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(54) Title: SUBSTITUTED 4-PROLINE DERIVATIVES AS IGLUR ANTAGONISTS

(57) Abstract: The present invention relates to compounds of Formula (I), combinations and use thereof for disease therapy, or pharmaceutically acceptable salt or solvate thereof, including all tautomers, stereoismers and polymorphs thereof, which are iGluR receptor inhibitors, and hence are useful in the treatment of psychiatric diseases or neurological disorders or a disease or disorder associated with abnormal activities of iGluR receptors.

Title

Substituted 4-proline derivatives as iGluR antagonists

Field of the invention

The present invention relates to a class of substituted pyrrolidine-2-carboxylic acid derivatives as iGluR receptor antagonist, their salt and solvates, pharmaceutical compositions comprising them, their use as medicament and in therapy, and preparation thereof. In particular, the invention relates to a class of substituted pyrrolidine-2-carboxylic acid derivatives as iGluR receptor antagonists, which is useful in the treatment of psychiatric diseases or neurological disorders or a disease or disorder associated with abnormal activities of iGluR receptors.

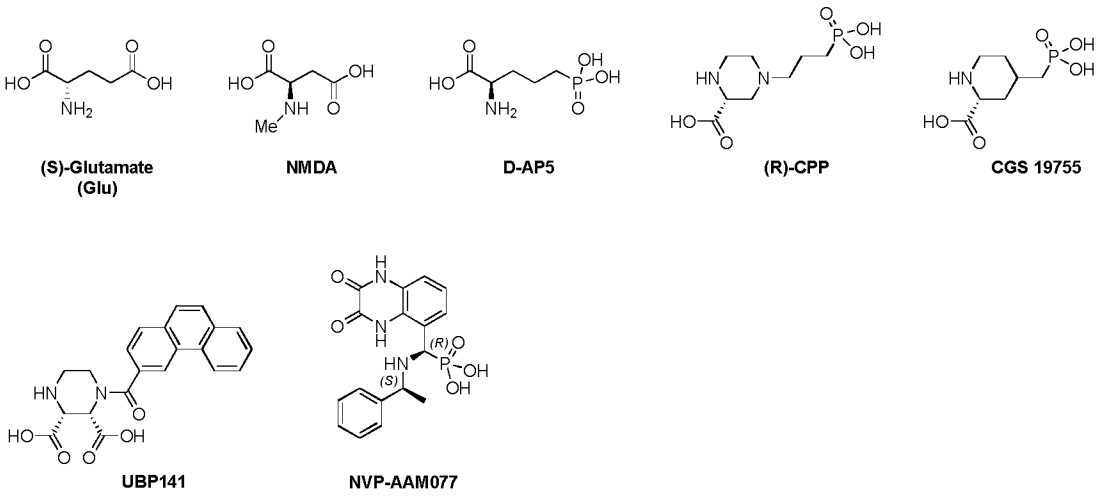
Background

In the mammalian central nervous system (CNS), (*S*)-glutamate (Glu) functions as the major excitatory neurotransmitter (Figure 1).[1] The glutamatergic neurotransmitter system is involved in a vast number of basic neuro-physiological processes such as memory, cognition, as well as neuronal plasticity and development.[2–9] Thus, psychiatric diseases or neurological disorders such as depression,[10–12] anxiety,[13–15] addiction,[16] migraine,[17] and schizophrenia[18–22] may be directly related to disordered glutamatergic neurotransmission. Moreover, *elevated synaptic Glu levels* or *excessive Glu signaling* is *neurotoxic* and will ultimately cause neuronal death.[23–26] Thus, it is believed that neurodegenerative diseases such as Alzheimer's,[27–31] Huntington's,[32] amyotrophic lateral sclerosis (ALS),[33] cerebral stroke,[34] and epilepsy[35] may indeed be the result of a malfunctioning glutamatergic neurotransmitter system which may be reversed by action of small molecule Glu ligands.[1]

Once released from the pre-synaptic neuron into the synapse, Glu activates a number of pre- and post-synaptic Glu receptors. On the basis of the pharmacological profile and ligand selectivity the Glu receptors have been grouped in two main classes: the fast acting ligand gated ion channels named the *ionotropic Glu receptors* (iGluRs), which comprise the AMPA receptors (subunits GluA1-4), kainate (KA) receptors (subunits GluK1-5), and NMDA receptors (subunits GluN1, GluN2A-D and GluN3A-C),[36] The second main class is the G-protein coupled *metabotropic Glu receptors* (mGluRs, subunits

mGluR1-8),[37] which produce a slower signal transduction through second messenger systems.

Functional NMDA receptors are tetrameric in structure, formed by the assembly of two heterodimers comprising one GluN1 subunit in combination with one of the GluN2A-D subunits.[36] The NMDA receptors are blocked (antagonized) by small-molecules acting as glycine antagonists, open channel blockers, non-competitive antagonists or competitive antagonists.[38] Within the latter class of NMDA blockers, small molecules such as D-AP5, (*R*)-CPP, CGS19755, UBP141 and NVP-AAM077[39] have been reported to antagonize the GluN2A-D subunits with varying degrees of subunit preference (2-10 fold).[38] Furthermore, peptides (e.g. Conantokin G) isolated from the venom of Conus geographus have shown to antagonize GluN1/GluN2B selectively over GluN1GluN2A (100 fold), but with only a 10-fold preference over GluN1/GluN2C and GluN1/2D.[40]

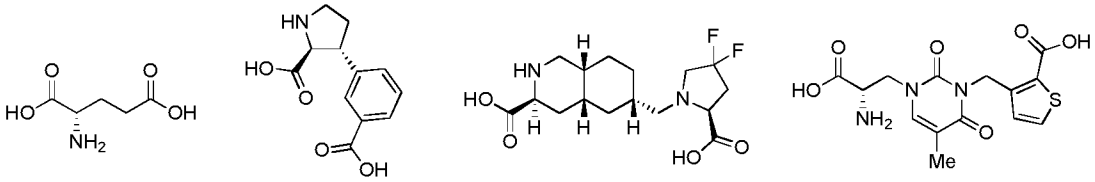


Chemical structures of (S)-Glu, NMDA and selected published competitive NMDA antagonists.

Further, disturbances of expression of KA receptors and function of KA receptors has been suggested to be linked to severe neurological- and psychiatric diseases.[138] Abnormal expression of KA subunit composition (GluK3 and GluK5) in the prefrontal cortex has been observed in schizophrenic subjects,[139] but also decreased expression of GluK2 and GluK3 from the medial dorsal thalamus to the dorsolateral prefrontal cortex and other cortical regions may be important to the pathophysiology of schizophrenia.[140] Furthermore, two population studies have suggested altered GluK3 expression

GRIK3 gene) as a risk factor,[141,142] whereas GluK2 (GRIK2 gene) in one Japanese study came out short.[143] In bipolar disorder the GluK3 receptor is suggested to play a role,[144] but also intervention of GluK2 may constitute a therapeutic target.[145] In an rodent (rat) model of pain, trigeminal caudal nucleus nerve terminals mainly express GluK2/GluK3 subunits, which evidence that differentiated expression of KA receptor subtypes plays a role at the various stages of pain transmission.[146]

To this date only selective antagonists for the GluK1 subtype has been reported.



(S)-Glutamate (Glu) | 1 (CNG-10100) | LY466195 | UBP310

iGluR antagonist 1 (CNG-10100) and examples of selective high-affinity GluK1 antagonists LY466195 and UBP310

(ref for UBP310: Dolman, N. P., More, J. C. A., Alt, A., Knauss, J. L., PentikÃ¤inen, O. T., Glasser, C. R., Bleakman, D., Mayer, M. L., Collingridge, G. L., and Jane, D. E. (2007) Synthesis and Pharmacological Characterization of N3-Substituted Willardiine Derivatives: Role of the Substituent at the 5-Position of the Uracil Ring in the Development of Highly Potent and Selective GLUK5 Kainate Receptor Antagonists, *J. Med. Chem. 50*, 1558-1570).

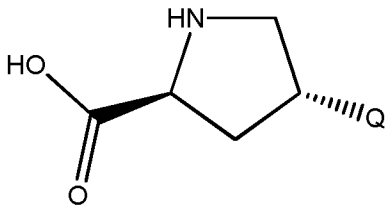
Hence, there is a strong need present for novel selective antagonists for iGluR or its subtypes such as GluA1-4, GluK1-5, or GluN1-3, which can be used to elucidate the role and function of iGluR receptors under both physiological and pathological conditions. Thus, new antagonists targeting iGluR receptors such as GluA1-4, GluK1-5, or GluN1-3 would therefore be useful in the treatment of disorders and diseases associated with these receptors. In particularly, it would be advantageously to identify antagonists having high affinity and at the same time high specificity to only one receptor or subgroup of receptors. Such compounds would be useful in the characterization of diseases related to these receptors, as well as for the treatment of diseases triggered by activity from or lack of activity from these receptors.

Therefore, the aim of the present invention is to provide improved antagonists having high affinity and selectivity to one or more iGluR receptors

such as GluA1-4, GluK1-5, or GluN1-3, preferably one selective iGluR receptor.

