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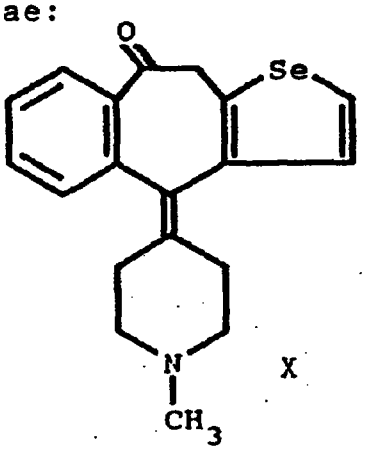
TITLE:

Selenophen Derivatives

DESCRIPTION

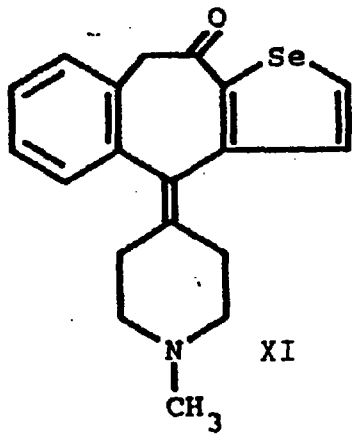
The invention relates to selenophen derivatives, to a process for their preparation and to pharmaceutical compositions containing them.

The invention provides selenophen derivatives of the formulae:



X

and

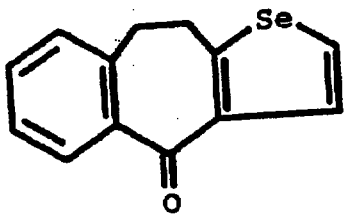


XI

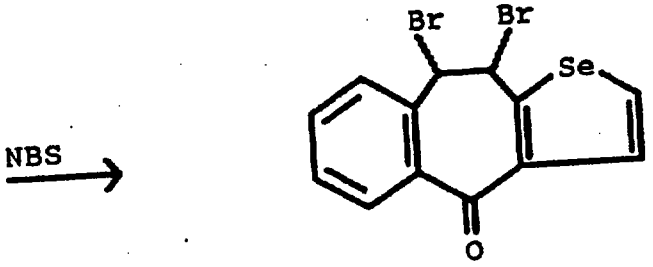
and their pharmaceutically acceptable salts.

The invention further provides a process for the preparation of the selenophen derivatives X and XI, the process comprising brominating 9,10-dihydro-4H-benzo[4,5]-cyclohepta[1,2-b]selenophen-4-one, reacting the resultant 9,10-dibromo-3H-benzo[4,5]cyclohepta[1,2-b]selenophen-4--one with methanol and treating the product with a strong inorganic base, reacting the resultant mixture of 9- and 10-methoxy-4H-benzo[4,5]cyclohepta[1,2-b]selenophen-4-one with a 1-methyl-4-piperidinylmagnesium halide, demethylating and dehydrating the resultant mixture of 4-hydroxy-4-(1-methyl-4-piperidyl)-9- and 10-methoxy--benzo[4,5]cyclohep[1,2-b]selenophen and separating the resultant compounds.

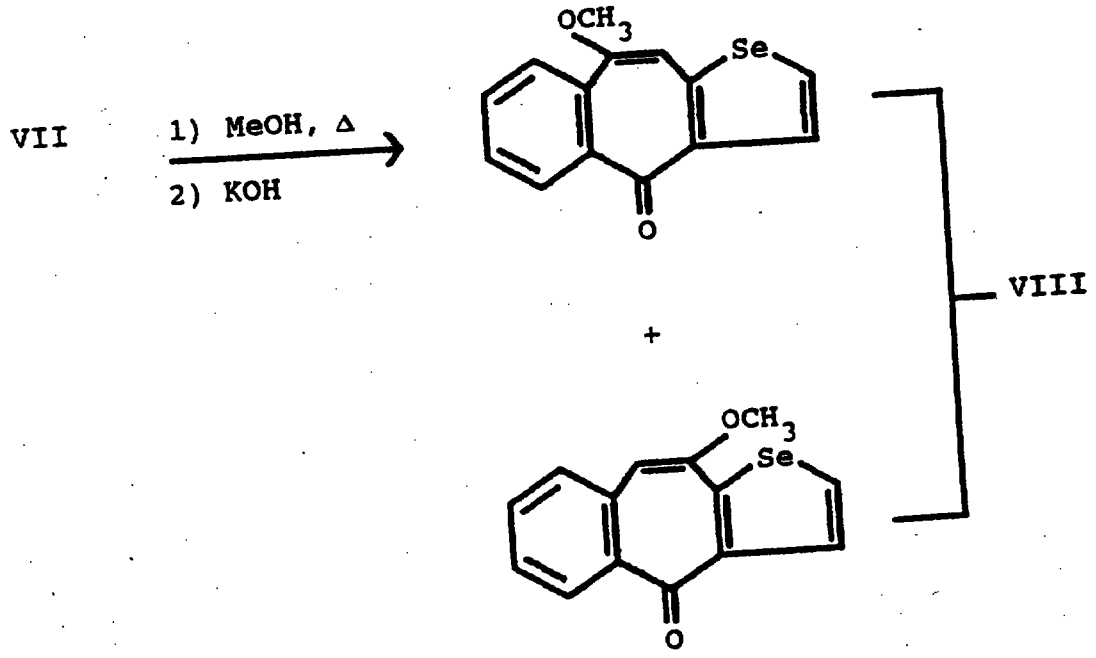
This process is illustrated by the following reaction scheme:

