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Norbornane compounds in pharmaceutical research

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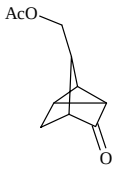
1. Introduction

This paper – a continuation of previously published reviews [1, 2] – presents an overview of papers published between 1989 and June 1997 on the biological activities of norbornanes. Chemical Abstracts were used as the main source of the literature research. The chapters were arranged according to biological activities.

2. Norbornanes as synthetic intermediates

In this chapter a series of norbornanes are dealt with, that is useful for the synthesis of either pharmacologically – effective compounds such as analogues of prostaglandins and thromboxane receptor antagonists, or other pharmaceutically – useful compounds such as reagents for optical resolution.



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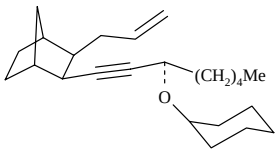

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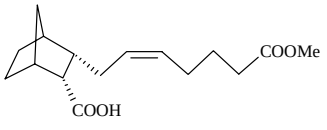

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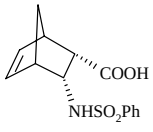

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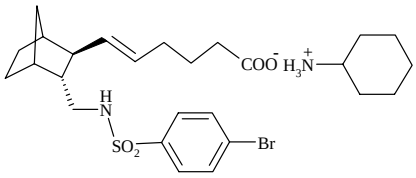

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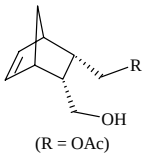
Compound **1** is an important intermediate for the synthesis of prostaglandins and their analogues via norbornandiene [3]. The starting substance for **2**, an analogue of prostaglandin-endo-peroxide, is norbornene [4]. The carbo-analogue of prostaglandin-endo-peroxide is synthesized from **3** [5].



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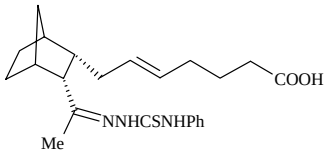

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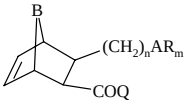

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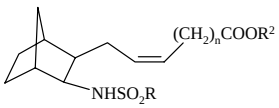

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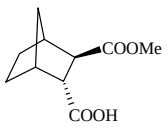

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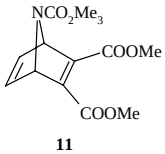

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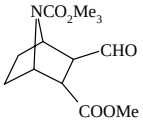

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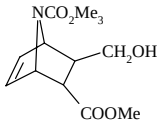

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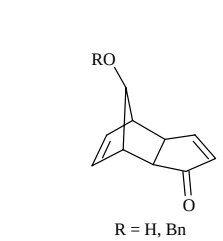
Compounds **4**–**8** [A = hetero atom, halogen; B = CH_2; Q = (un)substituted oxazolidinoyl; R = hydrocarbyl; m = 0, 1; ≥1] and **9** [R = (un)substituted aryl, aralkyl; R^2 = an amine residue] are intermediates for thromboxane receptor antagonists [6–11]. **10** is the main intermediate of S-1452 (**50a**) [12].

11 and the reduced compounds **12** and **13** are interesting starting materials for the synthesis of potent thromboxane receptor antagonists and other bioactive compounds [13]. The dimeric cyclopentadiene **14** is used for the synthesis of carboprostacycline [14]. **15** [R^{3-5} = H, alkyl, (un)substituted aryl] is useful for the preparation of optically-active vinyl alcohols as intermediates for prostaglandine syntheses [15].



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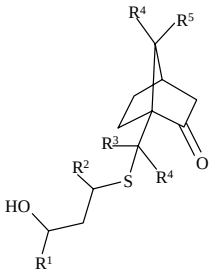

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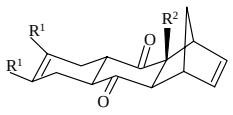

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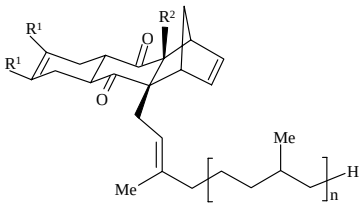

R^1 = H, Me; R^2 = H, Me; n = 0-9

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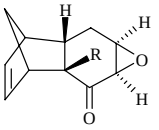

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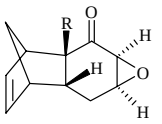

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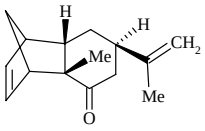

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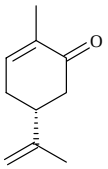
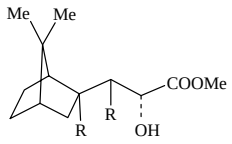


20a

Via **16** and **17**, both hexahydro alkenylmethano anthrachinone derivatives, some new naphthochinone derivatives (vitamine K) can be prepared [16]. Optically active carvones, e.g. **20a**, can be obtained via the intermediates **18**, **19** and **20** [R = alkyl, hydrocarbonyl, aralkyl, H] [17]. The chiral compound **21** [R = H or double bond] is a key substance for the synthesis of aspartyl dipeptide sweeteners of the type **22** [18].

For the synthesis of iridoides and eicosanoides optically-active-norbornene derivatives, such as **23**, can be used [19]. Alicyclic alcohols of type **24** are very useful as intermediates for the synthesis of agrochemicals and pharmaceuticals, and can be prepared via the dienes of type **25** [n = 1] [20]. Via **26**, **27** and **28** the elaeocarpus alkaloids (+)-elaeokanine A and (+)-elaeokanine C can be obtained with a new synthetic pathway [21].



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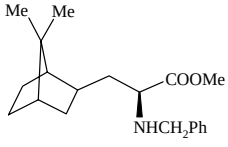

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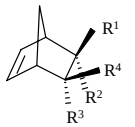

R^{1-3} = H, alkyl, aryl

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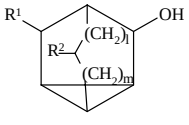

R^1, R^2 = H, CH_2OH; l, m = 0,1

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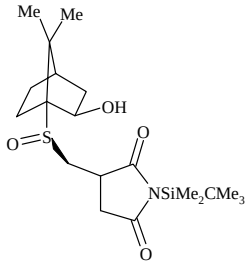

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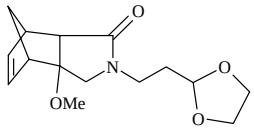

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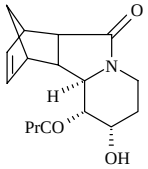

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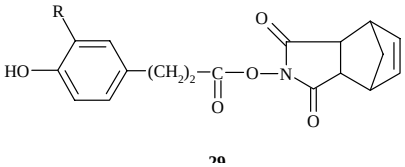
Compound **29** [R = I] is used for the iodination of amino acids and peptides [22]. Amino hydroxybornanes, such as **30** [R = furfuryl, (1-methylpyrrol-2-yl)-methyl, benzyl], are used as ligands for the synthesis of optically-active muscones [23]; **31** is very important for the preparation of terpenoids and nucleosides [24]. Carbamates with a substituted benzylamine group [R = **32**], yield with amines substituted derivatives of urea [25].

Via oxazolones, such as **33**, some aminohydroxy acids, such as statine- and hydroxyglutaminic acid, can be prepared. These are key-parts of bioactive peptides [26]. Starting from **34** [n = 0, 1] (*S*)-glutaminic acid and (*S*)-2-amino adipoic acid are synthesized [27]. *exo*-2-Norborneol is prepared from **35** [28] and 2-cyclopenten-1-one ethylene acetal (**36**) with a dienophil yields the 2-norbornanone ethylene acetal **37** [29].