Summary of the invention

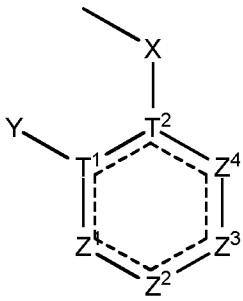
With this background, it is an object of the present invention in a first embodiment to provide a compound of Formula (I)



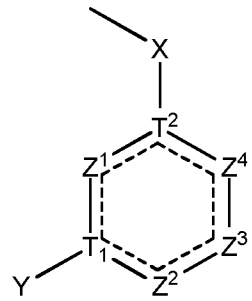
(I),

and pharmaceutically acceptable derivatives, the tautomers and stereoisomers, and protected compounds tereof, wherein

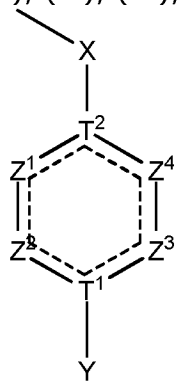
Q represents compounds of Formula (Ia), (Ib), (Ic), (Id), or (Ie);



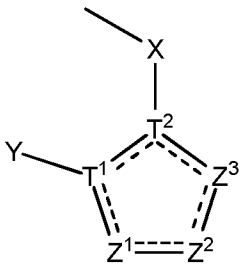
(Ia),



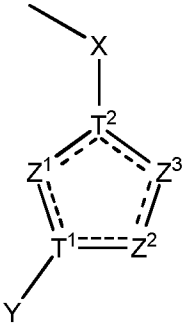
(Ib),



(1c),



(Id), or



(Ie)

---- in each case may represent if appropriate the presence of at least one double bond between two adjacent ringatoms forming the ring system consisting of T^1, T^2, Z^1, Z^2, Z^3 and optionally Z^4,

X is C, NH, O or S,

T^1 is C, or CH,

T^2 is C, or CH,

Y is COR^1, substituted or unsubstituted C_1-C_6-alkyleneCOR^1, $PO(OR^1)_2$, substituted or unsubstituted C_1-C_6-alkylene$PO(OR_1)_2$, SO_2OR_1, substituted or unsubstituted C_1-C_6-alkyleneSO_2OR^1, $SO_2N(R^1)_2$, or C_1-C_6-alkylene$SO_2N(R^1)_2$, wherein one or more $-CH_2-$ groups forming the alkylene group may optionally be replaced by –CH=CH- or –C≡C-,

Z^1 is CR^2, $C(R^2)_2$, N, S, O, or NR^3,

Z^2 is CR^2, $C(R^2)_2$, N, S, O, or NR^3,

Z^3 is CR^2, $C(R^2)_2$, N, S, O, or NR^3,

Z^4 is absent, CR^2, $C(R^2)_2$, N, S, O, or NR^3,

wherein if appropriate the residues Z^1, Z^2, Z^3 and Z^4, cannot represent adjacent O or S,

R^1 is independently selected from the group comprising H, OR^4, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, $COOR^4$, N(OH)H, or NHR^4,

R^2 is independently selected from the group comprising R^4, O, OR^4, C_1-C_6-alkyl OR^4, halogen, N(OH)H, $N(OH)R^4$, NHR^4, COR^4, C_1-C_6-alkyl COR^4, $COOR^4$, C_1-C_6-alkyl $COOR^4$, $CONHR^4$, C_1-C_6-alkyl $CONHR^4$, or SO_2NHR^4,

R^3 is independently selected from the group comprising R^4, O, OR^4, or halogen,

R^4 is independently selected from the group comprising H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, phenyl, C_1-C_6-alkylphenyl, or saturated or unsaturated C_5- or C_6-cycloalkyl, saturated or unsaturated C_5- or C_6-heterocyclyl, or saturated or unsaturated C_1-C_6-alkyl C_5- or C_6-heterocyclyl, wherein C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, phenyl, C_1-C_6-alkylphenyl, or saturated or unsaturated C_5- or C_6-cycloalkyl, saturated or unsaturated C_5- or C_6-heterocyclyl, or saturated or unsaturated C_1-C_6-alkyl C_5- or C_6-heterocyclyl may be substituted with one or more substituents selected from the group comprising C_1-C_6-alkyl, C_1-C_6-alkoxy, aryl, halogen, O, and amine,

R^1 may together with Z^1, Z^2, or Z^3 or

Z^2 may together with Z^1 or Z^3, or

Z^3 may together with Z^4,

optionally form if appropriate a saturated or unsaturated C_5- or C_6-cycloalkyl or a 5- or 6-membered heterocyclyl, wherein the saturated or unsaturated C_5- or C_6-cycloalkyl or the 5- or 6-membered heterocyclyl may be

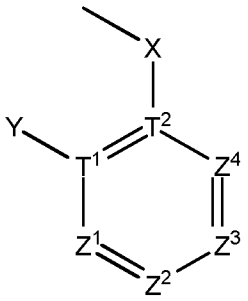
substituted with one or more substituents selected from the group comprising R_2, OR_4 or R_4,

halogen represents Cl, Br, or I, and

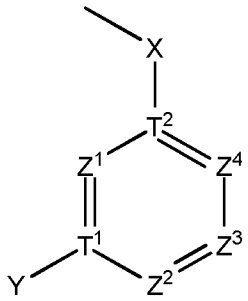
with the proviso that Z^1, Z^2, Z^3 and Z^4 are not all CH, and with the proviso that T^1 and T^2 are not both C, when R^1 is OH.

In one particular embodiment of the present invention, T^1, T^2, Y, Z^1, Z^2, Z^3, and optionally Z^4 represents an aromatic, conjugated, saturated or unsaturated ring system. Thus, compounds comprising Formula (I), wherein

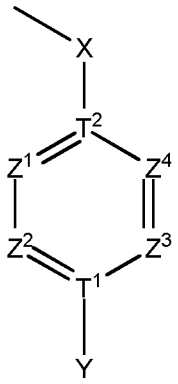
Q represents compounds of Formula (Ia2), (Ib2), (Ic2), (Id2), or (Ie2),



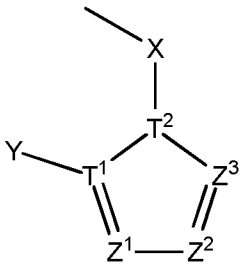
(Ia2),



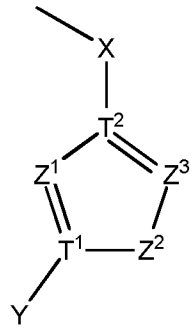
(Ib2),



(1c2),



(Id2), or



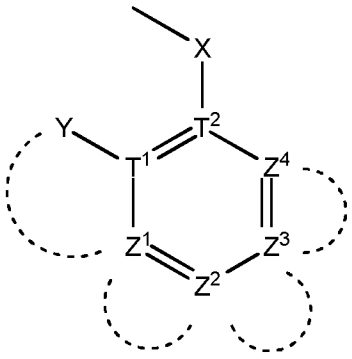
(Ie2),

wherein

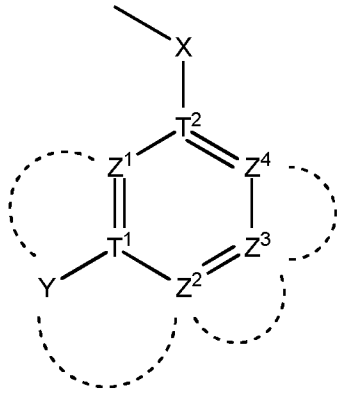
X, T^1, T^2, Y, Z^1, Z^2, Z^3, Z^4, R^1, R^2, R^3, R^4 and halogen have the same meaning as defined above are also part of the present invention.

In yet another embodiment of the present invention, the compound of Formula (I) as previously described can comprise additional ringforming structures. Thus, compounds comprising Formula (I), wherein

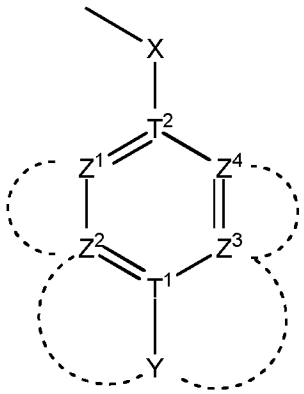
Q represents compounds of Formula (Ia3), (Ib3), (Ic3), (Id3), or (Ie3), wherein



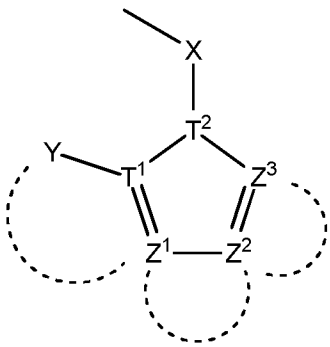
(Ia3),



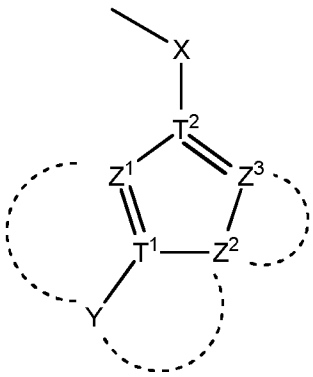
(Ib3),



(1c3),



(Id3), or



(Ie3),

wherein

R^1 and (Z^1, Z^2, or Z^3),

Z^2 and Z^1 or Z^3), or

Z^3 and Z^4,

form if appropriate a saturated or unsaturated C_5- or C_6-cycloalkyl or a 5- or 6-membered heterocyclyl ring, the heterocyclyl ring containing one, two, three or four heteroatoms selected from the group comprising sulfur,

oxygen and nitrogen, and the saturated or unsaturated C_5- or C_6-cycloalkyl or the 5- or 6-membered heterocyclyl ring may be substituted with one or more substituents selected from the group comprising OR_4 or R_4,

X, T^1, T^2, Y, Z^1, Z^2, Z^3, Z^4, R^1, R^2, R^3, R^4 and halogen have the same meaning as defined above, are also part of the present invention.