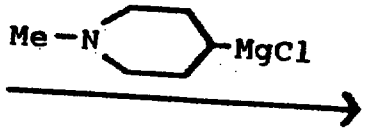


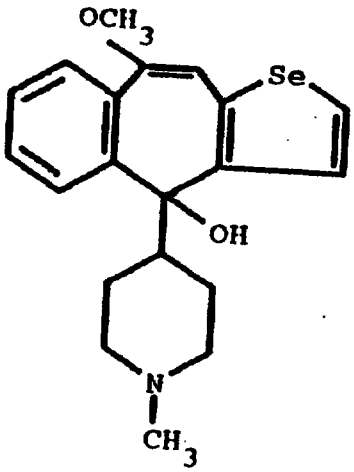
VI



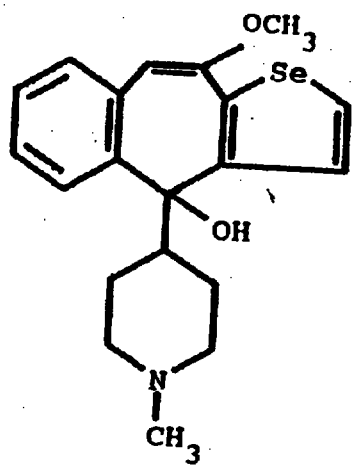
VII



VIII  IX



+



IX

X

XI

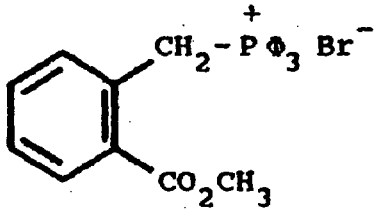
The bromination is preferably effected with a stoichiometric excess of N-bromosuccinimide in an inert aprotic solvent such as carbon tetrachloride. The reaction may be effected under reflux in the presence of a peroxide, preferably dibenzoylperoxide.

The reaction with methanol is suitably carried out under reflux. The strong inorganic base is then added, preferably in excess. Potassium hydroxide is suitable as the base. Continued heating, e.g. at 60-90°C, facilitates the completion of the reaction.

The Grignard compound used to introduce the piperidyl group into the molecule is preferably 1-methyl-4--piperidylmagnesium chloride. It is desirably used in stoichiometric excess. This reaction may be conducted at ambient temperature in an aprotic solvent such as tetrahydrofuran.

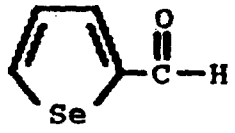
Demethylation and dehydration may be effected by heating with hydrochloric acid at about 100°C. Separation of the compounds X and XI may be by chromatography.

The starting material for the above described process according to the invention, that is 9,10-dihydro-4H--benzo[4,5]cyclohepta[1,2-b]selenophen-4-one VI, may be prepared from o-methoxycarbonylbenzyl-triphenyl-phosphonium bromide I and 2-formyl-selenophen II according to the following reaction scheme:

