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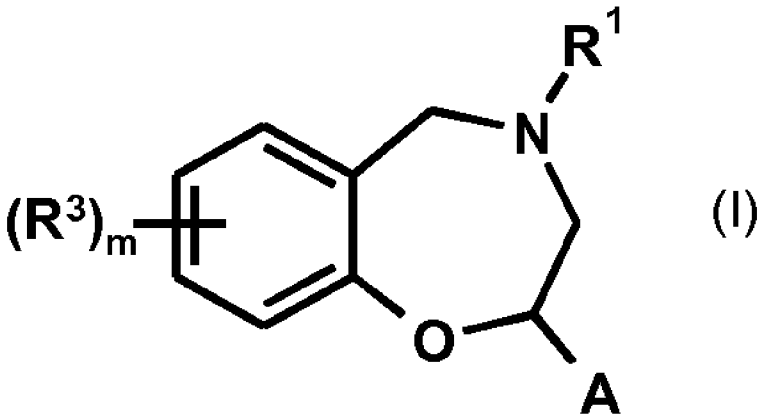
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(54) Title: PESTICIDAL COMPOUNDS



(57) Abstract: A method of combating and controlling insects, acarines, nematodes or molluscs which comprises applying to a pest, to a locus of a pest, or to a plant susceptible to attack by a pest an insecticidally, acaricidally, nematicidally or molluscicidally effective amount of a compound of formula (I), wherein R^1 is R^4, YR^5 or ZR^6; Y is CO or C=S; Z is S, S(O), SO_2 or PO_2; and A is an optionally substituted phenyl or an optionally substituted heteroaromatic ring, wherein R^1 to R^6 are defined organic groups; new compounds are also provided.

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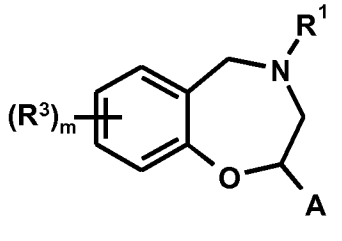
PESTICIDAL COMPOUNDS

The present invention relates to a method of combating and controlling insect, acarine, mollusc and nematode pests with certain tetrahydrobenzoxazepine derivatives, to defined tetrahydrobenzoxazepine derivatives, processes for preparing them, to insecticidal, acaricidal, molluscicidal and nematicidal compositions comprising them.

Tetrahydrobenzoxazepine derivatives with spasmolytic, antihistaminic and cataleptic properties are disclosed in DE2116222.

It has now surprisingly been found that certain tetrahydrobenzoxazepines have insecticidal properties.

The present invention therefore provides a method of combating and controlling insects, acarines, nematodes or molluscs which comprises applying to a pest, to a locus of a pest, or to a plant susceptible to attack by a pest an insecticidally, acaricidally, nematicidally or molluscicidally effective amount of a compound of formula (I):



(I)

wherein R^1 is R^4, YR^5 or ZR^6

Y is C=O or C=S

Z is S, S(O), SO_2 or PO_2;

A is an optionally substituted phenyl or an optionally substituted heteroaromatic ring;

each R^3 is independently halogen, hydroxy, nitro, azido, cyano, thiocyanato, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocyclyl, formyl, optionally substituted alkylcarbonyl, optionally substituted hydroxyiminoalkyl, optionally substituted alkoxyiminoalkyl, optionally substituted arylcarbonyl, optionally substituted heteroarylcarbonyl, optionally substituted alkoxycarbonyl, optionally substituted alkenyloxycarbonyl, optionally substituted alkynyloxycarbonyl, optionally substituted aryloxycarbonyl, optionally substituted heteroaryloxycarbonyl, aminocarbonyl, optionally substituted alkylaminocarbonyl, optionally substituted dialkylaminocarbonyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, optionally substituted dialkyloxyphosphoryl, optionally substituted trialkylsilyl, optionally substituted alkylthio, optionally substituted alkylsulfinyl, optionally substituted alkylsulfonyl, optionally substituted arylthio, optionally substituted arylsulfinyl, optionally substituted arylsulfonyl, aminosulfonyl, optionally substituted alkylaminosulfonyl, optionally substituted dialkylaminosulfonyl or $R^{31}R^{32}N$ where R^{31} and R^{32} are, independently, hydrogen, optionally

substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, formyl, optionally substituted alkylcarbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, optionally substituted alkylaminocarbonyl, optionally substituted dialkylaminocarbonyl optionally substituted alkoxycarbonyl or R^{31} and R^{32} together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further heteroatoms selected from O, N or S and which may be optionally substituted by one or two C_{1-6} alkyl groups, or 2 adjacent groups R^3 together with the carbon atoms to which they are attached form a 4, 5, 6, or 7 membered carbocyclic, heteroaromatic or heterocyclic ring which may be optionally substituted by halogen; m is 0, 1, 2, 3 or 4;

R^4 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, cyano, NO, dialkyloxyphosphoryl, optionally substituted (amino)(alkyloxy)phosphoryl, optionally substituted (alkylamino)(alkyloxy) phosphoryl, optionally substituted bis(alkylamino) phosphoryl, bis(dialkylamino) phosphoryl, or $NR^{41}R^{42}$ where R^{41} and R^{42} are independently hydrogen, COR^{43}, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl or R^{41} and R^{42} together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further heteroatoms selected from O, N or S and which may be optionally substituted by one or two C_{1-6} alkyl groups; or R^{41} and R^{42} together with the N atom to which they are attached form $N=CR^{44}R^{45}$ where R^{44} and R^{45} are independently hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl or R^{44} and R^{45} together with the N atom to which they are attached form a five, six or seven-membered carbocyclic or heterocyclic ring which may contain one or two heteroatoms selected from O, N or S and which may be optionally substituted by one or two C_{1-6} alkyl groups ; R^{43} is H, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aryl, optionally substituted aryloxy optionally substituted heteroaryl, optionally substituted heteroaryloxy or $NR^{46}R^{47}$; R^{46} and R^{47} are independently H, optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl;

R^5 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxycarbonyl, optionally substituted alkylcarbonyl, aminocarbonyl, optionally substituted alkylaminocarbonyl, optionally substituted dialkylaminocarbonyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, optionally substituted heterocyclyloxy, optionally

substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted alkylthio, optionally substituted arylthio, optionally substituted heteroarylthio, optionally substituted heterocyclylthio, $NR^{51}R^{52}$ where R^{51} and R^{52} are independently hydrogen, COR^{53}, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl or R^{51} and R^{52} together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further heteroatoms selected from O, N or S and which may be optionally substituted by one or two C_{1-6} alkyl groups; R^{53} is H, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aryl, optionally substituted aryloxy optionally substituted heteroaryl, optionally substituted heteroaryloxy;

R^6 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, $NR^{61}R^{62}$ where R^{61} and R^{62} are independently hydrogen, COR^{63}, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl or R^{61} and R^{62} together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further heteroatoms selected from O, N or S and which may be optionally substituted by one or two C_{1-6} alkyl groups; R^{63} is H, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aryl, optionally substituted aryloxy optionally substituted heteroaryl, optionally substituted heteroaryloxy or $NR^{66}R^{67}$; R^{66} and R^{67} are independently H, optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl; or a salt or N-oxide thereof.

The compounds of formula (I) may exist in different geometric or optical isomers or tautomeric forms. This invention covers all such isomers and tautomers and mixtures thereof in all proportions as well as isotopic forms such as deuterated compounds.

Each alkyl moiety either alone or as part of a larger group (such as alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl) is a straight or branched chain and is, for example, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl or neo-pentyl. The alkyl groups are suitably C_1 to C_{12} alkyl groups, but are preferably C_1-C_{10}, more preferably C_1-C_8, even more preferably preferably C_1-C_6 and most preferably C_1-C_4 alkyl groups.

When present, the optional substituents on an alkyl moiety (alone or as part of a larger group such as alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl) include one or more of halogen, nitro, azido, trialkylsilyl, trialkylsilyloxy, cyano, NCS-, C_{3-7} cycloalkyl (itself optionally substituted with C_{1-6} alkyl or halogen), C_{5-7} cycloalkenyl (itself optionally substituted with C_{1-6} alkyl or halogen), hydroxy, C_{1-10} alkoxy, C_{1-10} alkoxy(C_{1-10})alkoxy, tri(C_{1-4})alkylsilyl(C_{1-6})alkoxy, C_{1-6} alkoxycarbonyl(C_{1-10})alkoxy, C_{1-10} haloalkoxy, aryl(C_{1-4})-alkoxy (where the aryl group is optionally substituted), C_{3-7} cycloalkyloxy

(where the cycloalkyl group is optionally substituted with C_{1-6} alkyl or halogen), C_{2-10} alkenyloxy, C_{2-10} alkynyloxy, SH, C_{1-10} alkylthio, C_{1-10} haloalkylthio, aryl(C_{1-4})alkylthio (where the aryl group is optionally substituted), C_{3-7} cycloalkylthio (where the cycloalkyl group is optionally substituted with C_{1-6} alkyl or halogen), tri(C_{1-4})alkylsilyl(C_{1-6})alkylthio, arylthio (where the aryl group is optionally substituted), C_{1-6} alkylsulfonyl, C_{1-6} haloalkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} haloalkylsulfinyl, arylsulfonyl (where the aryl group may be optionally substituted), tri(C_{1-4})alkylsilyl, aryldi(C_{1-4})alkylsilyl, (C_{1-4})alkyldiarylsilyl, triarylsilyl, formyl, C_{1-10} alkylcarbonyl, HO_2C, C_{1-10} alkoxycarbonyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6} alkyl)aminocarbonyl, N-(C_{1-3} alkyl)-N-(C_{1-3} alkoxy)aminocarbonyl, C_{1-6} alkylcarbonyloxy, arylcarbonyloxy (where the aryl group is optionally substituted), di(C_{1-6})alkylaminocarbonyloxy, =O, =S, oximes such as =NOalkyl, =NOhaloalkyl and =NOaryl (itself optionally substituted), aryl (itself optionally substituted), heteroaryl (itself optionally substituted), heterocyclyl (itself optionally substituted with C_{1-6} alkyl or halogen), aryloxy (where the aryl group is optionally substituted), heteroaryloxy, (where the heteroaryl group is optionally substituted), heterocyclyloxy (where the heterocyclyl group is optionally substituted with C_{1-6} alkyl or halogen), amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkylcarbonylamino, N-(C_{1-6})alkylcarbonyl-N-(C_{1-6})alkylamino, C_{2-6} alkenylcarbonyl, C_{2-6} alkynylcarbonyl, C_{3-6} alkenyloxycarbonyl, C_{3-6} alkynyloxycarbonyl, aryloxycarbonyl (where the aryl group is optionally substituted) and arylcarbonyl (where the aryl group is optionally substituted).

Alkenyl and alkynyl moieties can be in the form of straight or branched chains, and the alkenyl moieties, where appropriate, can be of either the (E)- or (Z)-configuration. The alkenyl and alkynyl groups are suitably C_2 to C_{12} alkenyl and alkynyl groups, but are preferably C_2-C_{10}, more preferably C_2-C_8, even more preferably preferably C_2-C_6 and most preferably C_2-C_4 alkenyl and alkynyl groups.

Examples are vinyl, allyl and propargyl.

When present, the optional substituents on alkenyl or alkynyl include those optional substituents given above for an alkyl moiety.

In the context of this specification acyl is optionally substituted C_{1-6} alkylcarbonyl (for example acetyl), optionally substituted C_{2-6} alkenylcarbonyl, optionally substituted C_{2-6} alkynylcarbonyl, optionally substituted arylcarbonyl (for example benzoyl) or optionally substituted heteroarylcarbonyl.

Halogen is fluorine, chlorine, bromine or iodine.

Halogen-substituted carbon-containing groups and compounds, such as, for example, halogen-substituted alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy or alkylthio, can be partially halogenated or perhalogenated, where in the case of polyhalogenation the halogen substituents can be identical or different. Examples of haloalkyl - as a group per se and also as a structural element of other groups and compounds, such as haloalkoxy or haloalkylthio - are methyl which is mono- to trisubstituted by fluorine, chlorine and/or bromine, such as CHF_2 or CF_3; ethyl which is mono- to pentasubstituted by fluorine, chlorine and/or bromine, such as CH_2CF_3, CF_2CF_3, CF_2CCl_3, CF_2CHCl_2, CF_2CHF_2, CF_2CFCl_2, CF_2CHBr_2, CF_2CHClF,

CF_2CHBrF or CClFCHClF; propyl or isopropyl which is mono- to heptasubstituted by fluorine, chlorine and/or bromine, such as $CH_2CHBrCH_2Br$, CF_2CHFCF_3, $CH_2CF_2CF_3$, $CF(CF_3)_2$ or $CH(CF_3)_2$; butyl or one of its isomers, mono- to nonasubstituted by fluorine, chlorine and/or bromine, such as $CF(CF_3)CHFCF_3$ or $CH_2(CF_2)_2CF_3$; pentyl or one of its isomers, mono- to undecasubstituted by fluorine, chlorine and/or bromine, such as $CF(CF_3)(CHF_2)CF_3$ or $CH_2(CF_2)_3CF_3$; and hexyl or one of its isomers, mono- to tridecasubstituted by fluorine, chlorine and/or bromine, such as $(CH_2)_4CHBrCH_2Br$, $CF_2(CHF)_4CF_3$, $CH_2(CF_2)_4CF_3$ or $C(CF_3)_2(CHF)_2CF_3$.

In the context of the present specification the terms "aryl", “aromatic ring” and "aromatic ring system" refer to ring systems which may be mono-, bi- or tricyclic. Examples of such rings include phenyl, naphthalenyl, anthracenyl, indenyl or phenanthrenyl. A preferred aryl group is phenyl.

In addition, the terms “heteroaryl”, "heteroaromatic ring” or “heteroaromatic ring system" refer to an aromatic ring system containing at least one heteroatom and consisting either of a single ring or of two or more fused rings. Preferably, single rings will contain up to three and bicyclic systems up to four heteroatoms which will preferably be chosen from nitrogen, oxygen and sulphur. Examples of such groups include furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, benzofuryl, benzisofuryl, benzothienyl, benzisothienyl, indolyl, isoindolyl, indazolyl, benzothiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, benzimidazolyl, 2,1,3-benzoxadiazole quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, benzotriazinyl, purinyl, pteridinyl and indolizinyl. Preferred examples of heteroaromatic radicals include pyridyl, pyrimidyl, triazinyl, thienyl, furyl, pyrrolyl, imidazolyl, oxazolyl, isoxazolyl, 2,1,3-benzoxadiazole, benzothienyl, and thiazolyl.

The terms heterocycle and heterocyclyl refer to a non-aromatic ring containing up to 10 atoms including one or more (preferably one or two) heteroatoms selected from O, S and N. Examples of such rings include 1,3-dioxolane, tetrahydrofuran and morpholine.

When present, the optional substituents on heterocyclyl include C_{1-6} alkyl and C_{1-6} haloalkyl as well as those optional substituents given above for an alkyl moiety.

Cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Cycloalkenyl includes cyclopentenyl and cyclohexenyl.

When present, the optional substituents on cycloalkyl or cycloalkenyl include C_{1-3} alkyl as well as those optional substituents given above for an alkyl moiety.

Carbocyclic rings include aryl, cycloalkyl and cycloalkenyl groups.

When present, the optional substituents on aryl or heteroaryl are selected independently, from halogen, nitro, cyano, NCS-, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy-(C_{1-6})alkyl, C_{2-6} alkenyl, C_{2-6} haloalkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl (itself optionally

substituted with C_{1-6} alkyl or halogen), C_{5-7} cycloalkenyl (itself optionally substituted with C_{1-6} alkyl or halogen), hydroxy, C_{1-10} alkoxy, C_{1-10} alkoxy(C_{1-10})alkoxy, tri(C_{1-4})alkyl-silyl(C_{1-6})alkoxy, C_{1-6} alkoxycarbonyl(C_{1-10})alkoxy, C_{1-10} haloalkoxy, aryl(C_{1-4})alkoxy (where the aryl group is optionally substituted with halogen or C_{1-6} alkyl), C_{3-7} cycloalkyloxy (where the cycloalkyl group is optionally substituted with C_{1-6} alkyl or halogen), C_{2-10} alkenyloxy, C_{2-10} alkynyloxy, SH, C_{1-10} alkylthio, C_{1-10} haloalkylthio, aryl(C_{1-4})alkylthio C_{3-7} cycloalkylthio (where the cycloalkyl group is optionally substituted with C_{1-6} alkyl or halogen), tri(C_{1-4})-alkylsilyl(C_{1-6})alkylthio, arylthio, C_{1-6} alkylsulfonyl, C_{1-6} haloalkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} haloalkylsulfinyl, arylsulfonyl, tri(C_{1-4})alkylsilyl, aryldi(C_{1-4})-alkylsilyl, (C_{1-4})alkyldiarylsilyl, triarylsilyl, formyl, C_{1-10} alkylcarbonyl, HO_2C, C_{1-10} alkoxycarbonyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6} alkyl)-aminocarbonyl, N-(C_{1-3} alkyl)-N-(C_{1-3} alkoxy)aminocarbonyl, C_{1-6} alkylcarbonyloxy, arylcarbonyloxy, di(C_{1-6})alkylamino-carbonyloxy, aryl (itself optionally substituted with C_{1-6} alkyl or halogen), heteroaryl (itself optionally substituted with C_{1-6} alkyl or halogen), heterocyclyl (itself optionally substituted with C_{1-6} alkyl or halogen), aryloxy (where the aryl group is optionally substituted with C_{1-6} alkyl or halogen), heteroaryloxy (where the heteroaryl group is optionally substituted with C_{1-6} alkyl or halogen), heterocyclyloxy (where the heterocyclyl group is optionally substituted with C_{1-6} alkyl or halogen), amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkylcarbonylamino, N-(C_{1-6})alkylcarbonyl-N-(C_{1-6})alkylamino, arylcarbonyl, (where the aryl group is itself optionally substituted with halogen or C_{1-6} alkyl) or two adjacent positions on an aryl or heteroaryl system may be cyclised to form a 5, 6 or 7 membered carbocyclic or heterocyclic ring, itself optionally substituted with halogen or C_{1-6} alkyl. Further substituents for aryl or heteroaryl include aryl carbonyl amino (where the aryl group is substituted by C_{1-6} alkyl or halogen), (C_{1-6})alkyloxycarbonylamino (C_{1-6})alkyloxycarbonyl-N-(C_{1-6})alkylamino, aryloxycarbonylamino (where the aryl group is substituted by C_{1-6} alkyl or halogen), aryloxycarbonyl-N-(C_{1-6})alkylamino, (where the aryl group is substituted by C_{1-6} alkyl or halogen), arylsulphonylamino (where the aryl group is substituted by C_{1-6} alkyl or halogen), arylsulphonyl-N-(C_{1-6})alkylamino (where the aryl group is substituted by C_{1-6} alkyl or halogen), aryl-N-(C_{1-6})alkylamino (where the aryl group is substituted by C_{1-6} alkyl or halogen), arylamino (where the aryl group is substituted by C_{1-6} alkyl or halogen), heteroaryl amino (where the heteroaryl group is substituted by C_{1-6} alkyl or halogen), heterocyclylamino (where the heterocyclyl group is substituted by C_{1-6} alkyl or halogen), aminocarbonylamino, C_{1-6} alkylaminocarbonyl amino, di(C_{1-6})alkylaminocarbonyl amino, arylaminocarbonyl amino where the aryl group is substituted by C_{1-6} alkyl or halogen), aryl-N-(C_{1-6})alkylaminocarbonylamino where the aryl group is substituted by C_{1-6} alkyl or halogen), C_{1-6} alkylaminocarbonyl-N-(C_{1-6})alkyl amino, di(C_{1-6})alkylaminocarbonyl-N-(C_{1-6})alkyl amino, arylaminocarbonyl-N-(C_{1-6})alkyl amino where the aryl group is substituted by C_{1-6} alkyl or halogen) and aryl-N-(C_{1-6})alkylaminocarbonyl-N-(C_{1-6})alkyl amino where the aryl group is substituted by C_{1-6} alkyl or halogen).

For substituted phenyl moieties, heterocyclyl and heteroaryl groups it is preferred that one or more substituents are independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylthio, C_{1-6} haloalkylthio, C_{1-6} alkylsulfinyl, C_{1-6} haloalkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} haloalkylsulfonyl, C_{2-6} alkenyl, C_{2-6} haloalkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, nitro, cyano, CO_2H, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, $R^{25}R^{26}N$ or $R^{27}R^{28}NC(O)$; wherein R^{25}, R^{26}, R^{27} and R^{28} are, independently, hydrogen or C_{1-6} alkyl. Further preferred substituents are aryl and heteroaryl groups.

It is to be understood that dialkylamino substituents include those where the dialkyl groups together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further heteroatoms selected from O, N or S and which is optionally substituted by one or two independently selected (C_{1-6})alkyl groups. When heterocyclic rings are formed by joining two groups on an N atom, the resulting rings are suitably pyrrolidine, piperidine, thiomorpholine and morpholine each of which may be substituted by one or two independently selected (C_{1-6}) alkyl groups.

Preferably the optional substituents on an alkyl moiety include one or more of halogen, nitro, cyano, HO_2C, C_{1-10} alkoxy (itself optionally substituted by C_{1-10} alkoxy), aryl(C_{1-4})alkoxy, C_{1-10} alkylthio, C_{1-10} alkylcarbonyl, C_{1-10} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6} alkyl)aminocarbonyl, (C_{1-6})alkylcarbonyloxy, optionally substituted phenyl, heteroaryl, aryloxy, arylcarbonyloxy, heteroaryloxy, heterocyclyl, heterocyclyloxy, C_{3-7} cycloalkyl (itself optionally substituted with (C_{1-6})alkyl or halogen), C_{3-7} cycloalkyloxy, C_{5-7} cycloalkenyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, tri(C_{1-4})alkylsilyl, tri(C_{1-4})alkylsilyl(C_{1-6})alkoxy, aryldi(C_{1-4})alkylsilyl, (C_{1-4})alkyldiarylsilyl and triarylsilyl.

Preferably the optional substituents on alkenyl or alkynyl include one or more of halogen, aryl and C_{3-7} cycloalkyl.

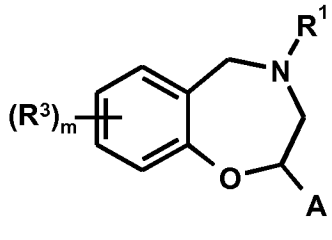
A preferred optional substituent for heterocyclyl is C_{1-6} alkyl.

Preferably the optional substituents for cycloalkyl include halogen, cyano and C_{1-3} alkyl.

Preferably the optional substituents for cycloalkenyl include C_{1-3} alkyl, halogen and cyano.

Preferably A is an unsubstituted or substituted phenyl, unsubstituted or substituted monocyclic 5- or 6-membered heteroaromatic ring system with one, two or three heteroatoms selected from N, O or S or an unsubstituted or substituted bicyclic 8-10-membered heteroaromatic ring system one, two or three heteroatoms selected from N, O or S; in each case the substituents on the ring being independently selected from halogen, cyano, C_{1-6} alkyl optionally substituted by halogen or C_1-C_6-alkoxy, C_1-C_6 alkoxy, and $R^{21}R^{22}N$, where R^{21} and R^{22} are, independently, hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-7} cycloalkyl(C_{1-4})alkyl, C_{2-6} haloalkyl, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkoxycarbonyl or R^{21} and R^{22} together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further heteroatoms selected from O, N or S and which may be optionally substituted by one or two C_{1-6} alkyl groups.

In an embodiment, independent of other embodiments, when A is an unsubstituted or substituted heteroaromatic ring, the compound of fomula (I) can be represented as a compound of formula (IB):

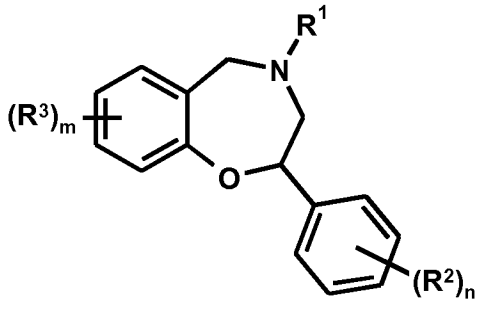

(IB)

wherein R^1 and R^3 are as defined for formula (I).

It is more preferred that A is an unsubstituted or substituted monocyclic 5- or 6-membered heteroaromatic ring system with one, two or three heteroatoms selected from N, O or S, the substituents being halogen, cyano, C_{1-6} alkyl, C_{1-6}-haloalkyl, C_1-C_6-alkoxy or C_{1-6}-haloalkoxy.

More preferably, A is unsubstituted or halo-substituted thiophene or cyano-substituted thiophene or unsubstituted or halo-substituted pyridyl.

In an embodiment, independent of other embodiments, A is an unsubstituted or substituted phenyl and so the compound of formula (I) can be represented as a compound of formula (IA):


(IA)

wherein R^1 and R^3 are as defined for formula (I) and each R^2 is independently halogen, hydroxy, nitro, azido, cyano, thiocyanato, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocyclyl, formyl, optionally substituted alkylcarbonyl, optionally substituted hydroxyiminoalkyl, optionally substituted alkoxyiminoalkyl, optionally substituted arylcarbonyl, optionally substituted heteroarylcarbonyl, optionally substituted alkoxycarbonyl, optionally substituted alkenyloxycarbonyl, optionally substituted alkynyloxycarbonyl, optionally substituted aryloxycarbonyl, optionally substituted heteroaryloxycarbonyl, aminocarbonyl, optionally substituted alkylaminocarbonyl, optionally substituted dialkylaminocarbonyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted

aryloxy, optionally substituted heteroaryloxy, optionally substituted dialkyloxyphosphoryl, optionally substituted trialkylsilyl, optionally substituted alkylthio, optionally substituted alkylsulfinyl, optionally substituted alkylsulfonyl, optionally substituted arylthio, optionally substituted arylsulfinyl, optionally substituted arylsulfonyl, aminosulfonyl, optionally substituted alkylaminosulfonyl, optionally substituted dialkylaminosulfonyl or $R^{21}R^{22}N$ where R^{21} and R^{22} are, independently, hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, formyl, optionally substituted alkylcarbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, optionally substituted alkylaminocarbonyl, optionally substituted dialkylaminocarbonyl optionally substituted alkoxycarbonyl or R^{21} and R^{22} together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further heteroatoms selected from O, N or S and which may be optionally substituted by one or two C_{1-6} alkyl groups, or 2 adjacent groups R^2 together with the carbon atoms to which they are attached form a 4, 5, 6, or 7 membered carbocyclic, heteroaromatic or heterocyclic ring which may be optionally substituted by halogen; n is 0, 1, 2, 3, 4 or 5; or a salt or N-oxide thereof.

Preferred groups for m, n, R^1, R^2 and R^3 in any combination thereof are set out below.

Preferably R^1 is hydrogen, CN, optionally substituted C_1-C_6-alkyl, optionally substituted C_2-C_6-alkenyl, optionally substituted C_2-C_6-alkynyl, formyl, dialkyloxyphosphoryl, optionally substituted alkylcarbonyl, optionally substituted alkylthiocarbonyl, optionally substituted alkoxycarbonyl, optionally substituted alkenyloxycarbonyl, aminocarbonyl, optionally substituted alkylaminocarbonyl, optionally substituted dialkylaminocarbonyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl; optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted alkyloxy, optionally substituted alkylamino, optionally substituted alkylthio, optionally substituted alkylsulfinyl, optionally substituted alkylsulfonyl.

More preferably R^1 is hydrogen, CN, C_1-C_6-alkyl [optionally substituted by halogen, COO C_1-C_6-alkyl, C_1-C_6-alkoxy, phenoxy (itself optionally substituted by halogen, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl), phenyl (itself optionally substituted by halogen, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl), thiophene (itself optionally substituted by halogen, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl), furan (itself optionally substituted by halogen, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl) or C_3-C_6 cycloalkyl], C_2-C_6-alkenyl optionally substituted by halogen, C_2-C_6-alkynyl optionally substituted by halogen, C_3-C_6 cycloalkyl optionally substituted by halogen or C_1-C_3-alkyl, C_1-C_6 alkylcarbonyl optionally substituted by halogen, C_1-C_6 alkyloxycarbonyl optionally substituted by halogen, C_2-C_6 alkenyloxycarbonyl optionally substituted by halogen, C_2-C_6 alkynyloxycarbonyl optionally substituted by halogen, C_3-C_6 cycloalkyloxycarbonyl optionally substituted by halogen or C_1-C_3-alkyl.

Even more preferably R^1 is hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_3-C_6 cycloalkyl, C_3-C_6 halocycloalkyl C_2-C_6-alkenyl, C_3-C_6-alkynyl, C_1-C_6-alkyloxycarbonyl, C_1-C_6-

haloalkyloxycarbonyl, C_2-C_6-alkenyloxycarbonyl, thienylmethyl (itself optionally substituted by halogen, CN, C_1-C_4 alkyl, C_1-C_4-haloalkyl).

Most preferably R^1 is hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_3-C_6 cycloalkyl, C_3-C_6 halocycloalkyl C_2-C_6-alkenyl, C_3-C_6-alkynyl, C_1-C_6-alkyloxycarbonyl, C_1-C_6-haloalkyloxycarbonyl, C_2-C_6-alkenyloxycarbonyl.

It is preferred that m is 0 or m is 1 and R^3 is halogen, C_1-C_6-haloalkyl,or C_1-C_6-alkoxy.

Preferably R^2 is halogen, cyano, C_{1-6} alkyl optionally substituted by halogen or C_1-C_6-alkoxy, C_1-C_6 alkoxy, $R^{21}R^{22}N$ where R^{21} and R^{22} are, independently, hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-7} cycloalkyl(C_{1-4})alkyl, C_{2-6} haloalkyl, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkoxycarbonyl or R^{21} and R^{22} together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further heteroatoms selected from O, N or S and which may be optionally substituted by one or two C_{1-6} alkyl groups, and n is 0, 1 or 2.

More preferably R^2 is halogen, cyano, C_{1-6} alkyl optionally substituted by halogen or C_1-C_6-alkoxy optionally substituted by halogen, and n is 0, 1 or 2.

It is most preferred that n is 0 or n is 1 or 2 and R^2 is halogen.

In an embodiment, a compound of the present invention is of formula (IA) wherein R^1 is hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_3-C_6 cycloalkyl, C_3-C_6 halocycloalkyl, C_2-C_6-alkenyl, C_3-C_6-alkynyl, C_1-C_6-alkyloxycarbonyl, C_1-C_6-haloalkyloxycarbonyl, C_2-C_6-alkenyloxycarbonyl, thienylmethyl (itself optionally substituted by halogen, CN, C_1-C_4 alkyl, C_1-C_4-haloalkyl); n is 0, 1 or 2; R^2 is halogen, cyano, C_{1-6} alkyl optionally substituted by halogen or C_1-C_6-alkoxy optionally substituted by halogen; m is 0 or m is 1; and R^3 is halogen, C_1-C_6-haloalkyl, or C_1-C_6-alkoxy.

In a preferred embodiment, a compound of the present invention is of formula (IA) wherein R^1 is hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_3-C_6 cycloalkyl, C_3-C_6 halocycloalkyl, C_2-C_6-alkenyl, C_3-C_6-alkynyl, C_1-C_6-alkyloxycarbonyl, C_1-C_6-haloalkyloxycarbonyl, C_2-C_6-alkenyloxycarbonyl; n is 0, 1 or 2; R^2 is halogen, cyano, C_{1-6} alkyl optionally substituted by halogen or C_1-C_6-alkoxy optionally substituted by halogen; m is 0 or m is 1; and R^3 is halogen, C_1-C_6-haloalkyl, or C_1-C_6-alkoxy.

In an especially preferred embodiment, a compound of the present invention is of formula (IA) wherein R^1 is C_1-C_6-alkyl; n is 1; R^2 is halogen; and m is 0, or a salt thereof.

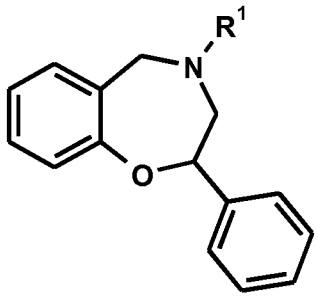
In an embodiment, a compound of the present invention is of formula (IB) wherein R^1 is hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_3-C_6 cycloalkyl, C_3-C_6 halocycloalkyl, C_2-C_6-alkenyl, C_3-C_6-alkynyl, C_1-C_6-alkyloxycarbonyl, C_1-C_6-haloalkyloxycarbonyl, C_2-C_6-alkenyloxycarbonyl, thienylmethyl (itself optionally substituted by halogen, CN, C_1-C_4 alkyl, C_1-C_4-haloalkyl); m is 0 or m is 1; R^3 is halogen, C_1-C_6-haloalkyl, or C_1-C_6-alkoxy; and A is an unsubstituted or substituted monocyclic 5- or 6-membered heteroaromatic ring system with one, two or three heteroatoms selected from N, O or S, the substituents being halogen, cyano, C_{1-6} alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy or C_1-C_6-haloalkoxy.

In a preferred embodiment, a compound of the present invention is of formula (IB) wherein R^1 is hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_3-C_6 cycloalkyl, C_3-C_6 halocycloalkyl, C_2-C_6-alkenyl, C_3-C_6-alkynyl, C_1-C_6-alkyloxycarbonyl, C_1-C_6-haloalkyloxycarbonyl, C_2-C_6-alkenyloxycarbonyl;; m is 0 or m is 1; R^3 is halogen, C_1-C_6-haloalkyl, or C_1-C_6-alkoxy; and A is unsubstituted or halo-substituted thiophene or cyano-substituted thiophene or unsubstituted or halo-substituted pyridyl.

In an especially preferred embodiment, a compound of the present invention is of formula (IB) wherein R^1 is C_1-C_6-alkyl or $C(O)OC_2$-C_6-alkenyl; m is 0; and A is unsubstituted or halo-substituted thiophene or cyano-substituted thiophene.

The compounds in Tables I to XVIII below illustrate the compounds of fomula (IA) of the invention.

Table I provides 39 compounds of formula Ia

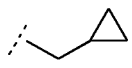


Ia

wherein the values of R^1 are given in Table 1.

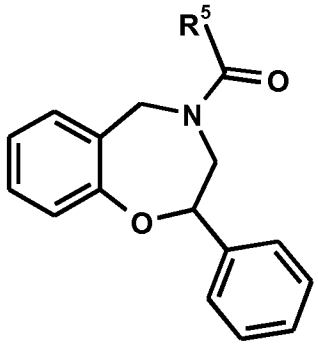
Table 1

Compound N°	R^1
I-1	H
I-2	methyl
I-3	ethyl
I-4	n-propyl
I-5	i-propyl
I-6	cyclopropyl
I-7	butyl
I-8	2-fluoroethyl
I-9	2,2-difluoroethyl

I-10	2,2,2-trifluoroethyl
I-11	2,2,3,3,3-pentafluoropropyl
I-12	allyl
I-13	propargyl
I-14	3,4,4-trifluoro-but-3-enyl
I-15	3-fluoropropyl
I-16	5-bromo-thiophen-2-ylmethyl
I-17	benzyl
I-18	3-bromo-thiophen-2-ylmethyl
I-19	1-furan-2-ylmethyl
I-20	5-methyl-thiophen-2-ylmethyl
I-21	3-methyl-thiophen-2-ylmethyl
I-22	1-furan-3-ylmethyl
I-23	CN
I-24	$CH(OSi(CH_3)_3)CF_3$
I-25	$CH(OSi(CH_3)_3)CF_2CF_3$
I-26	$CH(N_3)CF_3$
I-27	CH_2CClF_2
I-28	$CH2CH_2CH_2Ph$
I-29	CH_2CH_2OPh
I-30	
I-31	$CH_2CH_2CH=CF_2$
I-32	$CH_2C\equiv CCH_3$
I-33	$CH_2CH_2C(O)OMe$
I-34	6-methyl-4-oxo-chroman-3-ylmethyl

I-35	CH_2OCH_3
I-36	$CH_2OCH_2CH_3$
I-37	CH_2OCH_2Ph
I-38	$CH_2OCH_2CH_2OCH_3$
I-39	CH_2SCH_3

Table II provides 15 compounds of formula Ib



Ib

wherein the values of R^5 are given in Table 2.

Table 2

Compound N°	R^5
II-1	CF_3
II-2	OMe
II-3	OEt
II-4	$OCHClCH_3$
II-5	OCH_2Cl
II-6	$OCH=CH_2$
II-7	$OC(Me)=CH_2$
II-8	OCH=CH(Me)
II-9	$OCH=CMe_2$
II-10	$OCH_2C\equiv CH$

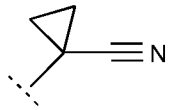
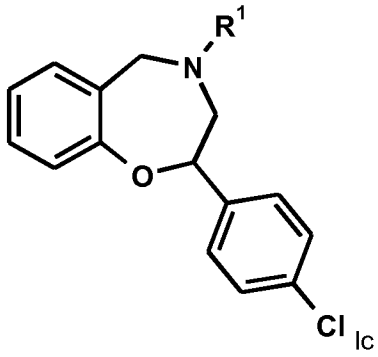
II-11	$OCH(CH_3)_2$
II-12	$OCCl_3$
II-13	
II-14	$C(CH_3)=CH_2$
II-15	$CH=CH_2$

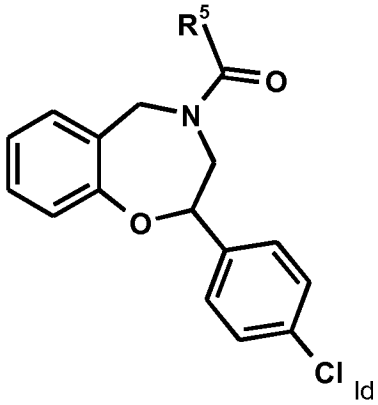
Table III provides 39 compounds of formula Ic



Ic

wherein the values of R^1 are given in Table 1.

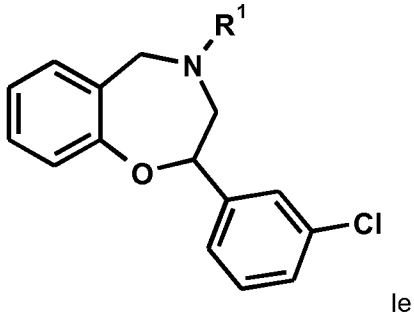
Table IV provides 15 compounds of formula Id



Id

wherein the values of R^1 are given in Table 2.

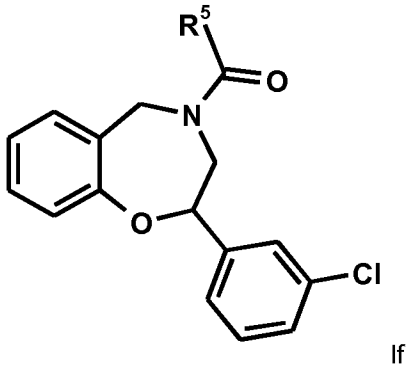
Table V provides 39 compounds of formula Ie



Ie

wherein the values of R^1 are given in Table 1.

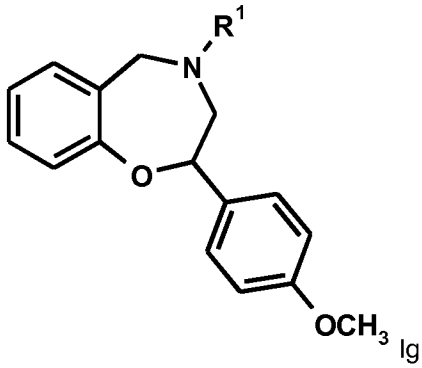
Table VI provides 15 compounds of formula If



If

wherein the values of R^1 are given in Table 2.

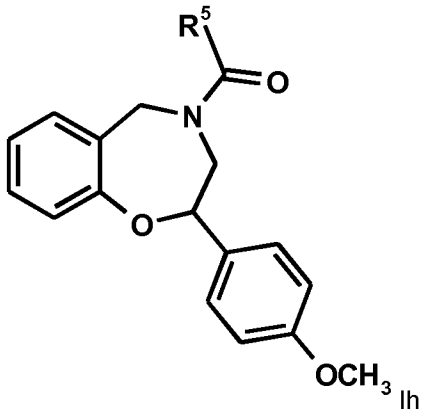
Table VII provides 39 compounds of formula Ig



Ig

wherein the values of R^1 are given in Table 1.

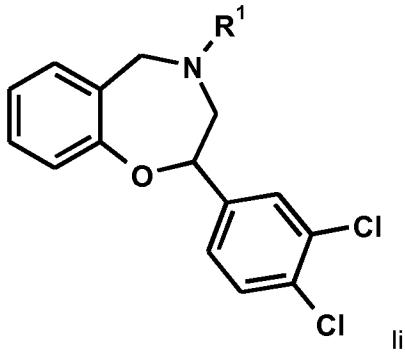
Table VIII provides 15 compounds of formula Ih



Ih

wherein the values of R^1 are given in Table 2.

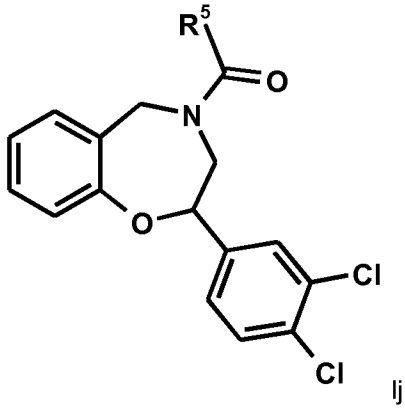
Table IX provides 39 compounds of formula Ii



Ii

wherein the values of R^1 are given in Table 1.

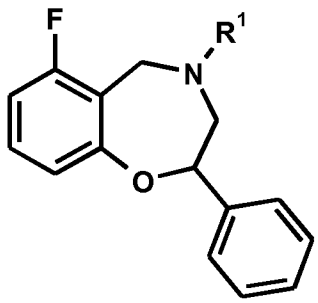
Table X provides 15 compounds of formula Ij



Ij

wherein the values of R^1 are given in Table 2.

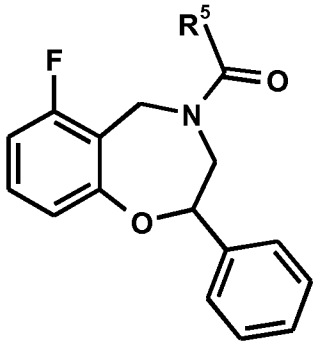
Table XI provides 39 compounds of formula Ik



Ik

wherein the values of R^1 are given in Table 1.