In particular, in yet a further embodiment, compounds selected from the group consisting of compounds of Formula (I) wherein the 5- or 6-membered ring is selected from the group consisting of pyrrolidine, pyrrole, tetrahydrofuran, furan, thiolane, thiophene, imidazolidine, pyrazolidine, imidazole, pyrazole, oxazolidine, isoxazolidine, oxazole, isoxazole, thiazolidine, isothiazolidine, thiazole, isothiazole, dioxolane, dithiolane, triazoles, furazan, oxadiazole, thiadiazole, dithiazole, tetrazole, piperidine, pyridine, oxane, pyran, thiane thiopyran, piperazine, diazines, morpholine, oxazine, thiomorpholine, thiazine, dioxane, dioxine, dithiane, dithiine, triazine, trioxane, or tetrazine, and wherein the 5- or 6-membered heterocyclic ring may be substituted with 1 to 3 substituents are comprised by the present invention.

Preferred compounds of the present invention are compounds comprising Formula (I), wherein

X is O or S,

T^1 is C,

T^2 is C,

Y is COOH,

Z^1 is CH,

Z^2 is CH,

Z^3 is CH,

Z^4 is absent or CH.

Further, in one embodiment of the invention, compounds of Formula (I), selected from the group consisting of

(2) (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(2-carboxyphenoxy)pyrrolidine-2-carboxylic acid,

(3) (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(3-carboxyphenoxy)pyrrolidine-2-carboxylic acid,

(4) (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(4-carboxyphenoxy)pyrrolidine-2-carboxylic acid,

(5) (2*S*,4*R*)-4-(2-carboxyphenoxy)pyrrolidine-2-carboxylic acid trifluoroacetic acid,

(6) (2*S*,4*R*)-4-(3-carboxyphenoxy)pyrrolidine-2-carboxylic acid hydrochloride,

(7) (2*S*,4*R*)-4-(4-carboxyphenoxy)pyrrolidine-2-carboxylic acid hydrochloride,

(16) (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-((2-carboxyphenyl)thio)pyrrolidine-2-carboxylic acid,

(18) (2*S*,4*R*)-4-((2-carboxyphenyl)thio)pyrrolidine-2-carboxylic acid trifluoroacetic acid,

(19) (2*S*,4*R*)-4-((3-carboxyphenyl)thio)pyrrolidine-2-carboxylic acid,

(20) (2*S*,4*R*)-1-*tert*-butyl 2-methyl 4-((methylsulfonyl)oxy)pyrrolidine-1,2-dicarboxylate,

(25) (2S,4R)-4-(2-(carboxymethyl)phenoxy)pyrrolidine-2-carboxylic acid,

(26) (2S,4R)-4-(3-(carboxymethyl)phenoxy)pyrrolidine-2-carboxylic acid,

(27) (2S,4R)-4-((3-carboxynaphthalen-2-yl)oxy)pyrrolidine-2-carboxylic acid,

(28) (2S,4R)-4-((2-carboxynaphthalen-1-yl)oxy)pyrrolidine-2-carboxylic acid,

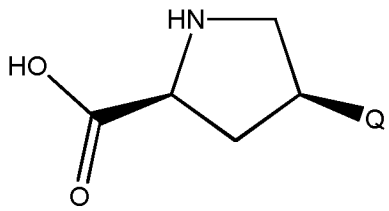
(29) (2S,4R)-4-((1-carboxynaphthalen-2-yl)oxy)pyrrolidine-2-carboxylic acid,

(30) (2S,4R)-4-(2,4-dicarboxyphenoxy)pyrrolidine-2-carboxylic acid,

(31) (2S,4R)-4-(2-carboxy-4-methylphenoxy)pyrrolidine-2-carboxylic acid,

(32) (2S,4R)-4-(4-acetyl-2-carboxyphenoxy)pyrrolidine-2-carboxylic acid, and (33) (2S,4R)-4-(2-carboxy-6-methylphenoxy)pyrrolidine-2-carboxylic acid, are particularly preferred.

In another particular embodiment, compounds of Formula (I) may have an altered stereochemistry. Thus, compounds of Formula (I) according to



(I),

wherein

Q , ----, T^1, T^2, Y, Z^1, Z^2, Z^3, Z^4, R^1, R^2, R^3, R^4 and halogen have the

same meaning as defined above, are also part of the invention.

Each of the described embodiments of the present invention is to be construed as disclosing the present invention either individually or in combination with the other embodiments.

Detailed description of the invention

In the following the present invention is described in more detail. All individual features and details can be individually applied to each embodiment and aspect of the compounds of Formula (I), its preparations, its formulations, its methods and its use.

The term "C_1-C_6 alkyl", unless otherwise indicated, denotes a straight chain or branched alkyl group with 1, 2, 3, 4, 5 or 6 carbon atoms. Suitable C_{1-6} alkyl groups include, for example, methyl, ethyl, propyl (e.g. n-propyl and isopropyl), butyl (e.g n-butyl, iso-butyl, sec-butyl and tert-butyl), pentyl (e.g. n- pentyl), and hexyl (e.g. n-hexyl).

The term "C_1-C_6 alkenyl", unless otherwise indicated, may be interpreted similarly to the term "alkyl". Alkenyl groups contain at least 1 double bond. Suitable alkenyl groups include ethenyl, propenyl, 1-butenyl, and 2-butenyl.

The term "C_1-C_6-alkynyl", unless otherwise indicated, may be interpreted similarly to the term "alkyl". Alkenyl groups contain at least 1 triple bond.

The term "C_1-C_6-alkylene", unless otherwise indicated, denotes a methylene, ethylene, propylene, butylene, pentylene, or hexylene group, wherein the methylene, ethylene, propylene, butylene, pentylene, or hexylene group optionally may be substituted with R_4, amine or halogen.

The term "saturated or unsaturated C_5- or C_6-cycloalkyl", unless otherwise indicated, denotes cyclic carbon rings comprising 5 or 6 carbon atoms, wherein either a single or double bond between the mutually adjacent carbon atoms exist. Suitable saturated or unsaturated C_5- or C_6-cycloalkyl groups include cyclopentane, cyclohexane, cyclopentene, cyclohexene, cyclopentadiene, cyclohhexadiene, and phenyl.

The term "5- or 6-membered heterocyclyl", unless otherwise indicated, denotes a heterocyclic compound, such as a carbocyclyl group, phenyl group, or aryl residue, having atoms of at least two different elements as

members of its ring. Suitable ring atoms in heterocyclic compound may be C, N, S, or O. Heterocyclic compounds according to the present invention may contain 3, 4, 5, 6, 7, 8 or even more rings atoms, preferably 5 or 6 ring atoms. Suitable saturated or unsaturated heterocyclic compounds may include

The term "halogen" comprises fluorine (F), chlorine (Cl), bromine (Br) and iodine (I), more typically F, Cl or Br.

All possible tautomers of the claimed compounds are included in the present invention. Tautomers are isomers of organic compounds that readily interconvert by a chemical reaction called tautomerization. This reaction commonly results in the formal migration of a hydrogen atom or proton, accompanied by a switch of a single bond and adjacent double bond.

The compounds of the invention have one or more asymmetric centers. Compounds with asymmetric centers give rise to enantiomers (optical isomers), diastereomers (configurational isomers) or both, and it is intended that all of the possible enantiomers and diastereomers in mixtures and as pure or partially purified compounds are included within the scope of this invention. The present invention is meant to encompass all isomeric forms of the compounds of the invention. The present invention includes all stereoisomers of compounds of Formula (I). Compounds of Formula (I) comprises although depending on the choice of T_2 at least one chiral centers, i.e. at the second position of pyrrolidine, a COOH group, and at the third position of pyrrolidine, a 5- or 6-membered ring, as indicated by the Q-group. Diastereomers differ from enantiomers in that these are pairs of stereoisomers that differ in all stereocenters. Diastereomers have different physical properties (unlike enantiomers) and different chemical reactivity. Diastereoselectivity is the preference for the formation of one or more than one diastereomer over the other in an organic reaction.

The independent syntheses of the enantiomerically or diastereomerically enriched compounds, or their chromatographic separations, may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates that are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration. If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers

or diastereomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods using chiral stationary phases, which methods are well known in the art.

Alternatively, any enantiomer or diastereomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

As compounds of Formula (I) contains at least 2 two asymmetric carbons, there are up to 4 possible configurations, which cannot be superimposable mirror images of each other.