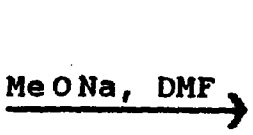


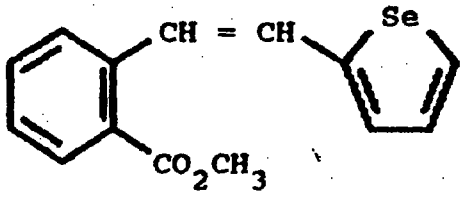
I

+

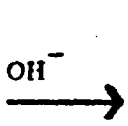


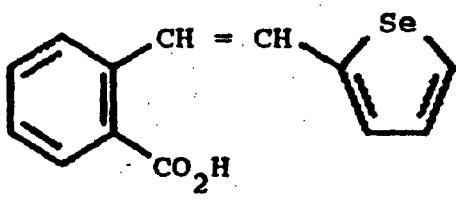
II



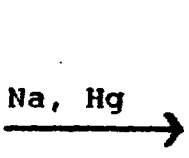


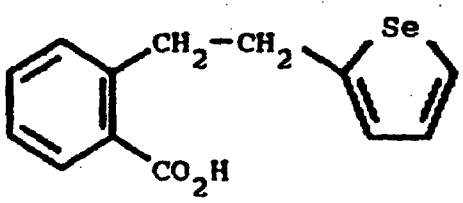
III



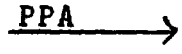


IV





V



VI

These steps are fully described in Examples 3 to 6 hereinbelow; the invention is not limited to this particular method for the preparation of compound VI. The process of the invention commences from compound VI, howsoever prepared.

The compounds of the invention are of interest for their anti-allergic activity, which has been found to be greater than that of closely related compounds such as are described in French Patent No. 2085695. The invention accordingly also provides a pharmaceutical composition comprising a selenophen derivative according to the invention or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable diluent or carrier.

Examples 1 to 6 below describe the preparation of the selenophen derivative VI, which is the starting material for the process according to the invention. The remaining Examples illustrate the invention.

EXAMPLE 1

o-Methoxycarbonylbenzyl-triphenylphosphonium bromide I

O-methoxycarbonylbenzyl bromide. This conventional reaction will not be further described.

EXAMPLE 2

2-formyl-selenophen II

This compound was prepared by the Vilsmeier-Haack reaction from selenophen, phosphorus oxychloride and dimethylformamide (DMF). This conventional reaction will not be further described. E_{10} = 88°C, yield 82%.

EXAMPLE 3

(Z+E)-2-(o-methoxycarbonylstyryl)-selenophen III

To a suspension of o-methoxycarbonylbenzyl-triphenyl-phosphonium bromide I (39 g, 75 mmol) in 150 ml of dry DMF, at -4°C, was added freshly prepared sodium methoxide (7 g; 0.13 mol). The red solution was stirred for 0.5 hour at the same temperature and 2-formyl-selenophen II (12 g, 75 mmol) in 35 ml DMF was added dropwise at -4°C. The solution was stirred for 1.5 hours at room temperature. Ice and dilute HCl (15%) were added and the mixture was extracted with diethyl ether. Partial elimination of diethyl ether was followed by filtration of ϕ_3PO. The filtrate was evaporated and the residue was extracted several times with hexane. Elimination of hexane gave III as a viscous product, a Z + E mixture (17.5 g, yield 80%).

IR (cm^{-1}): 1720 (C=O); 1620 (C=C); 1600 (ϕ); 1570 (selenophen)

^{1}HNMR ($CDCl_3$) (60 MHz) TMS
δ: 7-8.1 (m, 9H); 3.95 (d, 3H, CH_3 Z/E = 2.5)
TLC rf: 0.76 ($CHCl_3$/MeOH, 95: 5 V/V)

EXAMPLE 4:

(Z+E)-2-(o-carboxystyryl)-selenophen IV

10 g (36 mmol) of III were stirred with 150 ml of aqueous NaOH (0.5N) at 80-100°C overnight.

Acidification and extraction with diethyl ether and evaporation gave IV as a Z + E mixture (6.8 g, yield 71%).
mp 134°C - TLC rf: 0.33 ($CHCl_3$/MeOH; 95: 5; V/V).

IR (cm^{-1}): 3500 - 3000 (OH) (chelate); 1690 (C=O); 1620 (C=O); 1600 (ϕ); 1570 (selenophen)
^{1}HNMR 60 MHz, $CDCl_3$
δ: 11.65 (1H, OH); 7-8.1 (m, 9H)

EXAMPLE 5:
2-(o-carboxyphenethyl)-selenophen V

Sodium (4.7 g) was melted in dry toluene (20 ml) then mercury (225 g) was slowly added with stirring and the mixture was heated at 120°C for 30 min. After elimination of toluene, the sodium amalgam was heated at 60°C and a solution of IV (12 g) in ethanol 95 (130 ml) was added. Vigourous stirring was continued for 1 hour at the same temperature. Mercury was decanted, washed twice with ethanol. The solution was diluted with water (600 ml) then filtered through activated charcoal. The filtrate was acidified with concentrated HCl and the solid was filtered, washed with water and dried (8.5 g, yield 70%).
m.p. 118°C - TLC rf: 0.36 ($CHCl_3$/MeOH 95: 5)
IR (cm^{-1}): 3100 - 2900 (OH) (chelate); 1690 (C=O); 1600 (ϕ); 1570 (selenophen)
^{1}HNMR 60 MHz $CDCl_3$ (TMS)
δ: 11.95 (1H, COOH); 7-8.2 (m, 7H); 3.3 (larg. sing., 4H, CH_2-CH_2)