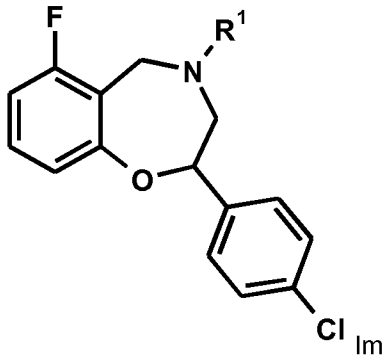
Table XII provides 15 compounds of formula Il



Il

wherein the values of R^1 are given in Table 2.

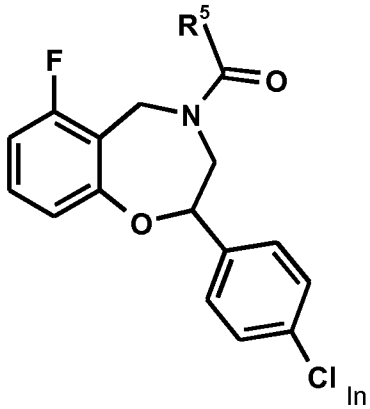
Table XIII provides 39 compounds of formula Im



Im

wherein the values of R^1 are given in Table 1.

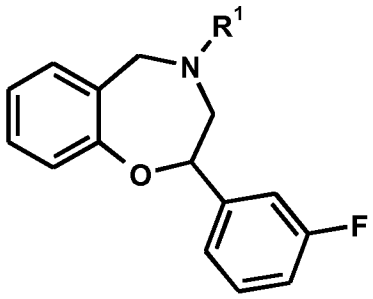
Table XIV provides 15 compounds of formula In



In

wherein the values of R^1 are given in Table 2.

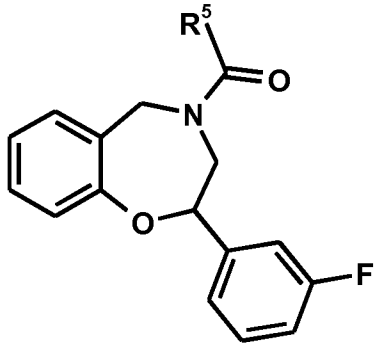
Table XV provides 39 compounds of formula Io



Io

wherein the values of R^1 are given in Table 1.

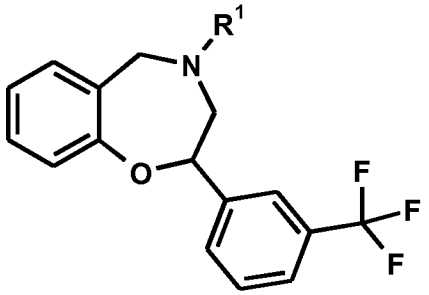
Table XVI provides 15 compounds of formula Ip



Ip

wherein the values of R^1 are given in Table 2.

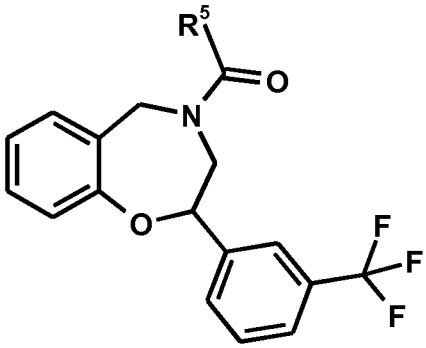
Table XVII provides 39 compounds of formula Iq



Iq

wherein the values of R^1 are given in Table 1.

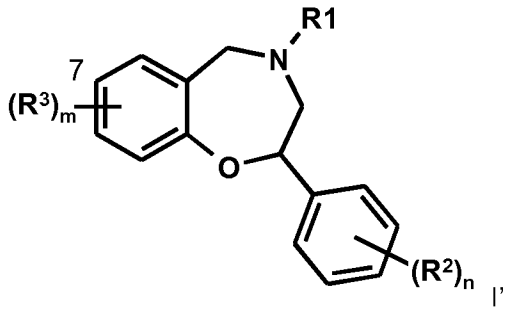
Table XVIII provides 15 compounds of formula Ir



Ir

wherein the values of R^5 are given in Table 2.

Certain compounds of formula (IA) are novel and as such form a further aspect of the invention. One group of novel compounds are those of formula (I')



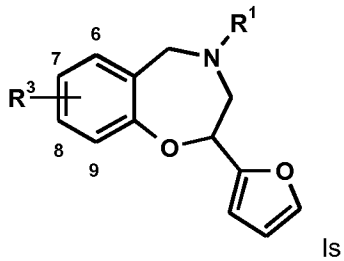
I'

wherein R^1, R^2, R^3, m and n are as defined for formula I above provided that when m and n are both zero then R^1 is other than hydrogen, C_1-C_4 alkyl, $COCH_3$ or $CH_2C(CH_3)=CH_2$ and

further provided that when n is zero and $(R^3)_m$ is 7-chloro or 7–methyl then R^1 is other than hydrogen, ethyl or *iso*-butyl.

The compounds in Tables XIX to XXXVIII below illustrate compounds of the invention, where A is a optionally substituted heteroaromatic ring..

Table XIX provides 41 compounds of formula Is

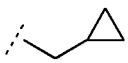


Is

wherein the values of R^1 and R^3 are given in Table 1.

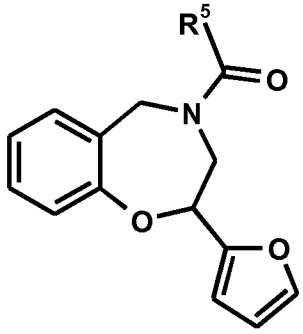
Table 1

Compound N°	R^1	R^3
I-40	H	H
I-41	methyl	H
I-42	ethyl	H
I-43	n-propyl	H
I-44	i-propyl	H
I-45	cyclopropyl	H
I-46	butyl	H
I-47	2-fluoroethyl	H
I-48	2,2-difluoroethyl	H
I-49	2,2,2-trifluoroethyl	H
I-50	2,2,3,3,3-pentafluoropropyl	H
I-51	allyl	H
I-52	propargyl	H
I-53	3,4,4-trifluoro-but-3-enyl	H
I-54	3-fluoropropyl	H

I-55	5-bromo-thiophen-2-ylmethyl	H
I-56	benzyl	H
I-57	3-bromo-thiophen-2-ylmethyl	H
I-58	1-furan-2-ylmethyl	H
I-59	5-methyl-thiophen-2-ylmethyl	H
I-60	3-methyl-thiophen-2-ylmethyl	H
I-61	1-furan-3-ylmethyl	H
I-62	CN	H
I-63	$CH(OSi(CH_3)_3)CF_3$	H
I-64	$CH(OSi(CH_3)_3)CF_2CF_3$	H
I-65	$CH(N_3)CF_3$	H
I-66	CH_2CClF_2	H
I-67	$CH2CH_2CH_2Ph$	H
I-68	CH_2CH_2OPh	H
I-69		H
I-70	$CH_2CH_2CH=CF_2$	H
I-71	$CH_2C\equiv CCH_3$	H
I-72	$CH_2CH_2C(O)OMe$	H
I-73	6-methyl-4-oxo-chromen-3-ylmethyl	H
I-74	CH_2OCH_3	H
I-75	$CH_2OCH_2CH_3$	H
I-76	CH_2OCH_2Ph	H
I-77	$CH_2OCH_2CH_2OCH_3$	H
I-78	CH_2SCH_3	H
I-79	CH_2CH_3	6-F

I-80	CH_2CH_3	7-OCH_2OCH_3

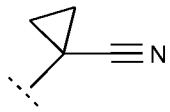
Table XX provides 15 compounds of formula It



It

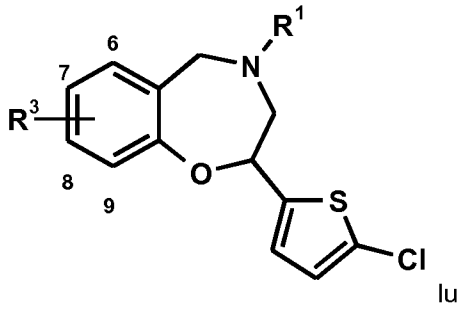
wherein the values of R^5 are given in Table 2.

Table 2

Compound N°	R^5
II-16	CF_3
II-17	OMe
II-18	OEt
II-19	$OCHClCH_3$
II-20	OCH_2Cl
II-21	$OCH=CH_2$
II-22	$OC(Me)=CH_2$
II-23	OCH=CH(Me)
II-24	$OCH=CMe_2$
II-25	$OCH_2C\equiv CH$
II-26	$OCH(CH_3)_2$
II-27	$OCCl_3$
II-28	

II-29	$C(CH_3)=CH_2$
II-30	$CH=CH_2$

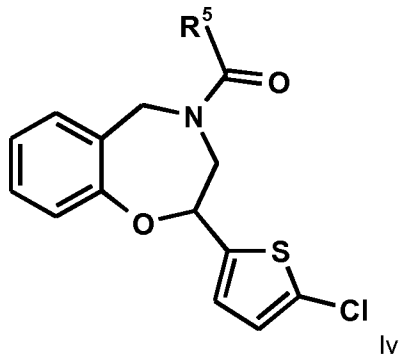
Table XXI provides 41 compounds of formula Iu



Iu

wherein the values of R^1 are given in Table 1.

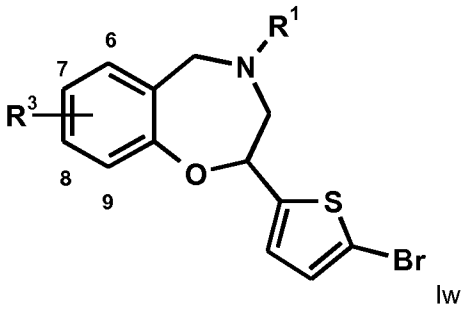
Table XXII provides 15 compounds of formula Iv



Iv

wherein the values of R^1 are given in Table 2.

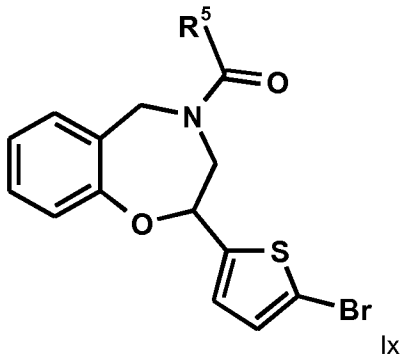
Table XXIII provides 41 compounds of formula Iw



Iw

wherein the values of R^1 are given in Table 1.

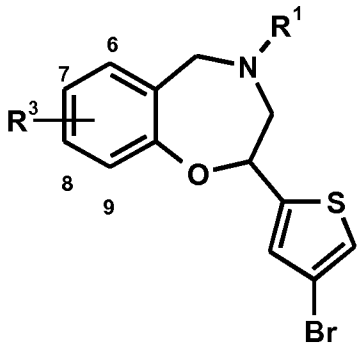
Table XXIV provides 15 compounds of formula Ix



Ix

wherein the values of R^1 are given in Table 2.

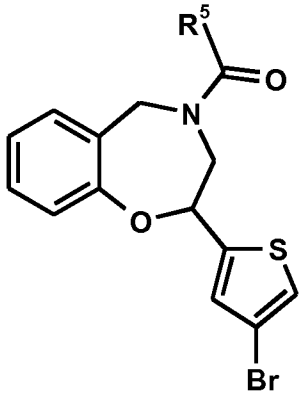
Table XXV provides 41 compounds of formula Iy



Iy

wherein the values of R^1 are given in Table 1.

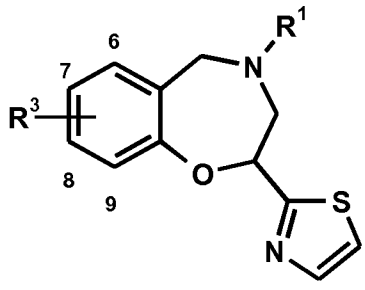
Table XXVI provides 15 compounds of formula Iz



Iz

wherein the values of R^1 are given in Table 2.

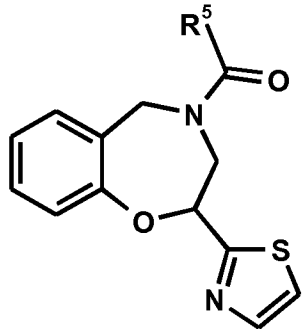
Table XXVII provides 41 compounds of formula Iaa



Iaa

wherein the values of R^1 are given in Table 1.

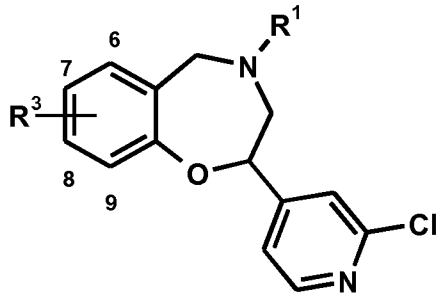
Table XXVIII provides 15 compounds of formula Iab



Iab

wherein the values of R^1 are given in Table 2.

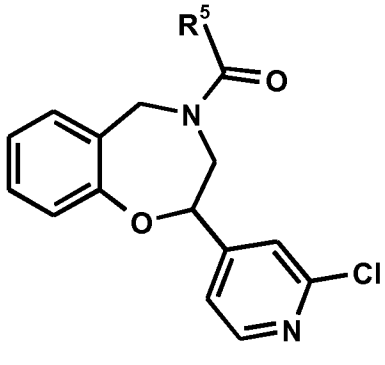
Table XXIX provides 41compounds of formula Iac



Iac

wherein the values of R^1 are given in Table 1.

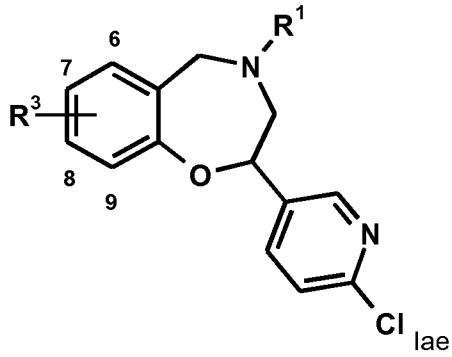
Table XXX provides 15 compounds of formula Iad



Iad

wherein the values of R^1 are given in Table 2.

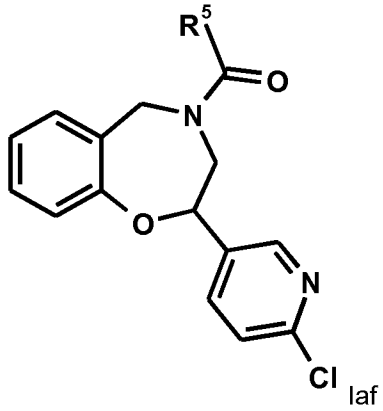
Table XXXI provides 41 compounds of formula Iae



Iae

wherein the values of R^1 are given in Table 1.

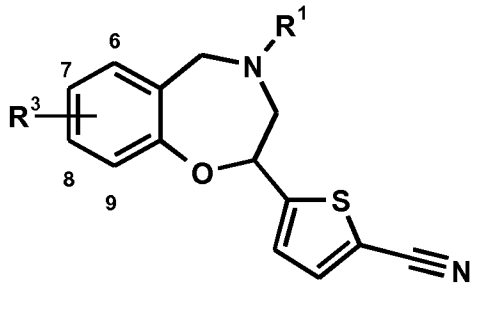
Table XXXII provides 15 compounds of formula Iaf



Iaf

wherein the values of R^1 are given in Table 2.

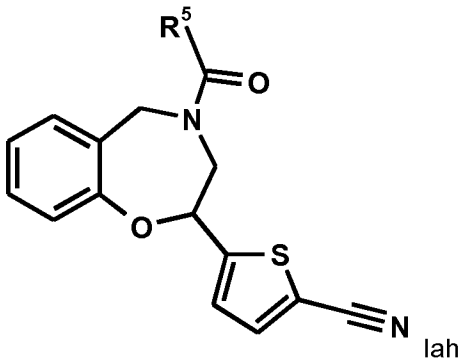
Table XXXIII provides 41 compounds of formula Iag



Iag

wherein the values of R^1 are given in Table 1.

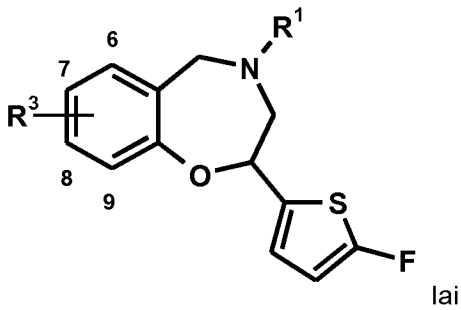
Table XXXIV provides 15 compounds of formula Iah



Iah

wherein the values of R^1 are given in Table 2.

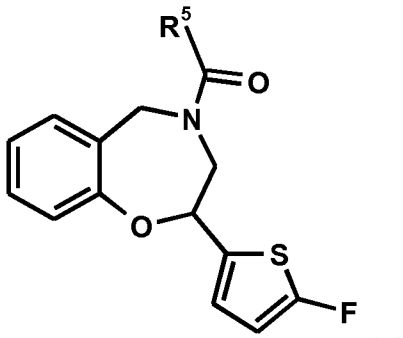
Table XXXV provides 41 compounds of formula Iai



Iai

wherein the values of R^1 are given in Table 1.

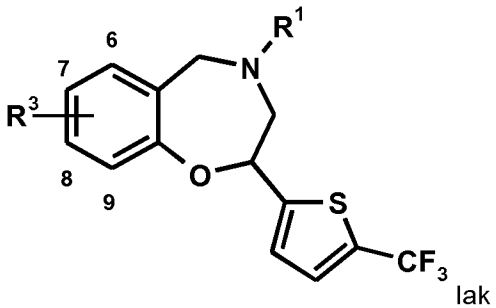
Table XXXVI provides 15 compounds of formula Iaj



laj

wherein the values of R^1 are given in Table 2.

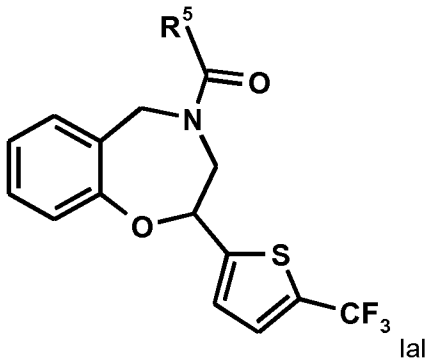
Table XXXVII provides 41 compounds of formula lak



lak

wherein the values of R^1 are given in Table 1.

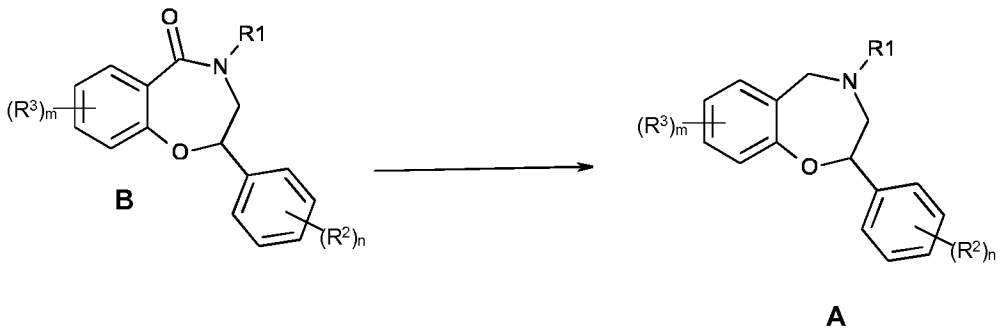
Table XXXVIII provides 15 compounds of formula lal



lal

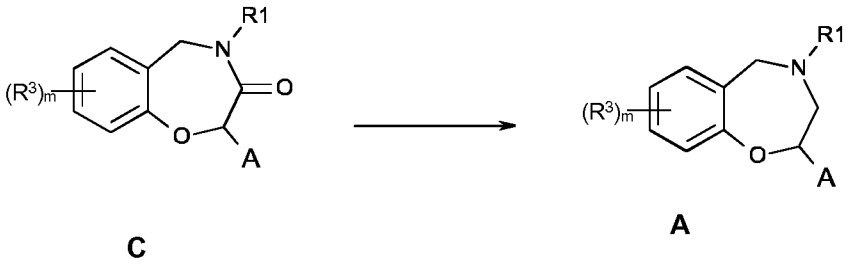
wherein the values of R^1 are given in Table 2.

The compounds of the invention may be made in a variety of ways. In the section that follows, R^1, R^2, R^3, m and n are defined for a compound of formulae 1, 1', IA and IB as appropriate.

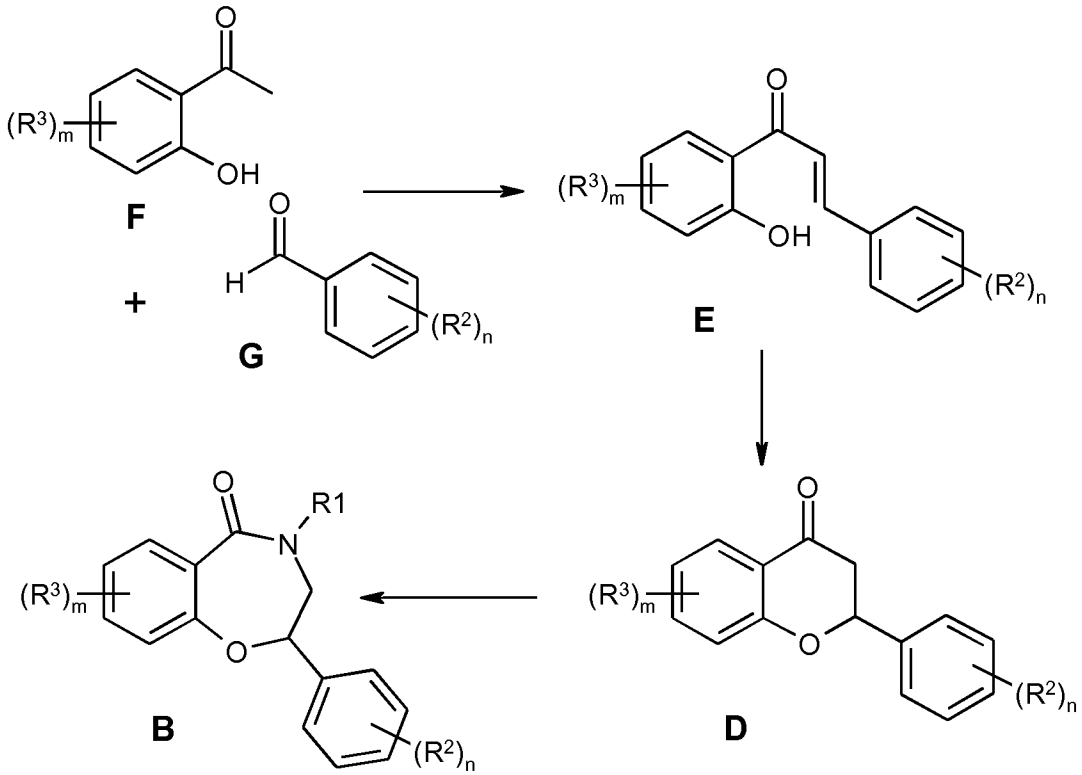


B

A



Thus a compound of formula A may be made from the reduction of an amide of formula B or C with a reducing agent such as lithium aluminium hydride (optionally in the presence of a Lewis acid such as aluminium chloride) or borane.



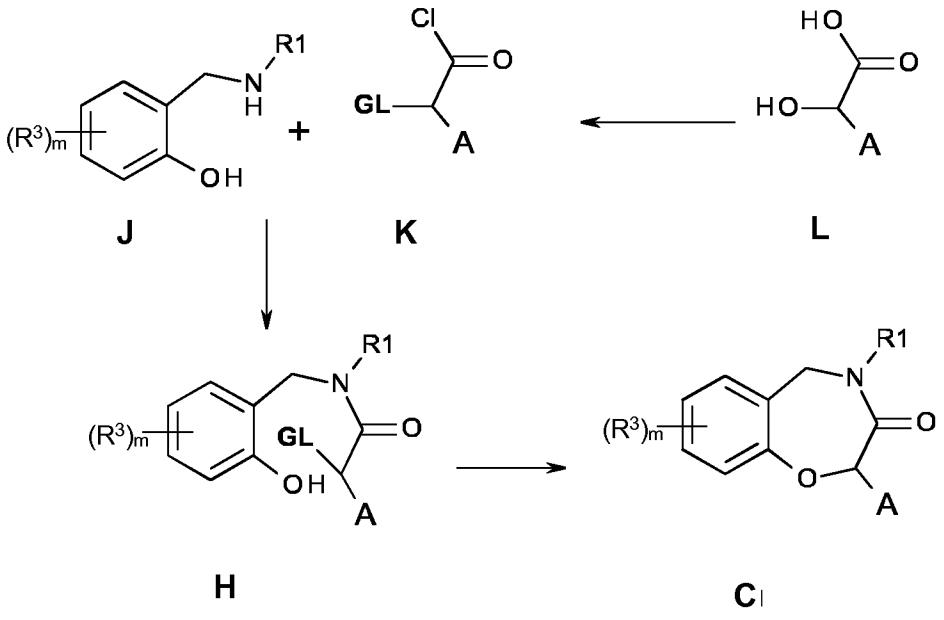
Compounds of formula B may be made from the flavanone D by Schmidt reaction or Beckmann rearrangement under known conditions by someone skilled in the art. A particularly convenient method of achieving such a transformation involves treating the compound D with sodium azide in trifluoroacetic acid, as described by G. Litkei and T. Patonay in Acta Chim. Acad. Sci. Hung. 1983, 114(1), 47-56.

Flavanones D are either known or may be made by methods known to those skilled in the art, for instance compounds of formula D may be synthesised from compounds of formula E by cyclisation under acidic conditions, as described in Indian J. Chem. 1997, 36B, 73-74.

Compounds of formula E are either known or may be made by methods known to someone skilled in the art, for instance compounds of formula E may be synthesised by

condensation of a 2-hydroxy-acetophenone of formula F and a benzaldehyde of formula G under standard conditions (such as potassium hydroxide in hydroalcoholic medium).

Compounds of formula F and G are either known or may be made by methods known by persons skilled in the art.



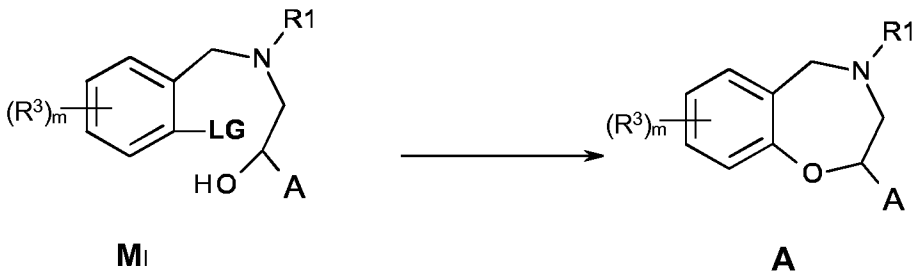
Compounds of formula C may be prepared by the cyclisation of a compound of formula H wherein LG is a leaving group such as chloro, bromo or sulfonate under basic conditions (such as treatment with sodium hydride or potassium carbonate in a polar solvent such as dimethylformamide).

Compounds of formula H may be obtained from the condensation of a 2-hydroxybenzylamine J and an acid chloride K under standard conditions (for instance by reacting J and K in dichloromethane in the presence of aqueous sodium bicarbonate).

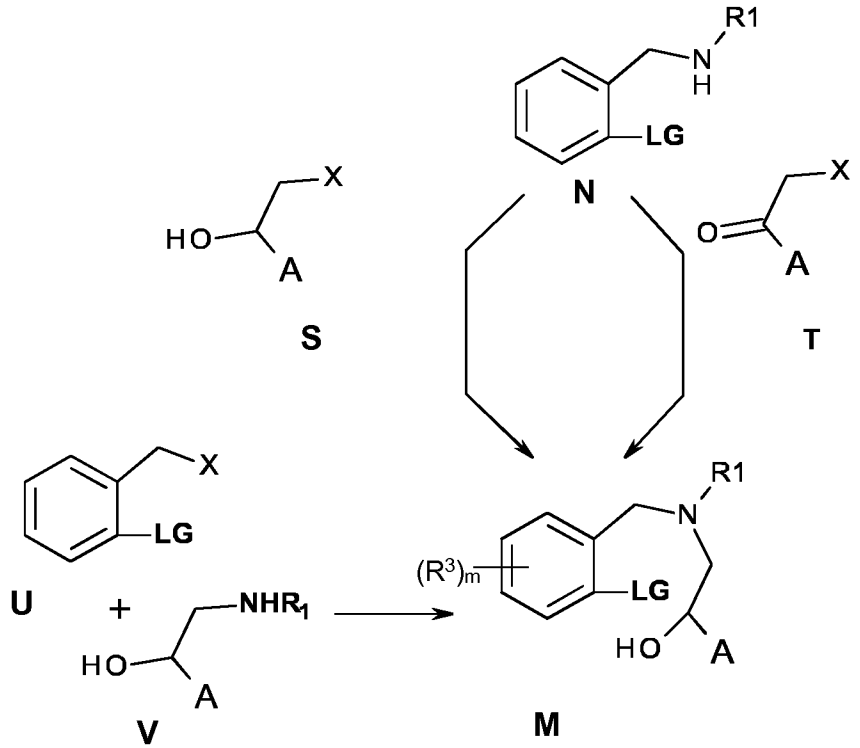
Compounds of formula J are either known or may be obtained by known methods to someone skilled in the art.

Acid chlorides of formula K may be made from a mandelic acid L under standard conditions. A particularly convenient method of achieving such a transformation when LG is chloro involves treating the compound L with thionyl chloride or oxalyl chloride in the presence of dimethylformamide in a solvent such as dioxan.

Mandelic acids of formula L are either known or may be made by methods known to those skilled in the art (for instance from the corresponding benzaldehyde).



Alternatively, compounds of formula A may be made from a compound of formula M, wherein LG is a leaving group such as fluoro, chloro, bromo, iodo or sulfonate, via intramolecular aromatic nucleophilic displacement. Such reactions are usually performed under basic conditions. A particularly convenient method of achieving such a cyclisation involves treating the compound M with sodium hydride in a solvent such as tetrahydrofuran, dimethylformamide or dimethylacetamide.

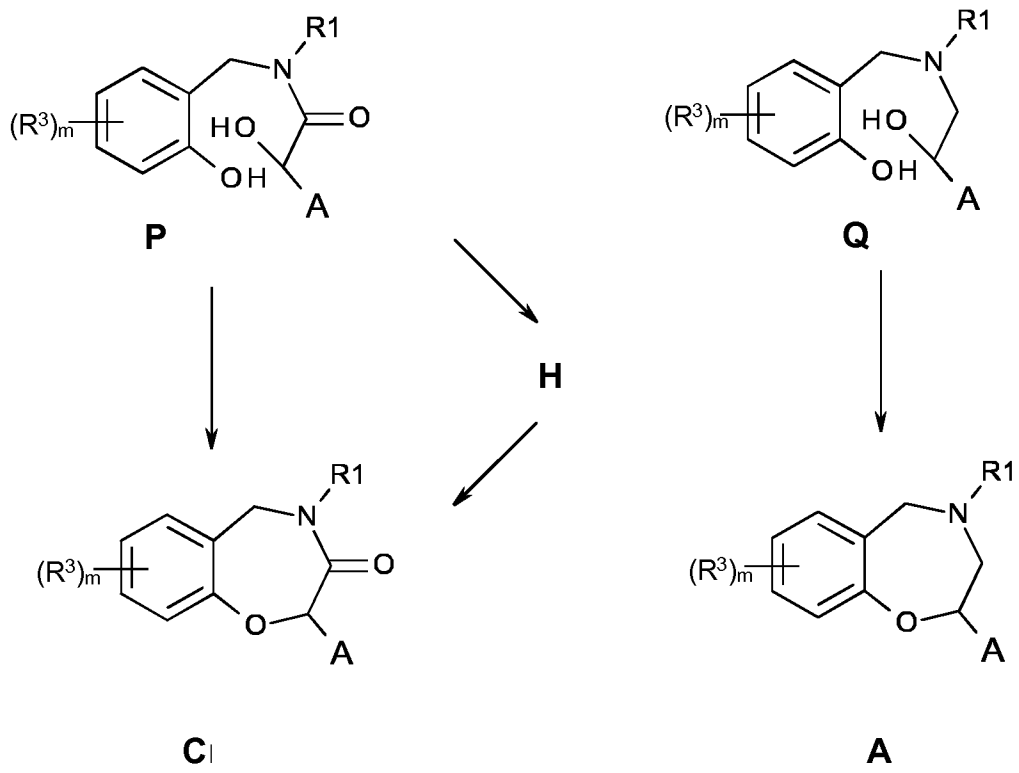


Compounds of formula M may be made in a variety of ways. For example, a compound a formula M may be derived from the condensation of an amine of formula N and a compound of formula S, wherein X is a halogen. Such reactions are usually performed under basic conditions.

Alternatively, a compound a formula M may be made by sequential treatment of a compound of formula N with a compound of formula T, wherein X is a halogen (optionally in the presence of a base) then with a reducing agent such as sodium borohydride.

Alternatively, a compound of formula M may be synthesised by condensation of a compound of formula U, wherin X is a halogen and an amino-alcohol of formula V. Such reactions are usually performed under basic conditions.

Compounds of formula N, S, T, U and V are either known compounds or may be prepared by known methods to someone skilled in the art.



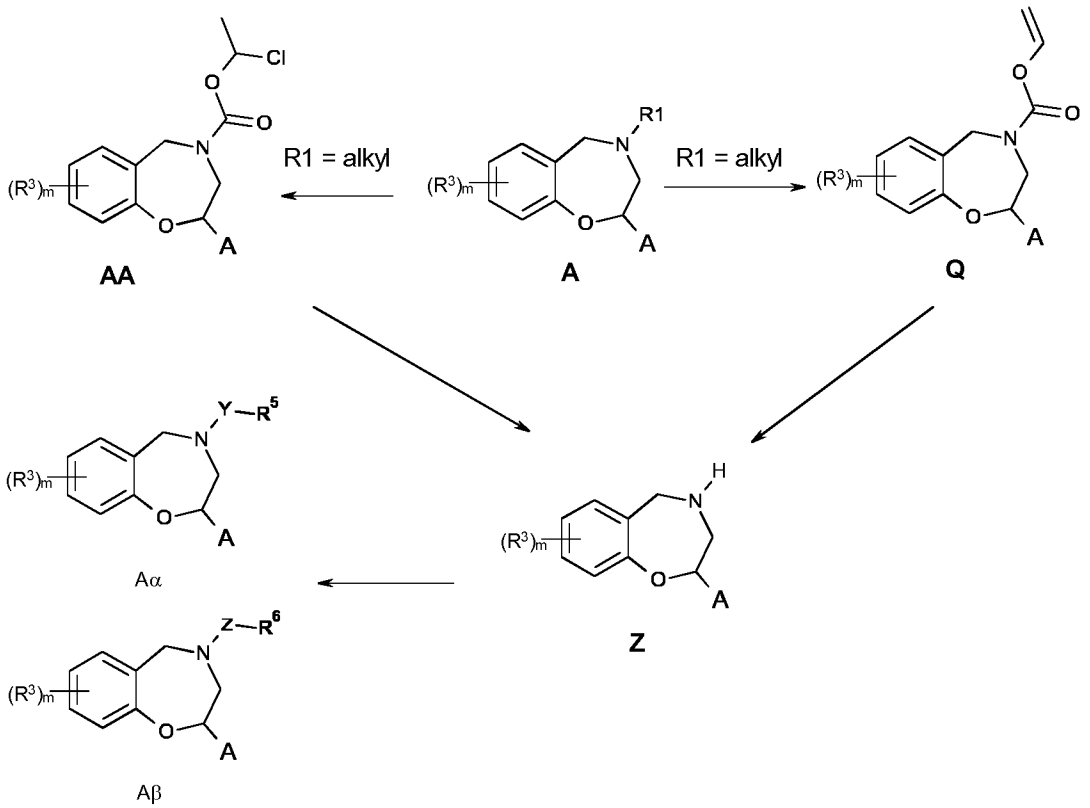
Alternatively, compounds of formula A (resp. C) may be made by cyclisation of compounds of formula P (resp. Q) under standard Mitsunobu conditions (such as treatment with triphenylphosphine and a dialkylazodicarboxylate in a solvent such as tetrahydrofuran).

A compound of formula P may be derived from the coupling of an amine of formula J and a mandelic acid of formula L under standard conditions.

A compound of formula Q may be made by coupling an amine of formula J and a compound of formula S or T.

Alternatively, compounds of formula C may be made by cyclisation of compounds of formula H as described previously; compounds of formula H may be obtained from compounds of formula P under standard conditions such as halogenation with thionyl chloride in the presence or not of a base.

The skilled person will readily recognise that it is possible to interconvert one compound of formula I into a different compound of formula I



Compounds of formula Aα and Aβ can be obtained by a variety of ways. For example, compounds of formula AA or AB may be obtained from a compound of formula Z by known methods to someone skilled in the art (e.g. acylation).

A compound of formula Z may be made by treatment of a compound of formula W with a strong acid such as hydrochloric acid in a solvent such as ethanol (as described for example in Tetrahedron Lett. 1977, 18, 1567-1570).

A compound of formula W may be derived by treatment of a compound of formula A wherein R1 is an alkyl group with vinyl chloroformate in a solvent such as tetrahydrofuran or dichloromethane.

A compound of formula AA may be derived by treatment of a compound of formula A wherein R1 is an alkyl group with 1-chloroethyl chloroformate in a solvent such as tetrahydrofuran or toluene.

Certain compounds of formulae C, H and M are novel and as such form a further aspect of the invention.

It must be recognised that some reagents and reaction conditions may not be compatible with certain functionalities that may be present in the molecules described. In such cases it may be necessary to employ standard protection/deprotection protocols comprehensively reported in the literature and well known to a person skilled in the art.

In addition in some cases it may be necessary to perform further routine synthetic steps not described herein to complete the synthesis of the desired compounds. An artisan

will also recognise that it may be possible to achieve the synthesis of the desired compounds by performing some of the steps of these synthetic routes in a different order to that described.

A person skilled in the art will also recognise that it may be possible to perform standard functional group interconversions or substitution reactions on the compounds described therein to introduce or modify substituents.

The compounds of formula (I) can be used to combat and control infestations of insect pests such as Lepidoptera, Diptera, Hemiptera, Thysanoptera, Orthoptera, Dictyoptera, Coleoptera, Siphonaptera, Hymenoptera and Isoptera and also other invertebrate pests, for example, acarine, nematode and mollusc pests. Insects, acarines, nematodes and molluscs are hereinafter collectively referred to as pests. The pests which may be combated and controlled by the use of the invention compounds include those pests associated with agriculture (which term includes the growing of crops for food and fibre products), horticulture and animal husbandry, companion animals, forestry and the storage of products of vegetable origin (such as fruit, grain and timber); those pests associated with the damage of man-made structures and the transmission of diseases of man and animals; and also nuisance pests (such as flies).

Examples of pest species which may be controlled by the compounds of formula (I) include: *Myzus persicae* (aphid), *Aphis gossypii* (aphid), *Aphis fabae* (aphid), *Lygus* spp. (capsids), *Dysdercus* spp. (capsids), *Nilaparvata lugens* (planthopper), *Nephotettixc incticeps* (leafhopper), *Nezara* spp. (stinkbugs), *Euschistus* spp. (stinkbugs), *Leptocorisa* spp. (stinkbugs), *Frankliniella occidentalis* (thrip), Thrips spp. (thrips), *Leptinotarsa decemlineata* (Colorado potato beetle), *Anthonomus grandis* (boll weevil), *Aonidiella* spp. (scale insects), *Trialeurodes* spp. (white flies), *Bemisia tabaci* (white fly), *Ostrinia nubilalis* (European corn borer), *Spodoptera littoralis* (cotton leafworm), *Heliothis virescens* (tobacco budworm), *Helicoverpa armigera* (cotton bollworm), *Helicoverpa zea* (cotton bollworm), *Sylepta derogata* (cotton leaf roller), *Pieris brassicae* (white butterfly), *Plutella xylostella* (diamond back moth), *Agrotis* spp. (cutworms), *Chilo suppressalis* (rice stem borer), *Locusta_migratoria* (locust), *Chortiocetes terminifera* (locust), *Diabrotica* spp. (rootworms), *Panonychus ulmi* (European red mite), *Panonychus citri* (citrus red mite), *Tetranychus urticae* (two-spotted spider mite), *Tetranychus cinnabarinus* (carmine spider mite), *Phyllocoptruta oleivora* (citrus rust mite), *Polyphagotarsonemus latus* (broad mite), *Brevipalpus* spp. (flat mites), *Boophilus microplus* (cattle tick), *Dermacentor variabilis* (American dog tick), *Ctenocephalides felis* (cat flea), *Liriomyza* spp. (leafminer), *Musca domestica* (housefly), *Aedes aegypti* (mosquito), *Anopheles* spp. (mosquitoes), *Culex* spp. (mosquitoes), *Lucillia* spp. (blowflies), *Blattella germanica* (cockroach), *Periplaneta americana* (cockroach), *Blatta orientalis* (cockroach), termites of the Mastotermitidae (for example *Mastotermes* spp.), the Kalotermitidae (for example *Neotermes* spp.), the Rhinotermitidae (for example *Coptotermes formosanus*, *Reticulitermes flavipes*, *R. speratu*, *R. virginicus*, *R. hesperus*, and *R. santonensis*) and the Termitidae (for example *Globitermes sulphureus*), *Solenopsis geminata* (fire ant), *Monomorium pharaonis* (pharaoh's ant), *Damalinia* spp. and *Linognathus* spp. (biting and

sucking lice), *Meloidogyne* spp. (root knot nematodes), *Globodera* spp. and *Heterodera* spp. (cyst nematodes), *Pratylenchus* spp. (lesion nematodes), *Rhodopholus* spp. (banana burrowing nematodes), *Tylenchulus* spp.(citrus nematodes), *Haemonchus contortus* (barber pole worm), *Caenorhabditis elegans* (vinegar eelworm), *Trichostrongylus* spp. (gastro intestinal nematodes) and *Deroceras reticulatum* (slug).