Pyrrolidine-2-carboxylic acid derivatives according to the invention can be prepared from the various examples given further below or by consulting handbooks within organic chemistry. Examples of such handbook – although not intending to be construed as limiting - are "Organic Chemistry, 2nd Edition, 2000, by Maitland Jones, Jr., and Organic Chemistry, 6th Edition, Robert T. Morrison, and Robert N. Boyd. The above referred handbooks are hereby incorporated by reference.

The term "pharmaceutically acceptable derivative" in present context includes pharmaceutically acceptable salts, which indicate a salt which is not harmful to the patient. Such salts include pharmaceutically acceptable basic or acid addition salts as well as pharmaceutically acceptable metal salts, ammonium salts and alkylated ammonium salts. A pharmaceutically acceptable derivative further includes hydrates, polymorphs, esters and prodrugs, or other precursors of a compound which may be biologically metabolized into the active compound, or crystal forms of a compound. Salts and solvates of the compounds of Formula (I) and physiologically functional derivatives thereof which are suitable for use in medicine are those wherein the counter-ion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counter-ions or associated

solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds and their pharmaceutically acceptable salts and solvates.

Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulfuric, nitric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, sulfamic, sulfanilic, succinic, oxalic, fumaric, maleic, malic, mandelic, glutamic, aspartic, oxaloacetic, methanesulfonic, ethanesulfonic, arylsulfonic (for example p-toluenesulfonic, benzenesulfonic, naphthalenesulfonic or naphthalenedisulfonic), salicylic, glutaric, gluconic, tricarballylic, cinnamic, substituted cinnamic (for example, phenyl, methyl, methoxy or halo substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic, 4-methoxybenzoic, 2- or 4- hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzeneacrylic (for example 1,4-benzenediacrylic), isethionic acids, perchloric, propionic, glycolic, hydroxyethanesulfonic, pamoic, cyclohexanesulfamic, salicylic, saccharinic and trifluoroacetic acid.

Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexylamine and [Lambda]/-methyl-D-glucamine.

Furthermore, some of the crystalline forms of the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e. hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention. The compounds, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

Organic molecules can form crystals that incorporate water into the crystalline structure without modification of the organic molecule. An organic molecule can exist in different crystalline forms, each different crystalline forms may contain the same number of water molecules pr organic molecule or a different number of water molecules pr organic molecule.

The term "administering" shall encompass the treatment of the vari-

ous disorders described with derivatives of the claimed compounds which convert to the active compound *in vivo* after administration to the subject. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The term "antagonist" in the present context refers to a substance that does not provoke a biological response itself upon binding to a receptor. Hence, antagonists have affinity to but no efficacy for their cognate receptors, and binding will disrupt the interaction and inhibit the function of e.g. an agonist.

The term "AMPA receptor" denotes a receptor family within the iGluRs receptors. The AMPA receptor comprises subunits such as, GluA1, GluA2, GluA3, or GluA4.

The term "KA" denotes a receptor family within iGluRs receptors. The KA receptor comprises subunits such as GluK1, GluK2, GluK3, GluK4, or GluK5.

The term "NMDA" denotes a receptor family within iGluRs receptors. The NMDA receptor comprises subunits such as GluN1, GluN2A, GluN2B, GluN2C, GluN2D, GluN3A, GluN3B, or GluN3C.

A receptor antagonist defined by the Formula (I), is thus capable of binding to the GluK1, GluK2, GluK3, GluK4, or GluK5 receptor, respectively. However, the receptor antagonist may optionally bind to other receptors, such as the AMPA receptor and NMDA receptor subunits.

The antagonist may be a selective antagonist, which only binds to and activates one type of receptor. Antagonist may bind reversible or irreversible depending on the antagonist–receptor complex.

The antagonist can also be an antagonist of several different types of receptors, and thus capable of binding to one or more different receptors, such AMPA receptors, KA receptors, and NMDA receptors. An antagonist may have high affinity to one or more iGluR receptors and at the same time having high selectivity to these one or more iGluR receptors. I.e. the antagonist has low affinity to the other iGluR receptors. Such antagonists are also part of the present invention.

The term "IC_{50}" is commonly used as a measure of antagonist drug potency and reflects the measure of the effectiveness of a compound in inhib-

iting biological or biochemical function. This quantitative measure indicates how much of a compound of Formula (I) is needed to inhibit 50% of the activity of a particular receptor. IC_{50} can be regarded as the functional strength of the different compounds of Formula (I).

IC_{50} is not a direct indicator of affinity although the two can be related at least for competitive agonists and antagonists by the Cheng-Prusoff equation.

The term "k_i" refers to the binding affinity, which describe the binding of compounds of Formula (I) to a receptor.

As used herein, the term "pharmaceutical composition" is intended to encompass a product comprising compounds of Formula (I) in the therapeutically effective amounts, as well as any product which results, directly or indirectly, from combinations of the claimed compounds.

The term "therapeutically effective amount" of a compound as used herein refers to an amount sufficient to cure, alleviate, prevent, reduce the risk of, or partially arrest the clinical manifestations of a given disease or disorder and its complications. An amount adequate to accomplish this is defined as a "therapeutically effective amount".

Compounds of Formula (I) according to the present invention may be used in pharmaceutical compositions and method for treatment of disorders, diseases in a subject, or conditions associated with the dysfunction of iGluR receptors, e.g. the AMPA receptors, KA receptors and NMDA receptors, and their corresponding subunits, GluA1-4, GluK1-5 and GluN1, GluN2A-D, and GluN3A-C. Thus, targeting iGluR or its subtypes such as GluA1-4, GluK1-5, GluN1-3 and its subtypes with antagonists according to the present invention would be helpful in the treatment of disorders and diseases associated with these receptors.

The terms "treatment" and "treating" as used herein refer to the management and care of a subject for the purpose of combating a condition, disease or disorder. The term is intended to include the full spectrum of treatments for a given condition from which the subject is suffering, such as administration of the active compound for the purpose of: alleviating or relieving symptoms or complications; delaying the progression of the condition, disease or disorder; curing or eliminating the condition, disease or disorder; and/or preventing the condition, disease or disorder, wherein "preventing" or

"prevention" is to be understood to refer to the management and care of a patient for the purpose of hindering the development of the condition, disease or disorder, and includes the administration of the active compounds to prevent or reduce the risk of the onset of symptoms or complications.

The term "subject" refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment. Treatment of animals, such as mice, rats, dogs, cats, cows, sheep and pigs, is, however, also within the scope of the present invention.

In one embodiment, compounds of Formula (I) may be used as a medicament, optionally in combination with one or more therapeutically acceptable diluents or carriers.

In a certain embodiment, the present invention relates to compounds of Formula (I) or pharmaceutical compositions thereof, or methods for treatment of diseases or conditions binding one of $GluK_1$, $GluK_2$, $GluK_3$, $GluK_4$, or $GluK_5$ receptors to obtain a beneficial therapeutic effect.

Further, in another aspect, the present invention relates to a method for treating a disease or disorder mediated by the GluK receptors, wherein the disease or disorder is selected from the group consisting of psychiatric diseases or neurological disorders or a disease or disorder associated with abnormal activities of GluK receptors in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of compounds of Formula (I) or a pharmaceutically acceptable derivative thereof, optionally together with a pharmaceutically acceptable carrier.

In yet a certain embodiment, the present invention relates to compounds of Formula (I) pharmaceutical compositions thereof, or methods, for treatment of disorders of the central nervous system, neuro-physiological processes such as memory, cognition; as well as neuronal plasticity and development, psychiatric diseases or neurological disorders such as depression, anxiety, addiction, pain, migraine, and schizophrenia, and neurodegenerative diseases; such as Alzheimer, Huntington disease, amyotrophic lateral sclerosis (ALS), cerebral stroke, and epilepsy; and diseases including aching, ADHD, Autism, Diabetes, Huntington's disease, ischemia, multiple sclerosis, Parkinson's disease (Parkinsonism), Rasmussen's encephalitis, seizures, AIDS dementia complex, amyotrophic lateral sclerosis, combined systems disease (vitamin B12 deficiency), drug addiction, drug tolerance, drug dependency,

glaucoma, hepatic encephalopathy, hydroxybutyric aminoaciduria, hyperhomocysteinemia and homocysteinuria, hyperprolinemia, lead encephalopathy, leber's disease, MELAS syndrome, MERRF, mitochondrial abnormalities (and other inherited or acquired biochemical disorders), neuropathic pain syndromes (e.g. causalgia or painful peripheral neuropathies), nonketotic hyperglycinemia, olivopontocerebellar atrophy, essential tremor, Rett syndrome, sulfite oxidase deficiency, Wernicke's encephalopathy or cancer.

In a preferred embodiment, the present invention relates to antagonist of compound of Formula (I) and its pharmaceutical compositions, which are administered in one or more daily doses of 0.5-1500 mg/day, preferably 0.5-200 mg/day, more preferably 0.5-60 mg/day, even more preferably 0.5-30 mg/day.

In a preferred embodiment, the present invention relates to antagonist of compound of Formula (I) suitable for oral, rectal, nasal, pulmonary, buccal, sublingual, transdermal or parenteral administration.