EXAMPLE 6:
9,10-dihydro 4H-benzo[4,5]cyclohepta[1,2-b]selenophen-4-one VI

A mixture of 30 g of polyphosphoric acid (PPA) and 30 ml of xylene was heated at 90°C and V (8 g) was added.

The stirring was continued for 1 hour at 90°C, then the mixture was poured on ice. After extraction with toluene and washing with aqueous NaOH (30%) then with water, the organic phase was dried (Na_2SO_4) and evaporated. The brown residue was chromatographed on silica gel column (eluent petroleum ether/diethyl ether (PE/E) 95: 5, then 90: 10) and gave VI (5 g, yield 67%).

TLC rf: 0.42 (PE/E: 70: 30)

IR (cm^{-1}): 1630 (C=O); 1600 (C=C (ϕ)); 1530 (selenophen)

^{1}HNMR 60 MHz $CDCl_3$ (TMS)

δ: 7.2 - 8.1 (m, 6H); 3,2 (larg. sing., 4H, CH_2-CH_2)

EXAMPLE 7:

9,10-dibromo-4H-benzo[4,5]cyclohepta[1,2-b]selenophen-4-one VII

A mixture of VI (4.6 g, 17.4 mmol), 57 ml of dry CCl_4, N-bromo-succinimide (6.6 g, 36 mmol) and dibenzoylperoxide (0.3 g) was refluxed for 3 hours with stirring. Succinimide was filtered off and washed with CCl_4 and the filtrate was eliminated.

The crude product obtained VII was worked up without purification.

IR (cm^{-1}): 1640 (C=O); 1595 (ϕ); 1540 (selenophen)

^{1}HNMR 60 Mz $CDCl_3$ (TMS)

δ: 7-8 (m, 6H); 6.05 (q, 1H, CHBr); 5.6 (q, 1H,CHBr)

EXAMPLE 8:

9- and 10-methoxy-4H-benzo[4,5]cyclohepta[1,2-b]-selenophen-4-one VIII (as a mixture)

A solution of crude product VII in methanol (80 ml) was refluxed with stirring for 6 hrs. Then KOH (3.3 g) was added and the mixture was heated for 6 hrs. The solid was filtered off at room temperature and the filtrate was eliminated. The residue was chromatographed on silica gel column (eluent PE/E 98: 2 then 95: 5) and yielded 2.52 g of VIII (50% on the two steps).

m.p.: 191°C (MeOH)
TLC: 0.22 (PE/E 70: 30) ratio 10/9 = 1.75
IR (cm^{-1}): 1580 (C=O); 1600 (C=C); 1540 (selenophen)
^{1}HNMR 60 MHz $CDCl_3$ (TMS)
δ: 8.65 (d. 1H, H_αSe); 8.25 (m, 1H, H_βSe); 7.6 (m, 4H, ϕ); 6.5 (large sing, 1H, H—C≡C—OMe); 4 (large sing., 3H, OMe)

EXAMPLE 9:

4-hydroxy-4-(1-methyl-4-piperidyl)-9- and 10-methoxy--benzo[4,5]-cyclohepta[1,2-b]selenophen IX

A solution of 4-chloro 1-methyl piperidine (4 g) in dry tetrahydrofuran (THF) (10 ml) was added dropwise to magnesium turnings covered with THF. The reaction was initiated by a drop of bromine, then the mixture was heated at 70°C for 2 hrs. After cooling, the mixture was diluted with 40 ml THF, then a solution of VIII (2.2 g) in 20 ml THF was added dropwise at room temperature and the mixture was stirred for 2 hrs, then poured in ice and NH_4Cl, and extracted with $CHCl_3$. The organic phase was washed with water, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel column (eluent $CHCl_3$, $CHCl_3$/MeOH 95: 5 then 90: 10) and gave IX (1.6 g, yield 54%).
TLC rf: 0.22 ($CHCl_3$/MeOH, 80: 20)
IR (cm^{-1}): 3400 (OH)
^{1}HNMR 60 MH_3 $CDCl_3$
δ: 7-8.1 (6H); 6.2 (sing large, 1H, CH≡C—OMe); 4.1 (1H, OH); 3.9 (2 peaks, 3H, OCH_3); 2.2 (sing, 3H, NCH_3); 1.8 - 2.7 (m, 9H)

EXAMPLE 10:

4-(1-methyl-4-piperidylidene)-9,10-dihydro-4H-benzo[4,5]-cyclo-penta[1,2-b]selenophen-9-one X and -10-one XI

1.2 g of IX were dissolved in 10 ml HCl (3N) and heated for 1 hour at 100°C with stirring.