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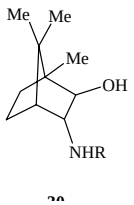

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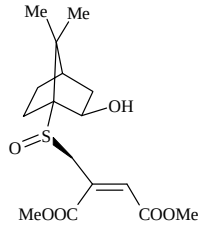

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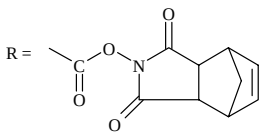

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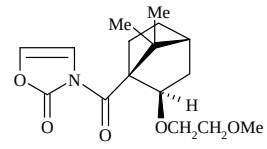

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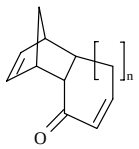

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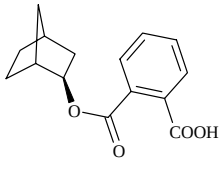

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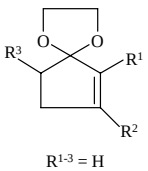

R^{1-3} = H

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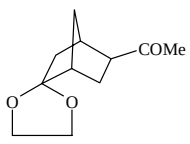

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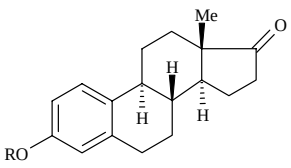
Estrones, like **38** [R = C_{1-20}alkyl] can be synthesized using norbornanes, e.g. **38** from **39** [30]. N-protected amino acids of the type **40** [X = CH_2; R = H, CH_3; R^1 = H] are useful for the preparation of bridged azatricyclic anhydrides, which are valuable substrates for peptide syntheses [31]. Polymers of such norbornanes, such as **41** [R^1 = CN, carbomethoxy; R^2 = organooligosilanyl, organooligosiloxanyl, organooligosilanylalkyl, organooligosiloxanylalkyl and alkyl] are used for the preparation of air-porous materials [32].

Sodium norbornyl monosulfate (**42**) is an intermediate for the synthesis of water soluble pharmaceuticals as well as for the optical resolution of racemic mixtures of organic bases [33]. Rigid bicyclo[2.2.1]heptanes, such as **43**, form protecting groups [34]. Derivatives, such as **44** [R^1 = halogen, CO_2R^3, $SiR^4R^5R^6$, CHO, $C(OH)R^7R^8$, SR^9; $R^{3-6,9}$ = lower alkyl, aryl; R^7 = H, alkyl, alkenyl, aryl; R^8 = alkyl, alkenyl, aryl] are intermediates for the synthesis of drugs, agrochemicals and starting materials for polymers and fragrances [35].

Compounds **45** and **46** can be used as intermediates for the synthesis of physiologically-active, naturally-occurring substances [36]. Chiral and electrophil glycine equivalents, such as compounds of the type **47** [R^1 = CH_3, propyl, t-butyl] [37] are new starting materials for the synthesis of optically active α-amino acids as well as of in position 4 substituted 2-oxazolidinones. Cyanoguanines, like **48** [ring is possible at the position 5 or 6] and **49** [ring is possible at the position 2 and 5, or 2 and 6] are monomeric pharmaceuticals and agrochemicals [38], or at least starting materials for such compounds [39, 40].



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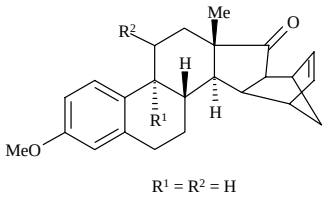

$R^1 = R^2 = H$

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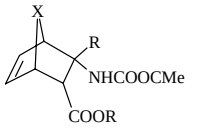

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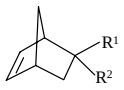

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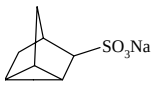

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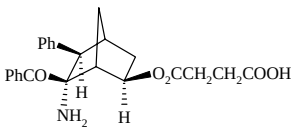

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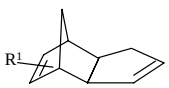

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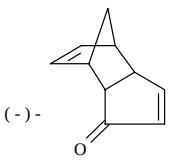

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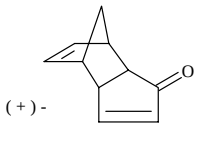

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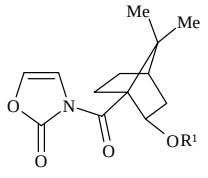

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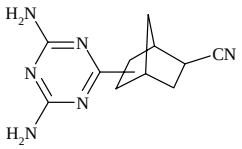

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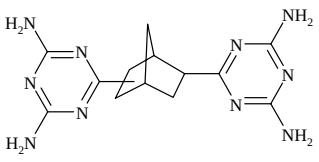

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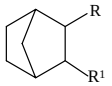
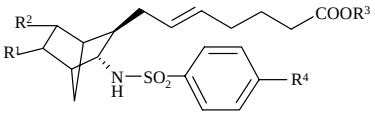
3. Receptor agonists and -antagonists

3.1. Analogues of prostaglandins and thromboxane antagonists





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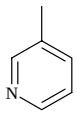
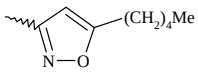
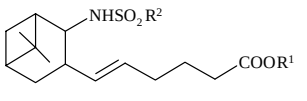




50	R	R^1	
a	S-1452 as Ca^{2+}-salt	$CH_2-CH=CH-(CH_2)_3COO^-$	$NH-SO_2-Ph$	[41–47]
b	EP-035	$CH_2-CH=CH-(CH_2)_3COOH$	$CH_2=N-O$	[48]
c		$CH_2-CH=CH-(CH_2)_3COOMe$	$NH-SO_2-Ph$	[49]
d		$CH_2-CH=CH-(CH_2)_3COONa$	$NH-SO_2-Ph$	[50]
e		$X-CO-NR_1-OR^2$ X = alkylene, alkenylene R^1, R^2 = H, C_{1-6}alkyl	$(CH_2)_nNH-SO_2-Ph-R^3$ R^3 = H, C_{1-6}alkyl, -alkoxy, OH halogen n = 0–2	[51]
f		$CH=CH-(CH_2)_3-R^1$ R^1 = carboxyl, -5-tetrazolyl	$NH-SO_2-PH-R^2$ R^2 = H, CH_3, OH, Cl, Br	[52]
g		$CH_2-CH=CH-(CH_2)_3COOH$		[53]
h	EP092 Z	the same	$C-CH_3$ | NHHCSNHPh	[54, 55]
i		$CO-(CH_2)_n-COOMe$ n = 4, 5	$CH:CHCH(OH)C_5H_{11}$ $CH:CHCOC_5H_{11}$ $COCH_2COC_5H_{11}$ $COC_7H_{11}CH(NH_2)CH_2CH(OH)C_5H_{11}$ $C(NH_2):CHCOC_5H_{11}$ ua.	[56]
j		$CH_2-CH=CH-(CH_2)_3COOH$	$NH-SO_2-Ph$	[57]
k		the same as salt of lysine	the same	[58]
l		$CH_2=CH-(CH_2)_3COOH$	$CH_2-NHSO_2-Ph-Br$	[59]
m		$CH_2-CH=CH-(CH_2)_3COOH$	$(CH_2)_2NHSO_2Ph$	[60]
n		$CO-(CH_2)_5-COOMe$		[61, 62]
o		$CO-(CH_2)_4-COOMe$ $(CH_2)_7H$	$S-(CH_2)_8-H$ or Ph $S-(CH_2)_2-COOEt$	[63]

Many analogues of prostaglandines have been synthesized. They have in common the capacity of inhibition of the aggregation of thrombocytes. Some of these compounds are **50a–o**, **51–53**. Compound **50** is called *domitroban calcium hydrate* [43] and acts also antiasthmatic [39] as well as being a useful radioligand for the investigation of the thromboxane-A_2-receptor if labelled with ^{125}I [40]. Also studies on the metabolites of **50a** and their receptor binding are known [41]. *Trans*-isomers show a better inhibitoring activity than the *cis*-isomers in tests with aortas of rats; in human plasma only tiny differences could be found [42]. Furthermore **50a** increases the reactivity of tumor cells to cancerostatics such as platin complexes in the case of resistent tumors of the lung [44]. **50a** is a good example of prostaglandine-D_2-antagonists which can be used against systemic mastocytosis, bronchoconstriction, as antiasthmatics, against allergic rhinitis and conjunctivitis, urticaria, ischemic disorders of blood supply