The invention therefore provides a method of combating and controlling insects, acarines, nematodes or molluscs which comprises applying an insecticidally, acaricidally, nematicidally or molluscicidally effective amount of a compound of formula (I), or a composition containing a compound of formula (I), to a pest, a locus of pest, or to a plant susceptible to attack by a pest, The compounds of formula (I) are preferably used against insects, acarines or nematodes.

The term "plant" as used herein includes seedlings, bushes and trees.

In order to apply a compound of formula (I) as an insecticide, acaricide, nematicide or molluscicide to a pest, a locus of pest, or to a plant susceptible to attack by a pest, a compound of formula (I) is usually formulated into a composition which includes, in addition to the compound of formula (I), a suitable inert diluent or carrier and, optionally, a surface active agent (SFA). SFAs are chemicals which are able to modify the properties of an interface (for example, liquid/solid, liquid/air or liquid/liquid interfaces) by lowering the interfacial tension and thereby leading to changes in other properties (for example dispersion, emulsification and wetting). It is preferred that all compositions (both solid and liquid formulations) comprise, by weight, 0.0001 to 95%, more preferably 1 to 85%, for example 5 to 60%, of a compound of formula (I). The composition is generally used for the control of pests such that a compound of formula (I) is applied at a rate of from 0.1g to10kg per hectare, preferably from 1g to 6kg per hectare, more preferably from 1g to 1kg per hectare.

When used in a seed dressing, a compound of formula (I) is used at a rate of 0.0001g to 10g (for example 0.001g or 0.05g), preferably 0.005g to 10g, more preferably 0.005g to 4g, per kilogram of seed.

In another aspect the present invention provides an insecticidal, acaricidal, nematicidal or molluscicidal composition comprising an insecticidally, acaricidally, nematicidally or molluscicidally effective amount of a compound of formula (I) and a suitable carrier or diluent therefor. The composition is preferably an insecticidal, acaricidal, nematicidal or molluscicidal composition.

In a still further aspect the invention provides a method of combating and controlling pests at a locus which comprises treating the pests or the locus of the pests with an insecticidally, acaricidally, nematicidally or molluscicidally effective amount of a composition comprising a compound of formula (I). The compounds of formula (I) are preferably used against insects, acarines or nematodes.

The compositions can be chosen from a number of formulation types, including dustable powders (DP), soluble powders (SP), water soluble granules (SG), water dispersible granules (WG), wettable powders (WP), granules (GR) (slow or fast release), soluble

concentrates (SL), oil miscible liquids (OL), ultra low volume liquids (UL), emulsifiable concentrates (EC), dispersible concentrates (DC), emulsions (both oil in water (EW) and water in oil (EO)), micro-emulsions (ME), suspension concentrates (SC), aerosols, fogging/smoke formulations, capsule suspensions (CS) and seed treatment formulations. The formulation type chosen in any instance will depend upon the particular purpose envisaged and the physical, chemical and biological properties of the compound of formula (I).

Dustable powders (DP) may be prepared by mixing a compound of formula (I) with one or more solid diluents (for example natural clays, kaolin, pyrophyllite, bentonite, alumina, montmorillonite, kieselguhr, chalk, diatomaceous earths, calcium phosphates, calcium and magnesium carbonates, sulphur, lime, flours, talc and other organic and inorganic solid carriers) and mechanically grinding the mixture to a fine powder.

Soluble powders (SP) may be prepared by mixing a compound of formula (I) with one or more water-soluble inorganic salts (such as sodium bicarbonate, sodium carbonate or magnesium sulphate) or one or more water-soluble organic solids (such as a polysaccharide) and, optionally, one or more wetting agents, one or more dispersing agents or a mixture of said agents to improve water dispersibility/solubility. The mixture is then ground to a fine powder. Similar compositions may also be granulated to form water soluble granules (SG).

Wettable powders (WP) may be prepared by mixing a compound of formula (I) with one or more solid diluents or carriers, one or more wetting agents and, preferably, one or more dispersing agents and, optionally, one or more suspending agents to facilitate the dispersion in liquids. The mixture is then ground to a fine powder. Similar compositions may also be granulated to form water dispersible granules (WG).

Granules (GR) may be formed either by granulating a mixture of a compound of formula (I) and one or more powdered solid diluents or carriers, or from pre-formed blank granules by absorbing a compound of formula (I) (or a solution thereof, in a suitable agent) in a porous granular material (such as pumice, attapulgite clays, fuller's earth, kieselguhr, diatomaceous earths or ground corn cobs) or by adsorbing a compound of formula (I) (or a solution thereof, in a suitable agent) on to a hard core material (such as sands, silicates, mineral carbonates, sulphates or phosphates) and drying if necessary. Agents which are commonly used to aid absorption or adsorption include solvents (such as aliphatic and aromatic petroleum solvents, alcohols, ethers, ketones and esters) and sticking agents (such as polyvinyl acetates, polyvinyl alcohols, dextrins, sugars and vegetable oils). One or more other additives may also be included in granules (for example an emulsifying agent, wetting agent or dispersing agent).

Dispersible Concentrates (DC) may be prepared by dissolving a compound of formula (I) in water or an organic solvent, such as a ketone, alcohol or glycol ether. These solutions may contain a surface active agent (for example to improve water dilution or prevent crystallisation in a spray tank).

Emulsifiable concentrates (EC) or oil-in-water emulsions (EW) may be prepared by dissolving a compound of formula (I) in an organic solvent (optionally containing one or more

wetting agents, one or more emulsifying agents or a mixture of said agents). Suitable organic solvents for use in ECs include aromatic hydrocarbons (such as alkylbenzenes or alkylnaphthalenes, exemplified by SOLVESSO 100, SOLVESSO 150 and SOLVESSO 200; SOLVESSO is a Registered Trade Mark), ketones (such as cyclohexanone or methylcyclohexanone) and alcohols (such as benzyl alcohol, furfuryl alcohol or butanol), N-alkylpyrrolidones (such as N-methylpyrrolidone or N-octylpyrrolidone), dimethyl amides of fatty acids (such as C_8-C_{10} fatty acid dimethylamide) and chlorinated hydrocarbons. An EC product may spontaneously emulsify on addition to water, to produce an emulsion with sufficient stability to allow spray application through appropriate equipment. Preparation of an EW involves obtaining a compound of formula (I) either as a liquid (if it is not a liquid at room temperature, it may be melted at a reasonable temperature, typically below 70°C) or in solution (by dissolving it in an appropriate solvent) and then emulsifiying the resultant liquid or solution into water containing one or more SFAs, under high shear, to produce an emulsion. Suitable solvents for use in EWs include vegetable oils, chlorinated hydrocarbons (such as chlorobenzenes), aromatic solvents (such as alkylbenzenes or alkylnaphthalenes) and other appropriate organic solvents which have a low solubility in water.

Microemulsions (ME) may be prepared by mixing water with a blend of one or more solvents with one or more SFAs, to produce spontaneously a thermodynamically stable isotropic liquid formulation. A compound of formula (I) is present initially in either the water or the solvent/SFA blend. Suitable solvents for use in MEs include those hereinbefore described for use in in ECs or in EWs. An ME may be either an oil-in-water or a water-in-oil system (which system is present may be determined by conductivity measurements) and may be suitable for mixing water-soluble and oil-soluble pesticides in the same formulation. An ME is suitable for dilution into water, either remaining as a microemulsion or forming a conventional oil-in-water emulsion.

Suspension concentrates (SC) may comprise aqueous or non-aqueous suspensions of finely divided insoluble solid particles of a compound of formula (I). SCs may be prepared by ball or bead milling the solid compound of formula (I) in a suitable medium, optionally with one or more dispersing agents, to produce a fine particle suspension of the compound. One or more wetting agents may be included in the composition and a suspending agent may be included to reduce the rate at which the particles settle. Alternatively, a compound of formula (I) may be dry milled and added to water, containing agents hereinbefore described, to produce the desired end product.

Aerosol formulations comprise a compound of formula (I) and a suitable propellant (for example *n*-butane). A compound of formula (I) may also be dissolved or dispersed in a suitable medium (for example water or a water miscible liquid, such as *n*-propanol) to provide compositions for use in non-pressurised, hand-actuated spray pumps.

A compound of formula (I) may be mixed in the dry state with a pyrotechnic mixture to form a composition suitable for generating, in an enclosed space, a smoke containing the compound.

Capsule suspensions (CS) may be prepared in a manner similar to the preparation of EW formulations but with an additional polymerisation stage such that an aqueous dispersion of oil droplets is obtained, in which each oil droplet is encapsulated by a polymeric shell and contains a compound of formula (I) and, optionally, a carrier or diluent therefor. The polymeric shell may be produced by either an interfacial polycondensation reaction or by a coacervation procedure. The compositions may provide for controlled release of the compound of formula (I) and they may be used for seed treatment. A compound of formula (I) may also be formulated in a biodegradable polymeric matrix to provide a slow, controlled release of the compound.

A composition may include one or more additives to improve the biological performance of the composition (for example by improving wetting, retention or distribution on surfaces; resistance to rain on treated surfaces; or uptake or mobility of a compound of formula (I)). Such additives include surface active agents, spray additives based on oils, for example certain mineral oils or natural plant oils (such as soy bean and rape seed oil), and blends of these with other bio-enhancing adjuvants (ingredients which may aid or modify the action of a compound of formula (I)).

A compound of formula (I) may also be formulated for use as a seed treatment, for example as a powder composition, including a powder for dry seed treatment (DS), a water soluble powder (SS) or a water dispersible powder for slurry treatment (WS), or as a liquid composition, including a flowable concentrate (FS), a solution (LS) or a capsule suspension (CS). The preparations of DS, SS, WS, FS and LS compositions are very similar to those of, respectively, DP, SP, WP, SC and DC compositions described above. Compositions for treating seed may include an agent for assisting the adhesion of the composition to the seed (for example a mineral oil or a film-forming barrier).

Wetting agents, dispersing agents and emulsifying agents may be surface SFAs of the cationic, anionic, amphoteric or non-ionic type.

Suitable SFAs of the cationic type include quaternary ammonium compounds (for example cetyltrimethyl ammonium bromide), imidazolines and amine salts.

Suitable anionic SFAs include alkali metals salts of fatty acids, salts of aliphatic monoesters of sulphuric acid (for example sodium lauryl sulphate), salts of sulphonated aromatic compounds (for example sodium dodecylbenzenesulphonate, calcium dodecylbenzenesulphonate, butylnaphthalene sulphonate and mixtures of sodium di-*iso*propyl- and tri-*iso*propyl-naphthalene sulphonates), ether sulphates, alcohol ether sulphates (for example sodium laureth-3-sulphate), ether carboxylates (for example sodium laureth-3-carboxylate), phosphate esters (products from the reaction between one or more fatty alcohols and phosphoric acid (predominately mono-esters) or phosphorus pentoxide (predominately di-esters), for example the reaction between lauryl alcohol and tetraphosphoric acid; additionally these products may be ethoxylated), sulphosuccinamates, paraffin or olefine sulphonates, taurates and lignosulphonates.

Suitable SFAs of the amphoteric type include betaines, propionates and glycinates.

Suitable SFAs of the non-ionic type include condensation products of alkylene oxides, such as ethylene oxide, propylene oxide, butylene oxide or mixtures thereof, with fatty alcohols (such as oleyl alcohol or cetyl alcohol) or with alkylphenols (such as octylphenol, nonylphenol or octylcresol); partial esters derived from long chain fatty acids or hexitol anhydrides; condensation products of said partial esters with ethylene oxide; block polymers (comprising ethylene oxide and propylene oxide); alkanolamides; simple esters (for example fatty acid polyethylene glycol esters); amine oxides (for example lauryl dimethyl amine oxide); and lecithins.

Suitable suspending agents include hydrophilic colloids (such as polysaccharides, polyvinylpyrrolidone or sodium carboxymethylcellulose) and swelling clays (such as bentonite or attapulgite).

A compound of formula (I) may be applied by any of the known means of applying pesticidal compounds. For example, it may be applied, formulated or unformulated, to the pests or to a locus of the pests (such as a habitat of the pests, or a growing plant liable to infestation by the pests) or to any part of the plant, including the foliage, stems, branches or roots, to the seed before it is planted or to other media in which plants are growing or are to be planted (such as soil surrounding the roots, the soil generally, paddy water or hydroponic culture systems), directly or it may be sprayed on, dusted on, applied by dipping, applied as a cream or paste formulation, applied as a vapour or applied through distribution or incorporation of a composition (such as a granular composition or a composition packed in a water-soluble bag) in soil or an aqueous environment.

A compound of formula (I) may also be injected into plants or sprayed onto vegetation using electrodynamic spraying techniques or other low volume methods, or applied by land or aerial irrigation systems.

Compositions for use as aqueous preparations (aqueous solutions or dispersions) are generally supplied in the form of a concentrate containing a high proportion of the active ingredient, the concentrate being added to water before use. These concentrates, which may include DCs, SCs, ECs, EWs, MEs SGs, SPs, WPs, WGs and CSs, are often required to withstand storage for prolonged periods and, after such storage, to be capable of addition to water to form aqueous preparations which remain homogeneous for a sufficient time to enable them to be applied by conventional spray equipment. Such aqueous preparations may contain varying amounts of a compound of formula (I) (for example 0.0001 to 10%, by weight) depending upon the purpose for which they are to be used.

A compound of formula (I) may be used in mixtures with fertilisers (for example nitrogen-, potassium- or phosphorus-containing fertilisers). Suitable formulation types include granules of fertiliser. The mixtures suitably contain up to 25% by weight of the compound of formula (I).

The invention therefore also provides a fertiliser composition comprising a fertiliser and a compound of formula (I).

The compositions of this invention may contain other compounds having biological activity, for example micronutrients or compounds having fungicidal activity or which possess plant growth regulating, herbicidal, insecticidal, nematicidal or acaricidal activity.

The compound of formula (I) may be the sole active ingredient of the composition or it may be admixed with one or more additional active ingredients such as a pesticide, fungicide, synergist, herbicide or plant growth regulator where appropriate. An additional active ingredient may: provide a composition having a broader spectrum of activity or increased persistence at a locus; synergise the activity or complement the activity (for example by increasing the speed of effect or overcoming repellency) of the compound of formula (I); or help to overcome or prevent the development of resistance to individual components. The particular additional active ingredient will depend upon the intended utility of the composition. Examples of suitable pesticides include the following:

a) Pyrethroids, such as permethrin, cypermethrin, fenvalerate, esfenvalerate, deltamethrin, cyhalothrin (in particular lambda-cyhalothrin), bifenthrin, fenpropathrin, cyfluthrin, tefluthrin, fish safe pyrethroids (for example ethofenprox), natural pyrethrin, tetramethrin, s-bioallethrin, fenfluthrin, prallethrin or 5-benzyl-3-furylmethyl-(E)-(1R,3S)-2,2-dimethyl- 3-(2-oxothiolan-3-ylidenemethyl)cyclopropane carboxylate;

b) Organophosphates, such as, profenofos, sulprofos, acephate, methyl parathion, azinphos-methyl, demeton-s-methyl, heptenophos, thiometon, fenamiphos, monocrotophos, profenofos, triazophos, methamidophos, dimethoate, phosphamidon, malathion, chlorpyrifos, phosalone, terbufos, fensulfothion, fonofos, phorate, phoxim, pirimiphos-methyl, pirimiphos-ethyl, fenitrothion, fosthiazate or diazinon;

c) Carbamates (including aryl carbamates), such as pirimicarb, triazamate, cloethocarb, carbofuran, furathiocarb, ethiofencarb, aldicarb, thiofurox, carbosulfan, bendiocarb, fenobucarb, propoxur, methomyl or oxamyl;

d) Benzoyl ureas, such as diflubenzuron, triflumuron, hexaflumuron, flufenoxuron or chlorfluazuron;

e) Organic tin compounds, such as cyhexatin, fenbutatin oxide or azocyclotin;

f) Pyrazoles, such as tebufenpyrad and fenpyroximate;

g) Macrolides, such as avermectins or milbemycins, for example abamectin, emamectin benzoate, ivermectin, milbemycin, spinosad or azadirachtin;

h) Hormones or pheromones;

i) Organochlorine compounds such as endosulfan, benzene hexachloride, DDT, chlordane or dieldrin;

j) Amidines, such as chlordimeform or amitraz;

k) Fumigant agents, such as chloropicrin, dichloropropane, methyl bromide or metam;

l) Chloronicotinyl compounds such as imidacloprid, thiacloprid, acetamiprid, nitenpyram or thiamethoxam;

m) Diacylhydrazines, such as tebufenozide, chromafenozide or methoxyfenozide;

n) Diphenyl ethers, such as diofenolan or pyriproxifen;

o) Indoxacarb;

p) Chlorfenapyr;

q) Pymetrozine;

r) Spirotetramat, Spiromesifen; or

s) Flubendiamid or Rynaxypyr

In addition to the major chemical classes of pesticide listed above, other pesticides having particular targets may be employed in the composition, if appropriate for the intended utility of the composition. For instance, selective insecticides for particular crops, for example stemborer specific insecticides (such as cartap) or hopper specific insecticides (such as buprofezin) for use in rice may be employed. Alternatively insecticides or acaricides specific for particular insect species/stages may also be included in the compositions (for example acaricidal ovo-larvicides, such as clofentezine, flubenzimine, hexythiazox or tetradifon; acaricidal motilicides, such as dicofol or propargite; acaricides, such as bromopropylate or chlorobenzilate; or growth regulators, such as hydramethylnon, cyromazine, methoprene, chlorfluazuron or diflubenzuron).

Examples of fungicidal compounds which may be included in the composition of the invention are (*E*)-*N*-methyl-2-[2-(2,5-dimethylphenoxymethyl)phenyl]-2-methoxy-iminoacetamide (SSF-129), 4-bromo-2-cyano-*N*,*N*-dimethyl-6-trifluoromethylbenzimidazole-1-sulphonamide, α-[*N*-(3-chloro-2,6-xylyl)-2-methoxyacetamido]-γ-butyrolactone, 4-chloro-2-cyano-*N*,*N*-dimethyl-5-*p*-tolylimidazole-1-sulfonamide (IKF-916, cyamidazosulfamid), 3-5-dichloro-*N*-(3-chloro-1-ethyl-1-methyl-2-oxopropyl)-4-methylbenzamide (RH-7281, zoxamide), *N*-allyl-4,5,-dimethyl-2-trimethylsilylthiophene-3-carboxamide (MON65500), *N*-(1-cyano-1,2-dimethylpropyl)-2-(2,4-dichlorophenoxy)propionamide (AC382042), *N*-(2-methoxy-5-pyridyl)-cyclopropane carboxamide, acibenzolar (CGA245704), alanycarb, aldimorph, anilazine, azaconazole, azoxystrobin, benalaxyl, benomyl, biloxazol, bitertanol, blasticidin S, bromuconazole, bupirimate, captafol, captan, carbendazim, carbendazim chlorhydrate, carboxin, carpropamid, carvone, CGA41396, CGA41397, chinomethionate, chlorothalonil, chlorozolinate, clozylacon, copper containing compounds such as copper oxychloride, copper oxyquinolate, copper sulphate, copper tallate and Bordeaux mixture, cymoxanil, cyproconazole, cyprodinil, debacarb, di-2-pyridyl disulphide 1,1'-dioxide, dichlofluanid, diclomezine, dicloran, diethofencarb, difenoconazole, difenzoquat, diflumetorim, *O*,*O*-di-*iso*-propyl-*S*-benzyl thiophosphate, dimefluazole, dimetconazole, dimethomorph, dimethirimol, diniconazole, dinocap, dithianon, dodecyl dimethyl ammonium chloride, dodemorph, dodine, doguadine, edifenphos, epoxiconazole, ethirimol, ethyl(*Z*)-*N*-benzyl-*N*-([methyl(methyl-thioethylideneaminooxycarbonyl)amino]thio)-β-alaninate, etridiazole, famoxadone, fenamidone (RPA407213), fenarimol, fenbuconazole, fenfuram, fenhexamid (KBR2738), fenpiclonil, fenpropidin, fenpropimorph, fentin acetate, fentin hydroxide, ferbam, ferimzone, fluazinam, fludioxonil, flumetover, fluoroimide, fluquinconazole, flusilazole, flutolanil, flutriafol, folpet, fuberidazole, furalaxyl, furametpyr, guazatine, hexaconazole,

hydroxyisoxazole, hymexazole, imazalil, imibenconazole, iminoctadine, iminoctadine triacetate, ipconazole, iprobenfos, iprodione, iprovalicarb (SZX0722), isopropanyl butyl carbamate, isoprothiolane, kasugamycin, kresoxim-methyl, LY186054, LY211795, LY248908, mancozeb, maneb, mefenoxam, mepanipyrim, mepronil, metalaxyl, metconazole, metiram, metiram-zinc, metominostrobin, myclobutanil, neoasozin, nickel dimethyldithiocarbamate, nitrothal-*iso*propyl, nuarimol, ofurace, organomercury compounds, oxadixyl, oxasulfuron, oxolinic acid, oxpoconazole, oxycarboxin, pefurazoate, penconazole, pencycuron, phenazin oxide, phosetyl-Al, phosphorus acids, phthalide, picoxystrobin (ZA1963), polyoxin D, polyram, probenazole, prochloraz, procymidone, propamocarb, propiconazole, propineb, propionic acid, pyrazophos, pyrifenox, pyrimethanil, pyroquilon, pyroxyfur, pyrrolnitrin, quaternary ammonium compounds, quinomethionate, quinoxyfen, quintozene, sipconazole (F-155), sodium pentachlorophenate, spiroxamine, streptomycin, sulphur, tebuconazole, tecloftalam, tecnazene, tetraconazole, thiabendazole, thifluzamid, 2-(thiocyanomethylthio)benzothiazole, thiophanate-methyl, thiram, timibenconazole, tolclofos-methyl, tolylfluanid, triadimefon, triadimenol, triazbutil, triazoxide, tricyclazole, tridemorph, trifloxystrobin (CGA279202), triforine, triflumizole, triticonazole, validamycin A, vapam, vinclozolin, zineb and ziram.

The compounds of formula (I) may be mixed with soil, peat or other rooting media for the protection of plants against seed-borne, soil-borne or foliar fungal diseases.

Examples of suitable synergists for use in the compositions include piperonyl butoxide, sesamex, safroxan and dodecyl imidazole.

Suitable herbicides and plant-growth regulators for inclusion in the compositions will depend upon the intended target and the effect required.

An example of a rice selective herbicide which may be included is propanil. An example of a plant growth regulator for use in cotton is PIX™.

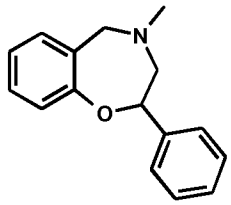
Some mixtures may comprise active ingredients which have significantly different physical, chemical or biological properties such that they do not easily lend themselves to the same conventional formulation type. In these circumstances other formulation types may be prepared. For example, where one active ingredient is a water insoluble solid and the other a water insoluble liquid, it may nevertheless be possible to disperse each active ingredient in the same continuous aqueous phase by dispersing the solid active ingredient as a suspension (using a preparation analogous to that of an SC) but dispersing the liquid active ingredient as an emulsion (using a preparation analogous to that of an EW). The resultant composition is a suspoemulsion (SE) formulation.

The invention is illustrated by the following Examples:

Mass spectra data were obtained for selected compounds of the following examples using positive electrospray 150-1000 m/z.

EXAMPLE E1.1

This Example illustrates the preparation of 4-methyl-2-phenyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



Step A: 2-Methylaminomethyl-phenol

200 g of salicylaldehyde and 210 ml of an 8M solution of methylamine in ethanol were dissolved in 1.6 L ethanol and stirred with 25 g 5% Pt/C under hydrogen. Hydrogen uptake stopped after 36.8 L were taken up. The catalyst was filtered and the solvent evaporated to yield 234.3 g of an orange oil which crystallised overnight.

Step B: 2-Chloro-N-(2-hydroxy-benzyl)-N-methyl-2-phenyl-acetamide

16.2 ml of DMF was added slowly to a solution of 14.9 ml of thionyl chloride in 25 ml dioxane, and then a solution of 15.2 g mandelic acid in 20 ml dioxane was slowly added. The reaction was slightly exothermic and was held during the addition at ca 25°C with an ice/water bath. This solution was then added to a rapidly stirred mixture of a solution of 50.4 g sodium bicarbonate in 300ml water and 13.7 g of the product of step A (2-methylaminomethyl-phenol) in 300 ml of dichloromethane. The mixture was stirred overnight, the organic phase dried and evaporated to yield 32.4 g of the product as a dark red oil.

Step C: 4-Methyl-2-phenyl-4,5-dihydro-benzo[f][1,4]oxazepin-3-one

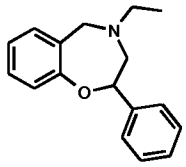
31.1 g of the product of step B (2-chloro-N-(2-hydroxy-benzyl)-N-methyl-2-phenyl-acetamide) was dissolved in 75 ml of DMF and stirred at 0°C. Sodium hydride was added in 5 portions causing an exothermic reaction, development of gas, and foaming. After the addition was complete the beige-brown suspension was stirred overnight at room temperature then poured onto ca 500 ml ice/water and extracted with ethyl acetate. The organic phase was dried and evaporated to yield 23.4 g of a brown amorphous crude product, which was chromatographed on silica with 5% EtOAc in dichloromethane to yield 20.46 g of the product as a resin.

Step D: 4-Methyl-2-phenyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine

A solution of 7.2 g of lithium aluminium hydride in 200 ml THF was heated at reflux while a solution of 20 g of the product from step C (4-Methyl-2-phenyl-4,5-dihydro-benzo[f][1,4]oxazepin-3-one) in 60 ml THF was added dropwise. Heating was continued overnight and the suspension was then cooled to 0-5°C and 10 ml of water was added dropwise causing a strongly exothemic reaction and development of gas. Then 10 ml of 4M aqueous NaOH was added dropwise and the white suspended material was filtered off and washed with THF. The solvent was evaporated to yield 18.24 g of the crude product as a yellow oil, which was chromatographed on silica with 50% EtOAc/hexane to yield 11.49 g of the product as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) 2.56 (s, 3H), 3.22 (m, 2H), 3.82 (d, 1H), 4.21 (d, 1H), 5.01 (m, 1H), 7.02-7.45 (m, 9H). MS (ES+) 240 (MH^+).

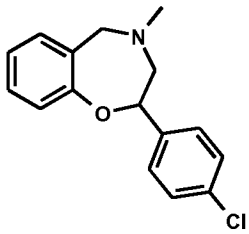
The following compounds were prepared according to procedures analogous to those described in Example E1.1:

Cpd n°	Compound	Structure	MH^+	1H NMR	M.p

				(°C)
E1.2		254	400MHz, $CDCl_3$: 1.2 (t, 3H), 2.7 (m, 2H), 3.25 (m, 2H), 3.8 and 4.2 (d, 2H), 4.95 (dd, 1H), 7.0-7.5 (m, 9H)	

EXAMPLE E2.1

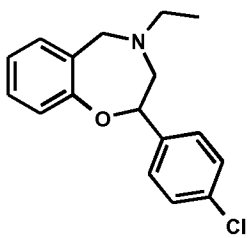
This Example illustrates the preparation of 2-(4-chloro-phenyl)-4-methyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



A stirred solution of 42 g of 4-methyl-2-(4-chloro-phenyl)-4,5-dihydro-benzo[f][1,4]oxazepin-3-one (prepared according to Example E1.1, steps A-C except for using 4-chloromandelic acid instead of mandelic acid in Step B) in 400 ml of tetrahydrofuran was heated to reflux and 150 ml of borane methylsulfide complex (2.0 M in THF) was added dropwise over 20 minutes; the solution was stirred at this temperature for 5 hours, then cooled to room temperature. The reaction was quenched by dropwise addition of 300 ml of 2M hydrochloric acid then basified to pH 13 with 200 ml of 4M sodium hydroxide; the mixture was then extracted with dichloromethane (3x1L), the organic layers dried over sodium sulphate and concentrated *in vacuo*; the residue was subjected to column chromatography (hexane:ethyl acetate 1:1) to yield 31.8 g of 2-(4-chloro-phenyl)-4-methyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine as a white solid. M.p 82-83°C; ^{1}H NMR (400 MHz, $CDCl_3$) 2.5 (s, 3H), 3.1 (d, 2H), 3.7 (d, 1H), 4.1 (d, 1H), 4.9 (t, 1H), 7.0 (m, 2H), 7.2 (m, 2H), 7.4 (s, 4H); MS (ES+) 274/276 (MH^+), 168/170 (M- CH_2PhO).

EXAMPLE E3.1

This Example illustrates the preparation of 2-(4-chloro-phenyl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



METHOD A:

Step A: 3-(4-Chloro-phenyl)-3-hydroxy-1-(2-hydroxy-phenyl)-propan-1-one

A solution of 10% NaOH in water (36 g) was added to an ice-cold solution of 10.54 g of 2'-hydroxyacetophenone in 15 ml of ethanol under stirring, followed by dropwise addition of a

solution of 10.21 g 4-chlorobenzaldehyde in 8 ml of ethanol. The reaction mixture was stirred further 2 hours under ice cooling and then kept in a refrigerator. After 16 hours the reaction mixture was poured into 150 ml of ice water. The water suspension was acidified by 1N-HCl to pH 2. The oily product was extracted with ethyl acetate and the combined organic phases were dried over sodium sulphate. The solution was filtered and then concentrated to give the crude product as a pale brown oil. Purification by column chromatography (hexane – ethyl acetate/14:1 -> 9:1) gave 1.2 g of (E)-3-(4-chloro-phenyl)-1-(2-hydroxy-phenyl)-propenone (mp 157-157°C) and 8.85 g of 3-(4-Chloro-phenyl)-3-hydroxy-1-(2-hydroxy-phenyl)-propan-1-one (mp 115-116°C).

Step B: 2-(4-Chlorophenyl)-chroman-4-one

A solution of 5.55 g of diethylazodicarboxylate (14.6 ml, 40% solution in toluene) was added dropwise to an ice-cold solution of 8.75 g of 3-(4-Chloro-phenyl)-3-hydroxy-1-(2-hydroxy-phenyl)-propan-1-one and 8.35 g of triphenylphosphine in 50 ml THF. The reaction mixture was stirred overnight at ambient temperature. The solvents were evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel (hexane-ethyl acetate /14:1 -> 9:1 -> 4:1) afforded the product 2-(4-chlorophenyl)-chroman-4-one as a white solid (6.8 g; mp 98-99°C).

Step C: 2-(4-Chloro-phenyl)-3,4-dihydro-2H-benzo[f][1,4]oxazepin-5-one

Sodium azide (6.5 g) was added in small portions to a solution of 2-(4-chlorophenyl)-chroman-4-one (6.47 g) in trifluoroacetic acid (250 ml) at room temperature under argon atmosphere. After 48 hours the trifluoroacetic acid was evaporated under reduced pressure and the oily residue was chromatographed on a silica gel column (hexane-acetone 4:1) giving 5.28 g of the desired product (2-(4-chloro-phenyl)-3,4-dihydro-2H-benzo[f][1,4]oxazepin-5-one). The following side products were obtained in minor quantities: 5-(4-chloro-phenyl)-4,5-dihydro-6-oxa-1,2,3,3a-tetraaza-benzo[e]azulene (0.26 g, m.p. 172.5-173.5 °C), 6-(4-chloro-phenyl)-6,7-dihydro-9H-5-oxa-9-aza-benzocyclohepten-8-one (0.12 g, m.p. 131-132.5°C) and 2-[5-(4-chlorophenyl)-4,5-dihydro-oxazol-2-yl]-phenol (0.14 g, m.p. 175-177°C).

Step D: 2-(4-Chloro-phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine

2-(4-Chloro-phenyl)-3,4-dihydro-2H-benzo[f][1,4]oxazepin-5-one (5.28 g) was dissolved in dry THF and cooled to 0°C under argon. Lithium aluminium hydride (1.68 g) was added in two portions, and the reaction mixture was stirred 18 hours at ambient temperature. An additional portion of lithium aluminium hydride (1.68 g) was then added to the reaction mixture and stirring was continued at reflux for 20 hours. The reaction mixture was cooled to 0°C and then 0.7 ml of 30% aqueous KOH was carefully added. The mixture was stirred at ambient temperature overnight and filtered. The cake was washed three times with dichloromethane. The combined organic layers were washed three times with water and the water phase was re-extracted with dichloromethane. The organic phases were combined, washed with brine and dried over sodium sulphate. After evaporation of the solvents the crude product was crystallized from the mixture of hexane / ethyl acetate. The product was filtered off (washed with small amount of cold hexane) giving 2.37 g of 2-(4-chloro-phenyl)-2,3,4,5-tetrahydro-

benzo[f][1,4]oxazepine as a white solid (mp 117-118.5 °C). The filtrate was evaporated and the residue was re-crystallized giving the next amount (1.33g) of the desired product (total yield 3.70 g).

Step E: 2-(4-Chloro-phenyl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine

A solution of 150 mg of 2-(4-chloro-phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4] oxazepine in 1.65 ml of acetic acid was heated to 55°C and 98 mg of sodium borohydride was added. After 22 hours and after 72 hours further sodium borohydride portions (each time 98mg) were added. The reaction mixture was stirred at 55°C for 4 days, then cooled to room temperature and quenched by addition of 10 ml of water and 5 pellets of sodium hydroxide. The mixture was extracted 4 times with dichloromethane. The combined organic phases were dried with sodium sulphate, filtered and concentrated *in vacuo*. The residue was subjected to column chromatography (hexane:ethyl acetate 3:1) to yield 91 mg of 2-(4-chloro-phenyl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4] oxazepine as a white solid. ; ^{1}H NMR (400 MHz, $CDCl_3$) 1.1 (t, 3H), 2.6 (m, 2H), 3.1 (m, 2H), 3.7 (d, 1H), 4.0 (d, 1H), 4.8 (d, 1H), 6.9-7.0 (m, 2H), 7.1-7.2 (m, 2H), 7.4 (s, 4H); MS (ES+) 288/290 (MH^+).

METHOD B: A solution of 35 g of 4-ethyl-2-(4-chloro-phenyl)-4,5-dihydro-benzo[f][1,4]oxazepin-3-one (prepared according to Example E1.1, steps A-C except for using ethylamine instead of methylamine in Step A and 4-chloromandelic acid instead of mandelic acid in Step B) in 800 ml of tetrahydrofuran was heated to reflux and 255 ml of borane methylsulfide complex (1.0 M in THF) was added dropwise over 30 minutes; the solution was stirred at this temperature for 2 hours, then cooled to room temperature and quenched by dropwise addition of 250 ml of methanol. The reaction mixture was stirred at room temperature for 2 hours the concentrated *in vacuo*. The residue was subjected to column chromatography (hexane:ethyl acetate 7:3) to yield 30 g of 2-(4-chloro-phenyl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine as a white solid. Mp 82°C; MS (ES+) 288/290 (MH^+).

METHOD C:

Step A: Ethyl-(2-fluoro-benzyl)-amine

To a solution of 6.2 g of 2-fluorobenzaldehyde in 80 ml of methanol was added 125 ml of a 2N solution of ethylamine in methanol and the resulting solution was stirred at room temperature for 2 hours. The solution was then cooled to 0°C and 3.7 g of sodium borohydride were added portion wise. Upon completion of the addition, the reaction mixture was stirred for 2 hours at room temperature then the solvent was removed *in vacuo*. The residue was partitioned between water and ethyl acetate, the organic layer was washed with brine, dried over sodium sulphate and concentrated *in vacuo* to afford 7.7 g of ethyl-(2-fluoro-benzyl)-amine as a yellow oil. MS (ES+) 154 (MH^+).

Step B: 1-(4-Chloro-phenyl)-2-[ethyl-(2-fluoro-benzyl)-amino]-ethanone

To a solution of 7.7 g of ethyl-(2-fluoro-benzyl)-amine and 18 ml of diisopropylethylamine in 250 ml of acetonitrile was added 14 g of 4'-chlorophenacyl bromide and the resulting mixture was stirred for 2 hours at 60°C. The reaction mixture was then cooled to room temperature, diluted with water and ethyl acetate, the organic layer was washed with water, dried over

sodium sulphate and concentrated *in vacuo* to afford 18 g of 1-(4-chloro-phenyl)-2-[ethyl-(2-fluoro-benzyl)-amino]-ethanone as a brown-orange oil. MS (ES+) 306/308 (MH^+).

Step C: 1-(4-Chloro-phenyl)-2-[ethyl-(2-fluoro-benzyl)-amino]-ethanol

To a solution of 18 g of 1-(4-chloro-phenyl)-2-[ethyl-(2-fluoro-benzyl)-amino]-ethanone in 600 ml of methanol were added 5.5 g of sodium borohydride portion wise. Upon completion of the addition, the reaction mixture was stirred overnight at room temperature, and then the solvent was removed *in vacuo*. The residue was partitioned between water and ethyl acetate, the organic layer was washed with brine, dried over sodium sulphate and concentrated *in vacuo*. The residue was subjected to silica gel chromatography (cyclohexane: ethyl acetate 8:2) to afford 14 g of 1-(4-chloro-phenyl)-2-[ethyl-(2-fluoro-benzyl)-amino]-ethanol as a yellow oil. MS (ES+) 308/310 (MH^+).

Step D: 2-(4-Chloro-phenyl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine

To a stirred suspension of 120 mg of sodium hydride (ca 60% in oil) in 5 ml of dimethylformamide under nitrogen was added a solution of 307 mg of 1-(4-chloro-phenyl)-2-[ethyl-(2-fluoro-benzyl)-amino]-ethanol in 5 ml of dimethylformamide and the resulting mixture was stirred for 2 hours at 80°C. The reaction mixture was cooled to room temperature, poured into ice water then extracted with ethyl acetate. The organic layer was washed with water then brine, dried over sodium sulphate and concentrated *in vacuo* to afford 295 mg of 2-(4-chloro-phenyl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine as a slightly yellow solid. MS (ES+) 288/290 (MH^+).

METHOD D:

Step A: Ethyl-(2-iodo-benzyl)-amine

To a solution of 2.32 g of 2-iodobenzaldehyde in 50 ml of methanol was added 25 ml of a 2N solution of ethylamine in methanol and the resulting solution was heated at 65°C for 1 hour. The solution was then cooled to 0°C and 0.74 g of sodium borohydride were added portion wise. Upon completion of the addition, the reaction mixture was stirred for 2 hours at room temperature then the solvent was removed *in vacuo*. The residue was partitioned between water and ethyl acetate; the organic layer was washed with brine, dried over sodium sulphate and concentrated *in vacuo* to afford 2.3 g of ethyl-(2-iodo-benzyl)-amine as a yellow oil. MS (ES+) 262/263 (MH^+).

Step B: 1-(4-Chloro-phenyl)-2-[ethyl-(2-iodo-benzyl)-amino]-ethanone

To a solution of 2.3 g of ethyl-(2-iodo-benzyl)-amine and 2.9 ml of N,N-diisopropylethylamine in 50 ml of acetonitrile was added 2.25 g of 4'-chlorophenacyl bromide and the resulting mixture was stirred for 2 hours at 60°C. The reaction mixture was then cooled to room temperature, diluted with water and ethyl acetate, the organic layer was washed with water, dried over sodium sulphate and concentrated *in vacuo* to afford 3.8 g of 1-(4-chloro-phenyl)-2-[ethyl-(2-iodo-benzyl)-amino]-ethanone as a yellow oil. MS (ES+) 414/416 (MH^+).

Step C: 1-(4-Chloro-phenyl)-2-[ethyl-(2-iodo-benzyl)-amino]-ethanol

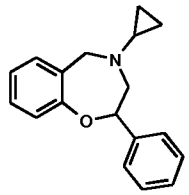
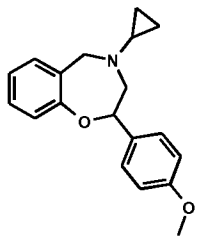
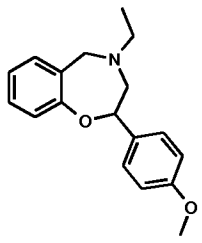
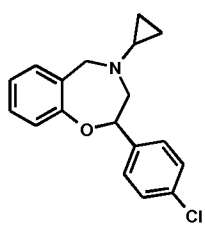
To a solution of 4 g of 1-(4-chloro-phenyl)-2-[ethyl-(2-iodo-benzyl)-amino]-ethanone in 100 ml of methanol was added 0.9 g of sodium borohydride portion wise. Upon completion of the

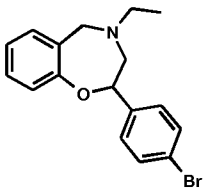
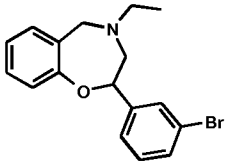
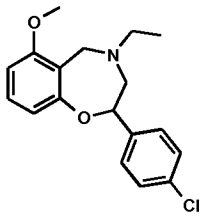
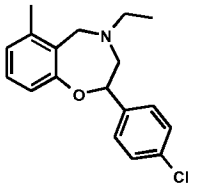
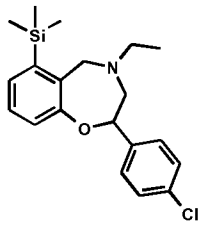
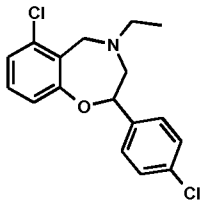
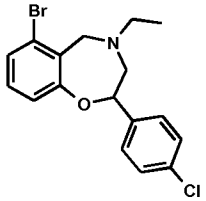
addition, the reaction mixture was stirred overnight at room temperature, and then the solvent was removed *in vacuo*. The residue was partitioned between water and ethyl acetate, the organic layer was washed with brine, dried over sodium sulphate and concentrated *in vacuo* to afford 4 g of 1-(4-chloro-phenyl)-2-[ethyl-(2-iodo-benzyl)-amino]-ethanol as a yellow oil. MS (ES+) 416/418 (MH^+).