After cooling, the solution was basified with NaOH and extracted with $CHCl_3$. The organic phase was dried and eliminated. A flash chromatography of the residue gave 2 products.
X eluted with $CHCl_3$/MeOH 99: 1
XI eluted with $CHCl_3$/MeOH 98: 2

TLC (eluent $CHCl_3$/MeOH 80: 20): (rf X: 0.61; rf XI: 0.51)
IR (cm^{-1}): 1645 (C=O); 1580 (ϕ); 1530 (selenophen)
^{1}HNMR
Product X: 60 MHz $CDCl_3$
δ: 7.2 (m, 6H); 3.7 and 4.2 (2d, 2H, CH_2—C=O); 2.3 (sing., 3H, NCH_3); 2-2.8 (m, 8H, piperidine)

Product XI: 500 MHz $CDCl_3$
δ: 8.25 (d, 1H, H_αSc); 7.25 (m, 5H); 4.25 and 3.8 (2 doublets, 2H, CH_2—C=O); 2.3 (sing, 3H, NCH_3); 2.8 and 2.7 (2m, 2H, equatorial H in α of N); 2.6 and 2.4 (2m, 4H, H in α of C=C); 2.2 and 2.1 (2m, 2H, axial H in α of N)

SALTS:
FUMARATES
Fumarate of XI

XI was dissolved in absolute ethanol and fumaric acid was added. The mixture was heated for few minutes and allowed to crystallize. After filtration, washing with ethanol and drying, pure fumarate was obtained, m.p.: 210-212°C

Fumarate of X

Proceeding similarly with X, the pure corresponding fumarate was obtained, m.p. 225°C.

TOXICITY

The toxicity of the compounds of the invention has been determined per os, by usual methods on mice. Their LD_{50} values are from about 300 mg/kg.

PHARMACOLOGY

The compounds of the invention appear as anti-allergic agents. However, compound XI shows higher activity than compound X; compound XI is an anti-allergic oral drug with histaminolytic and antianaphylactic properties. It prevents bronchial asthma. It is a powerful histamine and ovalbumine antagonist, and has been compared with ketotifen in pharmaceutical tests which are summarized as follow.

1°) Inhibition on ovalbumine immum bronchospasme

In the ovalbumine-induced bronchospasm in anaesthetized passively sensitized guinea-pigs, compound XI and ketotifen, administered 1 hour before the injection of ovalbumine, inhibit the bronchoconstriction (>90%) in a dose-dependant-manner respectively with following ED_{50} (P.O.)

compound XI: $5.72.10^{-8}$ M/kg

ketotifen: $9.41.10^{-8}$M/kg

At 0.1 mg/kg and 0.05 mg/kg (P.O.), the kinetic study shows that the compound XI significantly inhibits the bronchoconstriction when administered 1 to 18 hours before ovalbumine injection. Ketotifen significantly inhibits the bronchoconstriction when administered 1 to 3 hours before ovalbumin injection; its activity then decreases from 6 to 15 hours. For both products, the activity disappears at 24 hours.

The kinetic results, after administration by oral route of the said compounds at 0.1 mg/kg and 0.05 mg/kg (P.O.), for 1 to several hours before ovalbumine injection (1 mg/kg), are reported respectively in tables 1 and 2.

The different symbols NS, *, ** and *** which may be found in the different tables, mean that the result is repectively not significative, significative, very significative and highly significative.

The same results are obtained in actively sensitized guinea pigs, after administration, by oral route, at 0.1 mg/kg (P.O.), 1 to 21 hours before ovalbumine injection (1 mg/kg); these results are reported in the following table 3.

In the case of passively sensitized rat, compound XI inhibits the bronchoconstriction in a dose-dependant manner whereas ketotifen has no effect in this model. The results are reported in following table 4.