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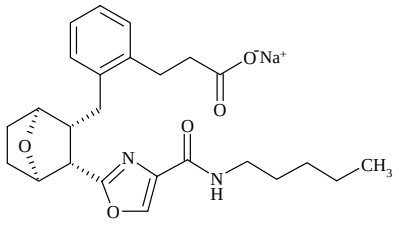

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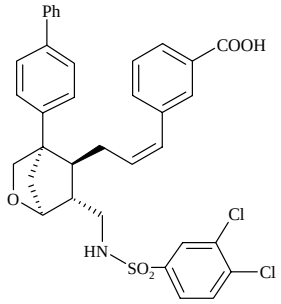

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and as antiinflammatory drugs [45]. **50b**, which acts as a PGI_2-mimeticum on blood platelets, is different from other specific thromboxane antagonists by virtue of its diphenyloxime part [46]. **50c** is a topical pharmacon against diseases of the bronchioles and, as such, is a prodrug of **50a**. It can be used therapeutically against asthma, acute or chronic bronchitis, emphysema and bronchiecstasis [47]. **50f** is useful in the therapy of thromboses, hypertonia, apoplexy, myocardial infarction, cerebral infarction, coronar insufficiency and disorders of the blood; it is stable, can be absorbed very fast and is not a partial agonist [50]. **50g** prevents the biosynthesis of thromboxane in human blood platelets [51]. **50n** is an analogue of prostaglandine-endoperoxide [59], and **50o** is an example of new, sulfur-containing bicycloheptane analogues of prostaglandines [61].

Compound **51** [R^1 = H, lower alkyl; R^2 = alkyl, aralkyl, aryl with various substituents] shows a remarkable activity in inhibition of thrombocyte aggregation, and is therefore useful against thromboses, embolisms, arteriosclerosis, myocardial infarction, shock and apoplexy [62]. *Ifetroban sodium* (**52**) is a potent selective antagonist of thromboxane receptors [63] and shows a dose-dependent cardioprotective activity [64]. **53** has been prepared as a TxA_2-receptor-antagonist [65].

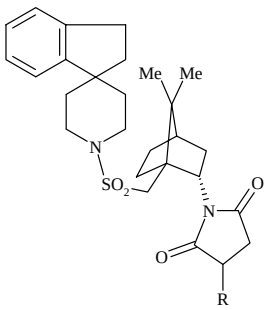
3.2. Antagonists of oxytocin

An essential key element for the activity as a non-peptidic antagonist of oxytocin is the camphoramino-succinimide group. Some examples are **54** [R = OH, alkylamino, carboxymethylamino, etc.], **55** [69] and **56** [70]. Further antagonists of oxytocine are **57** [71], **58** [$R = Q^2$, R^{16} = 2-methylphenyl, R^{17} = H, 4(5)-imidazoacetyl, m = 0, n = 1, Y = SO_2], **59** [72] and **60** [R^{12} = H, alkoxycarbonyl, (un)substituted alkyl; R^{13} = H, alkoxyl, aralkoxyl, alkoxycarbonylamino, (un)substituted amino, (un)substituted heterocylic, (un)substituted alkyl] [74].

Compound **59** is useful in the therapy of premature pains in labour, dysmenorrhea and for the inhibition of labour-pains before a caesarean section [73]. By administration of **60** an increase in fertility rates and survival of farm-animals could be observed [74].

3.3. $5HT_{1A}/5HT_2$ Receptor ligands

An example in this series is *tandospirone* (**61**) which shows anxiolytic and antidepressive activity [75]. A new administration form has been reported [76]. **61** is available as *Sediel*® on the Japanese market against psychosomatic disorders, depressions, anxiety, stress, sleeplessness, paranoidal psychoses and neurotic depressions [77]. Further examinations of its pharmacokinetic, -dynamic and clinical usage have been performed [78]. Another anxiolytic acting compound is *deramciclan fumarate (Egypt-3886)* (**62**), which acts as a less sedating, non-BDA-type-anxio-



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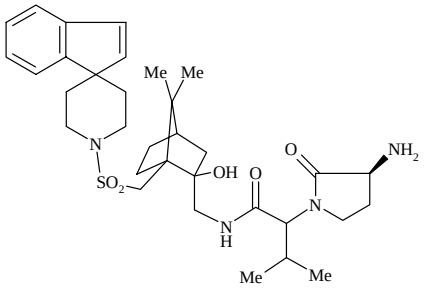

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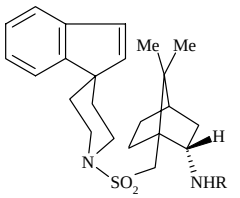

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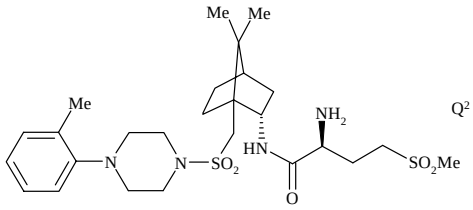

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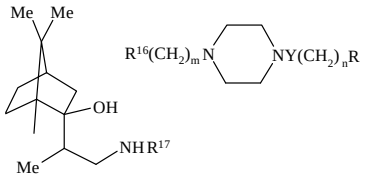

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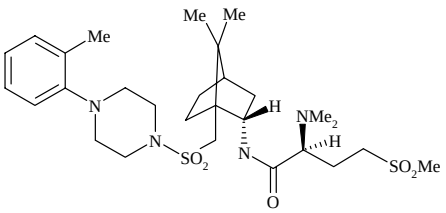

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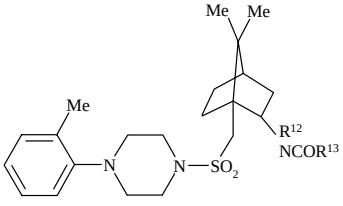

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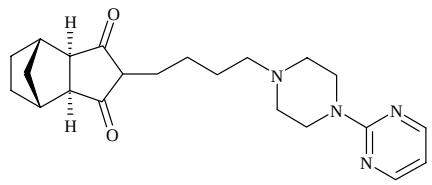

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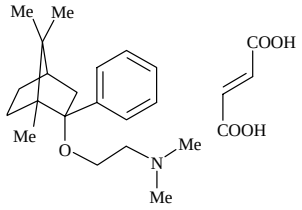

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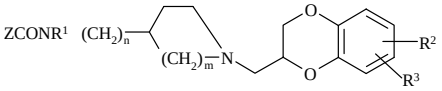

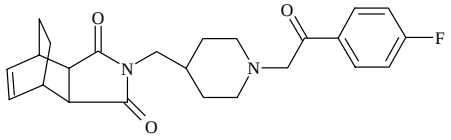

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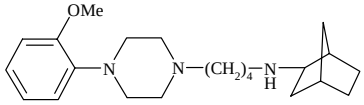

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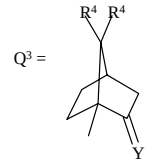

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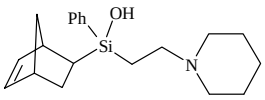
lyticum without non-wanted muscle relaxing side effects. The affinity of **62** to $5HT_2$ receptors is comparable with that of *cypoheptadin* [79]. **63** is an antagonist of the serotonine 5 HT_2 receptor [80]. The piperazine derivate **64** shows an increased affinity to $5HT_{1A}$ receptors [81]. Another antagonist is compound **65** [$Z = Q^3$, $Y = H_2$, O, R^1 = H, alkyl, R^2R^3 = H, alkyl, alkoxy, OH, halogen, (di)(alkyl)amino, alkylamido and sulfonamido, m = 1–3, n = 0, 1] [82].

3.4. Ligands of muscarinic receptors

Sila-biperiden (**66**) is the silicon analogue of *biperiden*, a well-known medicament against Morbus Parkinson. Both are competitive inhibitors at the muscarinic receptors M_{1-4}, showing a somewhat greater affinity towards M_1 [83]. Muscarinic activity has also been attributed to the carboxyl analogues of 1-azabicycloheptane (crystalline mixture of the diastereomers **67** and **68**) [84].