According to the present invention, the antagonist of compound of Formula (I) is administered to subjects in need of treatment in pharmaceutically effective doses. A therapeutically effective amount of a compound according to the present invention is an amount sufficient to cure, prevent, reduce the risk of, alleviate or partially arrest the clinical manifestations of a given disease or its complications. The amount that is effective for a particular therapeutic purpose will depend on the severity and the sort of the disease as well as on the weight and general state of the subject. The antagonists of the present invention may be administered one or several times per day, such as from 1 to 4 times per day, such as from 1 to 3 times per day, such as from 1 to 2 times per day, wherein administration from 1 to 3 times per day is preferred.

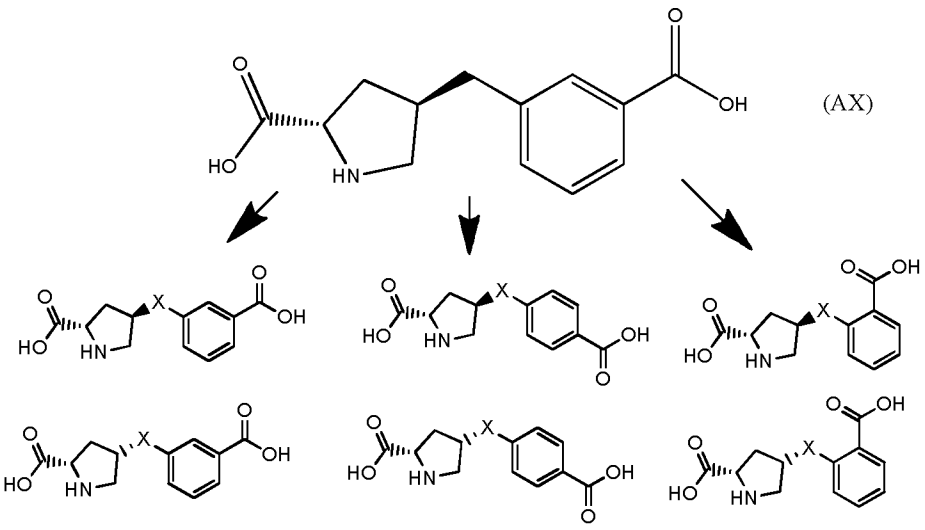
The antagonists of the present invention may be administered simultaneously, sequentially or separately in combination with one or more second active ingredients selected from the group of agents having affinity to one or more receptors or transporters in the CNS or in any way otherwise related to the treatment of the same diseases, disorders or conditions as the antagonists of the present invention.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive

or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T. W. Greene & P. G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991, fully incorporated herein by reference. The protecting groups may be removed at a convenient subsequent stage using methods known from the art. Thus, compounds of Formula (I) of the present invention may be in the form of their protected compounds.

Results and discussion

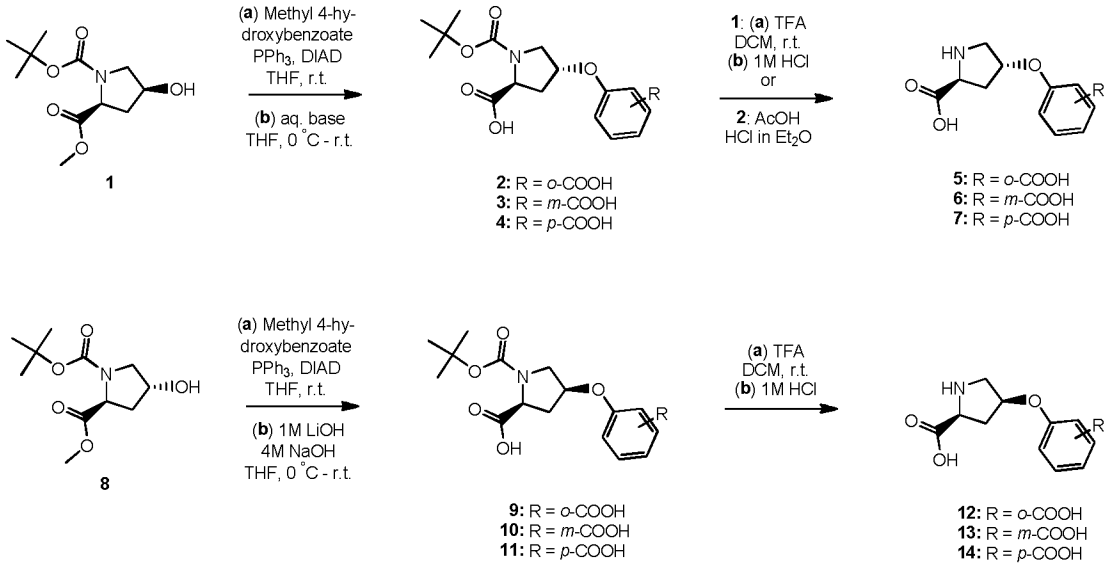
Based on ligand conformational analysis and the vast structural information on the GluA2 & GluK1 ligand binding domains, (2S,4R)-4-(3-carboxybenzyl)pyrrolidine-2-carboxylic acid (**AX**, CNG-10200) was designed. Succeeding its synthesis, pharmacological characterization of **AX** showed medium range micromolar binding affinity to NMDA receptors. Thus, **AX** defined a new lead structure for the discovery of subtype selective iGluR antagonists.



Scheme 1. Chemical structures designed iGluR antagonist AX (CNG-10200) and repositioning of the distal carboxylic acid group, replacement and/or changing of the steric configuration of the bridging carbon atom (X) between the two ring structures.

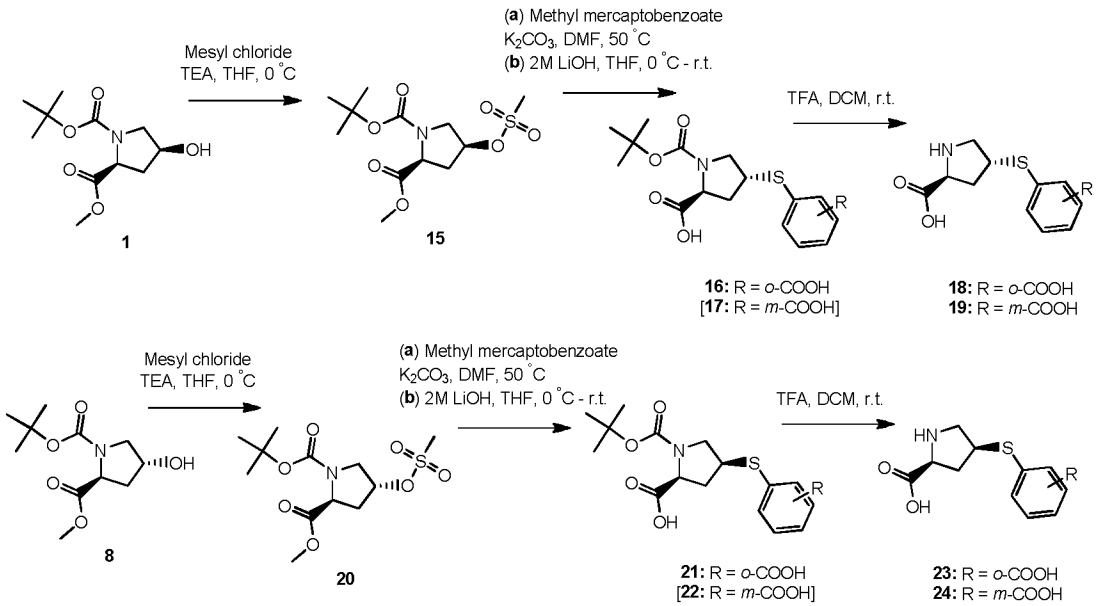
The preparation of carboxyphenoxy antagonists of the present invention followed generally the below outlined synthesis scheme. A more detailed

description is given further below. Further substitutions in the phenyl group or benzylring can be made by methods being well known to the skilled person.



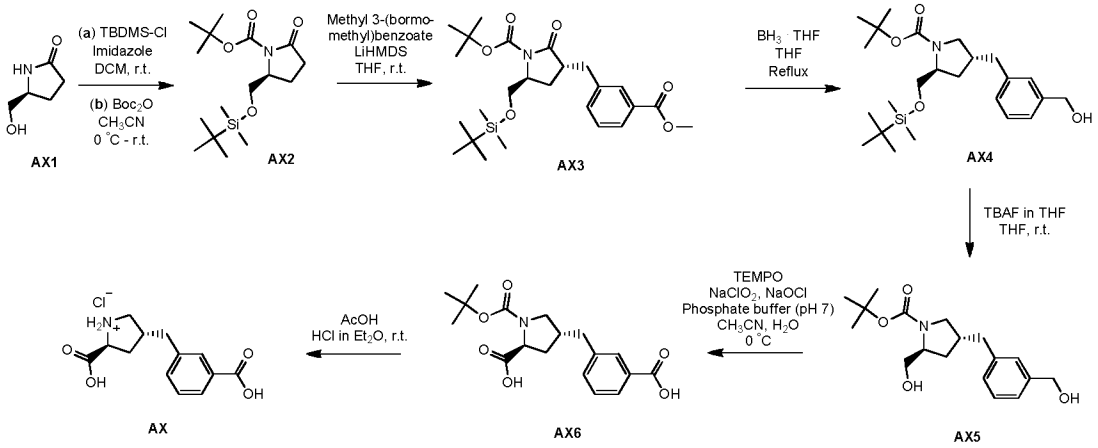
Reaction scheme 1: Synthesis of the phenol ether 4-CPP analogues

The preparation of carboxy-thiophenyl antagonists of the present invention followed generally the below outlined synthesis scheme. A more detailed description is given further below. Further substitutions in the phenyl group or benzylring can be made by methods being well known to the skilled person.