2°) Inhibition on histamine immun bronchospasme

In the histamine (15 mg IV) induced bronchospasm in artificially ventilated anaesthetized guinea pig, compound XI and ketotifen administered 1 hour before the injection of histamine, inhibit significantly the bronchoconstriction in a dose-dependant-manner, respectively with the following ED 50 (P.O.): compound XI $1.69\ 10^{-8}$ M/kg

ketotifen $6.35\ 10^{-8}$ M/kg

But the kinetic study shows that compound XI totally inhibits the bronchospasm during the first 9 hours then shows a regularly decreasing inhibition and reaches a plateau between 15 and 24 hrs.

Ketotifen shows a maximum effect during only the first 3 hours.

The kinetic results of the administration of compound XI and ketotifen by oral route at 0.1 mg/kg (P.O.), 1 to 27 h before histamine injection (15 mg IV), are reported in table 5.

3°) B.S.A.-induced immune lethality in mouse

Compound XI shows a protective effect at 0.275 mg/kg (P.O.). At the same dose, ketotifen has no effect.
The results of anaphylactic shock, in actively sensitized mouse, are reported in table 6.

4°) Antagonistic activity against PAF effects

In vitro: effects on aggregation (IC_{50}) induced by PAF ($5\ 10^{-10}$ M), rat washed platelets are as follow:
IC_{50} Compound XI $2\ .\ 10^{-6}$ M
IC_{50} Ketotifen 10^{-5} M

In vivo: in the PAF induced bronchospasm in artificially-ventilated anaesthetized guinea pig, compound XI administrated 1 hour before the injection of PAF, significantly inhibits the bronchospasm at 0.1 mg/kg. Ketotifen is less active.

The dose-effect on PAF induced bronchoconstriction (60 mg/kg IV), are reported in table 7.

PRESENTATION-POSOLOGY

For oral administration, in human therapy, the compounds of the invention may be presented in gelatine capsules or phials, containing 0.05 to 0.1 mg of active ingredient per dose unit. Usual posology is from 0.05 to 0.4 mg per diem.

TABLE I

Pretreatment period	Controls	Compound XI (0.1 mg/kg PO)		ketotifen (0.1 mg/kg PO)	
	% of broncho-constriction	% of broncho-constriction	% of effect	% of broncho-constriction	% of effect
1 h	84.5 ± 6.0 (n = 31)	6.9 ± 1.0 (n = 13) ***	-91.5 ± 1.3	8.3 ± 3.2 (n = 12) ***	-90.2 ± 3.8
3 h	62.3 ± 11.1 (n = 16)	3.9 ± 1.1 (n = 5)***	-93.7 ± 1.7	7.3 ± 3.0 (n = 5) ***	-88.3 ± 4.8
6 h	62.3 ± 11.1 (n = 16)	15.0 ± 11.5 (n = 6) *	-75.9 ± 18.4	31.9 ± 17.9 (n = 6) NS	-48.8 ± 28.8
9 h	77.1 ± 12.2 (n = 6)	35.7 ± 18.8 (n = 6) *	-60.1 ± 21.1	66.9 ± 19.7 (n = 6) NS	-25.1 ± 22.0
15 h	78.8 ± 10.2 (n = 11)	38.9 ± 13.7 (n = 10) *	-50.7 ± 17.3	77.5 ± 10.6 (n = 10) NS	-5.9 ± 13.3
18 h	96.8 ± 1.7 (n = 10)	36.8 ± 17.5 (n = 6) **	-62.0 ± 18.1	54.0 ± 18.6 (n = 6) *	-44.3 ± 19.2
21 h	96.8 ± 1.7 (n = 10)	73.3 ± 14.2 (n = 6) Lim*	-24.3 ± 14.7	88.3 ± 7.6 (n = 6) NS	-8.8 ± 7.9
24 h	62.3 ± 11.1 (n = 16)	45.4 ± 15.2 (n = 6) NS	-27.1 ± 24.4	67.3 ± 15.0 (n = 6) NS	+8.3 ± 24.0

TABLE II

Pretreatment period	Controls	Compound XI (0.05 mg/kg PO)		ketotifen (0.05 mg/kg PO)	
	% of broncho-constriction	% of broncho-constriction	% of effect	% of broncho-constriction	% of effect
1 h	88.4 ± 6.9 (n = 17)	13.2 ± 5.4 (n = 6)***	-85.1%	44.9 ± 15.9 (n = 6) **	-49.2%
3 h	89.6 ± 6.2 (n = 19)	17.7 ± 7.0 (n = 7)***	-80.5%	5.7 ± 1.7 (n = 6)***	-93.6%
6 h	96.7 ± 1.9 (n = 11)	38.3 ± 16.5 (n = 7)***	-60.4%	82.9 ± 14.0 (n = 5) NS	-14.3% NS
9 h	96.8 ± 3.2 (n = 6)	49.2 ± 16.7 (n = 6) *	-49.2%	80.3 ± 19.7 (n = 5) NS	-17.1%
15 h	65.9 ± 19.0 (n = 6)	61.6 ± 18.7 (n = 6)	-6.5% NS	64.3 ± 18.3 (n = 6)	-2.4% NS
18 h	98.0 ± 1.4 (n = 9)	50.7 ± 20.4 (n = 6) *	-48.3%	100 ± 0 (n = 5) NS	+2.0% NS
21 h	98.0 ± 1.4 (n = 9)	94.6 ± 4.4 (n = 5)	-3.5% NS	94.4 ± 3.2 (n = 5)	-3.2% NS