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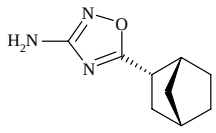

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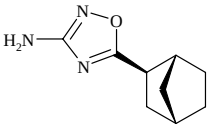
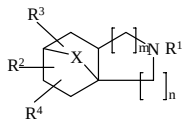


68

3.5. Dopamine D_2 receptor antagonists

Compounds of type **69** [R^1 = alkyl, R^{2-4} = H, halogen, alkyl, etc.] act antidyskinetic and can be used for the treatment of psychoses caused either physiologically and/or contingent upon drug-misuse [85]. Other dopamine D_2 receptor antagonists are compounds of type **70** [R^2 = CR^3R^4OH, COR^3, CHR^3R^4; R^3 = (cyclo)alkyl, phenyl, naphthyl, heteroaryl, etc.; R^4 = H, alkyl; X,Y = H, halogen] [86-88].



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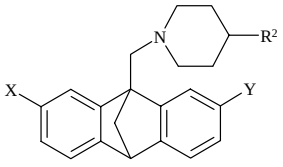

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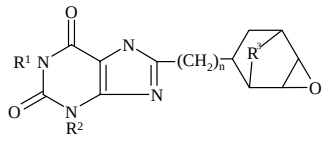
3.6. Adenosine receptor ligands

Purine or xanthine derivatives such as **71** [R^1, R^3 = H, C^{1-4}alkyl; $R^3 = CH_2$; n = 0–4] are known to be potent, selective agonistic or antagonistic ligands of adenosine receptors [89]. Another xanthine derivative acting as an adenosine receptor antagonist is **72** *(N-0861)*, which is able to inhibit disturbances of the cardial rhythm, whereby the adenosine induced positive-inotropic response is retained and the heart-time-volume is not decreased [90]. The compounds of the type **73** [R^1 = alkyl, alkenyl, alkinyl; R^2 = H, alkyl, alkenyl, unsubstituted benzyl; R^3 = C of an (un)saturated 5,6 or 7 membered ring heterocyclus with one or more O and/or S and substituted with either Q or Q^1] are xanthines with specific affinity to adenosine A_1-receptors, which can be used against alzheimer or senile dementia, diseases often encountered with the elderly [91].



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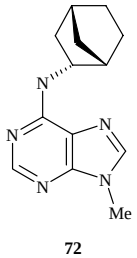

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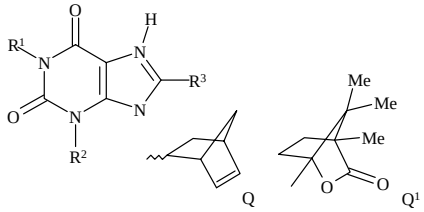

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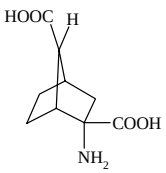
3.7. Other receptor ligands

Compound **74** is a competitive antagonist to $mGluR_{1a}$-receptors [92], and **75** is a ligand of the cholecystokinine and/or gastrine receptor [93]. **76** and **77** are antagonists to adrenergic α_2-receptors [94]. **78** is known to be a specific imidazoline$_1$-receptor-ligand without any activity to α_2-re-



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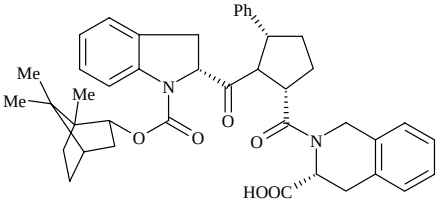

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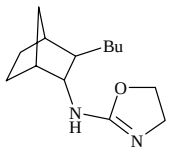

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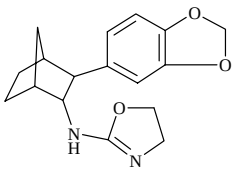

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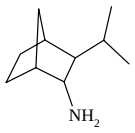

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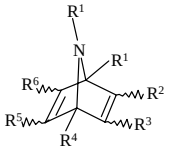


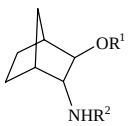
79

ceptors and without any physiologically response [95]. Compounds of type **79** [$R^{1,4}$ = H, (un)substituted alkyl; R^2 = H, alkyl, alkenyl, heterocyclyl(thio), aminoheterocyclylamino, carbamoyl, etc.; $R^{3,5,6}$ = H, (un)substituted alkyl, amino, halogen, etc.; R^2R^3 can form a ring; R^7 = H, (un)substituted alkyl, aryl, cycloalkyl] are ligands of cholinergic receptors and can be used for treatment of disorders of cholinergic equilibrium [96].

4. Analogues and inhibitors of enzymes

4.1. Protein kinase C

A group of structurally-modified bicyclic or tricyclic compounds of great interest, such as **80** and **81** [R^2 = COC_6H_4OH], can be classified as protein kinase C-(PKC)-inhibitors. Both reduce the activity of most of the PKC-isoenzymes and are selective to the c-AMP-dependent protein kinase (PKA) [97]. Other inhibitors of PKC are compounds of the type **82** [R = $CO(CH_2)_{14}CH_3$-n, $(CH_2)_{15}-CH_3$-n; R^1 = H, CH_2OH] [98, 99].



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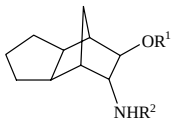

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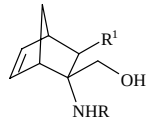
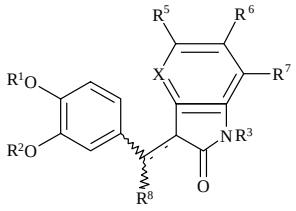


82

4.2. Phosphodiesterase

Substituted indolones, such as **83** and especially the example **84** [R^1 = alkyl, phenylalkyl; R^2 = the same, then cycloalkyl and polycycloalkyl; R^3 = H, alkyl, alkoxycarbonyl, (un)substituted $CONH_2$; R^{5-7} = halogen, alkoxy, cycloalkoxy, NO_2, acyloxy; R^9 = H, alkyl; X = N, (un)substituted CH; dotted lines are possible double bonds] show many interesting properties. As inhibitors of phosphodiesterase IV they can be used in the treatment of AIDS, asthma, rheumatic arthritis, osteoarthritis, bronchitis, etc. [100]. **85**, a *rolipram* derivative (*CP-80633*) [101] with a tetrahydropyrimidinone nucleus instead of a pyrrolidinone ring [102] shows antiinflammatory and bronchodilatatoric activities. **85** increases *in vitro* the intracellular concentration of cAMP and inhibits in human cells the liberation of tumor necrosis factor (TNF). Furthermore, it shows anaphylactic and antiemetic activities [101]. **86** also shows antiinflammatory properties for which it can be used against asthma and skin edemas [103]. **87** [R = H; RR = bond, CH : CHCH : CH, $(CH_2)_3$] acts as an selective inhibitor of the calcium independent phosphodiesterase and also inhibits the specific binding of tritium-labelled *rolipram* at cerebral membranes of rats. Some of the derivatives of **87** show in preclinical experiments with mice antidepressive activities [104,105]. Derivatives of **88** [R^1 = alkyl, cycloalkyl, aloxyalkyl; R^2 = H, halogen, alkyl, cycloalkyl, alkoxy, alkoxycarbonyl, haloalkyl, haloalkoxy, alkylthio, alkylsulfonyl, alkylsulfinyl, CN, NO_2; R^3 = H, $O(CH_2)_nQ^1Q^2$, $O(CH_2)_mN(CH_2)_nQ^1Q^2$; m, n = 1–18] are inhibitors of the phosphodiesterase and show calcium-antagonistic, antihypertensive properties and inhibit the aggregation of thromocytes, for which they are used as dilatators of coronary vessels and against thrombosis [106].