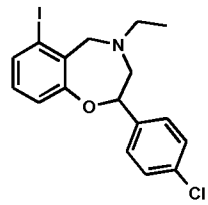
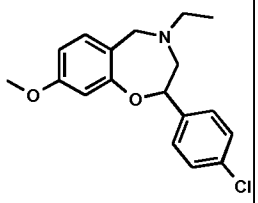
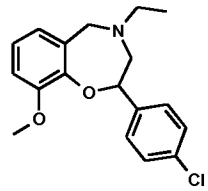
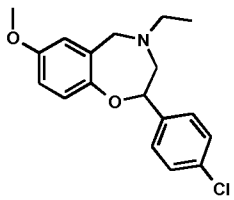
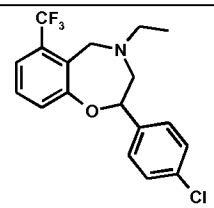
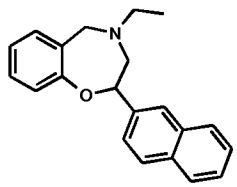
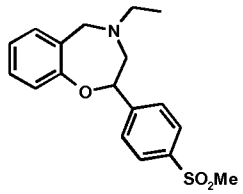
Step D: 2-(4-Chloro-phenyl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine

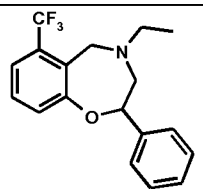
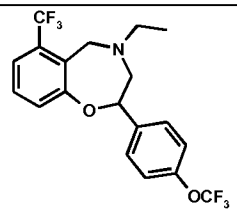
A mixture of 308 mg of 1-(4-chloro-phenyl)-2-[ethyl-(2-iodo-benzyl)-amino]-ethanol, 19 mg copper(I) iodide and 207 mg of potassium carbonate in 3 ml of dimethylacetamide were heated under microwave conditions at 220°C for 10 min. The reaction mixture was then poured into water, extracted with ethyl acetate, the organic layer was dried over sodium sulphate, concentrated in vacuo and the residue subjected to silica gel chromatography (cyclohexane:ethyl acetate 8:2) to afford 190 mg of 2-(4-chloro-phenyl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine as a pale yellow solid. MS (ES+) 288/290 (MH^+).

The following compounds were prepared according to procedures analogous to those described in Example E3.1:

Cpd n°	Structure	MH^+	1H NMR	M.p (°C)
E3.2		266	$CDCl_3$: 0.5 (d,4H); 1.9 (q, 1H), 3.15 (dd, 1H); 3.20 (d, 1H); 3.8 (d, 1H); 4.1 (d, 1H); 4.9 (d, 1H); 6.9-7.3 (m, 9H)	
E3.3		296		98°C
E3.4		284		52°C
E3.5		300/302		89-90°C

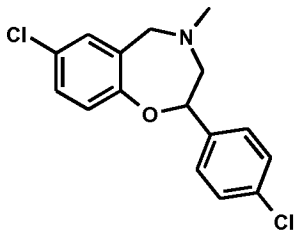
E3.6		332/334		117°C
E3.7		332/334		93°C
E3.8		318/320		76°C
E3.9		302/304	$CDCl_3$: 1.1 (t, 2H), 2.1 (s, 3H), 2.6 (m, 2H), 3.05 (dd, 1H); 3.1 (d, 1H); 3.7 (d, 1H); 4.1 (d, 1H); 4.7 (d, 1H); 6.8-7.1 (m, 3H), 7.3 (m,4H)	73-74°C
E3.10		360/362	$CDCl_3$: 0.0 (s, 9H), 1.1 (t, 2H), 2.6 (m, 2H), 3.05 (dd, 1H); 3.1 (d, 1H); 3.7 (d, 1H); 4.1 (d, 1H); 4.8 (d, 1H); 6.9-7.4 (m, 7H)	
E3.11		322/324	$CDCl_3$: 1.1 (t, 2H), 2.6 (m, 2H), 3.1 (dd, 1H); 3.15 (d, 1H); 3.8 (d, 1H); 4.1 (d, 1H); 4.8 (d, 1H); 6.9 (t, 1H), 7.0 (d, 1H), 7.2 (d, 1H), 7.3 (d, 2H), 7.4 (d, 2H)	78-79°C
E3.12		366/368	$CDCl_3$: 1.1 (t, 2H), 2.6 (m, 2H), 3.2 (dd, 1H); 3.25 (d, 1H); 3.8 (d, 1H); 4.2 (d, 1H); 4.9 (d, 1H); 6.9 (t, 1H), 7.15 (d, 1H), 7.4 (d, 2H), 7.45 (d, 2H), 7.5 (d, 1H)	87°C

E3.13		414/416	$CDCl_3$: 1.1 (t, 2H), 2.5 (m, 2H), 3.05 (dd, 1H); 3.1 (m, 1H); 3.75 (d, 1H); 4.1 (d, 1H); 4.8 (dd, 1H); 6.7 (t, 1H), 7.1 (d, 1H), 7.3 (d, 2H), 7.35 (d, 2H), 7.6 (d, 1H)	86°C
E3.14		318/320	$CDCl_3$: 0.95 (t, 2H), 2.4 (m, 2H), 2.90 (dd, 1H); 2.95 (dd, 1H); 3.55 (s, 3H), 3.6 (d, 1H); 3.8 (d, 1H); 4.7 (dd, 1H); 6.4 (m, 2H), 6.9 (d, 1H), 7.2 (s, 4H)	
E3.15		318/320	$CDCl_3$: 1.15 (t, 2H), 2.6 (m, 2H), 3.2 (dd, 1H); 3.25 (dd, 1H); 3.75 (s, 3H), 3.8 (d, 1H); 4.2 (d, 1H); 4.9 (dd, 1H); 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (t, 1H), 7.4 (d, 2H), 7.5 (d, 2H)	99°C
E3.16		318/320	$CDCl_3$: 1.2 (t, 2H), 2.6 (m, 2H), 3.1 (dd, 1H); 3.2 (dd, 1H); 3.75 (d, 1H); 3.8 (s, 3H); 4.15 (d, 1H); 4.8 (dd, 1H); 6.7 (m, 2H), 7.0 (d, 1H), 7.4 (s, 4H)	
E3.17		356/358		
E3.18		304		
E3.19		332		111°C

E3.20		322		
E3.21		406		

EXAMPLE E4.1

This Example illustrates the preparation of 7-chloro-2-(4-chloro-phenyl)-4-methyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



Step A: (E)-1-(5-Chloro-2-hydroxy-phenyl)-3-(4-chloro-phenyl)-propenone

60 ml of a aqueous solution of NaOH (60%) was added to an ice-cold solution of 5.00 g of 4-chloro-2'-hydroxyacetophenone and 4.12 g of 4-chloro-benzaldehyde in 120 ml of ethanol under stirring. The reaction mixture was stirred further at room temperature for 21 hours. After 16 hours the reaction mixture was poured into 400 ml of 1N-HCl. The solid was filtered, and the filtrate was extracted with ethyl acetate. The solid was dissolved in ethyl acetate and combined with the organic phases, which were dried over sodium sulphate, filtered and then concentrated. 2 Purifications by column chromatography ([A] toluene – dichloromethane 3:2 and [B] hexane – ethyl acetate 9:1) gave of 2.88 g of (E)-1-(5-chloro-2-hydroxy-phenyl)-3-(4-chloro-phenyl)-propenone.

Step B: 6-Chloro-2-(4-chloro-phenyl)-chroman-4-one

To a solution of 964 mg of (E)-1-(5-Chloro-2-hydroxy-phenyl)-3-(4-chloro-phenyl)-propenone in 140 ml of ethanol was added 66 mg of tetrabutylammonium iodide and 14.5 ml of HCl. The reaction mixture was stirred 23 hours at 80°C. The reaction mixture was diluted with 100 ml of ice water and extracted three times with chloroform. The combined organic phases were dried over sodium sulphate, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (hexane-dichloromethane 1:1) afforded the product 6-chloro-2-(4-chloro-phenyl)-chroman-4-one (724 mg).

Step C: 7-Chloro-2-(4-chloro-phenyl)-3,4-dihydro-2H-benzo[f][1,4]oxazepin-5-one

Sodium azide (1.48 g) was added in small portions to a solution of 6-chloro-2-(4-chloro-phenyl)-chroman-4-one (1.67 g) in trifluoroacetic acid (57 ml) at room temperature under

argon atmosphere. After 30 hours 100 ml of water and 100 ml of diethyl ether were added and the phases were separated. The aqueous phase was extracted twice with diethyl ether. The combined organic phases were dried over sodium sulphate, filtered and concentrated under reduced pressure. The oily residue was chromatographed on a silica gel column (hexane-acetone 3:1) giving 1.29 g (73.8%) of the desired product 7-chloro-2-(4-chloro-phenyl)-3,4-dihydro-2H-benzo[f][1,4]oxazepin-5-one along with the side-product 9-chloro-5-(4-chloro-phenyl)-4,5-dihydro-6-oxa-1,2,3,3a-tetraaza-benzo[e]azulene (0.114 g).

Step D: 7-Chloro-2-(4-chloro-phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine

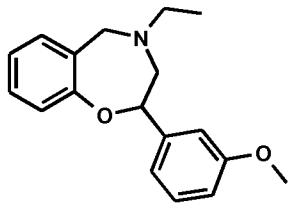
7-Chloro-2-(4-chloro-phenyl)-3,4-dihydro-2H-benzo[f][1,4]oxazepin-5-one (512 mg) was dissolved in 2.5 ml of dry THF. Lithium aluminium hydride (89 mg) was added, and the reaction mixture was stirred 23 hours at room temperature. An additional portion of lithium aluminium hydride (89 mg) was then added to the reaction mixture and stirring was continued at reflux for 7 hours. The reaction mixture was cooled to 0°C and then 2 ml of 30% aqueous KOH was carefully added. The mixture was stirred 17 hours at ambient temperature and filtered. The cake was washed two times with dichloromethane. The combined organic layers were washed with 25 ml of water and the water phase was re-extracted three times with dichloromethane. The organic phases were combined, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The oily residue was chromatographed on a silica gel column (hexane-acetone 5:1) to afford 358 mg of the desired product 7-chloro-2-(4-chloro-phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine. ^{1}H NMR (250 MHz, $CDCl_3$) 3.0 (dd, 1H), 3.2 (dd, 1H), 3.7 (d, 1H), 3.9 (d, 1H), 4.5 (dd, 1H), 6.8 (m, 1H), 7.0 (m, 2H), 7.2-7.3 (m, 4H), 7.4 (s, 1H).

Step E: 7-Chloro 2-(4-chloro-phenyl)-4-methyl-2,3,4,5-tetrahydro-benzo[f][1,4] oxazepine

To a solution of 145 mg of 7-chloro-2-(4-chloro-phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine in 0.89 ml of formic acid was added 0.44 ml of solution of formaldehyde (35%). The mixture was stirred 19 hours at 80°C. Then the reaction mixture was cooled to room temperature and quenched by addition of 20 ml of water and 0.03 ml of concentrated HCl (37%). The mixture was extracted 4 times with dichloromethane. The aqueous phase was treated with sodium hydroxide (until pH of 11 was reached) and extracted twice with dichloromethane. The last two organic phases were combined, dried with sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified on preparative HPLC to yield 109 mg of 7-chloro 2-(4-chloro-phenyl)-4-methyl-2,3,4,5-tetrahydro-benzo[f][1,4] oxazepine.

EXAMPLE E5.1

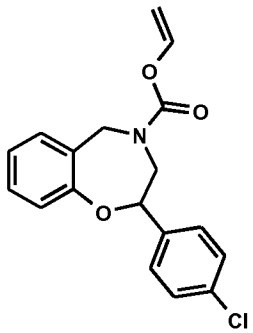
This Example illustrates the preparation of 4-ethyl-2-(3-methoxy-phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



To a stirred solution of 1.48 g of 2-({ethyl-[2-hydroxy-2-(3-methoxy-phenyl)-ethyl]-amino}-methyl)-phenol (prepared from salicaldehyde, ethylamine and 3'-methoxy-phenacyl bromide according to the procedures described in Example E3.1, method C, steps A-C) and 1.93 g of triphenylphosphine in 150 ml of tetrahydrofuran at -10°C was added dropwise a solution of 1.64 g of di-tert-butyl-azodicarboxylate in 10 ml of tetrahydrofuran. The solution was stirred at room temperature for 15 hours, then concentrated *in vacuo*. The residue was dissolved in dichloromethane and treated with 4.5 ml of trifluoroacetic acid for 1 hour. The reaction mixture was basified with 2M sodium hydroxide, the organic layer was separated, dried over sodium sulphate and concentrated *in vacuo*. The residue was subjected to column chromatography (cyclohexane:ethyl acetate 8:2) to yield 55 mg of 4-ethyl-2-(3-methoxy-phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine as a colorless resin. ^{1}H NMR (400 MHz, $CDCl_3$) 1.1 (t, 3H), 2.6 (m, 2H), 3.0 (m, 2H), 3.7 and 4.1 (d, 2H), 3.8 (s, 3H), 4.8 (d, 1H), 6.8-7.3 (m, 8H); MS (ES+) 284 (MH^+).

EXAMPLE E6.1

This Example illustrates the preparation of 2-(4-chloro-phenyl)-2,3-dihydro-5H-benzo[f][1,4]oxazepine-4-carboxylic acid vinyl ester.



METHOD A:

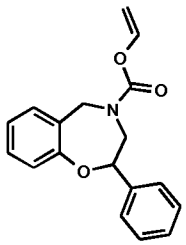
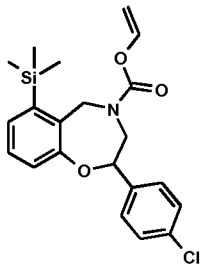
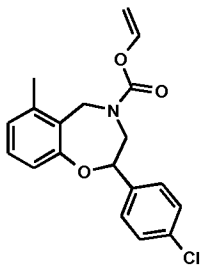
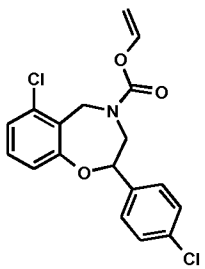
To a solution of 150 mg of 2-(4-chloro-phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4] oxazepine (Example E7.1) in 2 ml of dichloromethane was added 459 mg of sodium carbonate and 0.053 ml of vinyl chloroformate. The reaction mixture was stirred 24 hours at room temperature, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC (column: MerckNW25) to yield 108 mg of 2-(4-chloro-phenyl)-2,3-dihydro-5H-benzo[f][1,4]oxazepine-4-carboxylic acid vinyl ester.

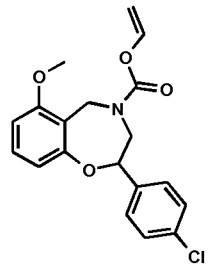
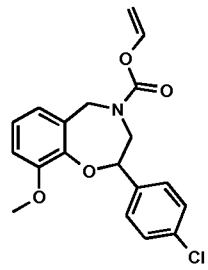
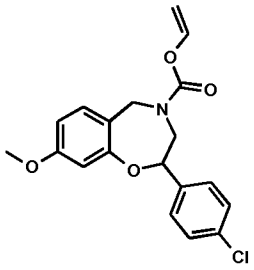
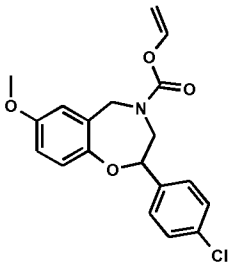
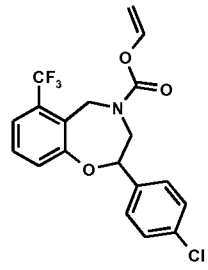
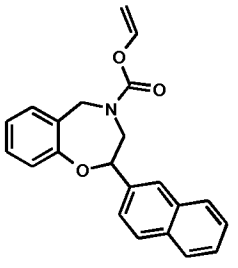
METHOD B:

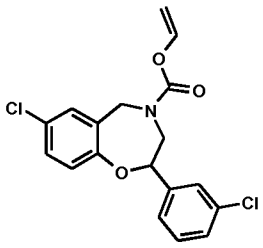
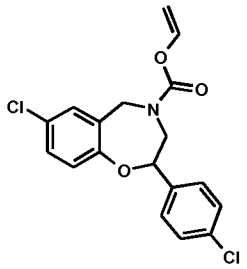
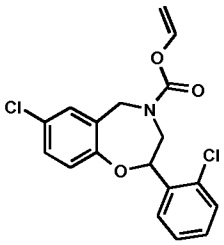
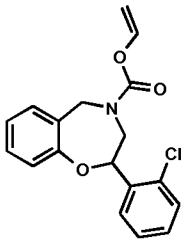
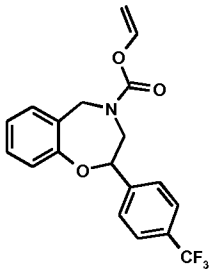
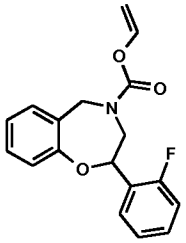
To a solution of 1.26 g of 2-(4-chloro-phenyl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4] oxazepine (Example E3.1) in 15 ml of THF was added 1.2 ml of vinyl chloroformate and the

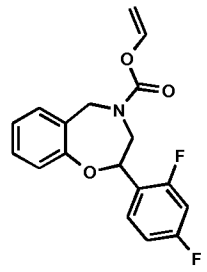
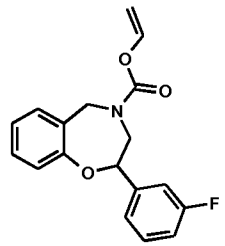
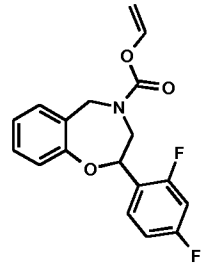
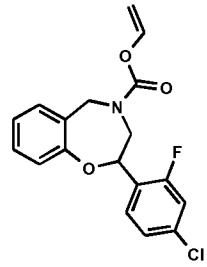
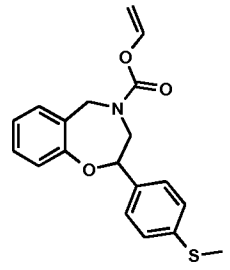
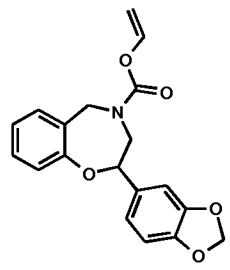
mixture was stirred 45 minutes at room temperature and 21 hours at 67°C. The reaction mixture was cooled to room temperature. Then 80 ml of ethyl acetate and 80 ml of a saturated solution of sodium hydrogen carbonate were added. The phases were separated and aqueous phase was extracted was extracted 2 times with ethyl acetate. The combined organic phases were dried with sodium sulphate, filtered and concentrated *in vacuo*. The residue was subjected to column chromatography (hexane:ethyl acetate 4:1) to yield 1.38 g of 2-(4-chloro-phenyl)-2,3-dihydro-5H-benzo[f][1,4]oxazepine-4-carboxylic acid vinyl ester. ^{1}H NMR (500 MHz, $CDCl_3$) 3.2-3.6 (m, 1H), 4.3-4.5 (m, 3H), 4.7-5.0 (m, 3H), 7.1-7.5 (m, 9H); MS (ES+) 330/332 (MH^+).

The following compounds were prepared according to procedures analogous to those described in Example E6.1:

Cpd n°	Structure	MH^+	1H NMR	M.p (°C)
E6.2		296		
E6.3		402/404		
E6.4		274/276		123-124°C
E6.5		364, 252/254		129°C

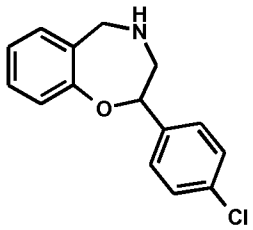
E6.6		360/362		
E6.7		360/362		
E6.8		360/362		
E6.9		360/362		
E6.10		398/400		99°C
E6.11		346		105°C

E6.12			250 MHz, $CDCl_3$: 3.2-3.5 (m, 1H), 4.1-4.5 (m, 3H), 4.6-4.9 (m, 3H), 6.8-7.0 (m, 1H), 7.0-7.5 (m, 7H).	
E6.13			250 MHz, $CDCl_3$: 3.1-3.5 (m, 1H), 4.1-4.5 (m, 3H), 4.6-4.9 (m, 3H), 6.8-7.0 (m, 1H), 7.0-7.5 (m, 7H).	
E6.14			250 MHz, $CDCl_3$: 3.0-3.3 (m, 1H), 4.1-4.5 (m, 3H), 4.5-4.8 (m, 2H), 4.8-5.1 (m, 1H), 6.8-6.9 (m, 1H), 6.9-7.4 (m, 6H), 7.4-7.7 (m, 1H).	
E6.15		339/332	400 MHz, $CDCl_3$: 3.3-3.4 (m, 1H), 4.3-4.6 (m, 3H), 4.7-4.9 (m, 2H), 5.0-5.2 (m, 1H), 7.0-7.4 (m, 8H), 7.7-7.8 (m, 1H).	
E6.16			400 MHz, $CDCl_3$: 3.4-3.7 (m, 1H), 4.4-4.6 (m, 3H), 4.8-5.1 (m, 3H), 7.1-7.5 (m, 5H), 7.6-7.9 (m, 4H).	
E6.17		314	400 MHz, $CDCl_3$: 3.4-3.6 (m, 1H), 4.3-4.6 (m, 3H), 4.7-5.0 (m, 2H), 5.1 (d, 1H), 7.0-7.4 (m, 8H), 7.6-7.8 (m, 1H).	

E6.18		332	400 MHz, $CDCl_3$: 3.4-3.6 (m, 1H), 4.3-4.6 (m, 3H), 4.7-5.0 (m, 2H), 5.0 (d, 1H), 6.8-7.4 (m, 7H), 7.5-7.8 (m, 1H).	96-97°C
E6.19		314	300 MHz, $CDCl_3$: 3.3-3.6 (m, 1H), 4.3-4.6 (m, 3H), 4.7-5.0 (m, 3H), 7.0-7.5 (m, 9H).	
E6.20		332	400 MHz, $CDCl_3$: 3.9-4.1 (m, 1H), 4.3-4.6 (m, 3H), 4.7-5.0 (m, 2H), 5.1 (d, 1H), 6.9-7.4 (m, 8H).	
E6.21		348/350	400 MHz, $CDCl_3$: 3.3-3.5 (m, 1H), 4.2-4.5 (m, 3H), 4.6-5.0 (m, 3H), 6.9-7.3 (m, 7H), 7.4-7.6 (m, 1H).	
E6.22		342	400 MHz, $CDCl_3$: 2.5 (2s, 3H), 3.3-3.6 (m, 1H), 4.3-4.6 (m, 3H), 4.7-5.0 (m, 3H), 7.0-7.5 (m, 9H).	
E6.23		340	400 MHz, $CDCl_3$: 3.3-3.6 (m, 1H), 4.4-4.6 (m, 3H), 4.6-5.0 (m, 3H), 6.0 (2s, 3H), 6.8-7.4 (m, 8H).	

EXAMPLE E7.1

This Example illustrates the preparation of 2-(4-chloro-phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



METHOD A:

2-(4-chloro-phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine can be prepared as described in Example E3.1, Method A (steps A-D) or a variant thereof.

METHOD B:

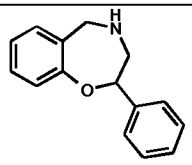
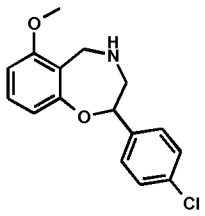
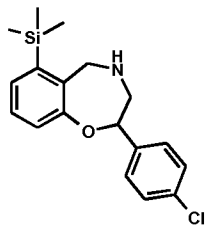
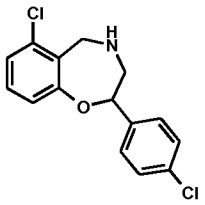
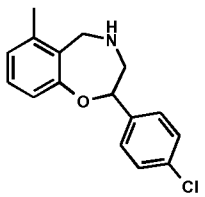
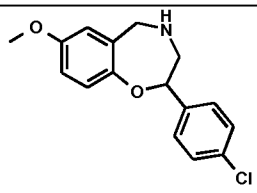
To a solution of 1.36 g of 2-(4-chloro-phenyl)-2,3-dihydro-5H-benzo[f][1,4] oxazepine-4-carboxylic acid vinyl ester (Example E6.1) in 20 ml of methanol was added 2.5 ml of concentrated HCl (37%) and the mixture was stirred 6.5 hours at 68°C. The reaction mixture was cooled to room temperature. Then 80 ml of ethyl acetate and 80 ml of a saturated aqueous solution of sodium hydrogen carbonate was added. The phases were separated and aqueous phase was extracted 2 times with ethyl acetate. The combined organic phases were dried with sodium sulphate, filtered and concentrated *in vacuo*. The residue was subjected to column chromatography (hexane:acetone 3:1) to yield 766 mg (m.p. 108-111°C) of 2-(4-chloro-phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine. ^{1}H NMR (250 MHz, $CDCl_3$) 3.1 (dd, 1H), 3.2 (dd, 1H), 3.9 (d, 1H), 4.1 (d, 1H), 4.6 (dd, 1H), 7.0 (d, 2H), 7.1 (d, 2H), 7.3 (s, 4H); MS (ES+) 260/262 (MH^+).

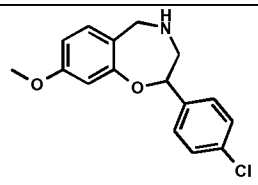
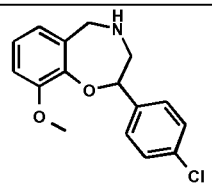
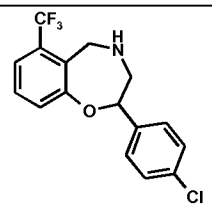
METHOD C:

To a solution of 1.26 g of 2-fluorobenzylamine in 50 ml acetonitrile were added 2.07 g of potassium carbonate and 2.33 g of 4'-chlorophenacyl bromide and the resulting mixture was stirred at room temperature for 3 hours, diluted with water then extracted with ethyl acetate. The organic layer was dried over sodium sulphate and concentrated *in vacuo* to afford crude 1-(4-chloro-phenyl)-2-(2-fluoro-benzylamino)-ethanone. The residue was dissolved in 100 ml methanol and 0.74 g of sodium borohydride was added portionwise over 2 hours. After 1 hour stirring, the solvent was removed *in vacuo*, the residue dissolved in ethyl acetate, washed with water, dried over sodium sulphate then concentrated *in vacuo*. The residue was subjected to column chromatography (ethyl acetate) to yield 1.2 g of 1-(4-chlorophenyl)-2-(2-fluoro-benzylamino)-ethanol as a white solid; M.p. 115-117°C. 307 mg of this compound was dissolved in 10 ml dimethylacetamide and treated with 90 mg of sodium hydride at 65°C for 12 hours. The reaction mixture was cooled to room temperature, poured into water and extracted with diethyl ether; the organic layer was washed with water and brine then dried over sodium sulphate and concentrated *in vacuo*. The residue was subjected to column

chromatography (ethyl acetate) to yield 270 mg of 2-(4-chloro-phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine as a yellow solid. M.p. 105-107°C.

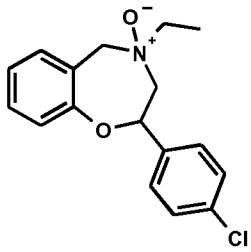
The following compounds were prepared according to procedures analogous to those described in Example E7.1:

Cpd n°	Structure	MH^+	1H NMR	M.p (°C)
E7.2		226		
E7.3		290/292		
E7.4		332		
E7.5		294/296	$CDCl_3$: 1.6 (br s, NH), 3.15 (dd, 1H), 3.4 (dd, 1H), 3.9 (d, 1H), 4.1 (d, 1H), 4.6 (dd, 1H), 6.9 (t, 1H), 7.0 (d, 1H), 7.2 (d, 1H), 7.3 (d, 2H), 7.4 (d, 2H)	
E7.6		274/276	$CDCl_3$: 2.1 (s, 3H), 3.1 (dd, 1H), 3.3 (dd, 1H), 3.85 (d, 1H), 4.05 (d, 1H), 4.5 (dd, 1H), 6.85 (t, 1H), 6.95 (d, 1H), 7.0 (d, 1H), 7.3 (s, 4H)	77°C
E7.7		290/292		98°C

E7.8		290/292		
E7.9		290/292		
E7.10		328/330		64°C

EXAMPLE E8.1

This Example illustrates the preparation of 2-(4-Chloro-phenyl)-4-ethyl-2,3-dihydro-5H-benzo[f][1,4]oxazepine 4-oxide.

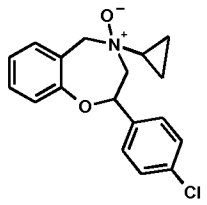
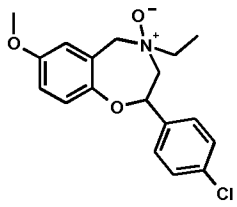
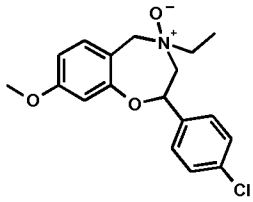
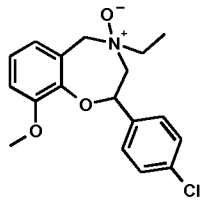
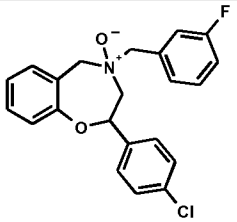
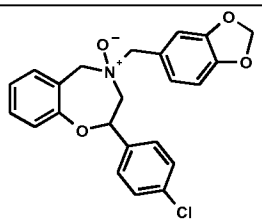
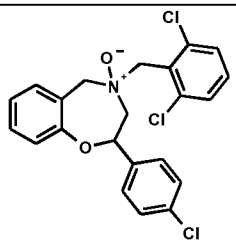


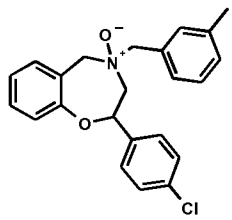
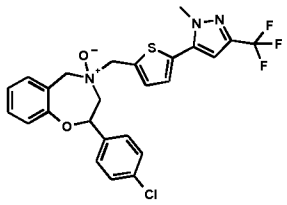
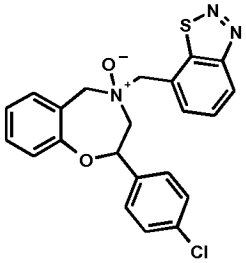
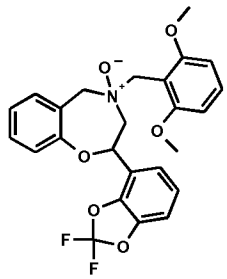
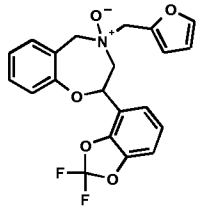
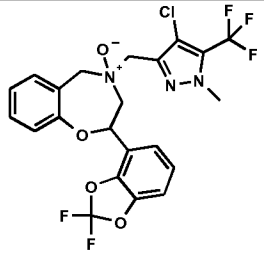
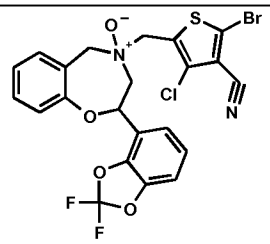
To a solution of 83 mg of 2-(4-chloro-phenyl)-4-ethyl-2,3-dihydro-5H-benzo[f][1,4]oxazepine (Example E3.1) in 5 ml of dichloromethane was added 78 mg of 3-chloro-perbenzoic acid and the mixture was stirred 6 hours at room temperature.

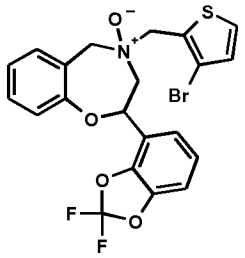
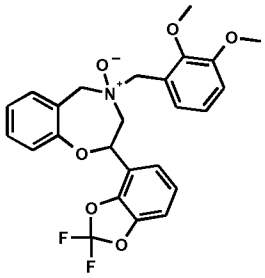
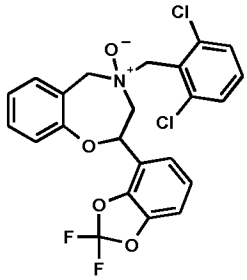
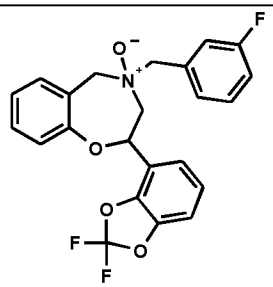
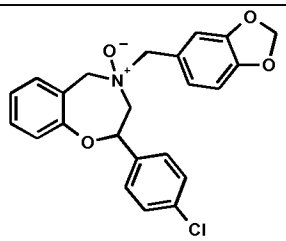
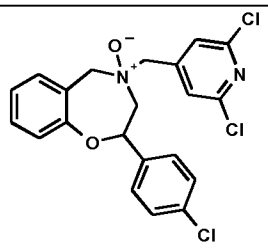
Then 10 ml of ethyl acetate and 10 ml of a saturated aqueous solution of sodium hydrogen carbonate were added. The phases were separated and aqueous phase was extracted was extracted with ethyl acetate. The combined organic phases were washed with water, dried with sodium sulphate, filtered and concentrated *in vacuo*. The residue was subjected to column chromatography (hexane: ethyl acetate 3:1) to yield 18 mg of 2-(4-chloro-phenyl)-4-ethyl-2,3-dihydro-5H-benzo[f][1,4]oxazepine 4-oxide. ^{1}H NMR (250 MHz, $CDCl_3$) 1.4 (t, 3H), 3.0-3.3 (m, 2H), 3.6-4.0 (m, 2H), 4.2-4.4 (m, 1H), 4.7-4.9 (m, 2H), 6.9-7.4 (m, 8H).

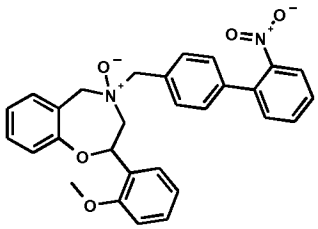
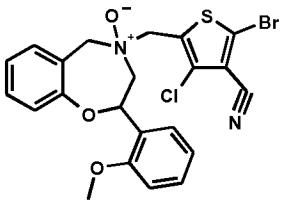
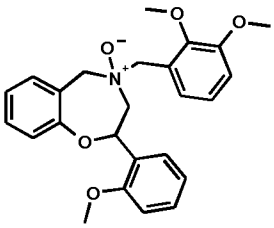
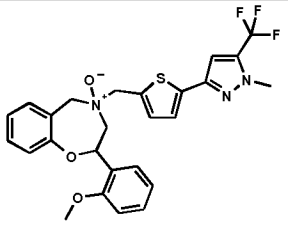
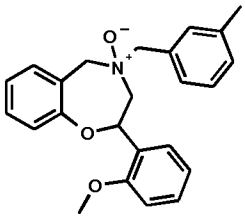
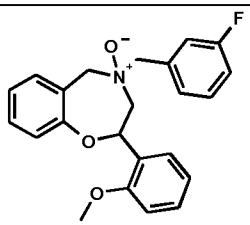
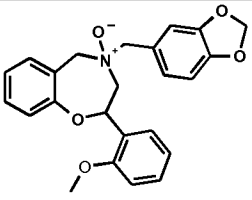
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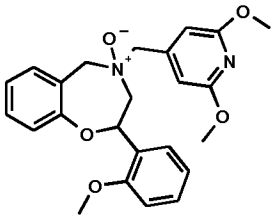
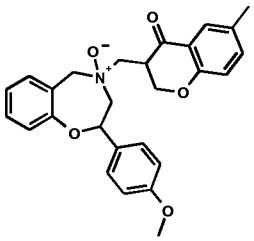
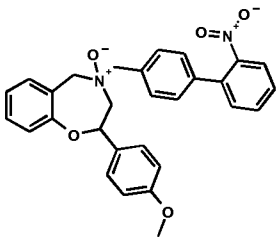
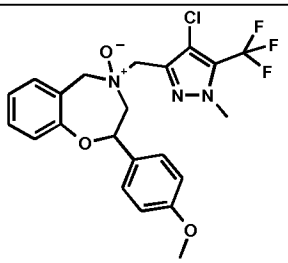
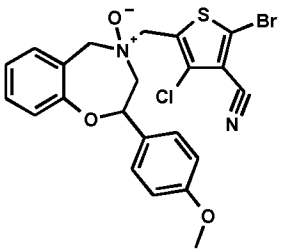
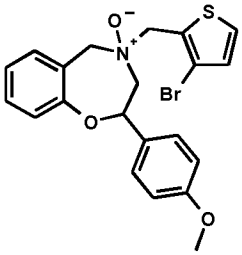
Compound	Structure	MH^+	M.p (°C)

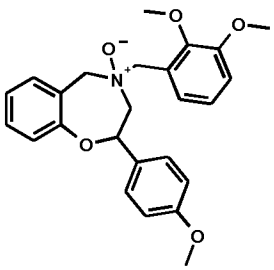
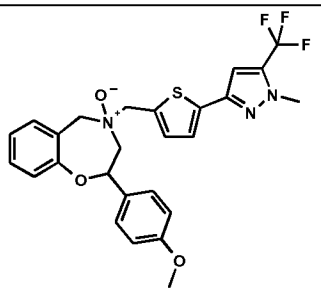
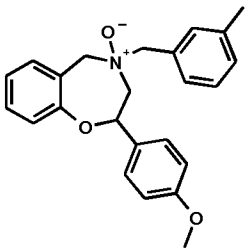
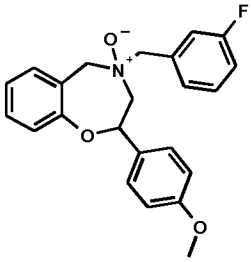
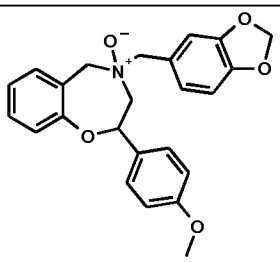
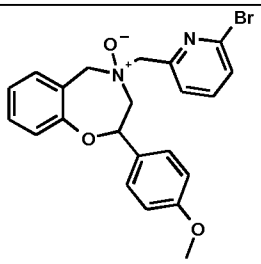
E8.2		316/318	135-137°C
E8.3		334/336	160°C
E8.4		334/336	
E8.5		334/336	66°C
E8.6		384	
E8.7		410	
E8.8		434	

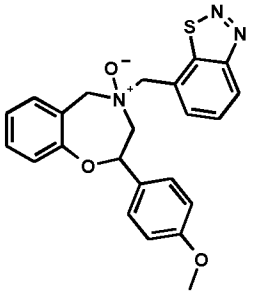
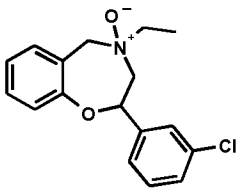
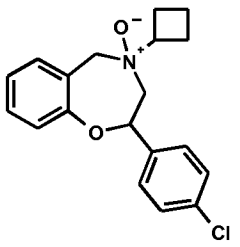
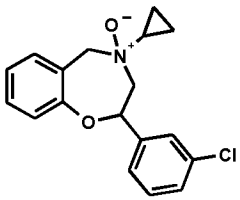
E8.9		380	
E8.10		520	
E8.11		424	
E8.12		472	
E8.13		402	
E8.14		518	
E8.15		555	

E8.16		496	
E8.17		472	
E8.18		480	
E8.19		364	
E8.20		456	
E8.21		481	

E8.22		483	
E8.23		505	
E8.24		422	
E8.25		516	
E8.26		376	
E8.27		380	
E8.28		406	

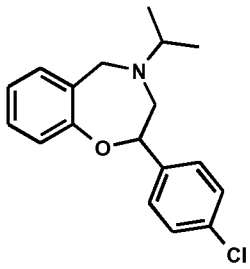
E8.29		423	
E8.30		444	
E8.31		483	
E8.32		468	
E8.33		456	
E8.34		446	

E8.35		422	
E8.36		516	
E8.37		376	
E8.38		380	
E8.39		406	
E8.40		441	

E8.41		420	
E8.42		330	
E8.43		330	
E8.44		316	

EXAMPLE E9.1

This Example illustrates the preparation of 4-isopropyl-2-(4-chloro-phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.

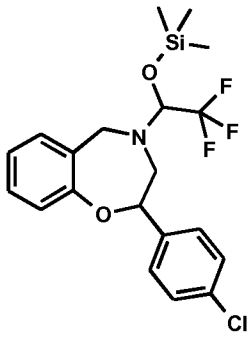


0.44 ml of acetone was added to a solution of 518 mg of 2-(4-chloro-phenyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (Example E7.1) and 138 mg of sodium cyanoborohydride in 10 ml of methanol (at pH 6, by addition of a few drops of acetic acid) at 0°C; the resulting mixture was stirred at room temperature for 2 hours. Water was added, and then solid sodium carbonate until pH 9-10, the mixture was extracted with dichloromethane, the organic layers dried over sodium sulphate and concentrated *in vacuo*. The residue was subjected to column chromatography (cyclohexane: ethyl acetate 9:1) to yield 500 mg of 4-isopropyl-2-(4-chloro-

phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine as a white solid. M.p. 85°C; ^{1}H NMR (400 MHz, $CDCl_3$) 1.1 and 1.2 (2 d, 6H), 2.9 (m, 2H), 3.1 (d, 1H), 3.2 (d, 1H), 3.8 and 3.9 (d, 2H), 4.9 (d, 1H), 7.0-7.4 (m, 8H); MS (ES+) 302/304 (MH^+).

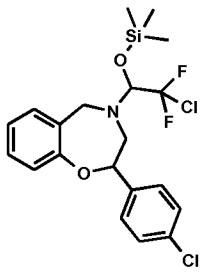
EXAMPLE E10.1

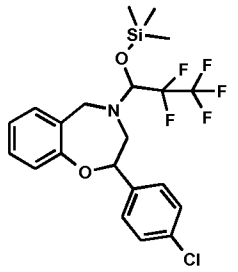
This Example illustrates the preparation of 2-(4-chloro-phenyl)-4-(2,2,2-trifluoro-1-trimethylsilanyloxy-ethyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



To a solution of 935 mg of 2-(4-chloro-phenyl)-2,3,4,5-tetrahydrobenzo [f][1,4]oxazepine (Example E7.1) in 15 ml of dichloromethane was added 3 g of 4Å molecular sieves then 0.49 ml of trifluoroacetaldehyde ethyl hemiacetal and the resulting mixture was stirred at room temperature for 24 hours. The brown suspension was filtered, the filtrate washed with 5% aqueous sodium bicarbonate, the organic layers dried over sodium sulphate and concentrated *in vacuo*. The residue was dissolved in 10 ml of tetrahydrofuran and 0.56 ml of trimethylsilylimidazole was added then the mixture was stirred overnight at room temperature. The solution was diluted with diethyl ether, washed with 5% aqueous sodium bicarbonate, the organic layer separated, dried over sodium sulphate and concentrated *in vacuo*. The residue was subjected to column chromatography (cyclohexane:ethyl acetate 9:1) to yield 796 mg of 2-(4-chloro-phenyl)-4-(2,2,2-trifluoro-1-trimethylsilanyloxy-ethyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine as a colorless oil. Mixture of diastereoisomers; MS (ES+) 430/432 (MH^+), 340/342 (M-OTMS).

