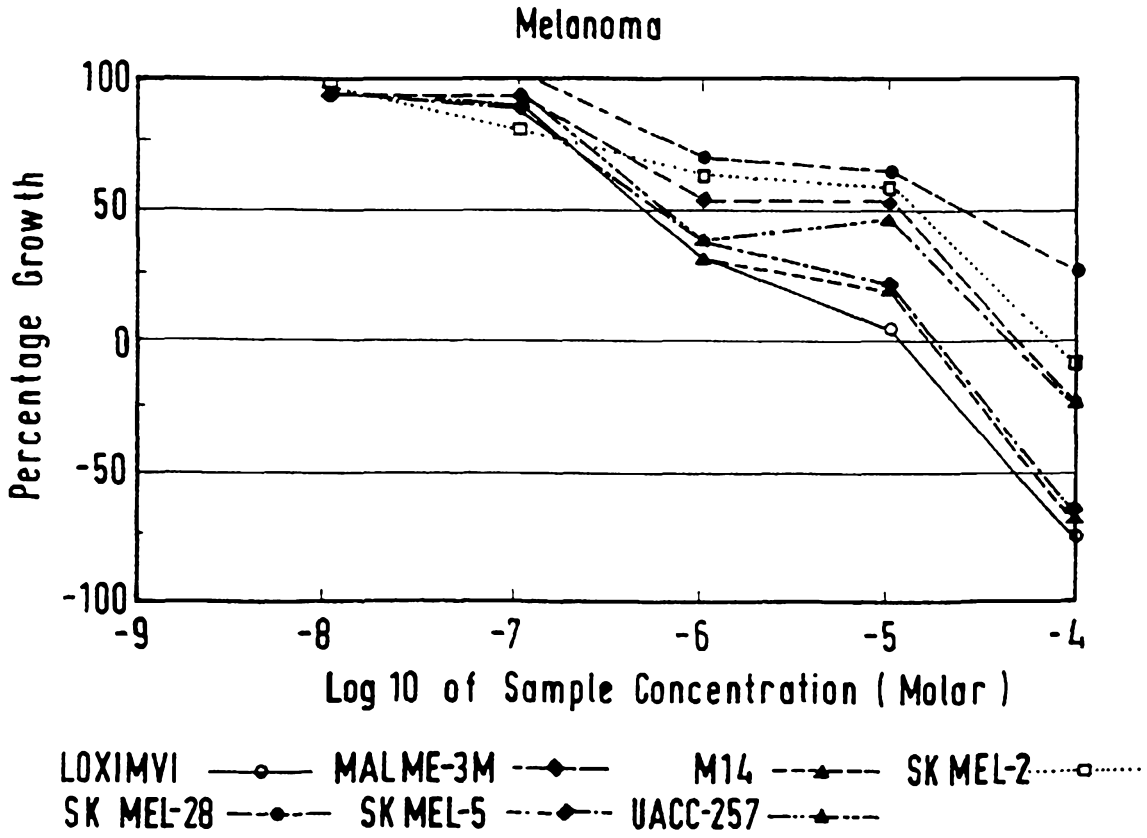
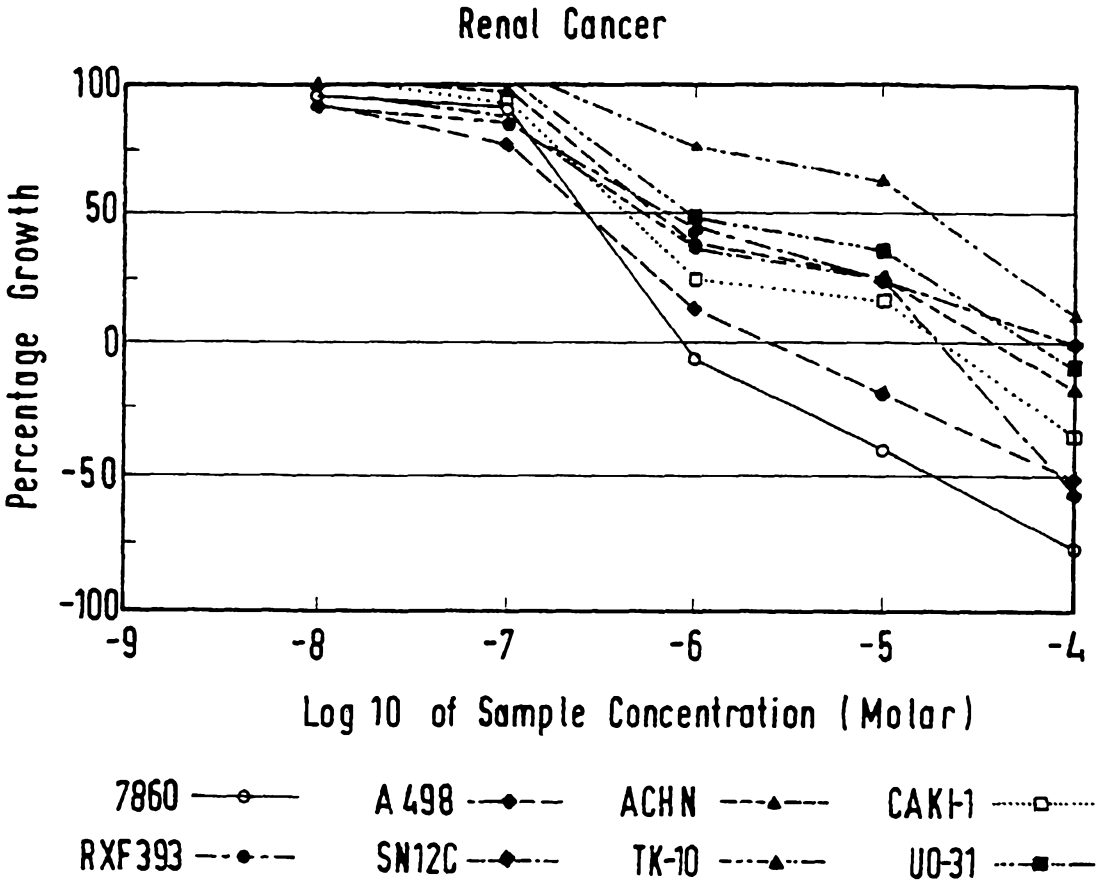

Melanoma
100
50
0
-50
-100
Percentage Growth
-9
-8
-7
-6
-5
-4
Log 10 of Sample Concentration (Molar)
LOXIMVI
MALME-3M
M14
SK MEL-2
SK MEL-28
SK MEL-5
UACC-257

FIG.9


Renal Cancer
Percentage Growth
100
50
0
-50
-100
-9
-8
-7
-6
-5
-4
Log 10 of Sample Concentration (Molar)
7860
A498
ACHN
CAKI-1
RXF393
SN12C
TK-10
UO-31