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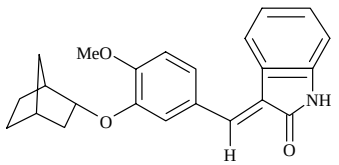

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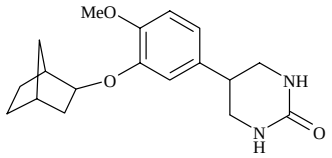

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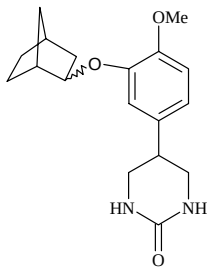

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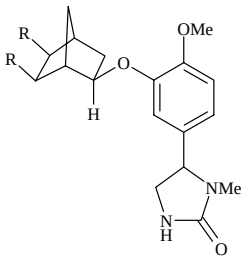

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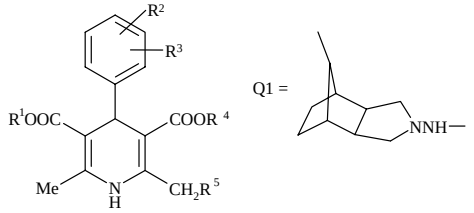

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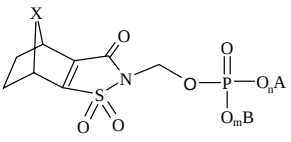
4.3. Others

Compounds such as **89** [A, B = alkyl, phenyl, CH_2-phenyl, 2-pyridinyl, m = 1, n = 0; A, B = alkyl, phenyl, alkoxyphenyl, m = n = 0; X = CH_2, $C(CH_3)_2$], act as inhibitors of several proteases and can therefore be used in the treatment of degenerative diseases, like emphysema, rheumatoic arthritis, pancreatitis, cystic fibrosis, bronchitis, etc. [107]. *Sulforphane* (**90**), an isothiocyanate which has been isolated from a certain variety of broccoli, activates phase-II-detoxification systems, which help to counteract the toxic and neoplastic effects of cancerogenes. **90** and the easily accessable norbornyl analogues **91**, **92** and **93** inhibit the formation of tumors. Among other analogues **92** was *in vivo* the best inductor of quinone reductase and glutathione transferase in various organs of mice. It is



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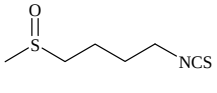

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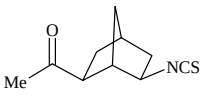

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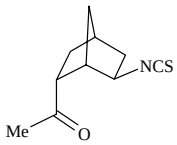

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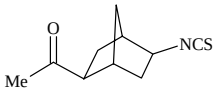

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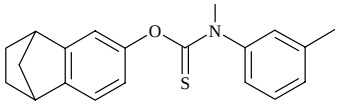

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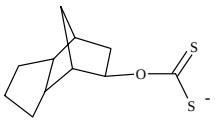

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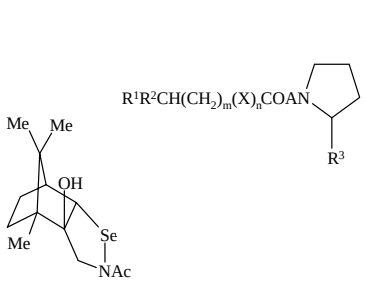

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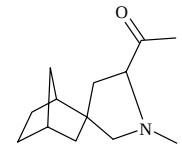

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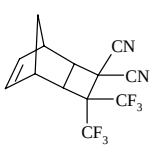
comparable with **90**, but as to the metabolism, more stable – like other bicyclic keto isothiocyanates – than **90** [108]. *Tolcyclate* (**94**) shows antimycotic properties thought to be caused by inhibition of the fungal DNA-synthesis. According to new research results, the inhibition of the fungal enzyme squalene epoxidase (SE) is responsible. SE together with HMG-CoA-reductase is an important factor in cholesterol biosynthesis. A new field of application can therefore be opened, namely the treatment of hypercholesteraemia, but the effects of fungal SE-inhibitors on the SE of mammals is not yet thoroughly investigated. **94** is a weak inhibitor of SE of ratliver [109]. Compound **95** interferes with phospholipase C dependent processes. The possible therapeutic advantage of such phospholipase C-inhibitors is stratified as the various functions of this group of phosphodiesterases. An example is the inhibition of the participation of neutrophiles in inflammatory processes or the application as antitumor-substances because of participation of phosphoinositol in cell-growth. Another speculative proposal is the use of phospholipase C inhibitors as potent medicaments in the treatment of adiposis [110]. Acylheterocyclocarbonyl-proline derivatives such as **96** are inhibitors of the prolinyl-endo-peptidase [R^1 = H, C_{1-20} alkyl, alkenyl, (substituted) C_{6-12} aryl; R^2 = H, OH, C_{1-6} alkyl, C_{1-21} alkoxyl, (substituted) C_{6-12} aryl, aryloxy, C_{7-13} aroyl; R^1R^2 = (substituted) benzylidene; R^3 = H, $HOCH_2$, HCO, COF_3, $R^6C:CR^7R^8$, $COCO_2R^9$ etc; R^4 and R^5 = H, C_1 alkyl, C_{5-8} cycloalkyl, (substituted) phenyl, phenylalkyl; R^6 = H, C_{1-6} alkyl, (substituted) C_{6-12} aryl; R^7 = H, C_{1-6} alkyl, C_{7-13} aroyl, Cyano; R^8 = C_{7-13} aroyl, cyano, arylalkanoyl; R^9 = H, C_{1-6} alkyl, (di)phenylalkyl; R^{10}, R^{11} = H, C_{1-8}, (substituted) C_{6-12} aryl, arylalkyl; $R^{10}R^{11}N$ = 5–10 membered substituted heterocyclus; A = Q^4; X = O, imino; m = 0-5; n = 0,1] [111]. **97**, a seleniumamide of camphor, acts as a glutathione-peroxidase mimetic [112].

5. Pesticides, antibacterially active substances, etc.

Cyano substituted polycyclusses like **98** possess pesticidal activities against a variety of arthropodes [113]. **99** is antibacterially active as well as being fungicidal [114]. **100** [R = CH_2OH, H] is a potent antibacterial compound [115] and **101** an anthelminthicum [116]. Thiosemicarbazones, as **102**, also show antibacterial and antituberculotic activities [117]. Aromatic ether-derivatives of bornanes, like **103** [R = Cl, Br, CH_3, C_2H_5, isopropyl] are analogues of juvenile insect hormones and therefore insecticides [118,119]. 2-Bornanol and various amino acids yield bactericidic esters of type **104** [R = BOC-NHCHR^{1}CO]. If R^1 = CH_2-phenyl, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$ then the compound is active against *Bacillus mycoides*, if R^1 = $CHCH_3$, $CH_2CHC(CH_3)_2$ then an activity also against *Bacillus subtilis* is observed [120].
Esters of type **105** [R = macrolide antibiotic or lincosamide-residue; R^1R^2 = H, alkyl, a = b = 0, 1; a ≠ b = 0, 1; A = Q, Q^1] can be used in the treatment of acne [121]. **106** can be used as an antioxidant, lubricant, insecticide and precursor of polymers [122]. *Sordarine* glycosides such as **107** [R^1 = H, halogen, OH, alkyl, alkoxy, alkoxycarbonyl; R^2 = H; R^1R^2 = O; R^3 = CH_2R^4; R^4 = H, OH, alkoxy, alkoxycarbonyl; X = O, S, CH_2] are fungicides [123–125].