TABLE III

Pretreatment period	Controls	Compound XI (0.1 mg/kg PO)		ketotifen (0.1 mg/kg PO)	
	% of broncho-constriction	% of broncho-constriction	% of effect	% of broncho constriction	% of effect
1 h	86.1 ± 10.5 (n = 8)	3.5 ± 1.1 (n = 6)***	-96.1 ± 1.3	3.6 ± 1.2 (n = 6)***	-95.8 ± 1.4
3 h	75.0 ± 11.7 (n = 12)	5.0 ± 1.6 (n = 6)***	-93.4 ± 2.1	3.3 ± 0.5 (n = 6)***	-95.6 ± 0.7
6 h	75.0 ± 11.7 (n = 12)	2.1 ± 0.6 (n = 6)***	-97.3 ± 0.8	42.1 ± 19.3 (n = 6) NS	-43.9 ± 25.8
9 h	91.2 ± 8.8 (n = 5)	35.5 ± 15.9 (n = 5) *	-61.1 ± 22.2	83.2 ± 16.1 (n = 6) NS	-8.8 ± 17.6
15 h	85.2 ± 14.8 (n = 5)	42.2 ± 16.6 (n = 6)	-50.6 ± 19.5	77.5 ± 14.8 (n = 6) NS	-9.0 ± 17.4
18 h	54.7 ± 13.6 (n = 10)	67.1 ± 19.0 (n = 6) NS	+22.7 ± 34.8	64.5 ± 19.5 (n = 6) NS	+17.9 ± 35.7
21 h	54.7 ± 13.6 (n = 10)	50.1 ± 21.6 (n = 5) NS	-8.3 ± 39.5	73.6 ± 15.5 (n = 6) NS	+34.4 ± 28.5

TABLE IV

Compounds	Dose mg/kg PO	n	Percentage of bronchoconstriction	Percentage of effect
Controls	---	15	38.5 ± 5.5	---
Compound XI	0.1	8	18.1 ± 6.3 *	-49.4%
	1	6	11.2 ± 2.7 *	-68.7%
Ketotifen	0.1	6	24.7 ± 5.1 NS	-31.0%
	1	6	46.3 ± 11.0 NS	+29.3%
Astemizole	5	5	8.6 ± 2.5 **	-76.0%

TABLE V

Time	Controls	Compound XI		ketotifen	
	% of broncho-constriction	% of broncho-constriction	% of effect	% of broncho-constriction	% of effect
1 h	79.4 ± 5.2 (n = 18)	2.0 ± 0.8 (n = 8)***	-97.5 ± 1.0	2.1 ± 0.8 (n = 9)***	-97.4 ± 1.0
3 h	79.4 ± 5.2 (n = 18)	1.0 ± 1.0 (n = 3)***	-98.8 ± 1.2	0 (n = 3)***	-100 ± 0
6 h	82.3 ± 8.1 (n = 5)	5.4 ± 3.2 (n = 6)***	-93.5 ± 3.8	18.2 ± 13.3 (n = 6)***	-77.8 ± 16.2
9 h	75.5 ± 10.6 (n = 6)	4.9 ± 1.7 (n = 6)***	-93.6 ± 2.3	22.1 ± 14.1 (n = 5)**	-71.5 ± 14.1
15 h	70.7 ± 7.6 (n = 12)	36.6 ± 8.4 (n = 10) *	-48.2 ± 11.8	51.4 ± 16.7 (n = 10) NS	-26.9 ± 16.7
18 h	91.0 ± 3.4 (n = 7)	34.9 ± 18.1 (n = 5)**	61.7 ± 19.9	54.6 ± 13.3 (n = 5) *	-39.8 ± 14.8
21 h	87.9 ± 4.5 (n = 6)	52.9 ± 9.7 (n = 6) *	37.6 ± 11.5	46.6 ± 14.9 (n = 6)**	-44.9 ± 17.6
24 h	65.7 ± 7.8 (n = 11)	37.9 ± 9.9 (n = 10) *	-42.3 ± 15.0	63.7 ± 15.1 (n = 6) NS	-3.0 ± 23.1
27 h	72.3 ± 10.8 (n = 5)	76.8 ± 10.2 (n = 5) NS	+6.3 ± 14.1	83.4 ± 5.9 (n = 6) NS	+15.4 ± 8.1