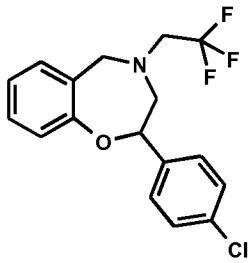
The following compounds were prepared according to procedures analogous to those described in Example E10.1:

Cpd n°	Structure	MH^+
E10.2		446/448, 356/358 (-OTMS)
E10.3		480/482, 390/392 (-OTMS)

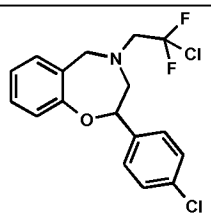
EXAMPLE E11.1

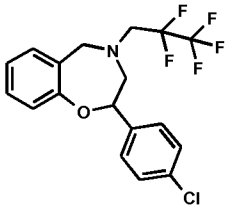
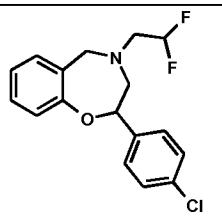
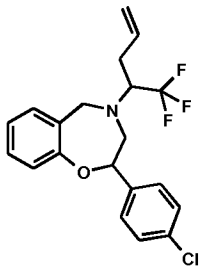
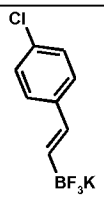
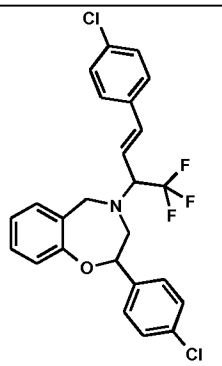
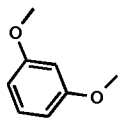
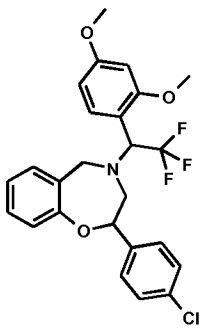
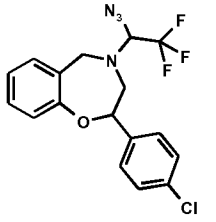
This Example illustrates the preparation of 2-(4-chloro-phenyl)-4-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine



To a solution of 685 mg of 2-(4-chloro-phenyl)-4-(2,2,2-trifluoro-1-trimethylsilanyloxy-ethyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine (Example E10.1) in 25 ml of dichloromethane was added 0.6 ml of triethylsilane then 0.25 ml of borontrifluoride etherate and the solution was stirred for 1 hour at room temperature. The reaction mixture was quenched by addition of sodium hydroxide 2N then extracted with diethyl ether; the organic layer was dried over sodium sulphate and concentrated *in vacuo*. The residue was subjected to column chromatography (cyclohexane:ethyl acetate 9:1) to yield 203 mg of 2-(4-chloro-phenyl)-4-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 3.0 (m, 2H), 3.2 (d, 1H), 3.3 (dd, 1H), 3.8 and 4.2 (d, 2H), 4.7 (d, 1H), 6.9-7.3 (m, 8H); MS (ES+) 342/344 (MH^+).

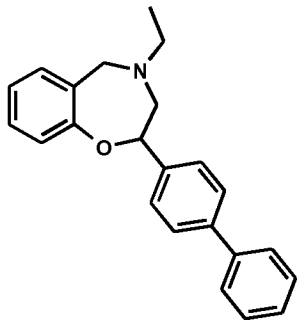
The following compounds were prepared according to procedures analogous to those described in Example E11.1:

Cpd n°	Reagent (T°C)	Compound Structure	MH^+	1H NMR
E11.2	Et_3SiH (RT)		358/360	$CDCl_3$: 3.0-3.4 (m, 4H), 3.8 and 4.2 (d, 2H), 4.7 (d, 1H), 6.9-7.3 (m, 8H)

E11.3	Et_3SiH (RT)		392/394	$CDCl_3$: 2.9-3.4 (m, 4H), 3.7 and 4.2 (d, 2H), 4.7 (d, 1H), 6.9-7.3 (m, 8H)
E11.4	Et_3SiH (RT)		324/326	$CDCl_3$: 2.9 (m, 2H), 3.1 (d, 1H), 3.2 (dd, 1H), 3.7 and 4.2 (d, 2H), 4.7 (d, 1H), 5.8 (tt, 1H), 6.9-7.3 (m, 8H)
E11.5	$allylSiMe_3$ (RT)		382/384	
E11.6	 (RT)		478/480	
E11.7	 (50°C)		478/480	$CDCl_3$:
E11.8	$TMSN_3$ (RT)		383/385	$CDCl_3$:

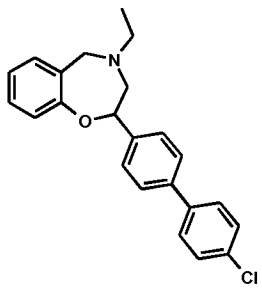
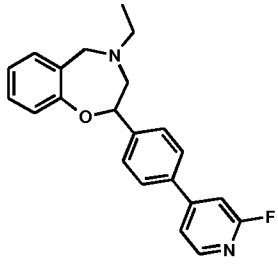
EXAMPLE E12.1

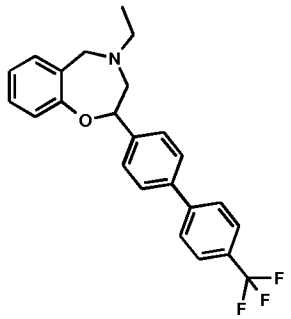
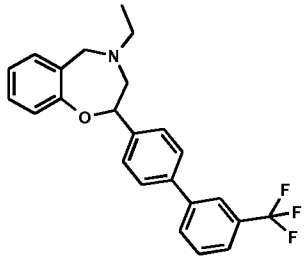
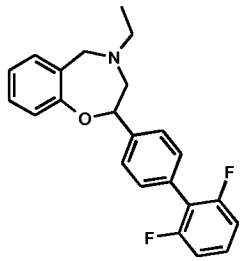
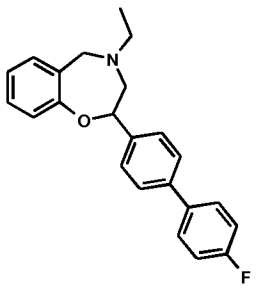
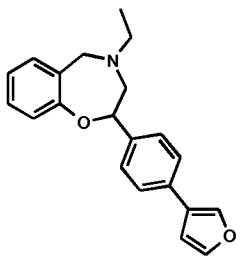
This Example illustrates the preparation of 2-biphenyl-4-yl-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.

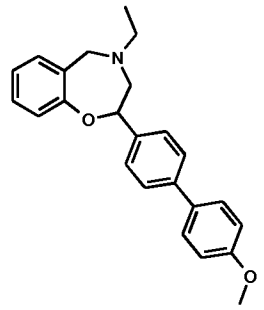
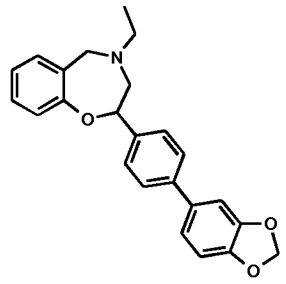
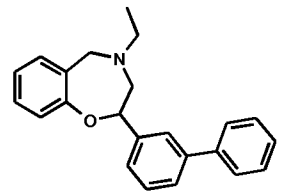
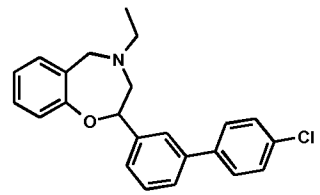


A dried, nitrogen-flushed flask was charged with 200 mg of 2-(4-bromo-phenyl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine (Example E3.6), 110 mg of phenyl boronic acid, 249 mg of potassium carbonate and 49 mg of $PdCl_2$(dppf); 10 ml of dimethylformamide were added and the resulting mixture was heated at 80°C for 24 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate, wahed with water and brine, the organic layers were dried over sodium sulphate and concentrated *in vacuo*. The residue was subjected to silica gel chromatography (ethyl acetate:cyclohexane 4:6) to afford 179 mg of 2-biphenyl-4-yl-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine as a white solid. M.p. 69-70°C; ^{1}H NMR (400 MHz, $CDCl_3$) 1.1 (t, 3H), 2.6 (m, 2H), 3.1 (d, 2H), 3.8 and 4.1 (d, 2H), 4.9 (d, 1H), 6.9-7.6 (m, 13H); MS (ES+) 330/331 (MH^+).

The following compounds were prepared according to procedures analogous to those described in Example E12.1:

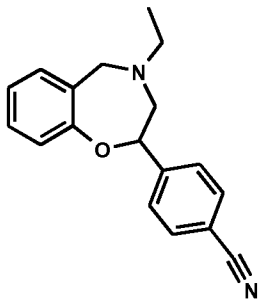
Cpd n°	Structure	MH^+	1H NMR	M.p (°C)
E12.2		364/366		92-93°C
E12.3		349		90-91°C

E12.4		398		89-90°C
E12.5		398		
E12.6		366		
E12.7		348		99-100°C
E12.8		320		82-83°C

E12.9		360		138-139°C
E12.10		374		103-104°C
E12.11		330	$CDCl_3$: 1.1 (t, 3H), 2.6 (m, 2H), 3.2 (m, 2H), 3.1 (d, 1H), 3.8 and 4.1 (d, 2H), 4.9 (dd, 1H), 7.0-7.7 (m, 13H)	
E12.12		364/366	$CDCl_3$: 1.1 (t, 3H), 2.6 (m, 2H), 3.2 (m, 2H), 3.1 (d, 1H), 3.8 and 4.1 (d, 2H), 4.9 (dd, 1H), 7.0-7.5 (m, 12H)	

EXAMPLE E13.1

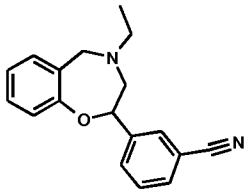
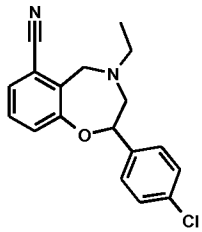
This Example illustrates the preparation of 4-(4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin-2-yl)-benzonitrile.



A dried, nitrogen-flushed flask was charged with 200 mg of 2-(4-bromo-phenyl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine (Example E3.6), 42.1 mg of zinc(II) cyanide, 11 mg of tris(dibenzylideneacetone)-dipalladium, 13 mg of diphenylphosphinoferrocene (dppf) and 5 mg of zinc powder; 10 ml of dimethylacetamide were added and the resulting mixture

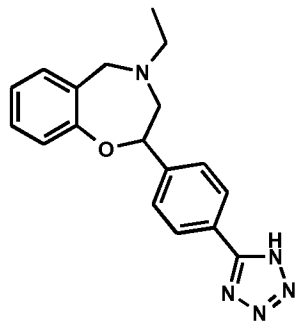
was heated at 120°C for 2 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate, washed with water and brine, the organic layers were dried over sodium sulphate and concentrated *in vacuo*. The residue was subjected to silica gel chromatography (ethyl acetate:cyclohexane 1:1) to afford 155 mg of 4-(4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin-2-yl)-benzonitrile as a yellow crystals. M.p. 92-93°C; ^{1}H NMR (400 MHz, $CDCl_3$) 1.1 (t, 3H), 2.6 (m, 2H), 3.0 (dd, 1H), 3.1 (d, 1H), 3.8 and 4.1 (d, 2H), 4.8 (d, 1H), 6.9-7.0 (m, 2H), 7.1 (d, 2H), 7.4 (d, 2H), 7.6 (d, 1H); MS (ES+) 279 (MH^+).

The following compounds were prepared according to procedures analogous to those described in Example E13.1:

Cpd n°	Structure	MH^+	1H NMR
E13.2		279	$CDCl_3$: 1.1 (t, 3H), 2.6 (m, 2H), 3.0 (dd, 1H), 3.1 (d, 1H), 3.75 and 4.05 (d, 2H), 4.9 (d, 1H), 7.0-7.7 (m, 8H)
E13.3		313/315	$CDCl_3$: 1.1 (t, 2H), 2.6 (m, 2H), 3.1 (dd, 1H); 3.2 (d, 1H); 3.8 (d, 1H); 4.0 (d, 1H); 5.0 (d, 1H); 7.0 (t, 1H), 7.2-7.5 (m, 6H)

EXAMPLE E14.1

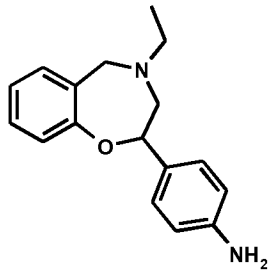
This Example illustrates the preparation of 4-ethyl-2-[4-(1H-tetrazol-5-yl)-phenyl]-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



A mixture of 140 mg of 4-(4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin-2-yl)-benzonitrile (Example E13.1), 89 mg of triethylamine hydrochloride and 43 mg of sodium azide in 10 ml of toluene was stirred at 95°C for 18 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, extracted with water (3x15 ml). The aqueous layers were basified with NaOH, the solution was saturated with sodium chloride and extracted with ethyl acetate to afford 65 mg of 4-ethyl-2-[4-(1H-tetrazol-5-yl)-phenyl]-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine as a yellow solid. M.p. 155°C; MS (ES+) 322 (MH^+).

EXAMPLE E15.1

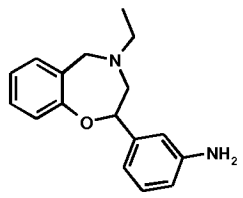
This Example illustrates the preparation of 4-(4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin-2-yl)-phenylamine.



200 mg of 2-(4-bromo-phenyl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine (Example E3.6), 2.5 mg of 2-dicyclohexylphosphinobiphenyl and 2.8 mg of tris-(dibenzylideneacetone)-dipalladium were charged in a dried, nitrogen-flushed flask. 0.72 ml of a lithium hexamethyldisalazane solution (1M in THF) and 2 ml of tetrahydrofuran were added and the resulting mixture was heated at 65°C overnight. After cooling to room temperature, the reaction mixture was quenched by addition of 3 ml 1M HCl, basified with diluted aqueous sodium hydroxide, extracted with dichloromethane. The organic layers were dried over sodium sulphate and concentrated *in vacuo*. The residue was subjected to silica gel chromatography (ethyl acetate with 1% triethylamine) to afford 140 mg of 4-(4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin-2-yl)-phenylamine as a yellow resin. ^1H NMR (400 MHz, $CDCl_3$) 1.1 (t, 3H), 2.55 (m, 2H), 3.1 (d, 2H), 3.6 (brs, 2H), 3.7 and 4.0 (d, 2H), 4.7 (t, 1H), 6.6-7.2 (m, 8H); MS (ES+) 269 (MH^+).

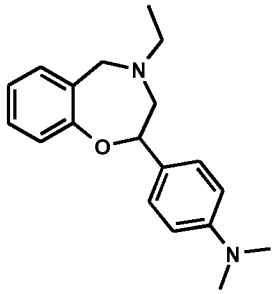
The following compounds were prepared according to procedures analogous to those described in Example E15.1:

Compound	Structure	MH^+	1H NMR	M.p (°C)

E15.2		269	$CDCl_3$: 1.1 (t, 3H), 2.55 (m, 2H), 3.1 (m 2H), 3.6 (brs, 2H), 3.7 and 4.0 (d, 2H), 4.7 (dd, 1H), 6.6-7.1(m, 8H)	

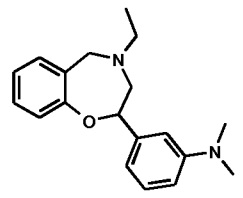
EXAMPLE E16.1

This Example illustrates the preparation of [4-(4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin-2-yl)-phenyl]-dimethyl-amine.



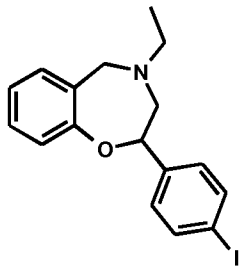
To a solution of 330 mg of 4-(4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin-2-yl)-phenylamine (Example E17.1) in 50 ml of acetonitrile were added 1.2 ml of 30% aqueous formaldehyde and 343 mg of sodium cyanoborohydride. The reaction mixture was stirred overnight at room temperature, basified with 25% aqueous ammonia and extracted with ethyl acetate; the organic layer was washed with brine, dried over sodium sulphate and concentrated *in vacuo*. The residue was subjected to silica gel chromatography (ethyl acetate:cyclohexane 1:1) to afford 252 mg of [4-(4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin-2-yl)-phenyl]-dimethyl-amine as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) 1.1 (t, 3H), 2.6 (m, 2H), 2.9 (s, 6H), 3.1 (d, 2H), 3.8 and 4.1 (d, 2H), 4.8 (dd, 1H), 6.6-7.3 (m, 8H; MS (ES+) 297 (MH^+).

The following compounds were prepared according to procedures analogous to those described in Example E16.1:

Cpd n°	Structure	MH^+	1H NMR	M.p (°C)
E16.2		297	$CDCl_3$: 1.1 (t, 3H), 2.6 (m, 2H), 2.9 (s, 3H), 3.2 (m, 2H), 3.1 (d, 1H), 3.8 and 4.1 (d, 2H), 4.8 (dd, 1H), 6.6-7.2 (m, 8H)	

EXAMPLE E17.1

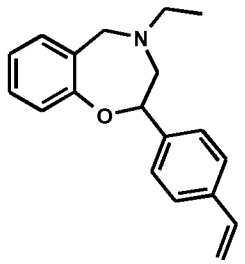
This Example illustrates the preparation of 4-ethyl-2-(4-iodo-phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



A dried, nitrogen-flushed flask was charge with 400 mg of 2-(4-bromo-phenyl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine (Example E3.6), 360 mg of sodium iodide, 11.4 mg of copper(I) iodide and 17 mg of *trans*-1,2-diaminocyclohexane; 20 ml of dioxin was added and the resulting mixture was heated at 110°C for 24 hours. After cooling to room temperature, the reaction mixture was diluted with 30% aqueous ammonia, poured into 20 ml water and extracted three times with dichloromethane. The organic layers were dried over sodium sulphate and concentrated *in vacuo*. The residue was crystallized from ethyl acetate to afford 395 mg of 4-ethyl-2-(4-iodo-phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine as a white solid. M.p. 147°C; ^{1}H NMR (400 MHz, $CDCl_3$) 1.2 (t, 3H), 2.6 (m, 2H), 3.2 (m, 2H), 3.8 and 4.1 (d, 2H), 4.9 (dd, 1H), 7.0-7.7 (m, 8H); MS (ES+) 380 (MH^+).

EXAMPLE E18.1

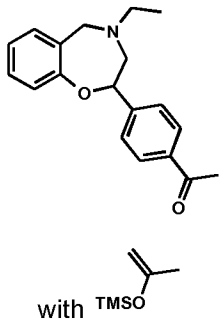
This Example illustrates the preparation of 4-ethyl-2-(4-vinyl-phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine



A dried, nitrogen-flushed flask was charged with 200 mg of 2-(4-bromo-phenyl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine (Example E3.6), 0.19 ml of vinyltributylstannane and 21 mg of palladium tetrakis(triphenylphosphine); 10 ml of toluene were added and the resulting mixture was heated at 110°C for 4 hours. The solvent was removed *in vacuo*, the residue treated for one hour in a biphasic mixture (ethyl acetate / 2N sodium hydroxide), the organic layer was separated, dried over sodium sulphate and concentrated *in vacuo*. The residue was subjected to silica gel chromatography (ethyl acetate:cyclohexane 3:7) to afford 110 mg of 4-ethyl-2-(4-vinyl-phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 1.2 (t, 3H), 2.7 (m, 2H),

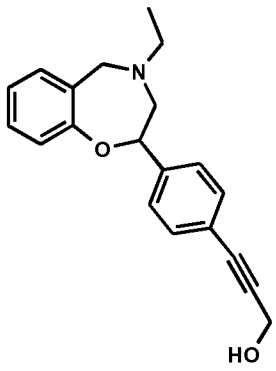
3.2 (d, 2H), 3.8 and 4.2 (d, 2H), 4.9 (dd, 1H), 5.3 (d, 1H), 5.8 (d, 1H), 6.7 (dd, 1H), 7.0-7.5 (m, 8H); MS (ES+) 280 (MH^+).

The following compounds were prepared according to procedures analogous to those described in Example E18.1:

Cpd n°	Compound Structure	MH^+	1H NMR	M.p (°C)
E18.2	 with	296	$CDCl_3$: 1.2 (t, 3H), 2.5 (s, 3H), 2.6 (m, 2H), 3.1 (m, 2H), 3.8 and 4.1 (d, 2H), 4.9 (dd, 1H), 6.9 (m, 2H), 7.1 (m, 2H), 7.4 (d, 2H), 7.9 (d, 2H)	

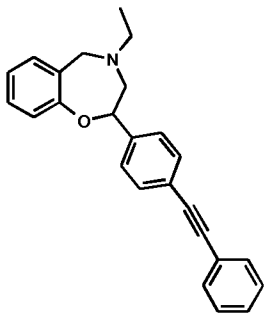
EXAMPLE E19.1

This Example illustrates the preparation of 3-[4-(4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin-2-yl)-phenyl]-prop-2-yn-1-ol.



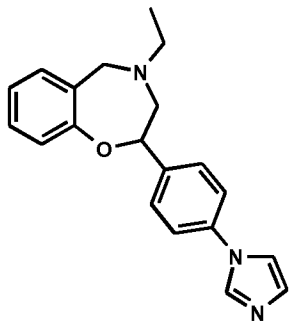
A dried, nitrogen-flushed flask was charged with 200 mg of 2-(4-bromo-phenyl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine (Example E3.6), 0.05 ml of propargyl alcohol, 4.5 mg of copper(I) iodide, 8.4 mg of bis(triphenyphosphine)-dichloropalladium and 0.1 ml of piperidine; 10 ml of dimethylformamide were added and the resulting mixture was heated at 80°C for 24 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over sodium sulphate and concentrated *in vacuo*. The residue was subjected to silica gel chromatography (ethyl acetate:cyclohexane 3:7) to afford 22 mg of 3-[4-(4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin-2-yl)-phenyl]-prop-2-yn-1-ol as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) 1.1 (t, 3H), 2.6 (m, 2H), 3.1 (m, 2H), 3.8 and 4.1 (d, 2H), 4.4 (s, 2H), 4.8 (dd, 1H), 7.0-7.43 (m, 8H); MS (ES+) 308 (MH^+).

The following compounds were prepared according to procedures analogous to those described in Example E19.1:

Cpd n°	Structure	MH^+	1H NMR	M.p (°C)
E19.2		354	$CDCl_3$: 1.1 (t, 3H), 2.7 (m, 2H), 3.1 (m, 2H), 3.8 and 4.1 (d, 2H), 4.4 (s, 2H), 5.0 (dd, 1H), 7.0-7.63 (m, 13H)	

EXAMPLE E20.1

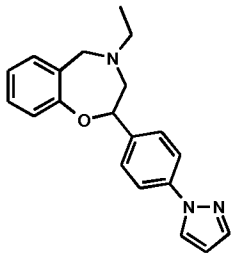
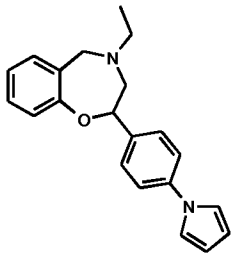
This Example illustrates the preparation of 4-ethyl-2-(4-imidazol-1-yl-phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



A dried, nitrogen-flushed flask was charge with 379 mg of 2-(4-iodo-phenyl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine (Example E17.1), 82 mg of imidazole, 9.5 mg of copper(I) iodide, 682 mg of cesium carbonate and 23 mg of trans-1,2-diaminocyclohexane; 2 ml of dimethylformamide was added and the resulting mixture was heated at 120°C for 24 hours. After cooling to room temperature, the reaction mixture was filtered over Hyflo, the filtrate was poured into water, extracted with ethyl acetate, the organic layers were dried over sodium sulphate and concentrated *in vacuo*. The residue was subjected to silica gel chromatography (ethyl acetate:cyclohexane 1:1) to afford 176 mg of 4-ethyl-2-(4-imidazol-1-yl-phenyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine as a colorless resin. ^1H NMR (400 MHz, $CDCl_3$) 1.1 (t, 3H), 2.6 (m, 2H), 3.1 (m, 2H), 3.8 and 4.1 (d, 2H), 5.0 (dd, 1H), 7.0-7.6 (m, 10H), 7.9 (s, 1H); MS (ES+) 320 (MH^+).

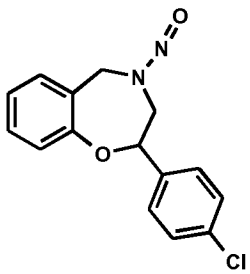
The following compounds were prepared according to procedures analogous to those described in Example E20.1:

Cpd n°	Structure	MH^+	1H NMR	M.p (°C)

E20.2		320	$CDCl_3$: 1.1 (t, 3H), 2.6 (m, 2H), 3.1 (m, 2H), 3.8 and 4.1 (d, 2H), 5.0 (dd, 1H), 6.5 (d, 1H), 7.0-7.7 (m, 9H), 7.9 (d, 1H)	
E20.3		319	$CDCl_3$: 1.2 (t, 3H), 2.7 (m, 2H), 3.2 (m, 2H), 3.7 and 4.2 (d, 2H), 5.0 (d, 1H), 6.4 (t, 2H), 7.1 (t, 2H), 7.0-7.6 (m, 4H)	

EXAMPLE E21.1

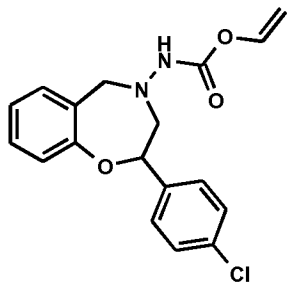
This Example illustrates the preparation of 2-(4-chloro-phenyl)-4-nitroso-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



A flask was charged with 6 g of wet silica in 80 ml of dichloromethane, 12.4 g of zinc chloride and 6.4 g of sodium nitrite. 8.0 g of 2-(4-chloro-phenyl)- 2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine (Example E7.1) in 20 ml dichloromethane was added; the resulting mixture was stirred at 25°C for 5 hours. The reaction mixture was diluted with water and ethyl acetate and filtered. The phases of the filtrate were separated and the organic layer was washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulphate and concentrated *in vacuo*. The residue was subjected to silica gel chromatography (hexane: ethyl acetate 5:1) to afford 7.8 g of 2-(4-chloro-phenyl)-4-nitroso-2,3,4,5-tetrahydro-benzo[f][1,4] oxazepine as a solid. M.p 79-81°C. MS (ES+) 289/291 (MH^+).

EXAMPLE E22.1

This Example illustrates the preparation of [2-(4-Chloro-phenyl)-2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-yl]-carbamic acid vinyl ester.



Step A: 2-(4-Chloro-phenyl)-2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-ylamine

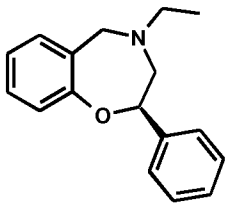
A solution of 2-(4-chloro-phenyl)-4-nitroso-2,3,4,5-tetrahydro-benzo[f][1,4] oxazepine (Example E21.1) in 6 ml of dry THF was added to suspension of 1.6 g lithium aluminium hydride in 6 ml of dry THF under stirring, and the mixture was stirred 17 hours at room temperature. The reaction mixture was stirred further 6 hours at 40°C and 20 hours at 50°C. During that time further 7 equivalents of lithium aluminium hydride were added. The reaction mixture was poured carefully into ice water and 1 N aqueous sodium hydroxide was added. The product was extracted four times with ethyl acetate and the combined organic phases were dried over sodium sulphate.The solution was filtered, concentrated and purified by column chromatography (hexane – ethyl acetate – Et_3N /2:8:1) to give 1.2 g of 2-(4-chloro-phenyl)-2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-ylamine which was used for the next step. ^1H NMR (300 MHz, $CDCl_3$) 3.0-3.5 (broad s, 2H), 3.3 (dd, 1H), 3.4 (dd, 1H), 3.9 (d, 1H), 4.4 (d, 1H), 4.9 (dd, 1H), 7.0-7.1 (m, 2H), 7.2-7.3 (m, 2H), 7.4 (s, 4H); MS (ES+) 275/277 (MH^+).

Step B: [2-(4-Chloro-phenyl)-2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-yl]-carbamic acid vinyl ester

0.082 ml of vinyl chloroformate was added drop wise to a mixture of 200 mg of 2-(4-chloro-phenyl)-2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-ylamine obtained in Step A in 6 ml of ethyl acetate and 6 ml of saturated aqueous sodium bicarbonate. The reaction mixture was stirred 3.5 hours at room temperature. Ethyl acetate was then added and the phases were separated. The aqueous phase was extracted with ethyl acetate. The combined organic phases were dried with sodium sulphate, filtered and the solvents were evaporated under reduced pressure. Purification of the residue with preparative HPLC (hexane-ethyl acetate) afforded the product [2-(4-chloro-phenyl)-2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-yl]-carbamic acid vinyl ester as a white crystals (106 mg; mp 61-62°C). ^1H NMR (400 MHz, $CDCl_3$) 3.4-3.6 (m, 2H), 4.1 (d, 1H), 4.5 (broad s, 1H), 4.6 (d, 1H), 4.7-4.8 (broad d, 1H), 4.9 (dd, 1H), 6.2 (broad s, 1H), 7.1-7.4 (m, 9H); MS (ES+) 345/347 (MH^+).

EXAMPLE E23.1

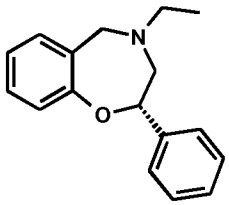
This Example illustrates the preparation of (*R*)-2-phenyl-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



The title compound was prepared from (*R*)-(-)-mandelic acid according to the method described in Example E1.1. MS (ES+) 254 (MH^+); $[\alpha]_D^{23}$ = -128.41° (*c* 0.03).

EXAMPLE E24.1

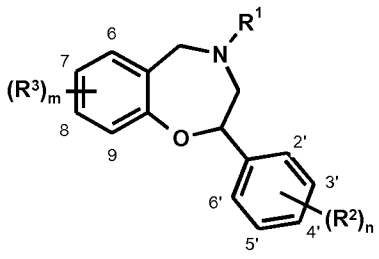
This Example illustrates the preparation of (*S*)-2-phenyl-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



The title compound was prepared from (*S*)-(-)-mandelic acid according to the method described in Example E1.1. MS (ES+) 254 (MH^+); $[\alpha]_D^{23}$ = +119.44° (*c* 0.016).

Further compounds listed in tables P1-P2 were prepared according to procedures similar to those described in examples E1-E24 or by general procedures published in the literature known to the person skilled in the art.

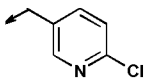
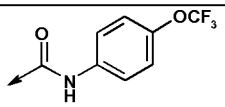
Table P1 : A compound of formula (I)

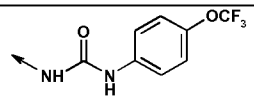
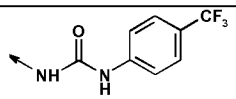


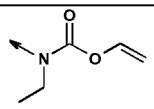
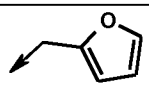
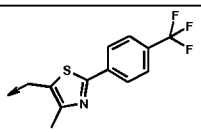
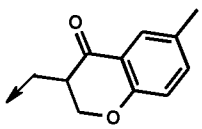
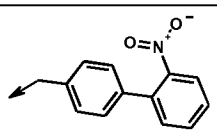
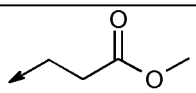
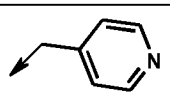
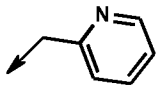
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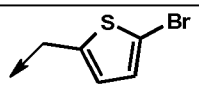
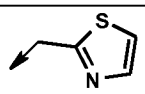
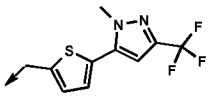
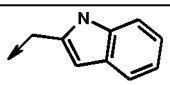
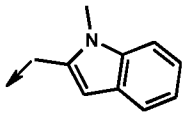
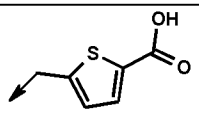
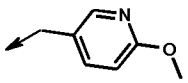
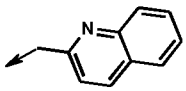
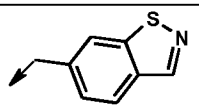
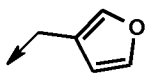
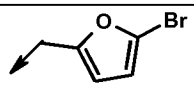
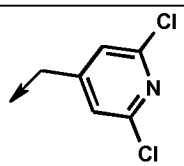
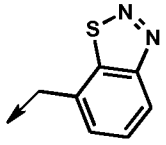
wherein the values are as given in the Table (a blank in the value for R3 signifies that m is zero):

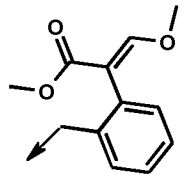
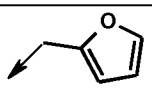
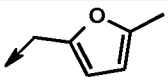
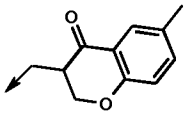
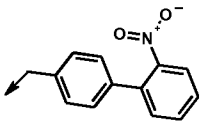
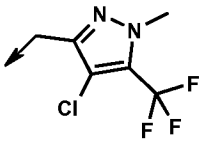
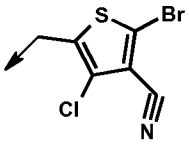
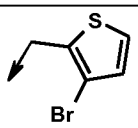
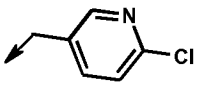
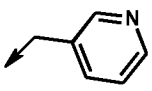
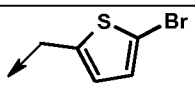
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 1	C(O)H	4'-Cl		syrup	
P1. 2	$CH_2CH_2CH_2F$	4'-Cl		syrup	320/322

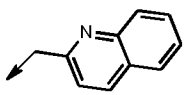
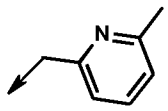
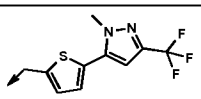
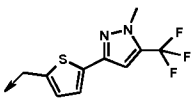
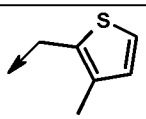
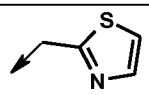
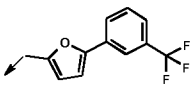
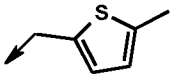
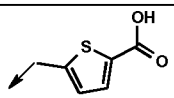
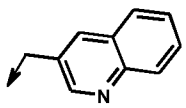
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 3		4'-Cl		syrup	
P1. 4	$CH_2CH_2CF=CF_2$	4'-Cl		syrup	
P1. 5	$CH_2C\equiv CH$	4'-Cl		syrup	298/300
P1. 6		4'-Cl		syrup	
P1. 7	$C(O)CF_3$	4'-Cl		syrup	356/358
P1. 8	$CH_2CH_2CH_3$	4'-Cl		syrup	
P1. 9	CN	4'-Cl		solid	
P1. 10	$C(NH)OCH_2CH_3$	4'-Cl		solid	
P1. 11	H	3'-Cl	7-Cl	syrup	294/296/298
P1. 12	CH_3	3'-Cl	7-Cl	syrup	
P1. 13	H	4'-F		syrup	
P1. 14	H	2'-Cl	7-Cl	113-115°C	
P1. 15	H	2',4'-Cl_2		108-109°C	
P1. 16	H	2'-Cl		97-98°C	
P1. 17	H	4'-CF_3		115-117°C	
P1. 18	H	4'-Br		110-111°C	
P1. 19	H	3'-Cl		syrup	260/262
P1. 20	H	4'-OCF_3		106-109°C	
P1. 21	CH_3	2'-Cl	7-Cl	syrup	
P1. 22	H	4'-Br	7-Cl	syrup	
P1. 23	CN	3'-Cl	7-Cl	syrup	
P1. 24	CN	4'-Cl	7-Cl	solid	
P1. 25	CN	2'-Cl	7-Cl	syrup	
P1. 26	$CH_2CH_2CH_2F$	3'-Cl	7-Cl	syrup	
P1. 27	$CH_2CH_2CH_2F$	4'-Cl	7-Cl	syrup	
P1. 28	$CH_2CH_2CH_2F$	4'-Cl	7-Cl	syrup	
P1. 29	CH_2CH_3	3'-Cl	7-Cl	syrup	322/324/326
P1. 30	CH_2CH_3	4'-Cl	7-Cl	syrup	

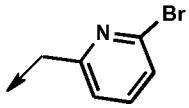
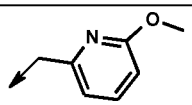
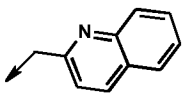
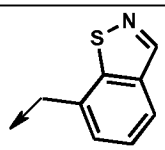
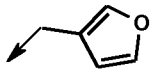
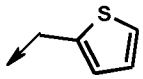
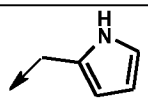
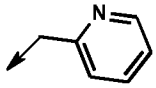
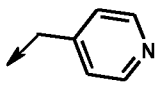
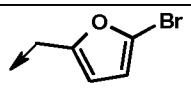
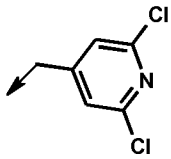
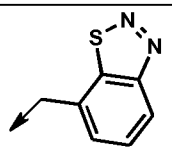
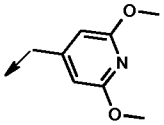
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 31	CH_2CH_3	2'-Cl	7-Cl	syrup	
P1. 32	$CH_2C\equiv CH$	3'-Cl	7-Cl	syrup	
P1. 33	$CH_2C\equiv CH$	2'-Cl	7-Cl	syrup	
P1. 34	$CH_2C\equiv CH$	4'-Cl	7-Cl	syrup	
P1. 35	CH_2CH_3	4'-Br	7-Cl	syrup	366/368/370
P1. 36	CH_2CH_3	4'-F		syrup	
P1. 37	CH_2CH_3	2'-Cl		syrup	
P1. 38	CH_2CH_3	4'-CF_3		syrup	
P1. 39	CH_3	2'-Cl		syrup	274/276
P1. 40	CH_3	4'-CF_3		syrup	
P1. 41	$CH_2C\equiv CH$	4'-CF_3		syrup	
P1. 42	$C(O)CH=CH_2$	4'-Cl		105-108°C	314/316
P1. 43	CH_2CH_3	2'-F		syrup	272
P1. 44	CH_2CH_3	2',4'-F_2		syrup	290
P1. 45	CH_2CH_3	3'-F		syrup	272
P1. 46	CH_2CH_3	2',6'-F_2		syrup	290
P1. 47	H	2'-F		syrup	244
P1. 48	H	2',4'-F_2		61-62°C	262
P1. 49	H	3'-F		syrup	244
P1. 50	H	2',6'-F_2		87-88°C	262
P1. 51	CH_2CH_3	4'-SCH_3		syrup	300
P1. 52	CH_2CH_3	2'-F,4'-Cl		syrup	306/308
P1. 53	CH_2CH_3	3'-OCH_2O-4'		syrup	298
P1. 54	H	4'-SCH_3		syrup	272
P1. 55	H	3'-OCH_2O-4'		syrup	270
P1. 56		4'-Cl		103-105°C	478/480
P1. 57	$NHC(O)CH_3$	4'-Cl		158-160°C	317/319
P1. 58		4'-Cl		103-105°C	462/464
P1. 59	$N=CH_2$	4'-Cl		syrup	287/289
P1. 60	$N=CH(CH_3)$	4'-Cl		syrup	301/303

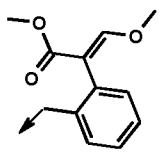
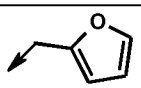
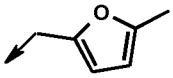
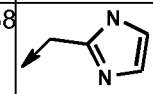
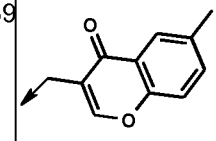
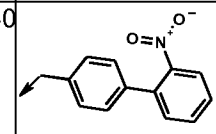
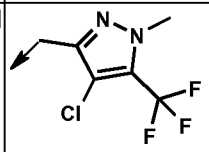
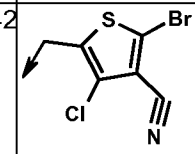
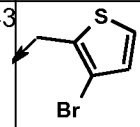
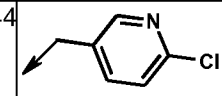
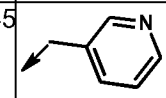
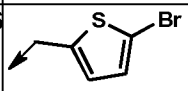
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 61	$N=CH(C_2H_5)$	4'-Cl		syrup	315/317
P1. 62	$N(CH_3)_2$	4'-Cl		syrup	303/305
P1. 63	$NCH(CH_3)_2$	4'-Cl		syrup	317/319
P1. 64	$NH(C_2H_5)$	4'-Cl		88-89°C	303/305
P1. 65	$N(C_2H_5)[C(O)CH_3]$	4'-Cl		solid	345/347
P1. 66		4'-Cl		solid	373/375
P1. 67	CH_2CH_3	4'-$P(O)(OEt)_2$		syrup	390/391/392
P1. 68	$-CH_2$Ph-3F	4'-Cl			368
P1. 69	$-CH_2$Ph-2,6-di-OCH3	4'-Cl			410
P1. 70	$-CH_2$Ph-2,3-di- OCH_3	4'-Cl			410
P1. 71	$-CH_2$Ph-2,3-OCH_2O	4'-Cl			288
P1. 72		4'-Cl			340
P1. 73		4'-Cl			515
P1. 74		4'-Cl			432
P1. 75		4'-Cl			471
P1. 76	$-CH_2$Ph-2,6-di-Cl	4'-Cl			418
P1. 77		4'-Cl			346,348
P1. 78		4'-Cl			351
P1. 79		4'-Cl			351