6. Compounds showing an influence on blood pressure and heart

Compound **108**, an aminopyridine with norbornyl residue, lowers blood pressure and leads to a significant improve-



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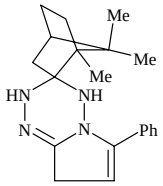

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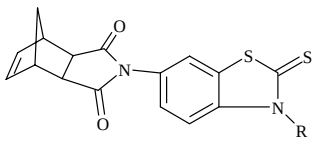

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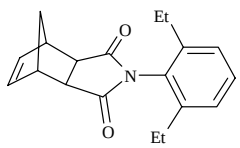

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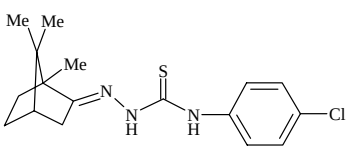

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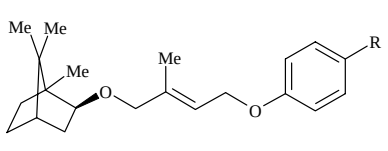

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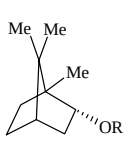

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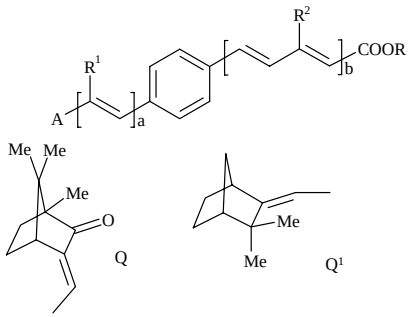

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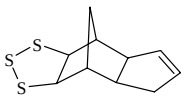

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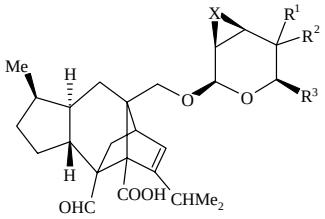

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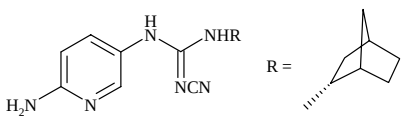
ment of fat metabolism by means of a decrease in triglycerides and increase in HDL-C-fraction [126]. *N*-aminopyridyl-*N′*-norbornyl-*N″*-cyanoguanidines and analogues, like **109**, are able to lower blood pressure by opening potassium channels, but with an unwanted side effect on the equilibrium of urine electrolytes. The alanine- and histidine derivatives of **109a** and **109b** avoid this effect by improved pharmacokinetics and without reduction of the blood-pressure lowering activity [127–129]. Spirosubstituted glutarimides, as described in formula **110** [A completes a 4–7 membered carboxyl ring; X is a bridge-group of formula II; Y is e.g. CH_2; $R^1 = H$, C_{1-4} alkyl; $R = R^4 = H$, C_{1-6} alkyl, benzyl, or an estergroup; R^2, $R^3 = H$, OH, C_{1-4} alkyl or alkoxy; R^5 = alkyl, alkenyl, alkinyl, arylalkinyl, cycloalkyl, cycloalkenyl, alkoxy, pyrroldinyl, piperidino, morpholino, piperazinyl or N-C_{1-4} alkyl-piperazinyl] are diuretics [130] and can be used against cardiovascular diseases like cardiac insufficiency, disorders of blood supply, angina pectoris, senile heart and hypertonia [131]. N-norbornene-dicarboximido-oxycarbonyl-aminoacid esters such as $R^2O_2CNHCHCH_2$-phenyl CO_2R^1 where by R^2 = **111**, and R^1 = (un)substituted alkyl, aryl,- act antihypertensive by means of inhibition of angiotensine converting enzyme (ACE) [132]. Other compounds with this effect are **112** (KRN 2391 as salt) [133], **113**, a cyclothiazide which shows also a diuretic effect [134] and **114** [R = H, $CH(CH_3)_2$] [135]. Furthermore cardiovascular active cyclopentyl hexenoic acids are known such as ZR′, whereby Z = **115** and $R' = CO_2R^{11}$, CH_2OR^{12} [R^{11} = H, alkyl, (substituted) carboxyl ring; R^{12} = H, CO-phenyl, CO-alkyl] and $Z^2 = Q^{5,6}$ [136]. Compounds **116** and **116a** show positive inotropic activities, but not the expected β-adrenoreceptor blocking effect [137]. For the treatment and prevention of ventricular disorders of the heart rhythm, atrial fibrillation and flutter bicycloheptanedicarboximides such as **117** [R^1 = group of formula II, R′ = group of formula II] can be used [138, 139], as well as compound **118** [140] and piperidinyl-cycloalkyldicarboximides of the type **119**, which represent a valuable protection of the ischemic heart muscle against cardiac insufficiency and disorders of rhythm [141]. Compounds such as **120** are esters and clearly show antiarrhythmic activity and act furthermore mildly hypotensive and local anaesthetic [142].

7. CNS-active compounds

Compound **121** [R^1 = 4-fluorophenylethyl group; X = CH_2; a = double bond] shows an antipsychotic and antidyskinetic effect [143]. Formula **122** is a compilation of a series of psychotropic effective compounds [A = CO; $B = Q^{1,2}$; $R^1 = R^2 = H$, alkyl, OH, C_{1-5} alkyl, C_{2-6} alkanoyloxy; R^1R^2 = O; E = F = CH_2] which have been prepared as highly selective neuroleptics, analgetics, antiallergenics or cardiavascular effective substances, whereby a possible variant is represented by the norbornyl residue [144]. Compounds of the type **123** [R = Q; A = CH_2] are psychotropic or anxiolytic effective butylheterocyclylpiper-



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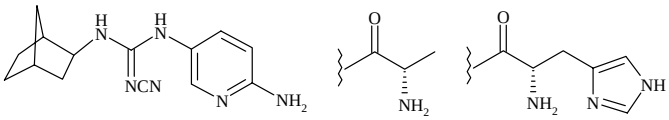

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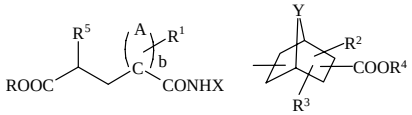

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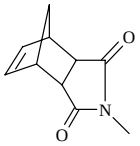

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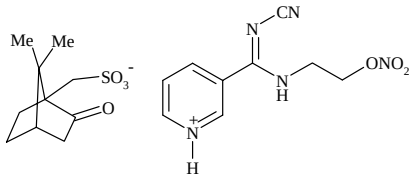

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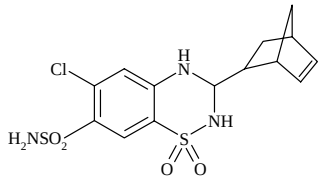

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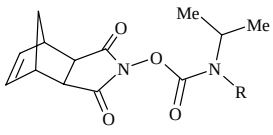

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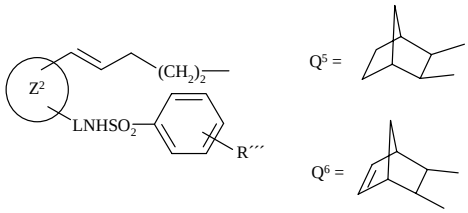

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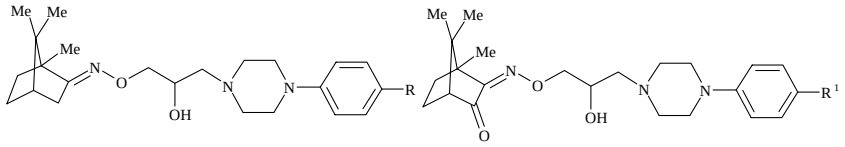

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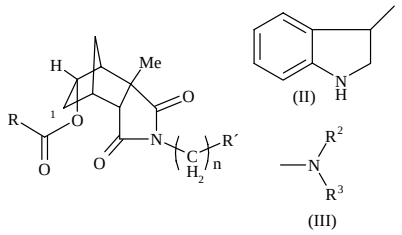

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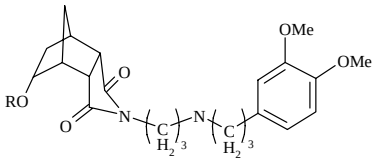

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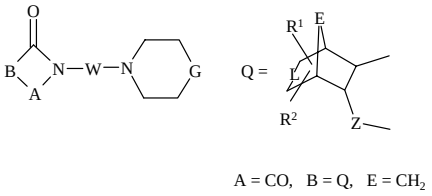

A = CO, B = Q, E = CH_2

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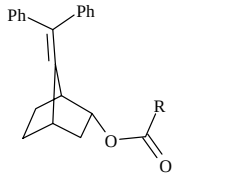
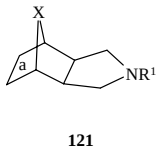


R = Me, CH_2Cl, $CHMe_2$, $CHEt_2$, ...