TABLE VI

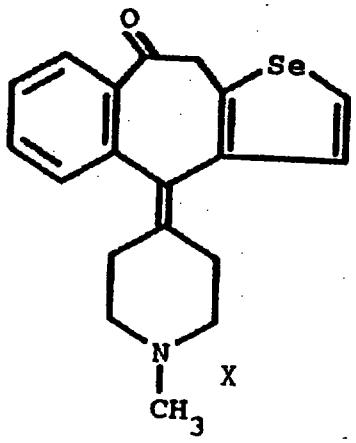
Compounds	Doses mg/kg PO	Mortality at 24 hours		
		Number of killed	% of mortality	% of variation
Controls	-	16/26	61.5	-
Ketotifen	0.250	5/10	50	-18.7 NS
	0.500	4/10	40	-35 NS
Compound XI	0.275	2/10	20	-67.5 **
	0.550	1/10	10	-83.7 ***
Mequitazine	2.5	3/10	30	-51.2 *
	10	3/10	30	-51.2 *

TABLE VII

Compounds	Dose mg/kg PO	n	Percentage of bronchoconstriction	Percentage of effect
Controls	-	18	78.3 ± 5.7	-
Compound XI	0.1	11	29.4 ± 7.9 ***	-62.5
	1	6	23.0 ± 9.7 ***	-70.6
Ketotifen	0.1	11	63.5 ± 9.6 NS	-18.9
	1	6	26.2 ± 14.8 ***	-66.5

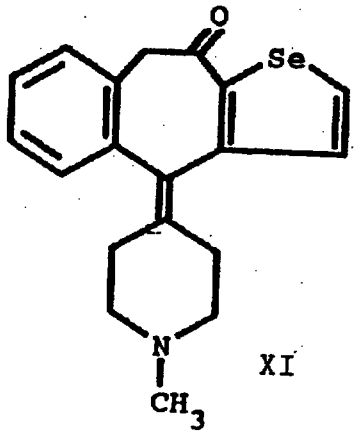
CLAIMS:

1. A selenophen derivative of the formula:



X

or



XI

or a pharmaceutically acceptable salt of such a selenophen derivative.

2. A process for the preparation of the selenophen derivatives X and XI, the process comprising brominating 9,10-dihydro-4H-benzo[4,5]cyclohepta[1,2-b]selenophen--4-one, reacting the resultant 9,10-dibromo-4H--benzo[4,5]cyclohepta-[1,2-b]selenophen-4-one with methanol and treating the product with a strong inorganic base, reacting the resultant mixture of 9- and 10-methoxy-4H-benzo[4,5]cyclohepta[1,2-b]selenophen-4-one with a 1-methyl-4-piperidinylmagnesium halide, demethylating and dehydrating the resultant mixture of 4-hydroxy-4-(1-methyl-4-piperidyl)-9- and 10-methoxy--benzo[4,5]cyclohepta[1,2-b]selenophen and separating the resultant compounds.

3. A process according to claim 2 in which the bromination is effected with a stoichiometric excess of N-bromosuccinimide under reflux in an inert aprotic solvent in the presence of dibenzoylperoxide.

* C L M S *

4. A process according to claim 2 or claim 3 in which the 9,10-dibromo-4H-benzo[4,5]cyclohepta[1,2-b] selenophen-4-one is refluxed with methanol, an excess of potassium hydroxide is added, and heating is continued at from 60 to 90°C.

5. A process according to any of claims 2 to 4 in which a stoichiometric excess of 1-methyl-4-piperidyl-magnesium chloride is used in an aprotic solvent at ambient temperature.

6. A process according to any of claims 2 to 5 in which the demethylation and dehydration is effected by heating with hydrochloric acid at about 100°C.

7. A process for the preparation of the selenophen derivatives X and XI, the process being substantially as described herein with reference to Examples 7 to 10.

8. A pharmaceutical composition comprising a selenophen derivative according to claim 1 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable diluent or carrier.

9. A pharmaceutical composition according to claim 8, the composition being in unit dose form and containing from 0.05 to 0.4 mg of the selenophen derivative or salt thereof.

* C L M S *