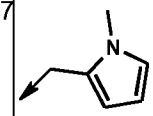
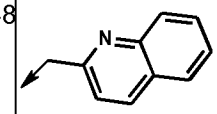
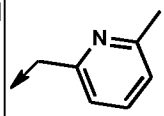
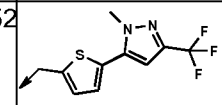
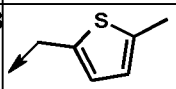
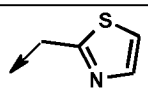
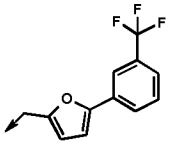
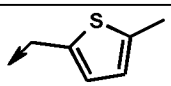
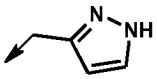
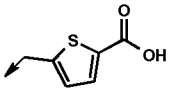
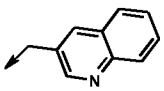
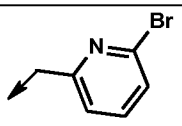
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 80		4'-Cl			434
P1. 81	$-CH_2Ph-3-CH_3$	4'-Cl			364
P1. 82		4'-Cl			357
P1. 83		4'-Cl			504
P1. 84		4'-Cl			389
P1. 85		4'-Cl			403
P1. 86		4'-Cl			400
P1. 87		4'-Cl			381
P1. 88		4'-Cl			401
P1. 89		4'-Cl			407
P1. 90		4'-Cl			407
P1. 91		4'-Cl			418
P1. 92		4'-Cl			419
P1. 93		4'-Cl			408

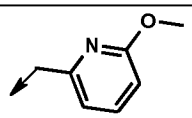
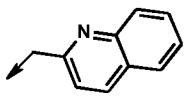
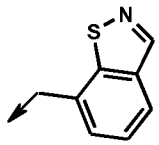
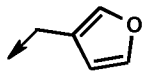
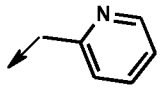
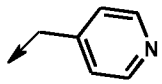
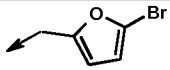
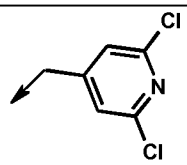
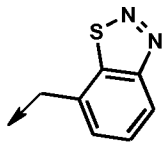
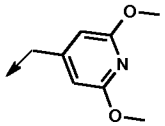
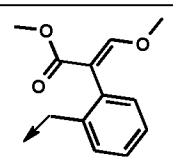
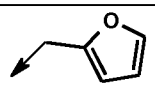
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 94		4'-Cl			464
P1. 95	-CH_2Ph-2,6-di-OCH_3	2',3'-$OCCF_2O$-			456
P1. 96		2',3'-$OCCF_2O$-			386
P1. 97		2',3'-$OCCF_2O$-			400
P1. 98		2',3'-$OCCF_2O$-			488
P1. 99		2',3'-$OCCF_2O$-			517
P1. 100		2',3'-$OCCF_2O$-			502
P1. 101		2',3'-$OCCF_2O$-			538
P1. 102		2',3'-$OCCF_2O$-			479
P1. 103		2',3'-$OCCF_2O$-			431
P1. 104		2',3'-$OCCF_2O$-			397
P1. 105		2',3'-$OCCF_2O$-			480

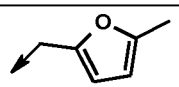
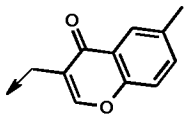
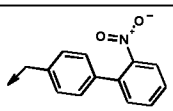
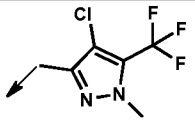
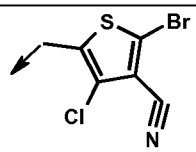
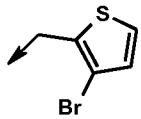
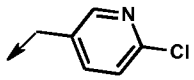
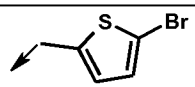
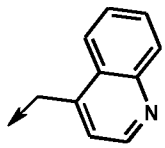
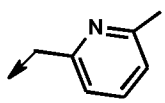
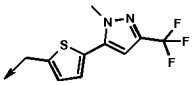
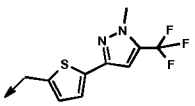
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 106		2',3'-$OCCF_2O$-			447
P1. 107	-CH_2Ph-2,3-di- OCH_3	2',3'-$OCCF_2O$-			456
P1. 108	-CH_2Ph-2,6-di-Cl	2',3'-$OCCF_2O$-			464
P1. 109		2',3'-$OCCF_2O$-			411
P1. 110		2',3'-$OCCF_2O$-			550
P1. 111		2',3'-$OCCF_2O$-			550
P1. 112		2',3'-$OCCF_2O$-			416
P1. 113	-CH_2(3-CH_3-Ph)	2',3'-$OCCF_2O$-			410
P1. 114		2',3'-$OCCF_2O$-			403
P1. 115		2',3'-$OCCF_2O$-			530
P1. 116	-CH_2Ph-3F	2',3'-$OCCF_2O$-			414
P1. 117		2',3'-$OCCF_2O$-			414
P1. 118		2',3'-$OCCF_2O$-			446
P1. 119	-CH_2Ph-3,4-OCH_2O	2',3'-$OCCF_2O$-			440
P1. 120		2',3'-OCCF2O-			447

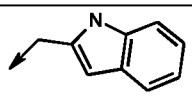
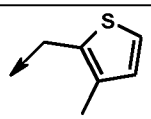
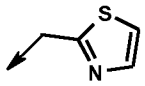
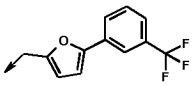
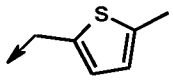
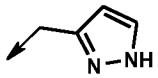
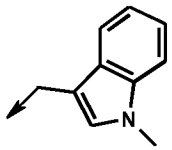
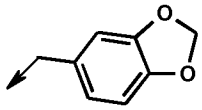
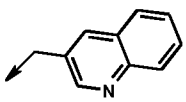
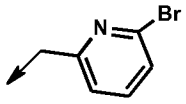
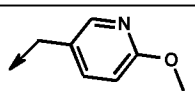
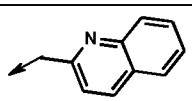
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 121		2',3'-OCCF$_2$O-			475
P1. 122		2',3'-OCCF$_2$O-			427
P1. 123		2',3'-OCCF$_2$O-			447
P1. 124		2',3'-OCCF$_2$O-			453
P1. 125		2',3'-OCCF$_2$O-			386
P1. 126		2',3'-OCCF$_2$O-			402
P1. 127		2',3'-OCCF$_2$O-			385
P1. 128		2',3'-OCCF$_2$O-			397
P1. 129		2',3'-OCCF$_2$O-			397
P1. 130		2',3'-OCCF$_2$O-			464
P1. 131		2',3'-OCCF$_2$O-			465
P1. 132		2',3'-OCCF$_2$O-			454
P1. 133		2',3'-OCCF2O-			457

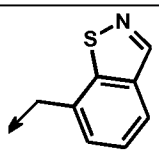
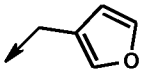
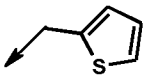
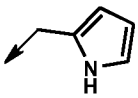
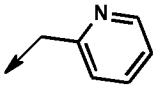
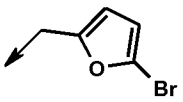
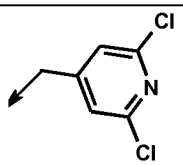
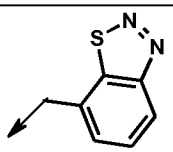
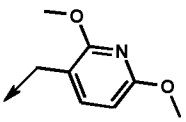
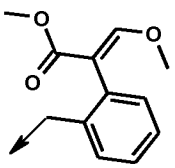
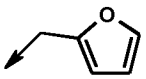
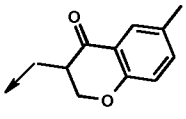
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 134		2',3'-$OCCF_2O$-			510
P1. 135	-CH_2Ph-2,6-di-OCH_3	2'-OCH_3			406
P1. 136		2'-OCH_3			436
P1. 137		2'-OCH_3			350
P1. 138		2'-OCH_3			336
P1. 139		2'-OCH_3			428
P1. 140		2'-OCH_3			467
P1. 141		2'-OCH_3			452
P1. 142		2'-OCH_3			489
P1. 143		2'-OCH_3			430
P1. 144		2'-OCH_3			381
P1. 145		2'-OCH_3			347
P1. 146		2'-OCH_3			430

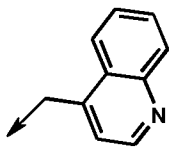
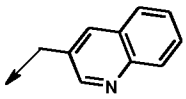
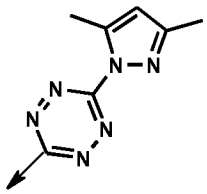
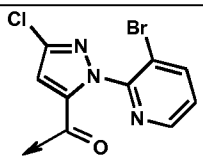
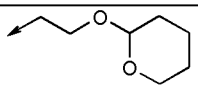
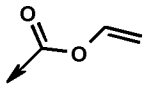
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 147		2'-OCH_3			349
P1. 148		2'-OCH_3			397
P1. 149	-CH_2Ph-2,3-di-OCH_3	2'-OCH_3			406
P1. 150	-CH_2Ph-2,6-di-Cl	2'-OCH_3			414
P1. 151		2'-OCH_3			361
P1. 152		2'-OCH_3			500
P1. 153		2'-OCH_3			366
P1. 154	-CH_2Ph-3CH_3	2'-OCH_3			460
P1. 155		2'-OCH_3			353
P1. 156		2'-OCH_3			480
P1. 157	-CH_2Ph-3F	2'-OCH_3			364
P1. 158		2'-OCH_3			366
P1. 159		2'-OCH_3			336
P1. 160		2'-OCH_3			396
P1. 161	-CH_2Ph-3,4-OCH_2O	2'-OCH_3			490
P1. 162		2'-OCH_3			397
P1. 163		2'-OCH_3			425

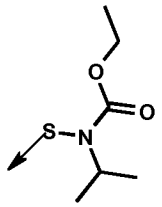
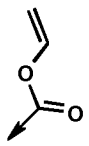
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 164		2'-OCH_3			377
P1. 165		2'-OCH_3			397
P1. 166		2'-OCH_3			403
P1. 167		2'-OCH_3			336
P1. 168		2'-OCH_3			347
P1. 169		2'-OCH_3			347
P1. 170		2'-OCH_3			414
P1. 171		2'-OCH_3			415
P1. 172		2'-OCH_3			404
P1. 173		2'-OCH_3			407
P1. 174		2'-OCH_3			460
P1. 175	-CH_2Ph-2,6-di-OCH_3	4'-OCH3			406
P1. 176		4'-OCH_3			336

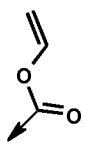
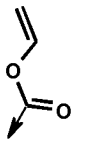
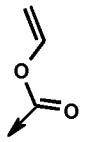
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 177		4'-OCH3			350
P1. 178		4'-OCH_3			428
P1. 179		4'-OCH3			467
P1. 180		4'-OCH_3			452
P1. 181		4'-OCH_3			489
P1. 182		4'-OCH_3			430
P1. 183		4'-OCH_3			381
P1. 184		4'-OCH_3			430
P1. 185		4'-OCH_3			397
P1. 186	-CH_2Ph-2,3-di-OCH3	4'-OCH_3			406
P1. 187	-CH_2Ph-2,6-di-Cl	4'-OCH_3			414
P1. 188		4'-OCH_3			361
P1. 189		4'-OCH_3			500
P1. 190		4'-OCH_3			500

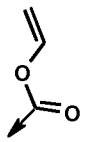
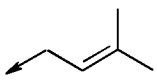
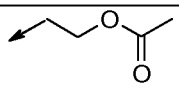
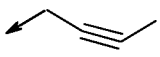
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 191		4'-OCH_3			385
P1. 192		4'-OCH_3			366
P1. 193	-CH_2Ph-3-CH_3	4'-OCH_3			360
P1. 194		4'-OCH_3			366
P1. 195		4'-OCH_3			480
P1. 196	-CH_2PH-3-F	4'-OCH_3			364
P1. 197		4'-OCH_3			366
P1. 198		4'-OCH_3			336
P1. 199		4'-OCH_3			399
P1. 200		4'-OCH_3			361
P1. 201		4'-OCH_3			397
P1. 202		4'-OCH_3			425
P1. 203		4'-OCH_3			377
P1. 204		4'-OCH_3			397

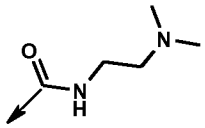
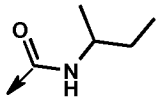
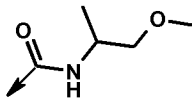
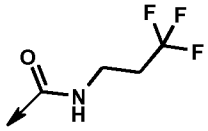
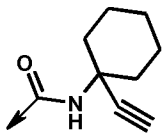
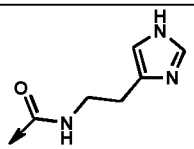
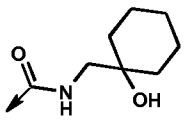
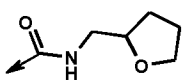
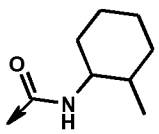
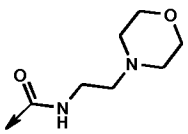
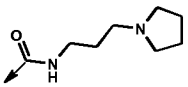
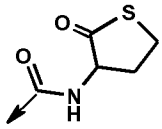
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 205		4'-OCH_3			403
P1. 206		4'-OCH_3			336
P1. 207		4'-OCH_3			352
P1. 208		4'-OCH_3			335
P1. 209		4'-OCH_3			347
P1. 210		4'-OCH_3			414
P1. 211		4'-OCH3			415
P1. 212		4'-OCH_3			404
P1. 213		4'-OCH_3			407
P1. 214		4'-OCH_3			460
P1. 215		3'-Cl			340
P1. 216		3'-Cl			432

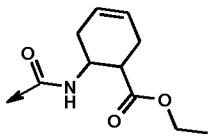
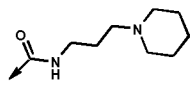
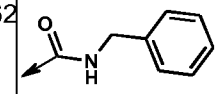
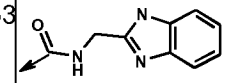
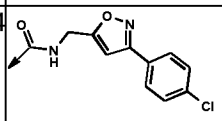
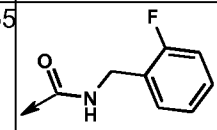
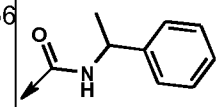
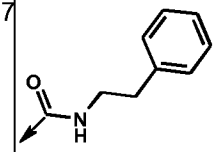
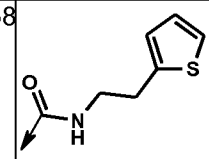
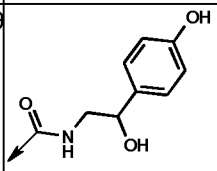
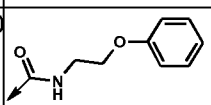
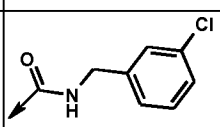
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 217		3'-Cl			401
P1. 218		3'-Cl			401
P1. 219		4'-Cl			$CDCl_3$: 1.6 (s, 3H), 2.3(s, 3H), 2.6 (s, 3H), 3.7-3.8 (dd, 2H), 4.7 (d, 1H), 4.75-4.8 (d, 1H), 5.0 (d, 1H), 6.0 (s, 1H) 7.0-7.1 (m, 2H), 7.2 (m, 2H), 7.3-7.5 (m, 4H)
P1. 220		4'-Cl			$CDCl_3$: 3.4-3.5 ,3.7-3.8 (2 x m, 1H ea), 4.2-4.4, 4.6-4.7 (2 x m, 1H ea), 4.8-5.0, 5.1-5.2 (2 x m, 1H), 6.4, 6.5 (2 x s, 1H), 7.0-8.5 (m, 11H)
P1. 221		4'-Cl			388,390
P1. 222	$-CH_2CH_3$	3'-Cl			$CDCl_3$: 1.2 (t, 3H), 2.6 (m, 2H), 3.1 (m, 2H); 3.7 (d, 1H); 4.1 (d, 1H); 4.8 (dd, 1H); 6.9-7.4 (m, 8H)
P1. 223		3'-Cl			$CDCl_3$: 3.3 (dd, 1H); 3.4 (dd, 1H); 4.3-4.5 (m, 1H); 4.7-4.9 (m, 1H); 7.0-7.5 (m, 8H)
P1. 224		4'-Cl			$CDCl_3$: 3.4 (br s, 2H); 3.8-4.0 (m, 1H); 4.1-4.3 (m, 1H); 4.5 (d, 1H), 4.8-4.9 (m, 1H), 5.0-5.1, 5.2-5.3 (2 x d, 1H ea) 7.0-7.5 (m, 6H), 7.8 (d, 2H)

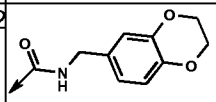
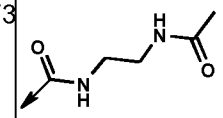
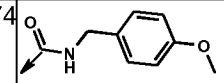
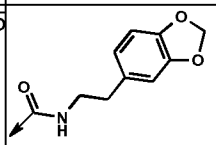
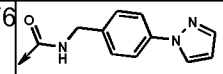
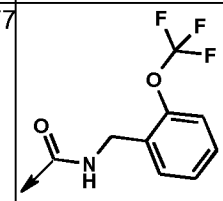
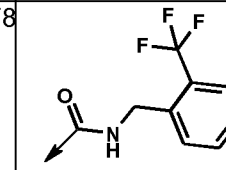
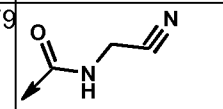
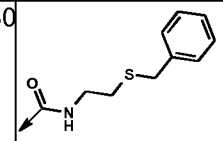
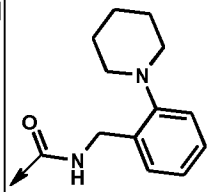
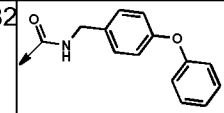
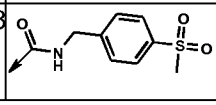
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 225		4'-Cl			$CDCl_3$: 1.1, 1.2 (2 x d, 3H ea), 1.3 (t, 3H), 3.6 (dd, 1H); 4.1-4.2 (m, 4H); 4.4 (d, 1H); 4.6 (d, 1H); 4.8 (d, 1H); 7.0-7.1 (m, 2H), 7.2-7.3 (m, 3H), 7.3-7.4 (m, 3H)
P1. 226	$-CH_3$	2'-OCH_3			$CDCl_3$: 2.6 (s, 3H), 3.2-3.5 (dd, 2H); 3.75 (s, 3H); 3.9 (d, 1H); 4.5 (d, 1H); 5.3 (d, 2H); 6.9-7.6 (m, 8H),
P1. 227		2'-OCH_3			$CDCl_3$: 3.2-3.4 (dd, 1H); 3.8 (s, 3H); 4..3-4.6 (m, 3H); 4.7-4.9 (m, 3H); 5.1 (t, 1H); 6.8-7.6 (m, 8H),
P1. 228	-H	2'-OCH_3			$CDCl_3$: 1.6 (br s, NH), 3.1(dd, 1H), 3.4 (dd, 1H), 3.7 (s, 3H), 4.0 (d, 2H), 5.0 (d, 1H), 6.8-7.6 (m, 8H)
P1. 229	$-CH_3$	4'-OCH_3			$CDCl_3$: 2.5 (s, 3H), 3.1(br s, 2H), 3.6 (dd, 1H), 3.8 (s, 3H), 4.1 (d, 1H), 4.8 (d, 1H), 6.8-7.3 (m, 8H)
P1. 230	$-CH_3$	3,4-di-OCH_3			$CDCl_3$: 2.5 (s, 3H), 3.1(br s, 2H), 3.7 (dd, 1H), 3.8 (s, 3H), 3.9 (s, 3H), 4.1 (d, 1H), 4.8 (d, 1H), 6.8-7.2 (m, 7H)
P1. 231	$-CH_3$	2',3'-OCF_2O			$CDCl_3$: 2.5 (s, 3H), 3.2 (br s, 2H), 3.7 (d, 1H), 4.2 (d, 1H), 5.1 (dd, 1H), 6.9-7.3 (m, 7H)

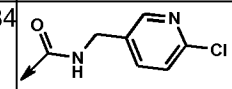
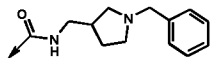
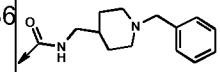
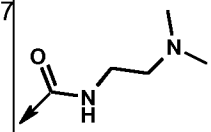
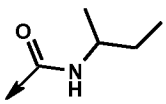
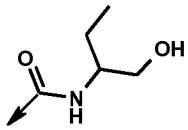
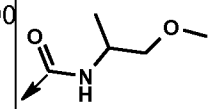
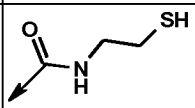
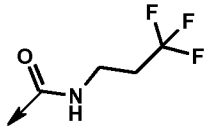
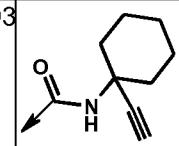
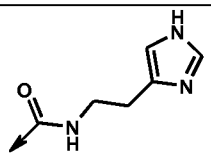
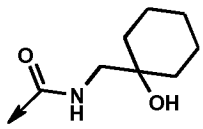
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 232		4'-OCH3			$CDCl_3$: 3.3-3.6 (dd, 2H); 3.8 (s, 3H); 4..3-4.5 (m, 3H); 4.6-4.9 (m, 3H); 5.1 (t, 1H); 6.8-7.6 (m, 8H),
P1. 233		3',4'-di-OCH_3			$CDCl_3$: 3.3-3.6 (dd, 2H); 3.8 (2 x s, 3H ea); 4..3-4.5 (m, 3H); 4.6-4.9 (m, 3H); 6.8-7.6 (m, 7H),
P1. 234		2',3'-OCF_2O			$CDCl_3$: 3.5-3.7 (m, 2H); 4..3-4.5 (m, 3H); 4.7-5.0 (m, 3H); 7.0-7.4 (m, 7H),
P1. 235	-H	4'-OCH_3			$CDCl_3$: 2.7-2.9 (m, 2H), 3.3 (s, NH), 3.8 (s, 3H), 3.9 (d, 1H), 4.1 (d, 1H), 4.3 (m, 1H) 6.7-7.3 (m, 8H)
P1. 236	-CO_2CH_3	4'-OCH_3			$CDCl_3$: 3.2-3.5 (m, 2H), 3.6(br d, 3H), 3.8 (s, 3H), 4.2-4.4 (m, 2H), 4.6-4.9 (m, 1H), 6.8-7.4 (m, 8H)
P1. 237	-H	2',3'-di-OCF_2O			$CDCl_3$: 1.7 (br s, 1H) 3.2 (dd, 1H), 3.5 (dd, 1H), 4.1 (dd, 2H), 4.8 (dd, 1H), 7.0-7.4 (m, 7H)
P1. 238		3'-Cl			$CDCl_3$: 0.5 (br d,4H); 1.9 (m, 1H), 3.15 (dd, 1H); 3.20 (d, 1H); 3.8 (d, 1H); 4.2 (d, 1H); 4.9 (dd, 1H); 7.0-7.5 (m, 8H)

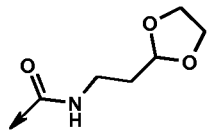
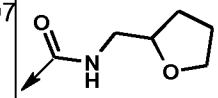
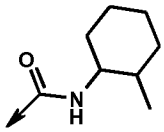
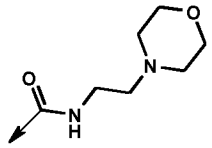
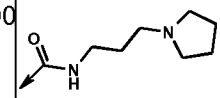
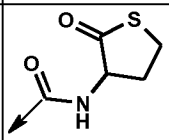
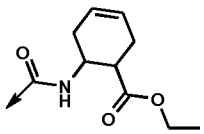
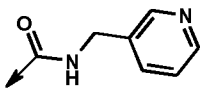
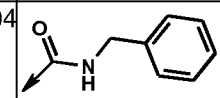
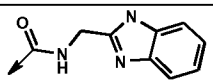
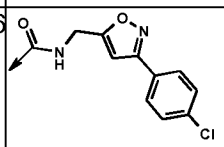
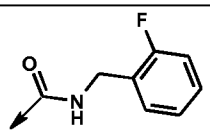
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 239		4'-Cl			$CDCl_3$: 0.9 (m, 2H); 1.6-1.8 (m, 2H), 1.8-1.9 (m, 2H); 2.1 (m, 1H); 2.8 (dd, 1H); 3.1 (dd, 2H); 3.7, 3.8 (2 x d, 1H ea); 4.8 (d, 1H), 6.9-7.4 (m, 8H)
P1. 240	$-CH_3$	4'-OCF_3			$CDCl_3$: 2.5 (s, 3H), 3.1(br s, 2H), 3.7 (d, 1H), 4.1 (d, 1H), 4.9 (dd, 1H), 7.0-7.1 (m, 2H), 7.2-7.3 (m, 4H), 7.5 (d, 2H)
P1. 241		4'-OCF_3			$CDCl_3$: 3.3-3.4 (dd, 1H); 3.4-3.6 (m, 1H); 4.2-4.5 (m, 4H); 4.7-4.9 (m, 2H); 7.0-7.6 (m, 8H),
P1. 242	-H	4'-OCF_3			$CDCl_3$: 1.57(br s, 1H), 3.1(dd, 1H), 3.3 (d, 1H), 3.9 (d, 1H), 4.1 (d, 1H), 4.7 (d, 1H), 7.0 (d, 2H), 7.1-7.3 (dd, 4H), 7.4 (d, 2H)
P1. 243	$-CH_2CH_3$	4'-OCF_3			$CDCl_3$: 1.2 (t, 3H), 2.6(q, 2H), 3.2 (m, 2H), 3.8 (d, 1H), 4.1 (d, 1H), 4.9 (d, 1H), 7.0 (m, 2H), 7.2-7.3 (dd, 4H), 7.4 (d, 2H)
P1. 244		4'-Cl			328,330
P1. 245		4'-Cl			346,348
P1. 246	CH_2CN	4'-Cl			299,301
P1. 247		4'-Cl			312,314

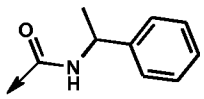
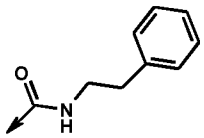
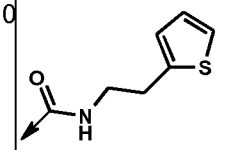
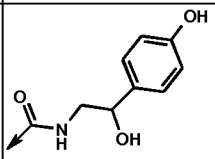
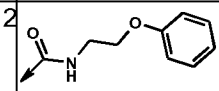
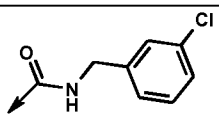
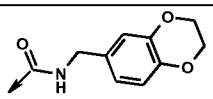
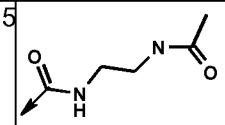
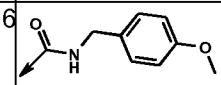
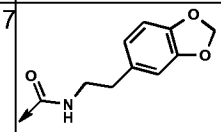
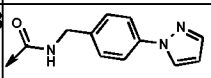
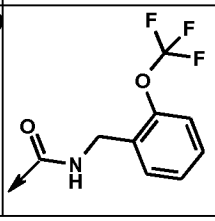
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 248		2'-OCH_3			370
P1. 249		2'-OCH_3			355
P1. 250		2'-OCH_3			371
P1. 251		2'-OCH_3			394
P1. 252		2'-OCH_3			405
P1. 253		2'-OCH_3			394
P1. 254		2'-OCH_3			411
P1. 255		2'-OCH_3			382
P1. 256		2'-OCH_3			395
P1. 257		2'-OCH_3			412
P1. 258		2'-OCH_3			410
P1. 259		2'-OCH_3			400

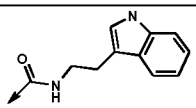
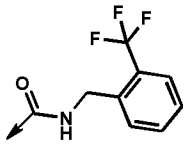
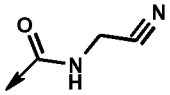
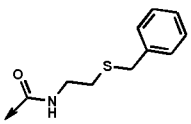
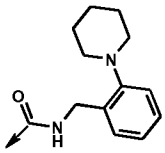
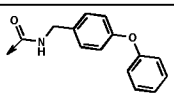
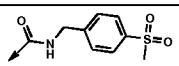
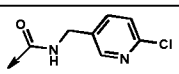
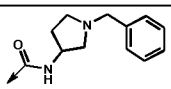
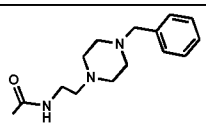
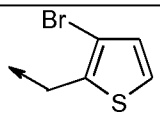
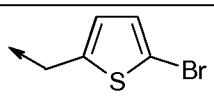
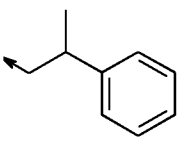
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 260		2'-OCH_3			451
P1. 261		2'-OCH_3			424
P1. 262		2'-OCH_3			389
P1. 263		2'-OCH_3			429
P1. 264		2'-OCH_3			490
P1. 265		2'-OCH_3			403
P1. 266		2'-OCH_3			403
P1. 267		2'-OCH_3			403
P1. 268		2'-OCH_3			409
P1. 269		2'-OCH_3			435
P1. 270		2'-OCH_3			419
P1. 271		2'-OCH_3			423

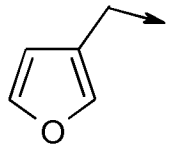
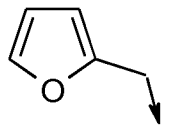
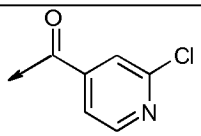
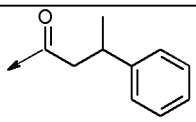
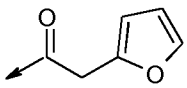
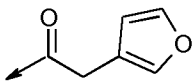
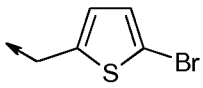
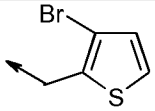
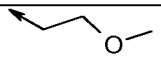
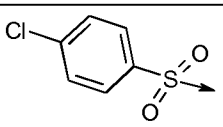
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 272		2'-OCH_3			447
P1. 273		2'-OCH_3			384
P1. 274		2'-OCH_3			419
P1. 275		2'-OCH_3			447
P1. 276		2'-OCH_3			455
P1. 277		2'-OCH_3			473
P1. 278		2'-OCH_3			457
P1. 279		2'-OCH_3			338
P1. 280		2'-OCH_3			449
P1. 281		2'-OCH_3			472
P1. 282		2'-OCH_3			481
P1. 283		2'-OCH_3			467

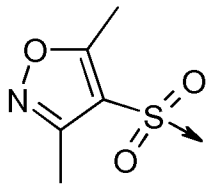
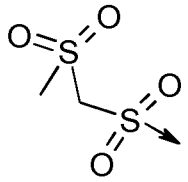
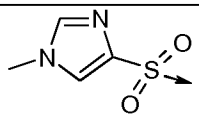
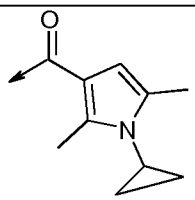
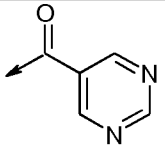
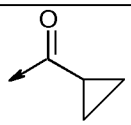
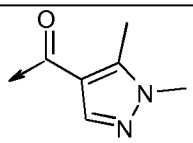
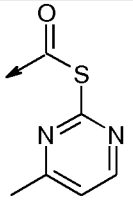
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 284		2'-OCH_3			424
P1. 285		2'-OCH_3			458
P1. 286		2'-OCH_3			501
P1. 287		2',3'-OCF_2O			420
P1. 288		2',3'-OCF_2O			405
P1. 289		2',3'-OCF_2O			421
P1. 290		2',3'-OCF_2O			421
P1. 291		2',3'-OCF_2O			409
P1. 292		2',3'-OCF_2O			445
P1. 293		2',3'-OCF_2O			455
P1. 294		2',3'-OCF_2O			443
P1. 295		2',3'-OCF_2O			461

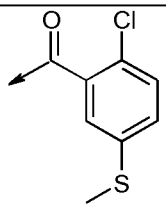
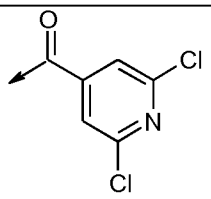
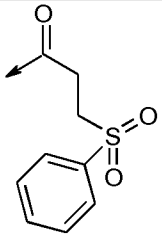
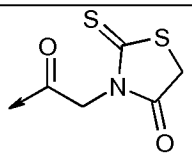
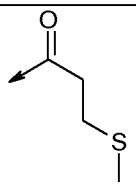
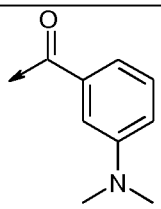
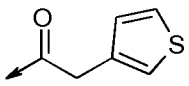
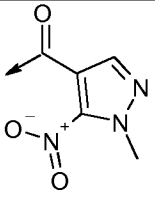
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 296		2',3'-OCF_2O			449
P1. 297		2',3'-OCF_2O			433
P1. 298		2',3'-OCF_2O			445
P1. 299		2',3'-OCF_2O			462
P1. 300		2',3'-OCF_2O			460
P1. 301		2',3'-OCF_2O			449
P1. 302		2',3'-OCF_2O			501
P1. 303		2',3'-OCF_2O			440
P1. 304		2',3'-OCF_2O			439
P1. 305		2',3'-OCF_2O			479
P1. 306		2',3'-OCF_2O			540
P1. 307		2',3'-OCF_2O			457

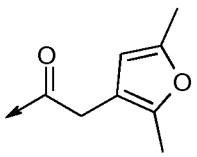
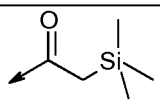
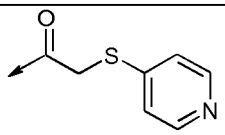
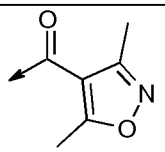
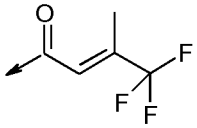
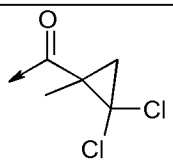
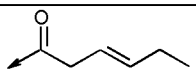
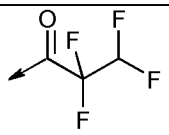
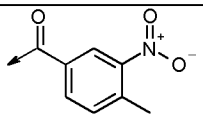
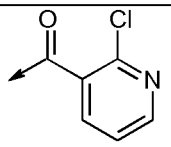
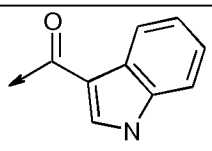
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 308		2',3'-OCF_2O			453
P1. 309		2',3'-OCF_2O			453
P1. 310		2',3'-OCF_2O			459
P1. 311		2',3'-OCF_2O			485
P1. 312		2',3'-OCF_2O			469
P1. 313		2',3'-OCF_2O			473
P1. 314		2',3'-OCF_2O			497
P1. 315		2',3'-OCF_2O			434
P1. 316		2',3'-OCF_2O			469
P1. 317		2',3'-OCF_2O			497
P1. 318		2',3'-OCF_2O			505
P1. 319		2',3'-OCF_2O			523

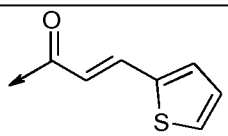
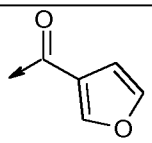
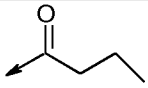
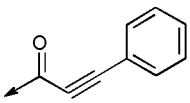
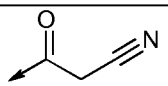
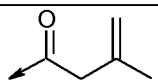
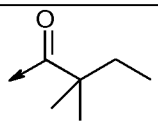
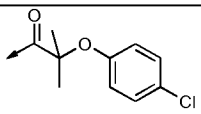
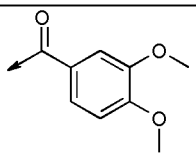
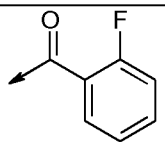
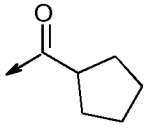
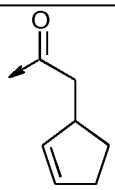
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 320		2',3'-OCF_2O			492
P1. 321		2',3'-OCF_2O			507
P1. 322		2',3'-OCF_2O			388
P1. 323		2',3'-OCF_2O			499
P1. 324		2',3'-OCF_2O			522
P1. 325		2',3'-OCF_2O			347
P1. 326		2',3'-OCF_2O			517
P1. 327		2',3'-OCF_2O			474
P1. 328		2',3'-OCF_2O			508
P1. 329		2',3'-OCF_2O			551
P1. 330					400,402
P1. 331					400,402
P1. 332					344

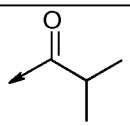
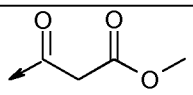
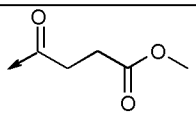
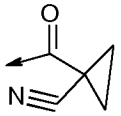
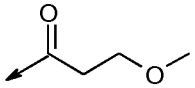
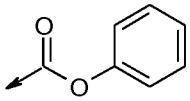
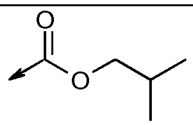
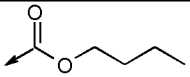
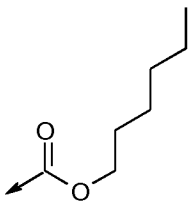
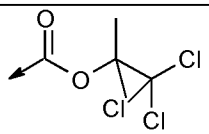
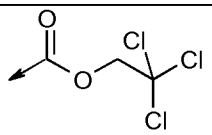
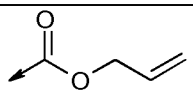
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 333					306
P1. 334					306
P1. 335	Et	4'-Cl	9-F		306,308
P1. 336	SO2Me	4'-Cl			
P1. 337	Et	4'-Cl	8-F		306,308
P1. 338	Et	4'-Cl	7-F		306,308
P1. 339		4'-Cl			399,401
P1. 340	$C(O)CH_3$	4'-Cl			302,304
P1. 341	Et	4'-Cl	6-F		306,308
P1. 342		4'-Cl			378,380
P1. 343		4'-Cl			340,342
P1. 344		4'-Cl			340,342
P1. 345		4'-Cl			434,436,438
P1. 346		4'-Cl			434,436,438
P1. 347	CO_2CH_3	4'-Cl			
P1. 348		4'-Cl			318,320
P1. 349		4'-Cl			
P1. 350	SO_2CF_3	4'-Cl			
P1. 351	SO_2iPr	4'-Cl			

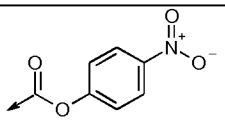
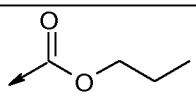
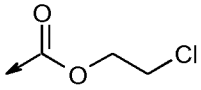
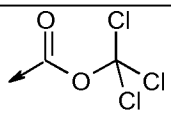
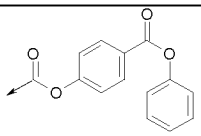
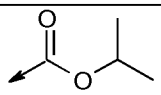
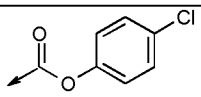
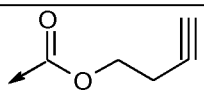
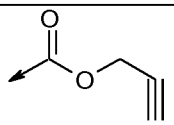
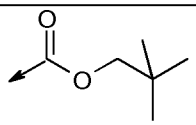
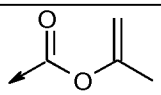
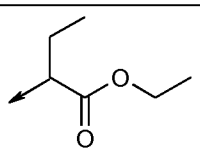
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 352	SO_2CH_2Ph	4'-Cl			
P1. 353	$SO_2CH_2CF_3$	4'-Cl			
P1. 354	$SO_2(CH_2)_2Cl$	4'-Cl			
P1. 355		4'-Cl			
P1. 356		4'-Cl			
P1. 357		4'-Cl			
P1. 358		4'-Cl			421,423
P1. 359		4'-Cl			340,342
P1. 360		4'-Cl			328,330
P1. 361		4'-Cl			382,384
P1. 362		4'-Cl			426,428

Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 363		4'-Cl			444,446,448
P1. 364		4'-Cl			433,435,437
P1. 365		4'-Cl			456,458
P1. 366		4'-Cl			433,435
P1. 367		4'-Cl			362,364
P1. 368		4'-Cl			407,409
P1. 369		4'-Cl			370,372
P1. 370		4'-Cl			413,415

Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 371		4'-Cl			424,426
P1. 372		4'-Cl			374,376
P1. 373		4'-Cl			411,413
P1. 374		4'-Cl			383,385
P1. 375		4'-Cl			396,398
P1. 376		4'-Cl			410,412,414,416
P1. 377		4'-Cl			356,358
P1. 378		4'-Cl			388,390
P1. 379		4'-Cl			423,425
P1. 380		4'-Cl			399,401
P1. 381		4'-Cl			403,405

Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 382		4'-Cl			396,398
P1. 383		4'-Cl			354,356
P1. 384		4'-Cl			330,332
P1. 385		4'-Cl			388,390
P1. 386		4'-Cl			327,329
P1. 387		4'-Cl			328,330
P1. 388		4'-Cl			358,360
P1. 389		4'-Cl			356,358,360
P1. 390		4'-Cl			424,426
P1. 391		4'-Cl			382.384
P1. 392		4'-Cl			356,358
P1. 393		4'-Cl			368,370

Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 394		4'-Cl			330.332
P1. 395		4'-Cl			360,362
P1. 396		4'-Cl			374,376
P1. 397		4'-Cl			353,355
P1. 398		4'-Cl			346,348
P1. 399		4'-Cl			380,382
P1. 400		4'-Cl			360,362
P1. 401		4'-Cl			360,362
P1. 402		4'-Cl			388,390
P1. 403		4'-Cl			462,464,466
P1. 404		4'-Cl			434,436,438
P1. 405		4'-Cl			344,346

Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 406		4'-Cl			425,427
P1. 407		4'-Cl			346,348
P1. 408		4'-Cl			366,368,370
P1. 409		4'-Cl			420,422,424
P1. 410		4'-Cl			500,502
P1. 411		4'-Cl			346,348
P1. 412	CO_2Et	4'-Cl			332,334
P1. 413	CO_2CH_2Cl	4'-Cl			352,354
P1. 414	$CO_2CH(CH_3)Cl$	4'-Cl			366,368
P1. 415		4'-Cl			414,416
P1. 416		4'-Cl			356,358
P1. 417		4'-Cl			342,344
P1. 418		4'-Cl			374,376
P1. 419		4'-Cl			344,346
P1. 420		4'-Cl			374,376

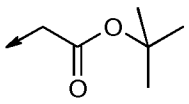
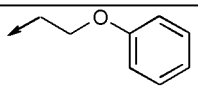
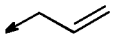
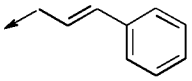
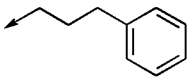
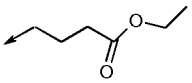
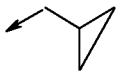
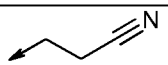
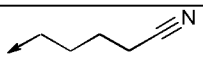
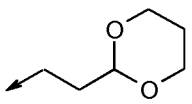
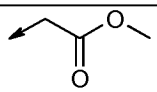
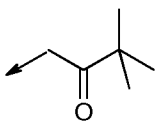
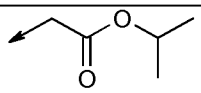
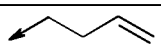
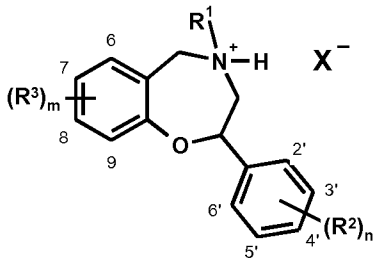
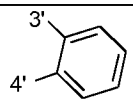
Line	R_1	R_2	R_3	M.p (°C)	MH^+/ NMR
P1. 421		4'-Cl			374,376
P1. 422		4'-Cl			380,382
P1. 423		4'-Cl			300,302
P1. 424		4'-Cl			376,378
P1. 425		4'-Cl			378,380
P1. 426		4'-Cl			374,376
P1. 427		4'-Cl			314,316
P1. 428		4'-Cl			313,315
P1. 429		4'-Cl			341,343
P1. 430		4'-Cl			374,376
P1. 431		4'-Cl			332,334
P1. 432		4'-Cl			358,360
P1. 433		4'-Cl			360,362
P1. 434		4'-Cl			314,316

Table P2 : A compound of formula (Ib)



(Ib)

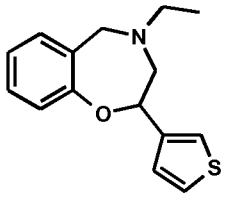
wherein the values are as given in the Table (a blank in the value for R3 signifies that m is zero):

Line	R_1	R_2	R_3	X^-	M.p (°C)
P2. 1	cyclopropyl	4'-Cl		Cl^-	92-94°C
P2. 2	C_2H_5	4'-Cl	7-OCH_3	Cl^-	170°C
P2. 3	C_2H_5	4'-Cl	8-OCH_3	Cl^-	135°C
P2. 4	C_2H_5	4'-Cl	9-OCH_3	Cl^-	200°C
P2. 5	H	4'-Cl		Cl^-	220-222°C
P2. 6	C_2H_5	4'-Cl	6-CF_3	Cl^-	220°C
P2. 7	C_2H_5			Cl^-	155-160°C
P2. 8	H	4'-Cl	6-CF_3	Cl^-	250°C
P2. 9	C_2H_5	4'-Cl	6-CF_3	Cl^-	215-216°C
P2. 10	CH_3	3'-Cl	7-Cl	Cl^-	246-247°C
P2. 11	H	3'-Cl	7-Cl	Cl^-	231-233°C
P2. 12	C_2H_5	4'-OCF_3	6-CF_3	Cl^-	205-206
P2. 13	CH_3	3'-Cl	7-Cl	Cl^-	246-247°C
P2. 14	H	3'-Cl	7-Cl	Cl^-	231-233°C
P2. 15	H	4'-Cl	7-Cl	Cl^-	243-245°C
P2. 16	H	2'-Cl	7-Cl	Cl^-	239-241°C
P2. 17	CH_3	4'-Cl	7-Cl	Cl^-	237-239°C
P2. 18	CH_3	2'-Cl	7-Cl	Cl^-	248-250°C
P2. 19	H	4'-Br	7-Cl	Cl^-	225-247°C
P2. 20	$CH_2C{\equiv}CH$	3'-Cl	7-Cl	Cl^-	218-220°C
P2. 21	$CH_2C{\equiv}CH$	4'-Cl	7-Cl	Cl^-	224-225°C
P2. 22	$CH_2C{\equiv}CH$	2'-Cl	7-Cl	Cl^-	222-223°C
P2. 23	CH_2CH_3	3'-Cl	7-Cl	Cl^-	235-237°C
P2. 24	CH_2CH_3	4'-Cl	7-Cl	Cl^-	222-225°C
P2. 25	CH_2CH_3	2'-Cl	7-Cl	Cl^-	240-242°C
P2. 26	$CH_2CH_2CH_2F$	3'-Cl	7-Cl	Cl^-	154-156°C
P2. 27	$CH_2CH_2CH_2F$	4'-Cl	7-Cl	Cl^-	169-171°C

Line	R_1	R_2	R_3	X^-	M.p (°C)
P2. 28	$CH_2CH_2CH_2F$	2'-Cl	7-Cl	Cl^-	196-197°C
P2. 29	H	2'-Cl		Cl^-	226-228°C
P2. 30	H	4'-CF_3		Cl^-	228-230°C
P2. 31	H	4'-Br		Cl^-	229-231°C
P2. 32	$CH_2C\equiv CH$	4'-Cl		Cl^-	211-212°C
P2. 33	NH_2	4'-Cl		Ph-COO^-	
P2. 34	CH_2CH_3	4'-Cl		Cl^-	93-96°C

EXAMPLE E25.1

This Example illustrates the preparation of 4-Ethyl-2-thiophen-3-yl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



Step A: 2-Ethylaminomethyl-phenol

6.72 g of salicylaldehyde and 25 ml of a 2M solution of ethylamine in methanol were dissolved in 16 ml ethanol and stirred with 0.84 g 5% Pt/C and 0.1 ml of concentrated H_2SO_4 under hydrogen at room temperature for 4 hours. Hydrogen uptake stopped after 2 hours. The catalyst was filtered and the solvent evaporated to yield 8.86 g of an orange oil. ^1H NMR ($CDCl_3$) 1.09 (t, 3H), 2.60 (q, 2H), 3.87 (s, 2H), 6.70-6.76 (m, 2H), 7.20 (broad s, 2H), 7.07-7.11 (m, 2H). MS (ES+) 152 (MH^+).

Step B: Hydroxy-thiophen-3-yl-acetic acid methyl ester

1.12 g of 3-thiophenecarboxaldehyde was dissolved in 5 ml of dichloromethane and stirred at room temperature. 0.62 g of Ytterbium triflate was added, followed by drop-wise addition of trimethylsilyl cyanide over 10 minutes. The dark brown mixture was stirred at room temperature for a few hours. Then the reaction mixture was quenched with a saturated aqueous solution of of sodium carbonate and extracted three times with diethyl ether. The combined organic phases were washed with a saturated aqueous solution of of sodium carbonate, dried ($MgSO_4$), filtered and evaporated to yield 1.9 g of a light brown oily product, which was dissolved in 12 ml of methanol. 4 ml of concentrated HCl were added and the mixture was heated to reflux with stirring for 3 hours. The methanol was evaporated and the residue was neutralized with a saturated aqueous solution of of sodium carbonate. The aqueous phase was extracted 2 times with ethyl acetate. The combined organic phases were washed with water, dried ($MgSO_4$), filtered and evaporated to yield 1.15 g of crude product as a brown liquid.

Step C: Hydroxy-thiophen-3-yl-acetic acid

1.15 g of crude product hydroxy-thiophen-3-yl-acetic acid methyl ester (Example E1, step B) was dissolved in 25 ml of tetrahydrofuran and stirred at 5°C. A solution of 0.294 g of lithium hydroxide monohydrate in 10 ml of water was added and the mixture was stirred at room temperature for a few hours (TLC control). The tetrahydrofuran was evaporated and the residue was acidified with diluted HCl. The aqueous phase was extracted 3 times with diethyl ether. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and evaporated to yield 0.57 g of crude product as a brown solid. The solid was triturated with hexane/diethyl ether and the solid was filtered off, washed with hexane/diethyl ether and dried to give 0.33 g of a tan, powdery solid.

Step D: 2-Chloro-N-ethyl-N-(2-hydroxy-benzyl)-2-thiophen-3-yl-acetamide

0.33 ml of DMF was added slowly to a cooled solution (15°C) of 0.31 ml of thionyl chloride in 10 ml dioxane, and then a solution of 0.25 g of hydroxy-thiophen-3-yl-acetic acid (Example E1, step C) in 10 ml dioxane was slowly added. The reaction was slightly exothermic and the temperature was held during the addition at ca 25°C with an ice/water bath. This solution was then added to a rapidly stirred mixture of a solution of 1.033 g sodium bicarbonate in 15 ml water and 0.31 g of 2-ethylamino-methyl-phenol (Example E1, step A) in 15 ml of dichloromethane and the mixture was stirred overnight. The phases were separated and the aqueous phase was extracted 3 times with dichloromethane. The combined organic phases were dried ($MgSO_4$), filtered and concentrated to yield 0.407 g of the product as a clear brown oil.

Step E: 4-Ethyl-2-thiophen-3-yl-4,5-dihydro-benzo[f][1,4]oxazepin-3-one

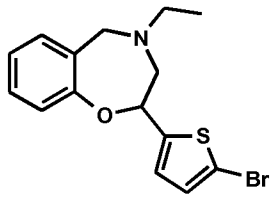
0.407 g of 2-chloro-N-ethyl-N-(2-hydroxy-benzyl)-2-thiophen-3-yl-acetamide (Example E1, step D) was dissolved in 8 ml of DMF and stirred at 0-5°C. 57 mg of sodium hydride (60% dispersion in oil) was added in 2 portions. After the addition was complete the suspension was stirred for ca. 24 hours at room temperature, then poured onto 10 ml of water and extracted four times with diethyl ether. The organic phases were dried ($MgSO_4$), filtered and evaporated to yield 0.318 g of a brown oil, which was chromatographed on silica (hexane -> 30% ethyl acetate in hexane) to yield 0.174 g of the product.

Step F: 4-Ethyl-2-thiophen-3-yl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine

1.44 ml of a 1M solution of lithium aluminium hydride in THF was heated at reflux while a solution of 0.16 g of 4-ethyl-2-thiophen-3-yl-4,5-dihydro-benzo[f][1,4] oxazepin-3-one (Example E1, step E) in 5 ml THF was added drop wise. Heating was continued for 4 hours and the reaction mixture was allowed to cool down to room temperature overnight. The reaction mixture was cooled in an ice bath and 3 ml of water was added drop wise. After stirring for 30 minutes the mixture was filtered and the filter cake was washed with ethyl acetate. The solvent of the filtrate was evaporated to yield 0.178 g of the crude product as a pale reddish brown oil, which was chromatographed on silica with 25% ethyl acetate in hexane to yield 61 mg of 4-ethyl-2-thiophen-3-yl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine. ^1H NMR ($CDCl_3$) 1.15 (t, 3H), 2.62 (m, 2H), 3.20 (dd, 1H), 3.30 (dd, 1H), 3.80 (d, 1H), 4.10 (d, 1H), 5.00 (dd, 1H), 7.00-7.08 (m, 2H), 7.14 (d, 1H), 7.15-7.3l (m, 4H). MS (ES+) 240 (MH^+).

EXAMPLE E26.1

This Example illustrates the preparation of 2-(5-Bromo-thiophen-2-yl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



Step A: (5-Bromo-thiophen-2-yl)-hydroxy-acetic acid methyl ester

24.8 g of 5-bromo-thiophene-2-carbaldehyde was dissolved in 65 ml of dichloromethane and stirred at room temperature. 8.1 g of Ytterbium triflate was added, followed by drop-wise addition of 20.8 ml of trimethylsilyl cyanide over 20 minutes. The dark brown mixture was stirred at room temperature for 5 hours. Then the reaction mixture was quenched with a saturated aqueous solution of of sodium carbonate and extracted three times with diethyl ether. The combined organic phases were washed with a saturated aqueous solution of of sodium carbonate, dried (Na_2SO_4), filtered and evaporated to yield 35 g of product, which was dissolved in 160 ml of methanol. 52 ml of concentrated HCl were added and the mixture was heated to reflux with stirring for 3 hours. The methanol was evaporated and the residue was neutralized with a saturated aqueous solution of of sodium carbonate. The aqueous phase was extracted 3 times with ethylacetate. The combined organic phases were washed with water, dried (Na_2SO_4), filtered and evaporated to yield 25 g of crude product. Flashchromatography (SiO_2, hexane-ethyl acetate 5:1) gave 17 g of the product. ^1H NMR ($CDCl_3$, 400 MHz) 3.51 (broad d, 1H), 3.82 (s, 3H), 5.35 (d, 1H), 6.87 (m, 1H), 6.96 (d, 1H).

Step B: (5-Bromo-thiophen-2-yl)-hydroxy-acetic acid

4.3 g of (5-bromo-thiophen-2-yl)-hydroxy-acetic acid methyl ester (Example E2, step A) was dissolved in 60 ml of tetrahydrofuran and stirred at 5°C. A solution of 0.75 g of lithium hydroxide monohydrate in 25 ml of water was added and the mixture was stirred at room temperature for 20 hours. The tetrahydrofuran was evaporated and the residue was acidified with 5% aqueous HCl. The aqueous phase was extracted 3 times with ethyl acetate. The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and evaporated to yield 2.9 g of crude product.

Step C: 2-(5-Bromo-thiophen-2-yl)-N-ethyl-2-hydroxy-N-(2-hydroxy-benzyl)-acetamide

1.4 g of (5-bromo-thiophen-2-yl)-hydroxy-acetic acid (Example E2, step B) was dissolved in 12 ml DMF, and then 4.0 ml of ethyldiisopropylamine, 0.95 g of 2-ethylaminomethyl-phenol (Example E1, step A) and 2.87 g of BOP were slowly added. This reaction mixture was stirred at room temperature for 16 hours, and then poured into 50 ml of ice water. The mixture was extracted 3 times with ethyl acetate and the combined organic phases were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography

(hexane:ethyl acetate 3:1) to yield 1.6 g of product. ^{1}H NMR ($CDCl_3$, 400 MHz) 1.08 (t, 3H), 3.19-3.37 (m, 2H), 4.26 (d, 2H), 4.46 (d, 1H), 4.55 (d, 1H), 5.37 (d, 1H), 6.66 (d, 1H), 6.78 (t, 1H), 6.84 (d, 1H), 6.91 (d, 1H), 7.06 (dd, 1H), 7.25 (td, 1H), 8.78 (s, 1H).

Step D: 2-(5-Bromo-thiophen-2-yl)-4-ethyl-4,5-dihydro-benzo[f][1,4]oxazepin-3-one

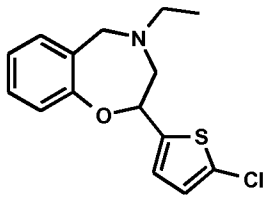
1.00 g of 2-(5-bromo-thiophen-2-yl)-N-ethyl-2-hydroxy-N-(2-hydroxy-benzyl)-acetamide (Example E2, step C) was dissolved in 25 ml of THF and stirred at room temperature under argon atmosphere. 1.4 g of sodium carbonate and then slowly 0.98 ml of thionylchloride were added. After the addition was complete the suspension was stirred for 1 hour at room temperature. The reaction mixture was filtered and the solvent removed under reduced pressure. The residue was neutralized (pH 7) with ice and triethylamine. The mixture was extracted 3 times with ethyl acetate. The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The crude product was dissolved in 30 ml of acetonitrile and 0.58 g of potassium carbonate was added. The mixture was stirred for 1.5 hours at room temperature and then filtered. The filtrate was concentrated under reduced pressure and the residue was dissolved in ethyl acetate. The organic phase was extracted with water and the water phase was extracted two times with ethyl acetate. The combined organic phases were dried (Na_2SO_4), filtered and evaporated. The residue was subjected to column chromatography on silica (hexane-ethyl acetate 5:1) to yield 0.4 g of the product. ^{1}H NMR ($CDCl_3$, 400 MHz) 1.18 (t, 3H), 3.59 (q, 2H), 4.53 (d, 1H), 4.60 (d, 1H), 5.96 (s, 1H), 6.93-6.97 (m, 2H), 7.01-7.10 (m, 2H), 7.20 (dd, 1H), 7.28 (td, 1H). MS (ES+) 352, 354 (MH^+).

Step E: 2-(5-Bromo-thiophen-2-yl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine

1.9 g of 2-(5-bromo-thiophen-2-yl)-4-ethyl-4,5-dihydro-benzo[f][1,4]oxazepin-3-one (Example E2, step D) in 20 ml of THF was heated in a flask equipped with a vigreux column and a descending cooler to 65°C and 7 ml of 2M solution of borandimethyl-sulfide in THF was added within 15 minutes. Heating was continued for 1 hour and the reaction mixture was allowed to cool down to room temperature overnight. The reaction mixture was treated with 16 ml of 2N HCl and stirred for 20 minutes. The pH was raised to pH 11 by addition of 4N NaOH and the mixture was extracted 3 times with dichloromethane. The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (SiO_2, hexane-ethyl acetate 5:1) to yield 1.25 g of 2-(5-bromo-thiophen-2-yl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine. ^{1}H NMR ($CDCl_3$, 400 MHz) 1.15 (t, 3H), 2.52-2.69 (m, 2H), 3.26 (dd, 1H), 3.34 (dd, 1H), 3.78 (d, 1H), 4.08 (d, 1H), 5.07 (dd, 1H), 6.76 (d, 1H), 6.96 (d, 1H), 7.02-7.08 (m, 2H), 7.14-7.25 (m, 2H). MS (ES+) 338, 340 (MH^+).

EXAMPLE E27.1

This Example illustrates the preparation of 2-(5-Chloro-thiophen-2-yl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



METHOD A:

Step A: (5-Chloro-thiophen-2-yl)-hydroxy-acetic acid methyl ester

2.5 g of 5-chloro-thiophene-2-carbaldehyde was dissolved in 10 ml of dichloromethane and stirred at room temperature. 100 mg of Ytterbium triflate was added, followed by drop-wise addition of 2.7 ml of trimethylsilyl cyanide over 10 minutes. The dark brown mixture was stirred at room temperature for 4 hours. Then the reaction mixture was quenched with a saturated aqueous solution of of sodium carbonate and extracted three times with diethyl ether. The combined organic phases were washed with a saturated aqueous solution of of sodium carbonate, dried (Na_2SO_4), filtered and concentrated. The residue was dissolved in 20 ml of methanol. 2 ml of concentrated HCl were added and the mixture was heated to reflux with stirring for 3 hours. The methanol was evaporated and the residue was neutralized with a saturated aqueous solution of of sodium carbonate. The aqueous phase was extracted two times with ethyl acetate. The combined organic phases were washed with water, dried (Na_2SO_4), filtered and concentrated. The residue was subjected to column chromatography (SiO_2, isohexane-ethyl acetate 1:1) gave 1.6 g of a white amorphous product. ^{1}H NMR ($CDCl_3$, 300 MHz) 3.66 (s, 1H), 3.83 (s, 3H), 5.30 (s, 1H), 6.79 (d, 1H), 6.87 (dd, 1H).

Step B: 2-(5-Chloro-thiophen-2-yl)-N-ethyl-2-hydroxy-N-(2-hydroxy-benzyl)-acetamide

1.6 g of (5-chloro-thiophen-2-yl)-hydroxy-acetic acid methyl ester (Example 3, step A) and 1.7 g of 2-ethylaminomethyl-phenol (Example E1, method A, step A) were mixed and heated at 125°C for 1.5 hours evaporating methanol to yield 3.1 g of crude product.

Step C: 2-(5-Chloro-thiophen-2-yl)-4-ethyl-4,5-dihydro-benzo[f][1,4]oxazepin-3-one

3.1 g of crude 2-(5-chloro-thiophen-2-yl)-N-ethyl-2-hydroxy-N-(2-hydroxy-benzyl)-acetamide (Example E3, method A, step B) was dissolved in 40 ml of THF and stirred at room temperature under argon atmosphere. 2.0 g of sodium carbonate and then at 0°C 3.5 ml of thionylchloride were added. After the addition was complete the suspension was stirred for 2 hours at room temperature. The reaction mixture was filtered and the solvent removed under reduced pressure. The crude product was dissolved in 30 ml of acetonitrile and 1.0 g of potassium carbonate was added at 0°C. The mixture was stirred for 3 hours at room temperature and then filtered. The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography on silica (isohexane-ethyl acetate 3:1) to yield 417 mg of the product. ^{1}H NMR ($CDCl_3$, 300 MHz) 1.18 (t, 3H), 3.61 (q, 2H), 4.54 (d, 1H), 4.60 (d, 1H), 5.93 (d, 1H), 6.81-6.27 (m, 6H).

Step D: 2-(5-Chloro-thiophen-2-yl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine

59 mg of $LiAlH_4$ was added to a mixture of 304 mg of $AlCl_3$ in 10 ml THF at 0°C under stirring. Then 340 mg of 2-(5-chloro-thiophen-2-yl)-4-ethyl-4,5-dihydro-benzo[f][1,4]oxazepin-3-one (Example E3, method A, step C) in 15 ml of THF was added and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched with water under nitrogen with cooling. The mixture was extracted two times with diethyl ether. The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography on silica (isohexane-ethyl acetate 1:1) to yield 213 mg of 2-(5-chloro-thiophen-2-yl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.

METHOD B:

Step A: Ethyl-(2-fluoro-benzyl)-amine

To a solution of 6.2 g of 2-fluorobenzaldehyde in 80 ml of methanol was added 125 ml of a 2N solution of ethylamine in methanol and the resulting solution was stirred at room temperature for 2 hours. The solution was then cooled to 0°C and 3.7 g of sodium borohydride were added portion wise. Upon completion of the addition, the reaction mixture was stirred for 2 hours at room temperature then the solvent was removed *in vacuo*. The residue was partitioned between water and ethyl acetate, the organic layer was washed with brine, dried over sodium sulphate and concentrated *in vacuo* to afford 7.7 g of ethyl-(2-fluoro-benzyl)-amine as a yellow oil.

Step B: 1-(5-Chloro-thiophen-2-yl)-2-[ethyl-(2-fluoro-benzyl)-amino]-ethanone

To a solution of 308 mg of ethyl-(2-fluoro-benzyl)-amine (Example E3, method B, step A) in 20 ml acetonitrile at room temperature was added 415 mg of potassium carbonate then 465 mg of 2-bromo-1-(5-chloro-thiophen-2-yl)-ethanone dissolved in a minimum of acetonitrile. The resulting reaction mixture was stirred at room temperature for 2 hours, at which time TLC and LCMS indicated complete formation of the product. The reaction mixture was diluted with water and extracted with ethyl acetate; the organic layer was washed with water then with brine, dried over sodium sulphate, filtered and concentrated *in vacuo* to afford 540 mg of 1-(5-chloro-thiophen-2-yl)-2-[ethyl-(2-fluoro-benzyl)-amino]-ethanone as a yellow oil. MS (ES+) 312/314 (MH^+).

Step C: 1-(5-Chloro-thiophen-2-yl)-2-[ethyl-(2-fluoro-benzyl)-amino]-ethanol

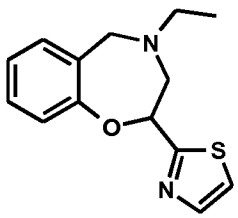
To a solution of 530 mg of 1-(5-chloro-thiophen-2-yl)-2-[ethyl-(2-fluoro-benzyl)-amino]-ethanone (Example E3, method B, step B) in 20 ml methanol was added 126 mg of sodium borohydride portion wise. Upon completion of the addition, the reaction mixture was stirred 2 hours at room temperature, and then the solvent was removed *in vacuo*. The residue was partitioned between water and ethyl acetate, the organic layer was washed with brine, dried over sodium sulphate, filtered and concentrated *in vacuo* to afford 496 mg of 1-(5-chloro-thiophen-2-yl)-2-[ethyl-(2-fluoro-benzyl)-amino]-ethanol as a brown oil, which was used as such. MS (ES+) 314/316 (MH^+).

Step D: 2-(5-Chloro-thiophen-2-yl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine

To a suspension of 51 mg of sodium hydride in 4 ml dimethylacetamide under N_2 was added a solution of 200 mg of 1-(5-chloro-thiophen-2-yl)-2-[ethyl-(2-fluoro-benzyl)-amino]-ethanol (Example E3, method B, step C) in 2 ml dimethylacetamide and the resulting mixture was stirred 1 hour at room temperature, then 2 hours at 60°C. The reaction mixture was cooled to room temperature, poured into water then extracted with diethyl ether. The organic layer was washed with water and brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was subjected to silica gel chromatography (cyclohexane: ethyl acetate 7:3) to afford 90 mg of 2-(5-chloro-thiophen-2-yl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) 1.17 (t, J = 6.95 Hz, 3H), 2.64 (m, 2H), 3.26 (dd, J = 14.3, 9.5 Hz, 1H), 3.35 (d, J = 14.3 Hz 1H), 3.80 and 4.10 (d, J = 14.2 Hz, 2H), 5.08 (d, J = 9.5 Hz, 1H), 6.78 (d, J = 3 Hz, 1H), 6.83 (d, J = 3 Hz, 1H), 7.05-7.25 (m, 4H). MS (ES+) 294/296 (MH^+).

EXAMPLE E28.1

This example illustrates the preparation of 4-Ethyl-2-thiazol-2-yl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



Step A: 2-Chloro-1-thiazol-2-yl-ethanone

According to the procedure described in WO03059911, a solution of 23.6 ml of 2-(trimethylsilyl)thiazole in 200 ml dichloromethane at 0°C under N_2 was treated drop wise with 24 ml of chloroacetyl chloride and the resulting solution was stirred at 0°C for 2 hours, then neutralised with saturated sodium bicarbonate until neutral pH. The aqueous layer was extracted with dichloromethane, washed with brine, dried over sodium sulphate, filtered and concentrated *in vacuo* to yield 25 g of a brown oil. Silica gel chromatography (cyclohexane: dichloromethane 1:1) afforded 17 g of 2-chloro-1-thiazol-2-yl-ethanone as a white solid. MS (ES+) 162/164 (MH^+).

Step B: 2-Ethylamino-1-thiazol-2-yl-ethanol

To a solution of 644 mg of 2-chloro-1-thiazol-2-yl-ethanone (Example E4, step A) in 10 ml methanol at 0°C under N_2 was added 300 mg of sodium borohydride portion wise. The resulting mixture was stirred at room temperature for 30 min., and then quenched by careful addition of 1N HCl until pH 4; the mixture was neutralised with saturated aqueous sodium bicarbonate, extracted with dichloromethane, dried over sodium sulphate, filtered then concentrated *in vacuo*. Silica gel chromatography (cyclohexane: ethyl acetate 1:1) afforded 600 mg of 2-chloro-1-thiazol-2-yl-ethanol as a yellow solid. MS (ES+) 164/166 (MH^+). This product was treated with 9.7 ml of ethylamine (2M in ethanol) and 150 mg of sodium iodide in a sealed tube at 60°C for 12 hours; the solution was concentrated *in vacuo* to afford 235 mg

of crude 2-ethylamino-1-thiazol-2-yl-ethanol, which was used as such. MS (ES+) 173/174 (MH^+).

Step C: 2-[Ethyl-(2-iodo-benzyl)-amino]-1-thiazol-2-yl-ethanol

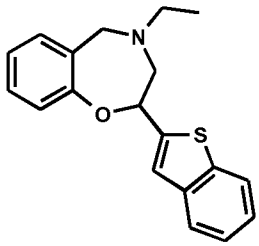
A solution of 930 mg of 2-ethylamino-1-thiazol-2-yl-ethanol (Example E4, step B) in 30 ml acetonitrile was treated with 1.9 ml of N,N-diisopropylethylamine and 1.6 g of 2-iodobenzyl bromide at room temperature for 1 hour. The reaction mixture was then concentrated *in vacuo* and subjected to silica gel chromatography (cyclohexane: ethyl acetate 8:2) to afford 475 mg of 2-[ethyl-(2-iodo-benzyl)-amino]-1-thiazol-2-yl-ethanol as a white solid. M.p. 83-84°C; MS (ES+) 389 (MH^+).

Step D: 4-Ethyl-2-thiazol-2-yl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine

A mixture of 194 mg of 2-[ethyl-(2-iodo-benzyl)-amino]-1-thiazol-2-yl-ethanol (Example E4, step C), 9.59 mg of copper(I) iodide and 103 mg of potassium carbonate in 3 ml of dimethylacetamide were heated in a sealed tube under microwave irradiation at 220°C for 10 min. The reaction mixture was then poured into water, extracted with ethyl acetate, the organic layer was dried over sodium sulphate, filtered, concentrated *in vacuo* and the residue subjected to silica gel chromatography (cyclohexane:ethyl acetate 1:1) to afford 102 mg of 4-ethyl-2-thiazol-2-yl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) 1.17 (t, 3H), 2.60 (m, 2H), 3.16 (dd, 1H), 3.70 (d, 1H), 3.78 and 4.08 (d, 2H), 5.14 (d, 1H), 6.98-7.17 (m, 4H), 7.30 (d, 1H), 7.72 (d, 1H). MS (ES+) 261 (MH^+).

EXAMPLE E29.1

This Example illustrates the preparation of 2-Benzo[b]thiophen-2-yl-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



Step A: Benzo[b]thiophen-2-yl-hydroxy-acetic acid ethyl ester

To 5.3 g of benzothiophene and 300 mg of Ytterbium triflate in 15 ml of dichloromethane was added at room temperature 4 g of oxo-acetic acid ethyl ester. The reaction mixture was stirred at room temperature for 2 hours. Then the solvent was evaporated and the residue was subjected to column chromatography (SiO_2, isohexane-ethyl acetate 2:1) gave 2.6 g of product as a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) 1.2 (t, 3H), 3.48 (d, 1H), 4.20 and 4.27 (m, 2H), 5.53 (d, 1H), 7.85 (s, 1H), 7.23-7.93 (m, 4H).

Step B: Benzo[b]thiophen-2-yl-hydroxy-acetic acid

4.3 g of Benzo[b]thiophen-2-yl-hydroxy-acetic acid ethyl ester (Example E5, step A) was dissolved in 45 ml of tetrahydrofuran and stirred at 5°C. A solution of 0.48 g of lithium hydroxide monohydrate in 15 ml of water was added drop wise over 10 minutes and the mixture was stirred at room temperature for a few hours. The tetrahydrofuran was evaporated

and the residue was acidified with diluted aqueous HCl. The aqueous phase was extracted 3 times with diethyl ether. The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated to yield 1.95 g of white amorphous product.

Step C: 2-Benzo[b]thiophen-2-yl-N-ethyl-2-hydroxy-N-(2-hydroxy-benzyl)-acetamide

1.4 g of Benzo[b]thiophen-2-yl-hydroxy-acetic acid (Example E5, step B) was dissolved in 15 ml DMF, and then 6.3 ml of ethyldiisopropylamine, 1.5 g of 2-ethylaminomethyl-phenol (Example E1, step A) and 4.4 g of BOP were added. The reaction mixture was stirred at room temperature for 2 hours and then poured into 150 ml of brine. The mixture was extracted 2 times with ethyl acetate and the combined organic phases were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography (isohexane:ethyl acetate 2:1) to yield 1.56 g of product as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) 0.943 (t, 3H), 3.18 (q, 2H), 4.27 (d, 1H), 4.56 (m, 2H), 5.61 (d, 1H), 6.81-7.95 (m, 9H), 9.04 (s, 1H).

Step D: 2-Benzo[b]thiophen-2-yl-4-ethyl-4,5-dihydro-benzo[f][1,4]oxazepin-3-one

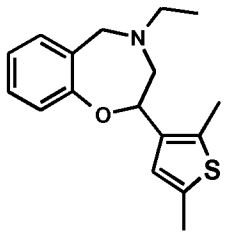
A solution of 1.41 g of triphenylphosphine in 20 ml of THF was cooled to 0°C and 3.0 ml of DEAD were added within 15 minutes under stirring. Then 1.56 g of 2-benzo[b]thiophen-2-yl-N-ethyl-2-hydroxy-N-(2-hydroxy-benzyl)-acetamide (Example E5, step C) in 20 ml THF was added. After the addition was complete the mixture was stirred for 30 minutes at 0°C and for 1 hour at room temperature. The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica (isohexane-ethyl acetate 3:1) to yield 970 mg of the product. ^{1}H NMR ($CDCl_3$, 300 MHz) 1.21 (t, 3H), 3.66 (m, 2H), 4.69 (s, 2H), 5.93 (d, 1H), 6.89-8.00 (m, 9H).

Step E: 2-Benzo[b]thiophen-2-yl-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine

159 mg of $LiAlH_4$ was added to a mixture of 822 mg of $AlCl_3$ in 30 ml of THF at 0°C under stirring. Then 973 mg of 2-benzo[b]thiophen-2-yl-4-ethyl-4,5-dihydro-benzo[f][1,4]oxazepin-3-one (Example E5, step D) in 15 ml of THF was added and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched with water under nitrogen with cooling. The mixture was extracted two times with diethyl ether. The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography on silica (isohexane-ethyl acetate 1:1) to yield 450 mg of 2-benzo[b]thiophen-2-yl-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) 1.19 (t, 3H), 2.71 (m, 2H), 3.43 (m, 2H), 3.86 (d, 1H), 4.15 (d, 1H), 5.32 (dd, 1H), 7.05-7.91 (m, 9H). MS (ES+) 310 (MH^+).

EXAMPLE E30.1

This Example illustrates the preparation of 2-(2,5-Dimethyl-thiophen-3-yl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



Step A: 2-Bromo-1-(2,5-dimethyl-thiophen-3-yl)-ethanone

4.7 g of 1-(2,5-dimethyl-thiophen-3-yl)-ethanone in 50 ml of chloroform was treated in two portions with 8.7 g of PBP and the mixture was stirred at room temperature for 2.5 hours. The reaction mixture was poured into ice water and extracted with diethyl ether. The organic layer was dried over sodium sulphate, filtered and concentrated *in vacuo* to afford 5.6 g of a brown oil, which was subjected to silica gel chromatography (isohexane: ethyl acetate 1:1) to afford 5.3 g of 2-Bromo-1-(2,5-dimethyl-thiophen-3-yl)-ethanone as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) 2.42 (s, 3H), 2.68 (s, 3H), 4.25 (s, 2H), 7.00 (s, 1H).

Step B: 1-(2,5-Dimethyl-thiophen-3-yl)-2-[ethyl-(2-hydroxy-benzyl)-amino]-ethanone

To a solution of 3.4 g of 2-ethylaminomethyl-phenol (Example E6, step A) in 30 ml acetonitrile at room temperature was added 3 ml of diisopropylethylamine and then in 3 portions 5.3 g of 2-Bromo-1-(2,5-dimethyl-thiophen-3-yl)-ethanone (Example E1, step A). The resulting reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* and purified by silica gel chromatography (isohexane: ethyl acetate 3:1) to afford 6.0 g of 1-(2,5-Dimethyl-thiophen-3-yl)-2-[ethyl-(2-hydroxy-benzyl)-amino]-ethanone as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) 1.10 (t, 3H), 2.40 (s, 3H), 2.69 (s, 3H), 2.71 (q, 2H), 3.82 (s, 2H), 3.84 (s, 2H), 6.76-7.12 (m, 5H).

Step C: 2-({[2-(2,5-Dimethyl-thiophen-3-yl)-2-hydroxy-ethyl]-ethyl-amino}-methyl)-phenol

To a solution of 6.0 g of 1-(2,5-Dimethyl-thiophen-3-yl)-2-[ethyl-(2-hydroxy-benzyl)-amino]-ethanone (Example E6, step B) in 50 ml methanol was added under cooling (ice bath) 740 mg of sodium borohydride portion wise. Upon completion of the addition, the reaction mixture was stirred 1 hour at room temperature, and then poured into ice water. The mixture was extracted with diethyl ether. The organic layer was washed with brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was subjected to column chromatography (isohexane: ethyl acetate 3:1) to afford 5.0 g of 2-({[2-(2,5-Dimethyl-thiophen-3-yl)-2-hydroxy-ethyl]-ethyl-amino}-methyl)-phenol. ^{1}H NMR ($CDCl_3$, 300 MHz) 1.11 (t, 3H), 2.28 (s, 3H), 2.64 (dd, 1H), 2.70 (m, 2H), 2.84 (dd, 1H), 3.37 (broad s, 4H), 4.93 (dd, 1H), 6.61-7.16 (m, 5H). MS (ES+) 288 (MH^+).

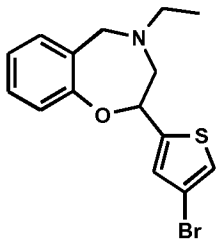
Step D: 2-(2,5-Dimethyl-thiophen-3-yl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4] oxazepine

10 ml of diethylazodicarboxylate (~40% in toluene) was added to an ice-cold solution of 5.3 g of triphenylphosphine in 50 ml THF within 15 minutes. A solution of 5.0 g of 2-({[2-(2,5-Dimethyl-thiophen-3-yl)-2-hydroxy-ethyl]-ethyl-amino}-methyl)-phenol (Example E6, step C) in 30 ml of THF was added drop wise. The reaction mixture was stirred 30 minutes under ice cooling and 1 hour at ambient temperature. The solvents were evaporated under reduced

pressure. Purification of the residue by column chromatography on silica gel (isohexane-ethyl acetate 3:1) afforded 1.9 g of the product 2-(2,5-dimethyl-thiophen-3-yl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4] oxazepine as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) 1.14 (t, 3H), 2.35 (s, 3H), 2.43 (s, 3H), 2.62 (m, 2H), 3.11 (dt, 1H), 3.25 (dd, 1H), 3.77 (dd, 1H), 4.05 (d, 1H), 4.89 (dd,1H), 6.78 (d,1H), 7.01-7.19 (m, 4H).

EXAMPLE E31.1

This Example illustrates the preparation of 2-(4-bromo-thiophen-2-yl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



Step A: (4-Bromo-thiophen-2-yl)-hydroxy-acetic acid methyl ester

24.8 g of 4-bromo-thiophene-2-carbaldehyde was dissolved in 65 ml of dichloromethane and stirred at room temperature. 8.1 g of Ytterbium triflate was added, followed by drop-wise addition of 20.8 ml of trimethylsilyl cyanide over 20 minutes. The dark brown mixture was stirred at room temperature for 6 hours. Then the reaction mixture was quenched with a saturated aqueous solution of of sodium carbonate and extracted three times with diethyl ether. The combined organic phases were washed with a saturated aqueous solution of of sodium carbonate, dried (Na_2SO_4), filtered and evaporated to yield 39 g of crude product, which was dissolved in 190 ml of methanol. 60 ml of concentrated HCl were added and the mixture was heated to reflux with stirring for 4 hours. The methanol was evaporated and the residue was neutralized with a saturated aqueous solution of of sodium carbonate. The aqueous phase was extracted 3 times with ethyl acetate. The combined organic phases were washed with water, dried (Na_2SO_4), filtered and evaporated to yield 25 g of crude product. Flashchromatography (SiO_2, hexane-acetone 9:1) gave 23 g of the product. ^{1}H NMR ($CDCl_3$, 400 MHz) 3.58 (d, 1H), 3.88 (s, 3H), 5.40 (d, 1H), 7.03 (m, 1H), 7.21 (d, 1H).

Step B: (4-Bromo-thiophen-2-yl)-hydroxy-acetic acid

22.6 g of (4-bromo-thiophen-2-yl)-hydroxy-acetic acid methyl ester (Example E7, step A) was dissolved in 330 ml of tetrahydrofuran and stirred at 5°C. A solution of 4 g of lithium hydroxide monohydrate in 135 ml of water was added and the mixture was stirred at room temperature for 20 hours. The tetrahydrofuran was evaporated and the residue was acidified with 5% aqueous HCl. The aqueous phase was extracted 3 times with ethyl acetate. The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and evaporated to yield 12 g of crude product.

Step C: 2-(4-Bromo-thiophen-2-yl)-N-ethyl-2-hydroxy-N-(2-hydroxy-benzyl)-acetamide

6.0 g of (4-bromo-thiophen-2-yl)-hydroxy-acetic acid (Example E7, step B) was dissolved in 50 ml DMF, and then 17.3 ml of ethyldiisopropylamine, 3.63 g of 2-ethylaminomethyl-phenol

(Example E1, step A) and 12.3 g of BOP were slowly added. This reaction mixture was stirred at room temperature for 16 hours, and then poured into 250 ml of ice water. The mixture was extracted 3 times with ethyl acetate and the combined organic phases were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography (hexane:ethyl acetate 2:1) to yield 6.8 g of product. ^1H NMR ($CDCl_3$, 300 MHz) 1.12 (t, 3H), 3.23-3.36 (m, 2H), 4.37 (d, 2H), 4.52 (d, 1H), 4.60 (d, 1H), 5.45 (d, 1H), 6.68-7.32 (m, 6H), 8.73 (s, 1H).

Step D: 2-(4-Bromo-thiophen-2-yl)-4-ethyl-4,5-dihydro-benzo[f][1,4]oxazepin-3-one

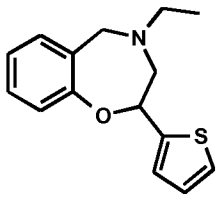
6.3 g of 2-(4-bromo-thiophen-2-yl)-N-ethyl-2-hydroxy-N-(2-hydroxy-benzyl)-acetamide (Example E7, step C) was dissolved in 170 ml of diethyl ether and stirred at room temperature under argon atmosphere. 9.0 g of sodium carbonate and then slowly 6.2 ml of thionylchloride were added. After the addition was complete the suspension was stirred for 20 hour at room temperature. The reaction mixture was poured on ice water and the mixture was extracted 3 times with ethyl acetate. The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The crude product was dissolved in 120 ml of dimethylformamide and 0.82 g of sodium hydride was added portion wise. The reaction mixture was stirred for 20 hours at room temperature and then poured on ice water. The aqueous phase was extracted three times with ethyl acetate. The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was subjected to column chromatography on silica (hexane-ethyl acetate 5:1) to yield 3.1 g of the product. ^1H NMR ($CDCl_3$, 400 MHz) 1.09 (t, 3H), 3.53 (m, 2H), 4.57 (d, 1H), 4.60 (d, 1H), 5.82 (s, 1H), 6.95-7.25 (m, 6H).