120

azines. In the case of Z = pyrimidinyl, the anxiolytic properties are dominant, whereas in the case of Z = 1,2-benzisothiazolyl, thieno[3,2-c]pyridyl or furo[3,2-c]pyridyl, an antipsychotic activity has been observed [145]. Bornanolglycosides such as **124** [R = H, acyl, alkyl], are sedatives and can be obtained by extraction of *Amomum xanthioides* [146]. Cyclic amides such as **125** are tranquilizers and neuroleptics [147-149]. **126** is an anticonvulsivum with an imidooxy partial structure [150]. **127** with two possible substituents **a** and **b** is anxiolytic effective and has the advantage of being orally administrable [151]. Camphor-1,2,4-triazines (**128**) with triazols (**a**) or tetrazols (**b**) show CNS stimulating activities [152].



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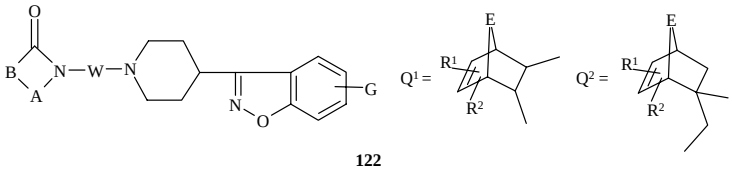

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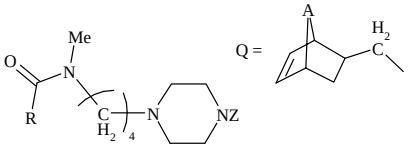

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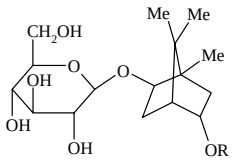

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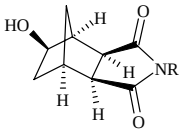

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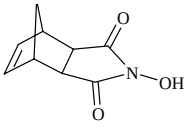

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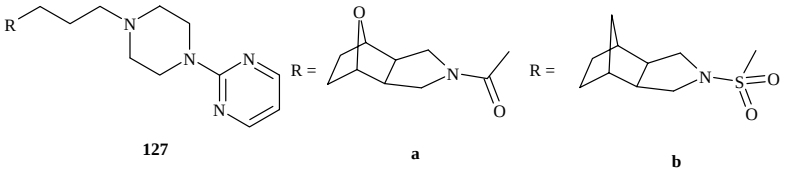
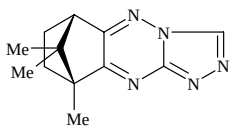


127 a b

8. Other norbornane compounds

Tricyclic compounds such as **129** [153], **130** [154] and **131** [155] possess good UV-filtering properties and can be used therefore as sun protectants. Other sunscreen products are **132** [$R^1 = Q^1$; $R^2 = NHCH_2CH{-}C_2H_5{-}C_4H_7$] [156] and benzylidene camphor derivatives, such as **133**, [157] and **134** [$R^1 = R^3 = OCH_3$; $R^2 = OH$, $R^4 = H$],



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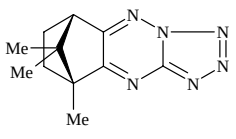

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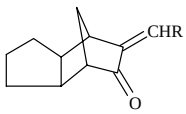

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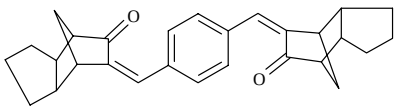

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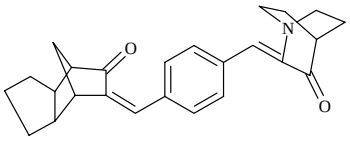

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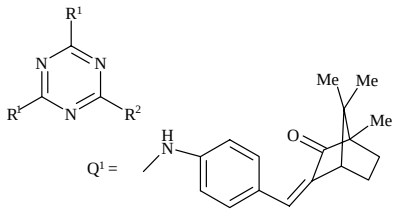

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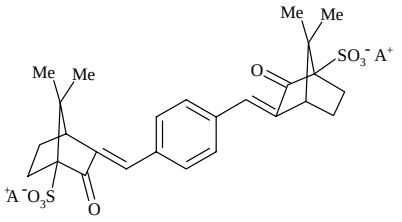

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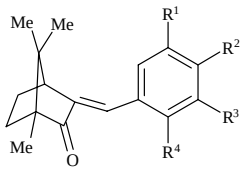

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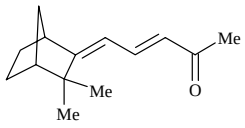


135

which act furthermore antiallergenic and antiphlogistic [158-162]. *Bornelone* (**135**), also a sunscreen product, nevertheless caused sometimes a type of contact allergy [163].

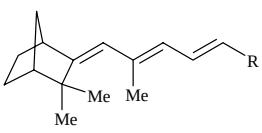
Compound **136** and various derivatives are useful in the treatment of skin cornification and disorders of skin function by means of an inflammation or an immunoallergic reaction [164]. **137** is topically as well as systemically effective against acne [165]. **138** [166, 167] and the thermal reaction products of **139** show antiviral activity [168]. **140** lowers the blood fat concentration [169] and **141** leads to a significant decrease in blood sugar level in genetically contingent fat mice [170, 171]. Compounds such as **142** which is a compilation of various bornyloxyethanols [$R^{1,2} = H$, C_2H_5] improve the flavour of perfume constituents, tensides, softeners or plasticizers, etc. [172].

Derivatives of borneol, as compilated in formula **143** [R^1 = amino(hydroxy)alkanoyl; $R^2 = R^3 = H$, OH, alkyl, alkoxy, acyloxy, sulfonyloxy, phosphoryl, amino; R^4 and $R^5 = H$, alkyl, alkoxyalkyl; $R^{4,5} = O$, alkylen; R^6 and $R^7 = H$, halogen, OH, NO_2, N_3, CN, amino, (un)substituted carboxylic acid, alkyl, alkoxy, acyloxy, acyl] have been synthesized as inhibitors of mitosis.

11 β-substituted ethano-estratrienes such as **144** [$R^1 = H$, C_{1-12} alkanoyl, benzoyl, C_{1-12} alkyl, C_{3-7} cycloalkyl or C_{4-8} alkylcycloalkyl; $R^2 = H$ or C_{1-12} alkanoyl; $R^3 = -(CH_2)_n-CO-NR^4R^5-(CH_2)_{n+1}$-$NR^4R^5$ or $-SO-R^4$; R^4 and $R^5 = H$, or partially fluorinated C_{1-8} alkyl groups; $n = 0-2$] show strong antiestrogenic activity. They can be used in the therapy of estrogene dependent diseases, such as hyperplasia of the prostate, breast carcinoma, anovulatoric infertility, carcinoma of the endometrium and melanoma [174]. **145** [$R1 = R^2 = R^3 = H$; AB = CH : CH] is an estratriene and useful as a contraceptive or against estrogene deficiency [175].

Compounds like **146** [R = alkyl or aralkyl; R^1 = aryl and R^2 = OH, OCO-alkyl or $R^1 = H$ and R^2 = OCO-alkyl] are potentially analgetic [176], as are also tropanol esters and tropane amineamides, as can be seen in formula **147** [A = phenylene or β-naphthylene, $R^1 = H$, CH_3, ter.-butyl; $R^2 = H$, CH_3, ethyl, $CH(CH_3)_2$, CH_2OH, phenyl; $R^4 = H$, CH_3, ethyl, $CH(CH_3)_2$, CH_2-phenyl; $R^5 = H$, CH_3; X = double bond, O, S, NH, NCH_3; Y = O, N, H] [177]. Carbanilic acid esters 2-(butyl-O)$-C_6H_4NHCO_2R$, with R = **148**, have been synthesized as local anaesthetics [178]. **149**, an aminopropionic acid derivative [179], **150** [180] and **151** [181] possess anti-inflammatory properties. **150** is antiallergically active and **151** shows an antidepressive effect.