Reaction scheme 2: Synthesis of the thiophenol ether 4-CPP analogues.

The preparation of carboxy-benzyl antagonists of the present invention followed generally the below outlined synthesis scheme. A more detailed description is given further below. Further substitutions in the benzylring can be made by methods being well known to the skilled person.



Reaction scheme 3: Synthesis of the thiophenol ether 4-CPP analogues.

Double protection of AX1 gave AX2 in high yield. Selective alkylation gave the trans diastereomer AX3, exclusively. Reduction of the endo-carbonyl group gave AX4 which was deprotected to the diol AX5. Double oxidation gave diacid AX6 which was finally deprotected under acidic conditions to give the target compound AX.

Pharmacological characterization

Analog **AX**, **5, 6, 7, 18,** and **19** were characterized pharmacologically in radio ligand binding assays at native iGluRs (rat synaptosomes) and cloned homomeric subtypes, GluK1-3, cf. Table 1. At native iGluRs **AX**, **7, 18,** and **19** showed neglictable affinity for AMPA receptors and KA receptors (>100 μM) but most interestingly, micro molar affinity for the NMDA receptors (IC_{50} < 100 μM). At cloned homomeric GluK1-3 receptors **AX** displayed no affinity (>100 μM), whereas **6**, and in particular **5** and **18** showed high affinity for the cloned homomeric GluK1 receptor.

	AMPA	**KA**	**NMDA**	**GluK1**	**GluK2**	**GluK3**
	IC_{50}	**IC_{50}**	**K_i**	**K_i**	**K_i**	**K_i**

(AX) 10-200	>100	>100	68	>100	>100	>100
(6), 10-201	>100	>100	>100	35.7	>100	>100
(7), 10-202	>100	>100	81	>100	>100	>100
(5), 10-203	>100	>100	>100	4	>100	>100
(18), 10-204	>100	>100	15	8	>100	16
(19), 10-205	>100	>100	68	>100	>100	>100
(25), 10-211						
(26), 10-212						
(27), 10-213						
(28), 10-214						
(29), 10-215						
(30), 10-216						
(31), 10-217						
(32), 10-218	>100	>100	>100		>100	30

Table 1. pharmacological characterization at native iGluR receptors as well as cloned homomeric GluK1-3 subtypes. All values in μM.

This section provides specific examples of selected targets molecules. However, it is to be understood that these examples outline the synthetic routes for other target molecules not specifically disclosed.

All reagents were obtained from commercial suppliers and used without further purification. Dry solvents were obtained differently. THF was distilled over sodium/benzophenone. Et_2O was dried over neatly cut sodium. All solvents were tested for water content using a Carl Fisher apparatus. Water - or air sensitive reactions were conducted in flame dried glassware under nitrogen with syringe-septum cap technique. Purification by DCVC (dry column vacuum chromatography) was performed with silica gel size 15-40μm (Merck, Silica gel 60). For TLC was used Merck TLC Silica gel F_{254} with appropriate spray reagents: $KMnO_4$ or Molybdenum blue. ^1H NMR and ^{13}C NMR spectra were obtained on a Varian Mercury Plus (300 MHz) and a Varian Gemini 2000 instrument (75 MHz), respectively. HPLC was done using Agilent Prep HPLC systems with Agilent 1100 series pump, Agilent 1200 series diode array, multiple wavelength detector (G1365B), and Agilent PrepHT High Performance Preparative Cartridge Column (Zorbax, 300 SB-C18 Prep HT, 21.2 × 250 mm,

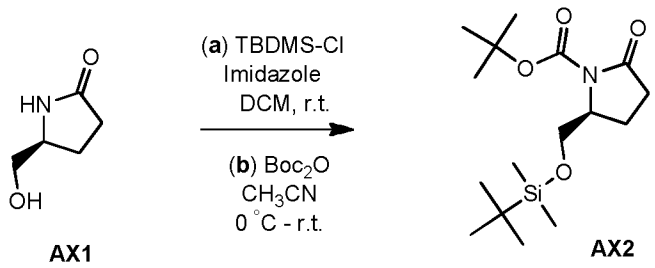
7 µm). Preparative HPLC was performed using Spectraseries UV100 with a JASCO 880-PU HPLC pump and an XTerra®Prep MS C18 ,(10µm, 10X300 mm) column. LC-MS was performed using an Agilent 1200 series solvent delivery system equipped with an autoinjector coupled to an Agilent 6400 series triple quadrupole mass spectrometer equipped with an electrospray ionization source. Gradients of 10% aqueous acetonitrile + 0.05% formic acid (buffer A) and 90% aqueous acetonitrile + 0.046% formic acid (buffer B) were employed or an Agilent 1200 system using a C18 reverse phase column (Zorbax 300 SB-C18, 21.1 mm – 250 mm) with a linear gradient of the binary solvent system of H_20/CH_3CN/TFA (A: 100/0/0.1 and B: 5/95/0.1) with a flow rate of 20 mL/min. Optical rotation was measured using a Perkin-Elmer 241 spectrometer, with Na lamp at 589 nm. Melting points were measured using an automated melting point apparatus, MPA100 OptiMelt (SRS) and are stated uncorrected. Compounds were dried either under high vacuum or freeze dried using a Holm & Halby, Heto LyoPro 6000 freezedrier.

Determination of binding affinities at native AMPA, KA and NMDA receptors was carried out as described in reference: Assaf, Z; Larsen, AP; Venskutonyte, R; Han, L; Abrahamsen, B; Nielsen, B; Gajhede, M; Kastrup, JS; Jensen, AA; Pickering, DS; Frydenvang, K; Gefflaut, T and Bunch,L* "Chemo-Enzymatic Synthesis of New 2,4-*Syn*-Functionalized (*S*)-Glutamate Analogues and Structure-Activity-Relationship Studies at Ionotropic Glutamate Receptors and Excitatory Amino Acid Transporters" *J. Med. Chem.* **2013**, *56*, 1614-1628

Determination of binding affinities at Cloned homomeric subtypes, GluK1, GluK2, GluK3 receptors was carried out as described in reference: Assaf, Z; Larsen, AP; Venskutonyte, R; Han, L; Abrahamsen, B; Nielsen, B; Gajhede, M; Kastrup, JS; Jensen, AA; Pickering, DS; Frydenvang, K; Gefflaut, T and Bunch,L* "Chemo-Enzymatic Synthesis of New 2,4-*Syn*-Functionalized (*S*)-Glutamate Analogues and Structure-Activity-Relationship Studies at Ionotropic Glutamate Receptors and Excitatory Amino Acid Transporters" *J. Med. Chem.* **2013**, *56*, 1614-1628

Compounds

(*S*)-*tert*-butyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-oxopyrrolidine-1-carboxylate (AX2):

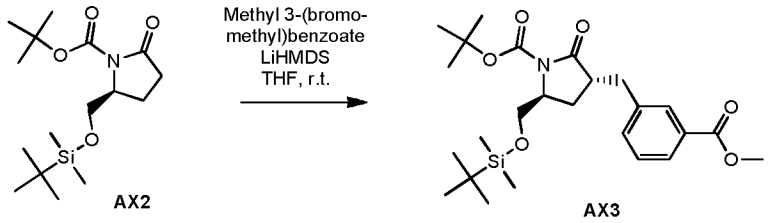


AX1 AX2

To a solution of (*S*)-pyroglutaminol (AX**1**) (1.00 g, 8.69 mmol, 1.00 equiv) in DCM (10 mL) was added imidazole (1.48 g, 21.7 mmol, 2.50 equiv) and TBDMS-Cl (1.56 g, 10.4 mmol, 1.20 equiv). The mixture was stirred at room temperatrue (r.t). for 24 hours. The solution was diluted with Et_2O (100 mL) and the organic phase was washed with H_2O (2 × 100 mL) and brine (2 × 100 mL) respectively. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a yellow oil (1.90 g).

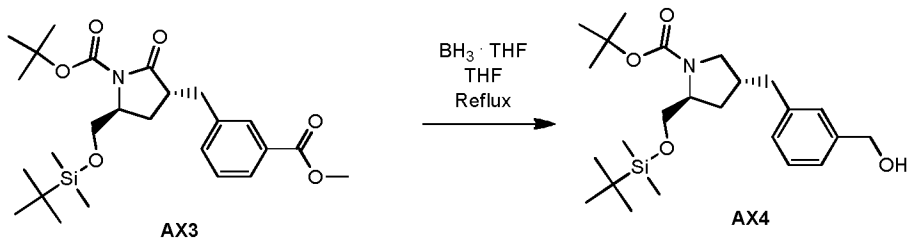
The crude oil (1.90 g, 8.2 mmol, 1.00 equiv) was dissolved in MeCN (70 mL), cooled to 0°C and added DMAP (0.11 g, 0.83 mmol, 0.11 equiv) and Boc_2O (3.60 g, 16.5 mmol, 1.99 equiv). The reaction mixture was left to stir at room temperature under nitrogen for 18 h. The organic phase was washed with brine (3 × 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a dark, red oil, which was purified using flash chromatography (EtOAc : heptane (1 : 9)) affording protected lactam AX**2** (2.61 g, 91 %) as a thick, yellow oil. ^{1}H NMR (300 mHz, $CDCl_3$): δ 0.04 (3H, s), 0.05 (3H, s), 0.88 (9H, s), 1.54 (9H, s), 1.95 – 2.20 (2H, m), 2.37 (1H, ddd, *J* = 18, 9, 2 Hz), 2.71 (1H, dt, *J* = 18, 11 Hz), 3.68 (1H, dd, *J* = 10, 2 Hz), 3.91 (1H, dd, *J* = 11, 4 Hz), 4.16 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.4, -5.3, 18.3, 21.3, 26.0, 28.2, 32.5, 59.0, 64.4, 82.7, 150.0, 174.9; OR: $[a]^{22}_D$: -71.57 (c = 0.55 g/100 mL; EtOAc); TLC: R_f: 0.13 (EtOAc : heptane (1 : 9)).