Step E: 2-(4-Bromo-thiophen-2-yl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine

2.28 g of 2-(4-bromo-thiophen-2-yl)-4-ethyl-4,5-dihydro-benzo[f][1,4]oxazepin-3-one (Example E7, step D) in 23 ml of THF was heated in a flask equipped with a vigreux column and a descending cooler to 65°C and 7 ml of 2M solution of borandimethyl-sulfide in THF was added within 20 minutes. Heating was continued for 5 hours and the reaction mixture was allowed to cool down to room temperature overnight. The reaction mixture was treated with 16 ml of 2N HCl and stirred for 5 minutes. The pH was raised to pH 11 by addition of 4N NaOH and the mixture was extracted 3 times with dichloromethane. The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (SiO_2, hexane-ethyl acetate 5:1) to yield 1.20 g of 2-(4-bromo-thiophen-2-yl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine. ^1H NMR ($CDCl_3$, 400 MHz) 1.16 (t, 3H), 2.53-2.71 (m, 2H), 3.28 (dd, 1H), 3.36 (dd, 1H), 3.81 (d, 1H), 4.10 (d, 1H), 5.10 (dd, 1H), 6.91 (s, 1H), 7.03-7.25 (m, 5H). MS (ES+) 338, 340 (MH^+).

EXAMPLE E32.1

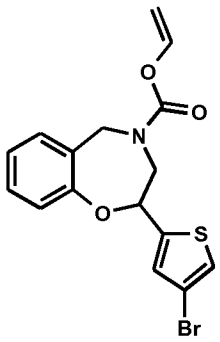
This Example illustrates the preparation of 4-ethyl-2-thiophen-2-yl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



A solution of 100 mg of 2-(4-bromo-thiophen-2-yl)-4-ethyl-4,5-dihydro-benzo[f][1,4]oxazepin-3-one (Example E7, step D) in 2 ml of THF was added to a solution 0.7 ml of 1M solution of lithium aluminium hydride in THF at 65°C. Heating was continued for 4 hours and the reaction mixture was cooled down to 0°C. The reaction mixture was treated with 2 ml of water and stirred for 30 minutes (white suspension formed). The mixture was filtered and the filter residue was washed several times with ethyl acetate. The phases of the filtrate were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (SiO_2, hexane-ethyl acetate 5:1) to yield 25 g of 4-ethyl-2-thiophen-2-yl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine. ^{1}H NMR ($CDCl_3$, 400 MHz) 1.15 (t, 3H), 2.55-2.70 (m, 2H), 3.31 (dd, 1H), 3.38 (m, 1H), 3.79 (d, 1H), 4.11 (d, 1H), 5.15 (dd, 1H), 7.00 (d, 1H), 7.02-7.32 (m, 6H). MS (ES+) 259 (MH^+).

EXAMPLE E33.1

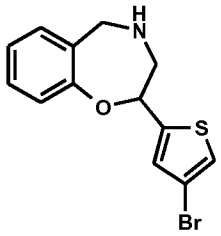
This Example illustrates the preparation of 2-(4-bromo-thiophen-2-yl)-2,3-dihydro-5H-benzo[f][1,4]oxazepine-4-carboxylic acid vinyl ester.



To a solution of 540 mg of 2-(4-bromo-thiophen-2-yl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine (Example E7) in 10 ml of THF was added 0.44 ml of vinyl chloroformate and the mixture was stirred 28 hours at reflux. The reaction mixture was cooled to room temperature and poured into 15 ml of ice water. The mixture was extracted was extracted 3 times with ethyl acetate. The combined organic phases were dried with sodium sulphate, filtered and concentrated *in vacuo*. The residue was subjected to column chromatography (hexane:ethyl acetate 20:1) to yield 300 mg of 2-(4-bromo-thiophen-2-yl)-2,3-dihydro-5H-benzo[f][1,4]oxazepine-4-carboxylic acid vinyl ester. ^{1}H NMR (400 MHz, $CDCl_3$) 3.45-3.69 (m, 1H), 4.31-4.67 (m, 3H), 4.77-5.01 (m, 3H), 6.98-7.40 (m, 7H). MS (ES+) 380, 382 (MH^+).

EXAMPLE E34.1

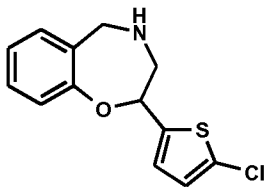
This Example illustrates the preparation of 2-(4-bromo-thiophen-2-yl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine



To a solution of 198 mg of 2-(4-bromo-thiophen-2-yl)-2,3-dihydro-5H-benzo[f][1,4]oxazepine-4-carboxylic acid vinyl ester (Example E9) in 4 ml of methanol was added 0.45 ml of concentrated HCl (37%) and the mixture was stirred 3 hours at 68°C. The reaction mixture was cooled to room temperature. Then 3 ml of ethyl acetate and 3 ml of a saturated aqueous solution of sodium hydrogen carbonate was added. The phases were separated and aqueous phase was extracted 3 times with ethyl acetate. The combined organic phases were dried with sodium sulphate, filtered and concentrated *in vacuo*. The residue was subjected to column chromatography (hexane:ethyl acetate 1:1 -> 1:2 -> 1:3) to yield 88 mg of 2-(4-bromo-thiophen-2-yl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine. ^{1}H NMR (400 MHz, $CDCl_3$) 1.85 (broad s, 1H), 3.30 (dd, 1H), 3.55 (dd, 1H), 3.88 (d, 1H), 4.13 (d, 1H), 4.39 (dd, 1H), 6.95 (s, 1H), 7.02-7.26 (m, 6H); MS (ES+) 310/312 (MH^+). As a side product 31 mg of ring-opened 2-({[2-(4-bromo-thiophen-2-yl)-2-methoxy-ethyl]-ethyl-amino}-methyl)-phenol was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) 1.85 (broad signal, 1H), 2.88 (dd, 1H), 2.99 (dd, 1H), 3.32 (s, 3H), 3.94 (d, 1H), 4.11 (d, 1H), 4.55 (dd, 1H), 6.78 (t, 1H), 6.84 (d, 1H), 6.92 (s, 1H), 7.00 (d, 1H), 7.19 (t, 1H), 7.21 (s, 1H).

EXAMPLE E35.1

This Example illustrates the preparation of 2-(5-chloro-thiophen-2-yl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



METHOD A:

Step A: 2-(5-Chloro-thiophen-2-yl)-2,3-dihydro-5H-benzo[f][1,4]oxazepine-4-carboxylic acid 1-chloro-ethyl ester

To a solution of 170 mg of 2-(5-chloro-thiophen-2-yl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine (Example E3) in 10 ml of toluene was added 1.2 ml of 1-chloroethyl chloroformate and the mixture was stirred under reflux for 2 hours. The reaction mixture was cooled to room temperature. Then 20 ml of ethyl acetate and 10 ml of a saturated solution of sodium hydrogen carbonate were added. The phases were separated and aqueous phase

was extracted. The combined organic phases were dried with sodium sulphate, filtered and concentrated *in vacuo*. The residue was used as such for the next step.

Step B: 2-(5-Chloro-thiophen-2-yl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine

A solution of 2-(5-chloro-thiophen-2-yl)-2,3-dihydro-5H-benzo[f][1,4]oxazepine-4-carboxylic acid 1-chloro-ethyl ester (Example E11, step A) in 20 ml of methanol was stirred 3 hours at 68°C. The reaction mixture was cooled to room temperature and the reaction mixture was concentrated *in vacuo*. The residue was subjected to column chromatography (dichloromethane-MeOH 95:5) to yield 89 mg of 2-(5-chloro-thiophen-2-yl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine. ^{1}H NMR (300 MHz, $CDCl_3$) 1.72 (br s, 1H), 3.27 (d, 1H), 3.32 (d, 1H), 3.95 (d, 1H), 4.10 (d, 1H), 4.82 (dd, 1H), 6.76 (d, 1H), 6.82 (d, 1H), 7.02-7.23 (m, 4H).

METHOD B:

Step A: 1-(5-Chloro-thiophen-2-yl)-2-(2-fluoro-benzylamino)-ethanol

1-(5-Chloro-thiophen-2-yl)-2-(2-fluoro-benzylamino)-ethanol was prepared from 2-fluorobenzylamine and 2-bromo-1-(5-chloro-thiophen-2-yl)-ethanone according to the procedure described in Example 3, method B, steps B-C. Alternatively, the title product was prepared as follows: A solution of 2.39 g of 2-bromo-1-(5-chloro-thiophen-2-yl)-ethanone in 50 ml chloroform was treated with 2.8 g of hexamethylenetetramine at 50°C for 1 hour, during which time a precipitate formed. The reaction mixture was cooled to room temperature and the solid collected by filtration, washed with chloroform and dried under vacuum. The solid was suspended in 50 ml ethanol and treated with a mixture of 15 ml ethanol and 25 ml of concentrated HCl. After the end of the addition, the clear solution was stirred at room temperature for 24 hours, during which time a precipitate formed. The solid was collected by filtration, washed with cold ethanol and dried under vacuum to yield 1.5 g of the hydrochloride salt of 2-amino-1-(5-chloro-thiophen-2-yl)-ethanone. MS (ES+) 312/314 (MH^+).

This product was reduced with 635 mg of sodium borohydride in 10 ml water at room temperature for 24 hours to afford after basification with 10% aqueous sodium hydroxide and extraction with dichloromethane 736 mg of 2-amino-1-(5-chloro-thiophen-2-yl)-ethanol as a solid. M.p. 75°C; MS (ES+) 178/180 (MH^+).

A solution of 265 mg of 2-amino-1-(5-chloro-thiophen-2-yl)-ethanol in 10 ml methanol at room temperature was treated sequentially with 0.16 ml of 2-fluorobenzaldehyde at room temperature for 2 hours , then with 111 mg of sodium borohydride at room temperature for 12 hours. The reaction mixture was concentrated *in vacuo* then partitioned between dichloromethane and water; the organic layer was dried over sodium sulphate and concentrated; the residue was subjected to silica gel chromatography (cyclohexane: ethyl acetate 1:1) to afford 300 mg of 1-(5-chloro-thiophen-2-yl)-2-(2-fluoro-benzylamino)-ethanol as a colorless solid. M.p. 88°C; MS (ES+) 286/288 (MH^+).

Alternatively, the title product was obtained by alkylation of 354 mg of 2-amino-1-(5-chloro-thiophen-2-yl)-ethanol with 0.23 ml of 2-fluorobenzyl bromide in 15 ml acetonitrile in the presence of 0.7 ml of N,N-diisopropylethylamine at room temperature for 24 hours;

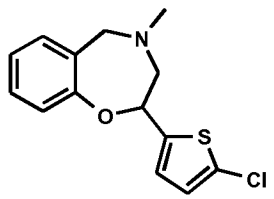
evaporation of the solvent and silica gel chromatography (cyclohexane: ethyl acetate 1:1) afforded 225 mg of the title product.

Step B: 2-(5-Chloro-thiophen-2-yl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine

To a suspension of 80 mg of sodium hydride in 3 ml dimethylacetamide under N_2 was added a solution of 285 mg of 1-(5-chloro-thiophen-2-yl)-2-(2-fluoro-benzylamino)-ethanol in 3 ml tetrahydrofuran and the resulting mixture was stirred at 65°C for 12 hours. A second portion of 40 mg of sodium hydride was added and the resulting mixture was stirred at 90°C for 3 hours. The reaction mixture was cooled to room temperature, poured into water then extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was subjected to silica gel chromatography (ethyl acetate) to afford 210 mg of 2-(5-chloro-thiophen-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) 1.72 (br s, 1H), 3.29 (dd, 1H), 3.35 (d, 1H), 3.80 and 4.10 (d, 2H), 4.82 (d, 1H), 6.75 (d, 1H), 6.76 (d, 1H), 7.05-7.26 (m, 4H). MS (ES+) 266/268 (MH^+).

EXAMPLE E36.1

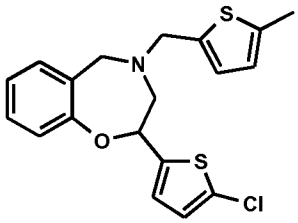
This Example illustrates the preparation of 2-(5-chloro-thiophen-2-yl)-4-methyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine.



74 mg of 2-(5-chloro-thiophen-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (Example E11) and 0.018 ml of methyl iodide in a mixture of 1 ml of ethyl acetate and 1 ml of a saturated aqueous solution of sodium hydrogen carbonate was stirred 3 hours at 60°C. The reaction mixture was cooled to room temperature. Then 5 ml of ethyl acetate was added and the phases were separated. The organic phase was washed with 5 ml of water, dried with sodium sulphate, filtered and concentrated *in vacuo*. The residue was subjected to column chromatography (hexane:ethyl acetate 3:1) to yield 25 mg of 2-(5-chloro-thiophen-2-yl)-4-methyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine. ^{1}H NMR (400 MHz, $CDCl_3$) 2.40 (s, 3H), 3.10-3.25 (m, 2H), 3.61 (d, 1H), 4.00 (d, 1H), 5.00 (d, 1H), 6.68 (d, 1H), 6.73 (d, 1H), 6.95-7.25 (m, 4H); MS (ES+) 380/282 (MH^+).

EXAMPLE E37.1

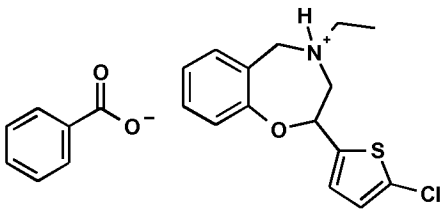
This Example illustrates the preparation of 2-(5-chloro-thiophen-2-yl)-4-thiophen-2-ylmethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine



80 mg of 2-(5-chloro-thiophen-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (Example E11) in 1 ml of dichloromethane was added to a solution of 5-methylthiophen-2-carbaldehyde in 1 ml of dichloroethane. 0.15 ml of acetic acid and a suspension of 210 mg sodium borohydride in 1 ml of dichloroethane and the mixture were stirred 20 hours at room temperature. The reaction mixture was treated with 2 ml of a saturated aqueous solution of sodium hydrogen carbonate extracted 3 times with dichloromethane. The combined organic phases were dried with sodium sulphate, filtered and concentrated *in vacuo*. The residue was subjected to column chromatography (hexane:ethyl acetate 19:1) to yield 75 mg of 2-(5-chloro-thiophen-2-yl)-4-thiophen-2-ylmethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine. ^{1}H NMR (400 MHz, $CDCl_3$) 2.49 (s, 3H), 3.30 (dd, 1H), 3.39 (d, 1H), 3.77-3.90 (m, 3H), 4.12 (d, 1H), 5.10 (d, 1H), 6.10 (d, 1H), 6.67 (d, 1H), 6.74 (d, 1H), 6.81 (d, 1H), 7.01-7.26 (m, 4H); MS (ES+) 376/378 (MH^+).

EXAMPLE E38.1

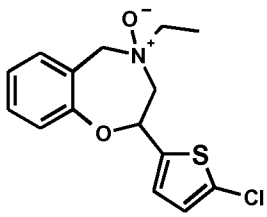
This Example illustrates the preparation of 2-(5-chloro-thiophen-2-yl)-4-ethyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin-4-ium benzoate.



58 mg of 2-(5-chloro-thiophen-2-yl)-4-ethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (Example E3) in 1 ml of diethyl ether was treated with 22.8 mg benzoic acid and stirred 1 hour at room temperature. The reaction mixture was concentrated *in vacuo* stirred with hexane, and filtered to give 74 mg of product.

EXAMPLE E39.1

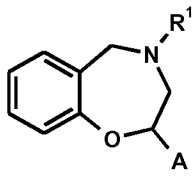
This Example illustrates the preparation of 2-(5-chloro-thiophen-2-yl)-4-ethyl-2,3-dihydro-5H-benzo[f][1,4]oxazepine 4-oxide.



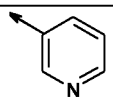
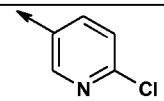
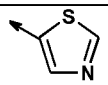
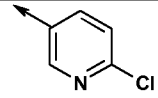
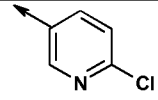
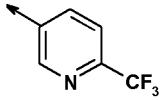
To a solution of 132 mg of 2-(5-chloro-thiophen-2-yl)-4-ethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (Example E3) in 2.5 ml of dichloromethane was added 123 mg of 3-chloro-perbenzoic acid and the mixture was stirred 5 hours at room temperature. Then 20 ml of ethyl acetate and 20 ml of a saturated aqueous solution of sodium hydrogen carbonate were added. The phases were separated and the aqueous phase was extracted was extracted with ethyl acetate. The combined organic phases were washed with water, dried with sodium sulphate, filtered and concentrated *in vacuo*. The residue was subjected to column chromatography (ethyl acetate:methanol 3:1) to yield 6 mg of 2-(5-chloro-thiophen-2-yl)-4-ethyl-2,3-dihydro-5H-benzo[f][1,4]oxazepine 4-oxide. ^{1}H NMR (400 MHz, $CDCl_3$) 1.32 (t, 3H), 3.04-3.26 (m, 2H), 3.81-4.0 (m, 2H), 4.32 (d, 1H), 4.78 (d, 1H), 4.89 (d, 1H), 6.69 (d, 1H), 6.73 (d, 1H), 7.01-30 (m, 4H); MS (ES+) 310/312 (MH^+).

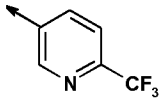
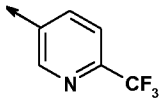
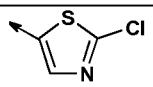
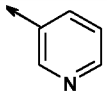
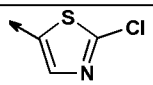
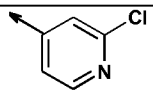
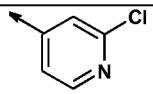
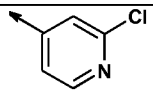
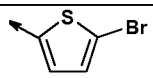
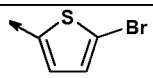
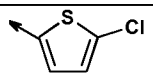
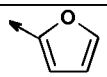
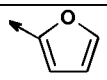
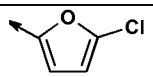
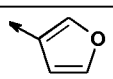
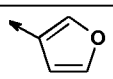
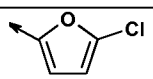
Further compounds listed in tables P3-P4 were prepared according to procedures similar to those described in examples E25.1-E39.1 or by general procedures published in the literature known to the person skilled in the art.

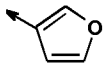
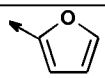
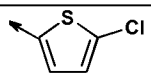
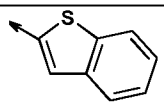
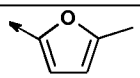
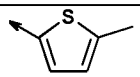
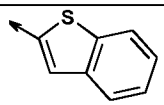
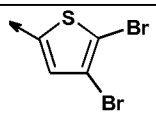
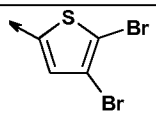
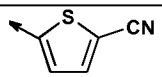
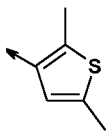
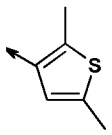
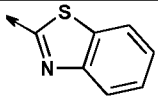
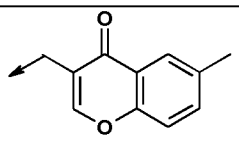
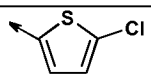
Table P3 : A compound of formula (I)


(I)

wherein the values are as given in the Table:

Line	R_1	A	M.p (°C)	MH^+
P3.1	CH_2CH_3		oil	255
P3.2	CH_2CH_3		oil	289/291
P3.3	CH_2CH_3		oil	261
P3.4	$C(=O)OCH=CH_2$		oil	331/333
P3.5	H		oil	261/263
P3.6	CH_2CH_3		oil	323/324

Line	R_1	A	M.p (°C)	MH^+
P3.7	$C(=O)OCH=CH_2$		100-102 °C	
P3.8	H		118-120 °C	
P3.9	CH_2CH_3		oil	295/297
P3.10	H		oil	
P3.11	$C(=O)OCH=CH_2$		oil	337/339
P3.12	CH_2CH_3		oil	289/291
P3.13	$C(=O)OCH=CH_2$		oil	331/333
P3.14	H		oil	261/263
P3.15	$C(=O)OCH=CH_2$		oil	380/382
P3.16	H		oil	310/312
P3.17	$C(=O)OCH=CH_2$		oil	336/338
P3.18	CH_2CH_3		oil	244
P3.19	H		oil	
P3.20	CH_2CH_3		oil	278/280
P3.21	CH_2CH_3		oil	244
P3.22	H		oil	
P3.23	H		oil	250/252

Line	R_1	A	M.p (°C)	MH^+
P3.24	$C(=O)OCH=CH_2$		oil	286
P3.25	$C(=O)OCH=CH_2$		oil	286
P3.26			oil	306/308
P3.27	H		oil	282
P3.28	CH_2CH_3		oil	258
P3.29	CH_2CH_3		oil	274
P3.30	$C(=O)OCH=CH_2$		oil	352
P3.31	CH_2CH_3		oil	416/418/420
P3.32	H		oil	388/390/392
P3.33	CH_2CH_3		oil	285
P3.34	$C(=O)OCH=CH_2$		wax	330
P3.35	H		wax	260
P3.36	CH_2CH_3		92-93 °C	311
P3.37			oil	438/440

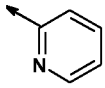
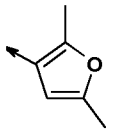
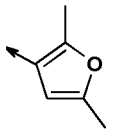
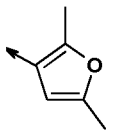
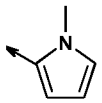
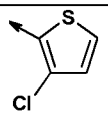
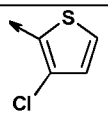
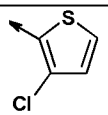
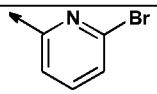
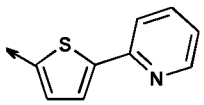
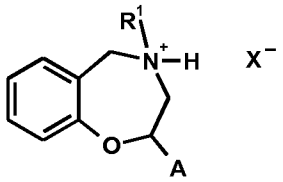
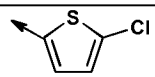
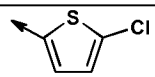
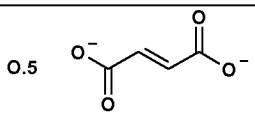
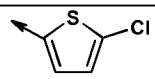
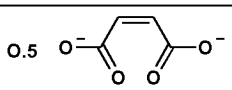
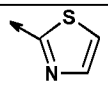
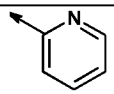
Line	R_1	A	M.p (°C)	MH^+
P3.38	CH_2CH_3		oil	255
P3.39	CH_2CH_3		oil	272
P3.40	$C(=O)OCH=CH_2$		oil	314
P3.41	H		oil	244
P3.42	CH_2CH_3		oil	257
P3.43	CH_2CH_3		oil	294/296
P3.44	$C(=O)OCH=CH_2$		oil	336/338
P3.45	H		oil	266/268
P3.46	CH_2CH_3		oil	333/335
P3.47	CH_2CH_3		oil	327

Table P4 : A compound of formula (Ib1)



(Ib1)

wherein the values are as given in the Table:

Line	R_1	A	X^-	M.p (°C)
P4.1	C_2H_5		Cl^-	110°C
P4.2	C_2H_5			140-141°C
P4.3	C_2H_5			110-111°C
P4.4	C_2H_5		Cl^-	resin
P4.5	CH_2CH_3		Cl^-	115-120°C

EXAMPLE 40

This Example illustrates the pesticidal/insecticidal properties of compounds of formula (I).

Test against were performed as follows:

Heliothis virescens (Tobacco budworm):

Eggs (0-24 h old) were placed in 24-well microtiter plate on artificial diet and treated with test solutions at an application rate of 200 ppm by pipetting. After an incubation period of 4 days, samples were checked for egg mortality, larval mortality, and growth regulation. The following compounds gave at least 80% control of *Heliothis virescens:*

P1.5, P1.32, P1.33, P1.338, P1.347, E26.1, E27.1, E28.1, P3.2, P3.1.

Plutella xylostella (Diamond back moth):

24-well microtiter plate (MTP) with artificial diet was treated with test solutions at an application rate of 18.2 ppm by pipetting. After drying, the MTP's were infested with larvae (L2)(10-15 per well). After an incubation period of 5 days, samples were checked for larval mortality, antifeedant and growth regulation. The following compounds gave at least 80% control of *Plutella xylostella:*

E3.5, E8.1, E14.1, P1.64.

Diabrotica balteata (Corn root worm):

A 24-well microtiter plate (MTP) with artificial diet was treated with test solutions at an application rate of 200 ppm (concentration in well 18 ppm) by pipetting. After drying, the MTP's were infested with larvae (L2) (6-10 per well). After an incubation period of 5 days, samples were checked for larval mortality, and growth regulation. The following compounds gave at least 80% control of *Diabrotica balteata:*

P1.2, P1.78, P1.129, P1.322, E27.1.

Aedes aegypti (Yellow fever mosquito):

10-15 Aedes larvae (L2) together with a nutrition mixture are placed in 96-well microtiter plates. Test solutions at an application rate of 2ppm are pipetted into the wells. 2 days later,

insects were checked for mortality and growth inhibition. The following compounds gave at least 80% control of *Aedes aegypti:*

E3.5, P1.2, P1.3, P1.25, P1.26.

Myzus persicae (Green peach aphid): Sunflower leaf discs are placed on agar in a 24-well microtiter plate and sprayed with test solutions at an application rate of 200 ppm. After drying, the leaf discs are infested with an aphid population of mixed ages. After an incubation period of 6 DAT, samples are checked for mortality and special effects (e.g. phytotoxicity). The following compounds gave at least 80% control of *Myzus persicae:*

E1.2, E2.1, E3.1, E3.2, E3.6, E6.1, E6.2, E7.1, E7.2, E3.7, E6.18, E6.19, E8.1, E8.11, E8.6, E8.7, E8.8, E8.9, E8.10, E8.14, E8.29, E8.31, E8.43, E8.44, E11.1, E10.2, E11.2, E11.8, E9.1, E10.3, E11.3, E11.4, E10.1, E12.1, E12.2, E3.5, E8.1, E8.2, E21.1, E5.1, E7.4, E23.1, P1.2, P1.3, P1.4, P1.5, P1.7, P1.8, P1.18, P1.19, P1.33, P1.42, P1.43, P1.45, P1.49, P1.64, P1.80, P1.82, P1.84, P1.90, P1.91, P1.68, P1.182, P1.184, P1.197, P1.193, P1.195, P1.192, P1.206, P1.207, P1.210, P1.176, P1.221, P1.222, P1.223, P1.229, P1.232, P1.235, P1.238, P1.247, P1,239, P1.333, P1.334, P1.341, P1.345, P1.347, P1.378, P1.397, P1.411, P1.412, P1.413, P1.414, P1.417, P1.419, P1.422, P1.425, P1.427, P1.431, P2.1, P2.5, P2.32, P2.34, E25.1, E26.1, E29.1, E31.1, E33.1, E34.1, E35.1, E36.1, E37.1, E38.1, E39.1, P3.15, P3.16, P3.17, P3.26, P3.33, P4.1, P4.2, P4.3..

Myzus persicae (Green peach aphid), systemic test: Roots of pea seedlings, infested with an aphid population of mixed ages, are placed directly in the test solutions at an application rate of 12.5 ppm. 6 days after introduction, samples are checked for mortality and special effects on the plant. The following compounds gave at least 80% control of *Myzus persicae:*

E1.1, E1.2, E3.4, E15.1, P2.34, P3.33.

Tetranychus urticae (Two-spotted spider mite): Bean leaf discs on agar in 24-well microtiter plates are sprayed with test solutions at an application rate of 200 ppm. After drying, the leaf discs are infested with mite populations of mixed ages. 8 days later, discs are checked for egg mortality, larval mortality, and adult mortality. The following compounds gave at least 80% control of *Tetranychus urticae:*

P1.2, E18.1, P1.64, E21.1, P1.243, P1.338, P1.441, P3.19.

Aonidiella aurantii (California red scale): Potato tubers are treated by dipping the in the test solution at an application rate of 100 ppm. One day later, tubers are infested with about 50 crawlers. 6-8 weeks after application samples are checked for the number of crawlers of the next generation (compared to the non treated samples). The following compounds gave at least 80% control of *Aonidiella aurantii:*

E3.1, E6.1, E1.2, P1.238, P2.34, E26.1, E27.1, P3.15, P3.16.

Bemisia tabaci (Whitefly): Bean plants are infested with 20-30 adults. After a 4 day egg laying period, adults are removed. N-2 nymps are treated after another 7 days in a spray chamber with the test solution at an application rate of 100 ppm. 3 weeks later, samples are checked for number of adults (compared to the non treated samples). The following compounds gave at least 80% control of *Bemisia tabaci:*

E3.1, E6.1, E7.1, E1.2, E3.5, P1.238, P2.34, E26.1, E27.1, P3.15, P3.16.

Aphis craccivora: Pea seedlings are infested with a mixed population and treated with diluted test solutions at an application rate of 200 ppm in a spray chamber. 6 days after treatment, samples are checked for mortality. The following compounds gave at least 80% control of *Aphis craccivora:*

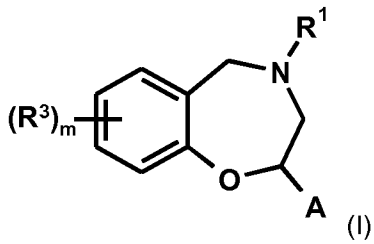
E2.1, E3.1, E3.2, E3.4, E6.1, P1.5, E1.2, E3.5, P1.235, P2.1, E8.2, P1.238, P2.5, P1.45, E6.19, P1.49, P2.34, E26.1, E27.1, E35.1, E36.1, E28.1, P3.15, P3.16, P3.17, P3.26, P3.33, P4.1, P4.2.

Aphis gossypii: Pea seedlings are infested with a mixed population and treated with diluted test solutions at an application rate of 200 ppm in a spray chamber. 6 days after treatment, samples are checked for mortality. The following compounds gave at least 80% control of *Aphis gossypii:*

E2.1, E3.1, E3.2, E3.4, E6.1, P1.5, E1.2, P1.223, E12.2, E3.5, P1.235, P2.1, E8.2, P1.225, P1.238, P1.239, P2.5, P1.45, E6.19, P1.49, P2.34, E26.1, E27.1, E28.1, E34.1, E35.1, E36.1, E37.1, E38.1, P3.15, P3.16, P3.17, P3.19, P3.26, P3.28, P3.33, P3.37, P4.1, P4.3.

CLAIMS

1. A method of combating and controlling insects, acarines, nematodes or molluscs which comprises applying to a pest, to a locus of a pest, or to a plant susceptible to attack by a pest an insecticidally, acaricidally, nematicidally or molluscicidally effective amount of a compound of formula (I):



(I)

wherein R^1 is R^4, YR^5 or ZR^6

Y is C=O or C=S

Z is S, S(O), SO_2 or PO_2;

A is an optionally substituted phenyl or an optionally substituted heteroaromatic ring;

each R^3 is independently halogen, hydroxy, nitro, azido, cyano, thiocyanato, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocyclyl, formyl, optionally substituted alkylcarbonyl, optionally substituted hydroxyiminoalkyl, optionally substituted alkoxyiminoalkyl, optionally substituted arylcarbonyl, optionally substituted heteroarylcarbonyl, optionally substituted alkoxycarbonyl, optionally substituted alkenyloxycarbonyl, optionally substituted alkynyloxycarbonyl, optionally substituted aryloxycarbonyl, optionally substituted heteroaryloxycarbonyl, aminocarbonyl, optionally substituted alkylaminocarbonyl, optionally substituted dialkylaminocarbonyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, optionally substituted dialkyloxyphosphoryl, optionally substituted trialkylsilyl, optionally substituted alkylthio, optionally substituted alkylsulfinyl, optionally substituted alkylsulfonyl, optionally substituted arylthio, optionally substituted arylsulfinyl, optionally substituted arylsulfonyl, aminosulfonyl, optionally substituted alkylaminosulfonyl, optionally substituted dialkylaminosulfonyl or $R^{31}R^{32}N$ where R^{31} and R^{32} are, independently, hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, formyl, optionally substituted alkylcarbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, optionally substituted alkylaminocarbonyl, optionally substituted dialkylaminocarbonyl optionally substituted alkoxycarbonyl or R^{31} and R^{32} together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further heteroatoms selected from O, N or S and which may be optionally substituted by one or two C_{1-6} alkyl groups, or 2 adjacent groups R^3

together with the carbon atoms to which they are attached form a 4, 5, 6, or 7 membered carbocyclic, heteroaromatic or heterocyclic ring which may be optionally substituted by halogen; m is 0, 1, 2, 3 or 4;

R^4 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, cyano, NO, dialkyloxyphosphoryl, optionally substituted (amino)(alkyloxy)phosphoryl, optionally substituted (alkylamino)(alkyloxy) phosphoryl, optionally substituted bis(alkylamino) phosphoryl, bis(dialkylamino) phosphoryl, or $NR^{41}R^{42}$ where R^{41} and R^{42} are independently hydrogen, COR^{43}, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl or R^{41} and R^{42} together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further heteroatoms selected from O, N or S and which may be optionally substituted by one or two C_{1-6} alkyl groups; or R^{41} and R^{42} together with the N atom to which they are attached form $N=CR^{44}R^{45}$ where R^{44} and R^{45} are independently hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl or R^{44} and R^{45} together with the N atom to which they are attached form a five, six or seven-membered carbocyclic or heterocyclic ring which may contain one or two heteroatoms selected from O, N or S and which may be optionally substituted by one or two C_{1-6} alkyl groups ; R^{43} is H, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aryl, optionally substituted aryloxy optionally substituted heteroaryl, optionally substituted heteroaryloxy or $NR^{46}R^{47}$; R^{46} and R^{47} are independently H, optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl;

R^5 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxycarbonyl, optionally substituted alkylcarbonyl, aminocarbonyl, optionally substituted alkylaminocarbonyl, optionally substituted dialkylaminocarbonyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, optionally substituted heterocyclyloxy, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted alkylthio, optionally substituted arylthio, optionally substituted heteroarylthio, optionally substituted heterocyclylthio, $NR^{51}R^{52}$ where R^{51} and R^{52} are independently hydrogen, COR^{53}, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl or R^{51} and R^{52} together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further heteroatoms selected from O, N or S and which may be optionally substituted by one or two C_{1-6} alkyl groups; R^{53} is H,

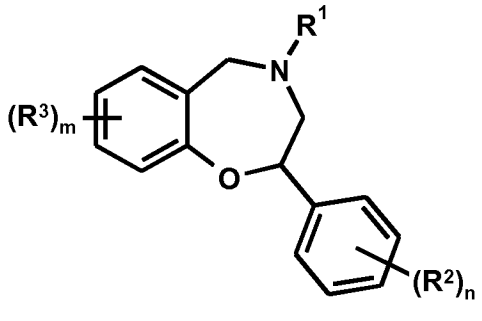
optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aryl, optionally substituted aryloxy optionally substituted heteroaryl, optionally substituted heteroaryloxy;

R^6 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, $NR^{61}R^{62}$ where R^{61} and R^{62} are independently hydrogen, COR^{63}, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl or R^{61} and R^{62} together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further heteroatoms selected from O, N or S and which may be optionally substituted by one or two C_{1-6} alkyl groups; R^{63} is H, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aryl, optionally substituted aryloxy optionally substituted heteroaryl, optionally substituted heteroaryloxy or $NR^{66}R^{67}$; R^{66} and R^{67} are independently H, optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl; or a salt or N-oxide thereof.

2. The method according to claim 1 wherein R^1 is selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_3-C_6 cycloalkyl, C_3-C_6 halocycloalkyl C_2-C_6-alkenyl, C_3-C_6-alkynyl, C_1-C_6-alkyloxycarbonyl, C_1-C_6-haloalkyloxycarbonyl, C_2-C_6-alkenyloxycarbonyl.

3. The method according to either claim 1 or claim 2 wherein m is 0 or m is 1 and R^3 is halogen, C_1-C_6-haloalkyl, or C_1-C_6-alkoxy.

4. The method according to any one of claims 1 to 3 wherein A is an optionally substituted phenyl and the compound is of the formula (IA)

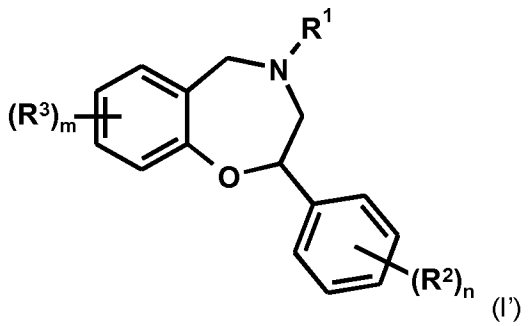


(IA)

wherein R^1 and R^3 are as defined for formula (I) in any one of claims 1 to 3 and each R^2 is independently halogen, hydroxy, nitro, azido, cyano, thiocyanato, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocyclyl, formyl, optionally substituted alkylcarbonyl, optionally substituted hydroxyiminoalkyl, optionally substituted alkoxyiminoalkyl, optionally substituted arylcarbonyl, optionally substituted heteroarylcarbonyl, optionally substituted

alkoxycarbonyl, optionally substituted alkenyloxycarbonyl, optionally substituted alkynyloxycarbonyl, optionally substituted aryloxycarbonyl, optionally substituted heteroaryloxycarbonyl, aminocarbonyl, optionally substituted alkylaminocarbonyl, optionally substituted dialkylaminocarbonyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, optionally substituted dialkyloxyphosphoryl, optionally substituted trialkylsilyl, optionally substituted alkylthio, optionally substituted alkylsulfinyl, optionally substituted alkylsulfonyl, optionally substituted arylthio, optionally substituted arylsulfinyl, optionally substituted arylsulfonyl, aminosulfonyl, optionally substituted alkylaminosulfonyl, optionally substituted dialkylaminosulfonyl or $R^{21}R^{22}N$ where R^{21} and R^{22} are, independently, hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, formyl, optionally substituted alkylcarbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, optionally substituted alkylaminocarbonyl, optionally substituted dialkylaminocarbonyl optionally substituted alkoxycarbonyl or R^{21} and R^{22} together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further heteroatoms selected from O, N or S and which may be optionally substituted by one or two C_{1-6} alkyl groups, or 2 adjacent groups R^2 together with the carbon atoms to which they are attached form a 4, 5, 6, or 7 membered carbocyclic, heteroaromatic or heterocyclic ring which may be optionally substituted by halogen; n is 0, 1, 2, 3, 4 or 5; or a salt or N-oxide thereof.

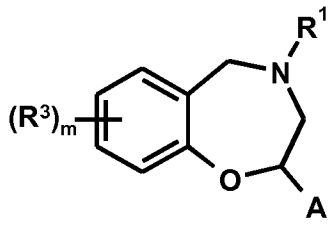
5. A compound of formula I'



(I')

wherein R^1 and R^3 and m are as defined for formula I in any one of claims 1 to 3 and R^2 and n are as defined for formula IA in claim 5, provided that when m and n are both zero then R^1 is other than hydrogen, C_1-C_4 alkyl, $COCH_3$ or $CH_2C(CH_3)=CH_2$ and further provided that when n is zero and $(R^3)_m$ is 7-chloro or 7–methyl then R^1 is other than hydrogen, ethyl or *iso*-butyl; or a salt or N-oxide thereof.

6. A compound of formula (IB)



(IB)

wherein R^1 and R^3 are as defined for formula (I) in any one of claims 1 to 3, and A is an optionally substituted heteroaromatic ring; or a salt or N-oxide thereof.

7. The compound according to claim 6 wherein A is unsubstituted or halo-substituted thiophene or cyano-substituted thiophene or unsubstituted or halo-substituted pyridyl.

8. An insecticidal, acaricidal, nematicidal or mollusicidal composition comprising an insecticidally, acaricidally, nematicidally mollusicidally effective amount of a compound as defined in any one of claims 5 to 7.

9. A method for the protection of plant propagation material from the attack by pests, which comprises treating the propagation material or the site, where the propagation material is planted, with a composition comprising a compound as defined in any one of claims 1 to 7.

10. A plant propagation material treated in accordance with the method described in claim 9.

11. A plant propagation material having adhered thereoto a compound as defined in any one of claims 1 to 7.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/066237

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/04 C07D413/06 C07D413/10 C07D417/04 C07D417/06
C07D267/14 A01N43/72
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A01N

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE pubchem [Online] 2010, XP002743384, retrieved from NCBI Database accession no. 45197848 compound 45197848 -----	5
X	DATABASE pubchem [Online] 2012, XP002743385, retrieved from NCBI Database accession no. 69478583 compound 69478583 ----- -/--	6,7

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 August 2015	31/08/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Grassi, Damian

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE pubchem [Online] 2012, XP002743386, retrieved from NCBI Database accession no. 69495859 compound 69495859 -----	6,7
X	DATABASE pubchem [Online] 2010, XP002743387, retrieved from NCBI Database accession no. 45203317 compound 45203317 -----	6,7
X	DATABASE pubchem [Online] 2010, XP002743388, retrieved from NCBI Database accession no. 45235437 compound 45235437 -----	6,7
A	Brewer et al.: J. Med. Chem., vol. 32 1989, page 2058-2062, XP055207572, Retrieved from the Internet: URL:http://pubs.acs.org/doi/pdf/10.1021/jm 00129a007 [retrieved on 2015-08-13] compound 43 -----	1-11
X	DATABASE pubchem [Online] 2009, XP002743389, retrieved from NCBI Database accession no. 42435407 compound 42435407 -----	5
X	DATABASE pubchem [Online] 2009, XP002743390, retrieved from NCBI Database accession no. 25290149 compound 25290149 ----- -/--	6,7

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE pubchem [Online] 2009, XP002743391, retrieved from NCBI Database accession no. 26400817 compound 26400817 -----	6,7
X	DATABASE pubchem [Online] 2009, XP002743392, retrieved from NCBI Database accession no. 42480309 compound 42480309 -----	6,7