Compound **152** [R^1 = (un)substituted aryl] is a carbo analogue of norcantharidine [182], palasonine (**153**), whose



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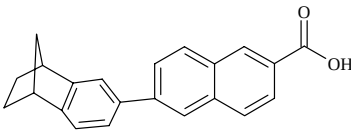

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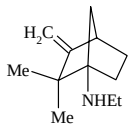

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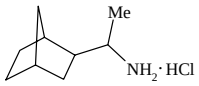

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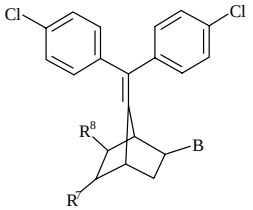

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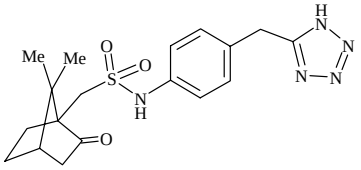

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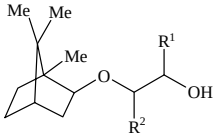

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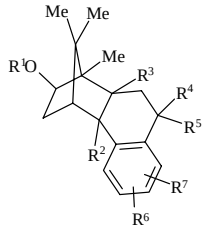

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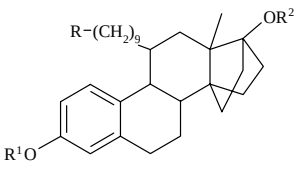

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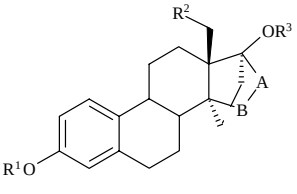

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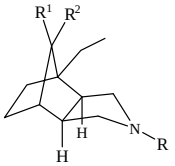

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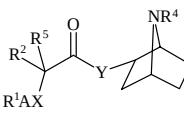

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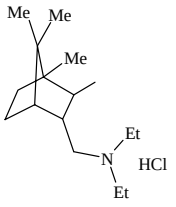

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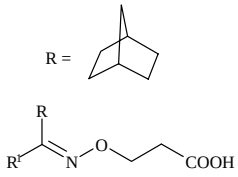

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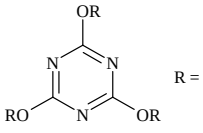

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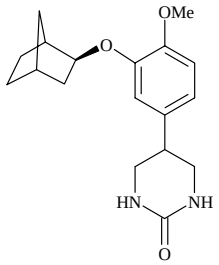

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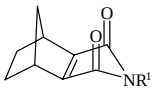

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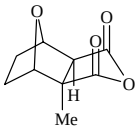

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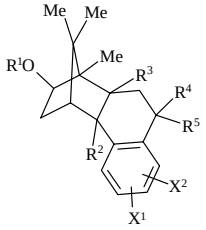

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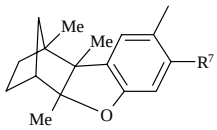

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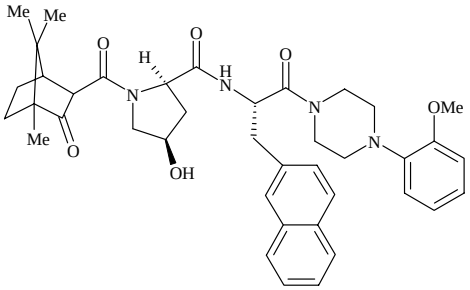

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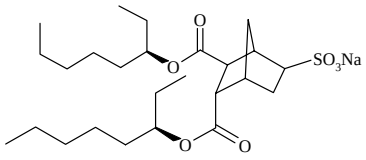

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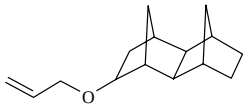

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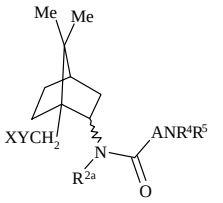

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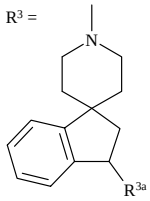
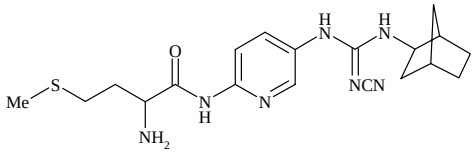
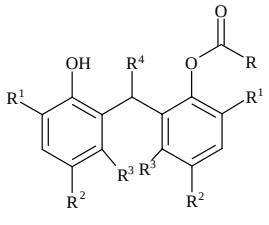




160

synthesis has been reported [183], and borneol esters such as **154** [R1 = (ub)substituted alkylacyl; R^2 = H, OH, alkyl, alkoxy, (un)substituted amino; R^2R^3 = O; R^3 = H, (un)substituted alkyl; R^4R^5 = O, (un)substituted alkylene, H, (un)substituted alkyl; X1, X^2 = H, halogen, OH, CN], [184, 185] all show tumor-inhibiting activities. Derivatives of dibenzofurane RCOZCOOH, with R = **155** [R^7 = H; Z = 2,6-naphthylene], inhibit cell differentiation [186]. Modified peptides like **156** have been prepared as antagonists of neurohormones [187]. **157** is a bicyclic surfactant, which forms reverse micelles for selective proteine extraction [188]. **158** is thixotropically active and useful for the fractionation of serum [189].

Derivatives of camphor such as **159** [example: $R^{2a} = R^{3a}$ = H; ANR^4R^5 = 3-piperidinyl; Y = SO_2; X = R^3] promote the release of mammalian and human growth hormones. This property can be used for acceleration of the growth of fat stock for economic reasons, or in humans against a deficiency of these hormones or in the treatment of diseases where the anabolic effect of these substance is



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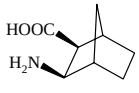

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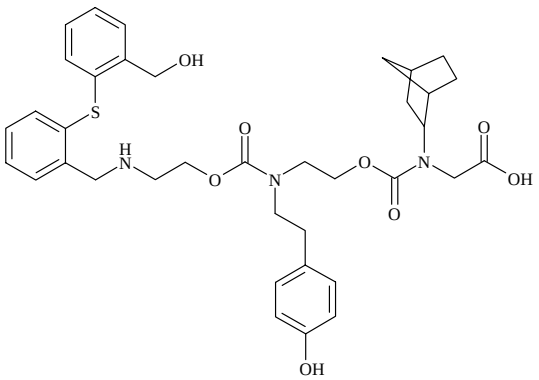

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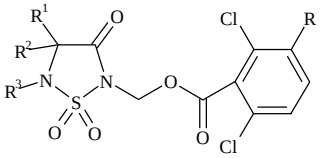

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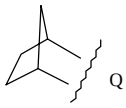

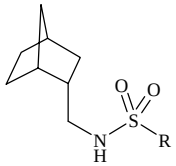

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desired [190, 191]. **160** [192, 193] and **161** [R = Q^1; $R^1 = R^2 = CCH_3$; $R^3 = H$; $R^4 = CH_3$; $R^{5-10} = H$; Y = Z = CH_2] are active as antioxidants [194].

Acylation of *N*-hydroxylated β-lactams in the presence of *Pseudomonas* sp lipase furnished optically-active precursors of the amino acid **162** [195]. Derivatives of glycine such as **163** have been prepared as opiate receptor ligands [196]. Compounds of the type **164** [R = H, 2-morpholinoethyl, 2-(1-pyrrolidinyl)ethyl; R^1 = H, alkyl, phenylalkyl, haloalkyl; R^2R^3 = Q etc.] have been tested in the treatment of degenerative diseases as inhibitors of human leucocyte elastase [197]. The sulfonamide **165** [R = 4-$NO_2C_6H_4$] shows anticonvulsive, analgetic and antiphlogistic properties [198].

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