(3*R*,5*S*)-(*tert*-Butoxycarbonyl)-5-(((*tert*-butyl)dimethylsilyloxy)methyl)-3-(3-(methoxycarbonyl)benzyl)-pyrrolidin-2-one (AX3):



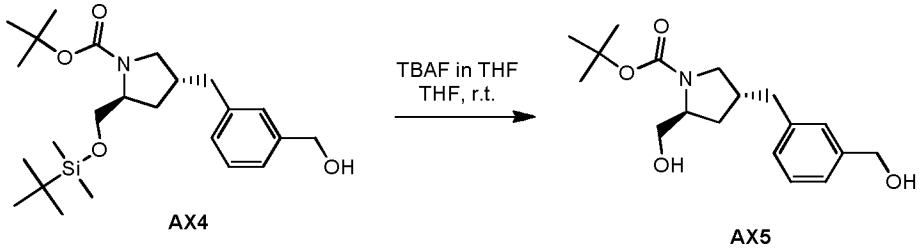
Lactam **AX2** (500 mg, 1.52 mmol, 1.00 equiv) was weight out in a dry flask that was afterwards purged with nitrogen. Dry THF (2 mL) was added and the solution cooled to -78 °C. 1M LiHMDS (1.80 mL, 1.80 mmol, 1.19 equiv) was drop wise added over the course of 10 min. and stirred for 2 h. Methyl 3-bromomethylbenzoate (454 mg, 1.98 mmol, 1.31 equiv) was dissolved in dry THF (2 mL) in a dry flask and drop wise added to the mixture of lactam **2** over the course of 15 min. The mixture was stirred for 3 h before removed from the cooling bath and allowed to warm up to room temperature. The mixture was quenched by addition of sat. NH_4Cl (4 mL) and transferred to a separation funnel containing EtOAc (5 mL). The aqueous phase was extracted with EtOAc (2 x 5 mL) and the combined organic phases was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using DCVC (0 – 28 % EtOAc in heptanes) to afford methyl ester AX**3** (467 mg, 64 %) as a dark, orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.00 (6H, s), 0.85 (9H, s), 1.55 (9H, s), 1.75 – 1.93 (2H, m), 1.95 – 2.07 (1H, m), 3.05 – 3.20 (1H, m), 3.30 – 3.40 (1H, m), 3.56 – 3.64 (1H, m), 3.83 – 3.93 (4H, m), 4.00 – 4.09 (1H, m), 7.33 – 7.40 (2H, m), 7.81 – 7.85 (1H, m), 7.85 – 7.90 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.39, -5.35, 18.3, 26.0, 28.3, 28.5, 37.1, 44.5, 52.2, 57.0, 64.2, 82.9, 127.7, 128.6, 129.8, 130.3, 133.4, 139.6, 150.0, 166.9, 175.4; LCMS: m/z $[M + H]^+$: calc: 378.2, found: 378.1; TLC: R_f: 0.37 (EtOAc : heptanes (1 : 4)); OR: $[a]^{20.5}_D$: -31.55 (c = 0.37 g/100 mL; Abs. EtOH).

(2*S*,4*R*)-(*tert*-Butoxycarbonyl)-2-(((*tert*-butyl)dimethylsilyloxy)methyl)-4-(3-(hydroxymethyl)benzyl)-pyrrolidine (AX4).



Methyl ester AX**3** (1.31 g, 2.75 mmol, 1.00 equiv) was weight out in a dry flask and dissolved in dry THF (10 mL). 1M BH_3 · THF complex (14.6 mL, 14.6 mmol, 5.31 equiv) was added and the mixture heated to reflux for 21 h. The mixture was cooled to 0 °C, added THF (35 mL) and subsequently H_2O (4.2 ml) was carefully added drop wise over the course of 30 min. 2M NaOH (22.3 ml) was carefully added drop wise over the course of 30 min and 30% H_2O_2 (7 ml) was added over the course of 15 min. After stirring for 5 min at 0 °C the mixture was removed from the icebath and left to stir for 1.5 h at room temperature. The mixture was transferred to a separation funnel containing sat. $NaHCO_3$ (75 mL) and EtOAc (75 mL). The aqueous phase was extracted with EtOAc (2 x 75 mL). The combined organic phases was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The mixture was purified using DVCV (0 - 100 % EtOAc in heptanes) to yield alcohol AX**4** (0.68 g, 56 %) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (6H, s), 0.88 (9H, s), 1.46 (9H, s), 1.55 – 1.85 (2H, m), 1.95 – 2.15 (1H, m), 2.50 – 2.75 (3H, m), 2.95 – 3.15 (1H, m), 3.35 – 3.55 (1.5H, m), 3.55 – 3.85 (2H, m), 3.85 – 3.95 (0.5H, m), 4.68 (2H, s), 7.08 (1H, d, *J* = 7 Hz), 7.12 – 7.25 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.1, 18.5, 26.1, 28.8, 34.1, 34.7, 37.9, 39.0, 39.9, 52.1, 52.5, 58.6, 58.8, 63.6, 64.0, 65.5, 79.2, 79.5, 124.8, 127.3, 128.0, 128.6, 140.7, 141.1, 154.5; LCMS: m/z $[M + H]^+$: calc: 380.2, found: 380.2 (- *t*-Bu); TLC: R_f : 0.46 (EtOAc : heptanes (1 : 1)); OR: $[a]^{20.5}_D$: -28.41 (c = 0.35 g/100 mL; Abs. EtOH).

(2*S*,4*R*)-*tert*-butyl 2-(hydroxymethyl)-4-(3-(hydroxymethyl)benzyl)pyrrolidine-1-carboxylate (AX5):

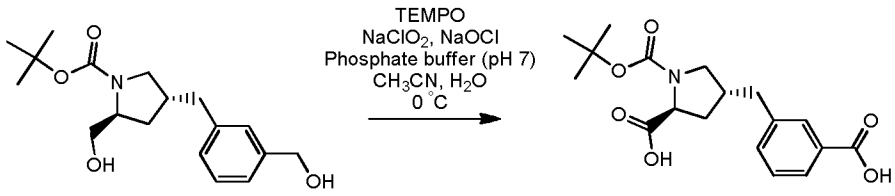


AX4 AX5

Silyl protected alcohol AX**4** (0.67 g, 1.55 mmol, 1.00 equiv) was dissolved in dry THF (11 mL) and added 1M TBAF in THF (4.66 mL, 4.66 mmol, 3.01 equiv). The mixture was left to stir at room temperature for 1 h before added sat. $NaHCO_3$ (40 mL). The mixture was transferred to a

separation funnel containing EtOAc (30 mL). The aqueous phase was extracted with EtOAc (2 x 50 mL) and the combined organic phase was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The mixture was purified using DVCV (0 – 100 % EtOAc in toluene) to yield diol AX**5** (0.26 g, 52 %) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 (9H, s), 1.60 – 2.05 (3H, m), 2.35 – 2.55 (1H, m), 2.55 – 2.70 (2H, m), 3.10 – 3.20 (1H, m), 3.42 (1H, dd, *J* = 10, 7 Hz), 3.52 – 3.65 (2H, m), 4.08 (1H, bs), 4.46 (1H, bs), 4.69 (2H, s), 7.07 (1H, d, J = 7 Hz), 7.16 (1H, s), 7.18 – 7.33 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.7, 34.3, 39.1, 39.4, 52.6, 59.6, 65.4, 68.0, 80.6, 125.0, 127.3, 128.0, 128.7, 140.4, 141.2; LCMS: m/z $[M + H]^+$: calc: 266.1, found: 266.1 (- *t*-Bu); TLC: R_f : 0.10 (EtOAc : heptanes (1 : 1)); OR: $[a]^{20.5}_D$: -14.11 (c = 0.25 g/100 mL; Abs. EtOH).

(2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(3-carboxybenzyl)pyrrolidine-2-carboxylic acid (AX6):



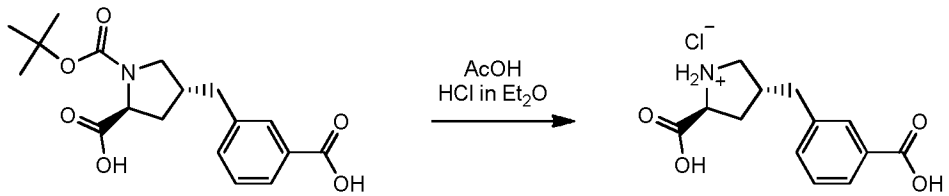
AX5 AX6

Diol AX**5** (180 mg, 0.56 mmol, 1.00 equiv) was dissolved in CH_3CN (2.4 ml) and added a sodium phosphate buffer (1.8 mL, pH = 6.7 (670 mM)) and TEMPO (12 mg, 0.08 mmol, 0.14 equiv). The reaction mixture was heated to 35°C and drop wise added a solution of $NaClO_2$ (200 mg, 2.21 mmol, 4.12 equiv) in H_2O (0.48 mL) and a solution of NaOCl (8 µL 10-13 % aqueous solution, app. 1 mg, app. 0.013 mmol, 0.023 equiv) in H_2O (0.24 mL) simultaneously over the course of 2 h. The lack of characteristic intermediate colorisation of mixture facilitated the addition of additional TEMPO (10 mg, 0.06 mmol, 0.11 equiv) and NaOCl (2 drops). This resulted in a dark coloring of the mixture that disappeared shortly after. The mixture was stirred for 18 h at 35 °C. The mixture was cooled to 0 °C, added H_2O (2 mL) and 2M NaOH (drop wise until pH = 10). The mixture was then drop wise added a solution of Na_2SO_3 (300 mg, 2.38 mmol, 4.25 equiv) in H_2O (2 mL). The mixture was stirred at room temperature for 30 min. The mixture was

transferred to a separation funnel and washed with Et_2O (2 x 20 mL). The aqueous mixture was made acidic using 4M HCl (a few drops, pH = 2) and extracted with Et_2O (3 x 20 mL). The pooled organic phases was washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield diacid AX**6** (122 mg, 62 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (4H, s), 1.50 (5H, s), 1.75 – 2.10 (1.46H, m), 2.25 – 2.40 (0.57H, m), 2.55 – 2.95 (3H, m), 3.00 – 3.20 (1H, m), 3.58 (0.57H, m), 3.80 (0.46H, m), 4.32 (0.46H, m), 4.42 (0.57H, d, *J* = 8 Hz), 7.33 – 7.44 (2H, m), 7.87 – 7.99 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4, 28.5, 35.0, 36.2, 38.4, 38.8, 39.2, 51.5, 51.8, 59.0, 80.7, 81.2, 128.3, 128.8, 129.7, 130.2, 134.0, 140.1, 153.8, 155.4, 171.6, 176.6, 178.7; LCMS: m/z $[M + H]^+$: calc: 350.2, found: 250.1 (-Boc); TLC: R_f : 0.46 (EtOAc : heptanes : AcOH (32 : 16 : 1)); OR: $[a]^{20.5}_D$: -3.42 (c = 0.38 g/100 mL; Abs. EtOH).

(2S,4R)-4-(3-carboxybenzyl)pyrrolidine-2-carboxylic acid, hydrochloride, (AX) 10-200:

(2*S*,4*R*)-4-(3-carboxybenzyl)-proline hydrochloride (AX) 10-200:



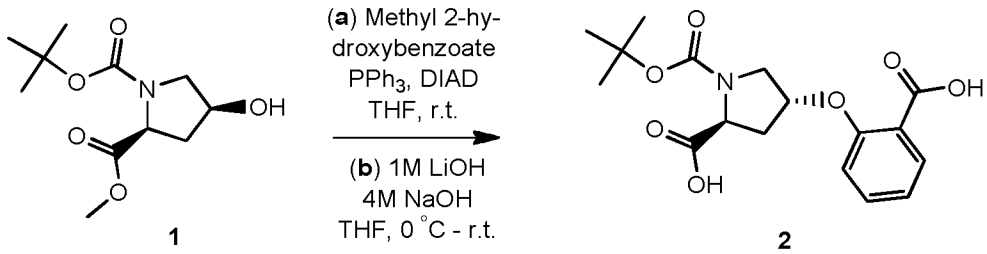
AX6 **AX**

Diacid AX**6** (121 mg, 0.35 mmol, 1.00 equiv) was dissolved in Et_2O (2 mL), cooled to 0 °C and added 1M HCl in Et_2O (4.18 mL, 4.18 mmol, 11.9 equiv). The mixture was stirred at room temperature for 18 h and concentrated *in vacuo* to yield proline salt **AX** (98 mg, 99 %) as a yellow foam. The mixture was triturated with CH_3CN twice to yield a white, colloid precipitate that was isolated by decantation and drying of the semi-solid *in vacuo*. ^{1}H NMR (300 MHz, D_2O): δ 2.05 – 2.18 (1H, m), 2.18 – 2.34 (1H, m), 2.57 – 2.75 (1H, m), 2.75 – 2.88 (2H, m), 2.98 – 3.10 (1H, m), 3.52 (1H, dd, *J* = 11, 7 Hz), 4.40 (1H, dd, *J* = 9, 4 Hz), 7.38 – 7.53 (2H, m), 7.78 – 7.88 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.5, 37.6, 39.1, 50.8, 60.5, 128.4, 129.5, 130.3, 130.4, 134.6, 140.4, 171.0, 173.3; LCMS: m/z [M +

H]$^+$: calc: 250.1, found: 250.1; OR: [a]$^{22}_D$: -16.76 (c = 0.34 g/100 mL; 2M NaOH).

Starting materials, compounds **1** (CAS 102195-79-9), **8** (CAS 102195-79-9) and CAS: 17342-08-4) are commercially available from a wide range of leading fine chemical suppliers such as Sigma-Aldrich, Combi-Blocks, and TCI.

(2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(2-carboxyphenoxy)pyrrolidine-2-carboxylic acid (2):



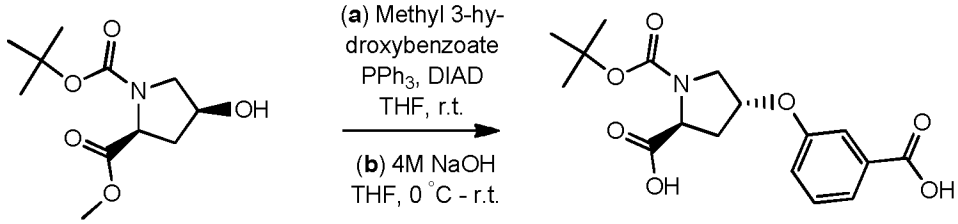
1 2

Proline analogue **1** (140 mg, 0.57 mmol, 1.00 equiv), methyl 2-hydroxybenzoate (108 mg, 0.71 mmol, 1.24 equiv), PPh_3 (140 mg, 0.69 mmol, 1.21 equiv) and DIAD (181 mg, 0.69 mmol, 1.21 equiv) were weight out in a dry flask and dissolved in dry THF (4 mL). The mixture was left to stir at room temperature for 18 h. The mixture was added a combination of Et_2O and THF (1 : 1, 20 mL) and washed with 2M NaOH (2 x 10 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The mixture was purified using DCVC (0 – 24 % EtOAc in toluene).

The mixture was dissolved in THF (6 mL), cooled to 0 °C and drop wise added 1M LiOH (6 mL) over the course of 2 min and subsequently 4M NaOH (1 mL) over the course of 2 min. The mixture was left to stir at 0 °C for 15 min and at room temperature for 20 h. The mixture was added H_2O (20 mL) and the aqueous phase washed with Et_2O (2 x 20 mL). The aqueous phase was added conc. HCl (pH ≈ 1) and extracted with a mixture of Et_2O and THF (1 : 1, 3 x 20 mL). The pooled organic phases was washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* The mixture was purified using DCVC (0 – 100 % EtOAc in heptanes containing 2 % AcOH) to yield diacid **2** (123 mg, 61 %) as a clear, colorless oil. ^{1}H NMR (300 MHz, ($CDCl_3$): δ 1.42/1.43 (9H, 2 x s), 2.30 – 2.50 (1H, m), 2.55 – 2.75 (1H, m), 3.67 – 3.95 (2H, m), 4.49 (0.5H, t, *J* = 8 Hz), 4.59 (0.5H, t, *J* = 8 Hz), 5.09

(1H, bs), 6.96 (1H, dd, *J* = 8, 5 Hz), 7.07 (1H, td, *J* = 8, 4 Hz), 7.50 (1H, m), 7.98 (1H, dm, *J* = 8 Hz); ^{13}C NMR (75 MHz, ($CDCl_3$): δ 28.3, 28.4, 35.3, 36.6, 51.7, 52.1, 57.8, 57.9, 76.8, 77.2, 81.5, 81.7, 114.8, 115.1, 119.7, 120.1, 122.1, 133.2, 133.4, 134.6, 134.7, 153.9, 155.3, 156.3, 168.6, 168.7, 177.1, 177.5; LCMS: m/z $[M + H]^+$: calc: 352.1, found: 252.2 (-Boc); HPLC: purity$_{254}$ = 100 %; TLC: R_f: 0.13 (EtOAc : heptanes : AcOH (40 : 20 : 1)); OR: $[a]^{35}_D$: -42.31 (c = 0.52 g/100 mL; Abs. EtOH).

(2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(3-carboxyphenoxy)pyrrolidine-2-carboxylic acid (3):



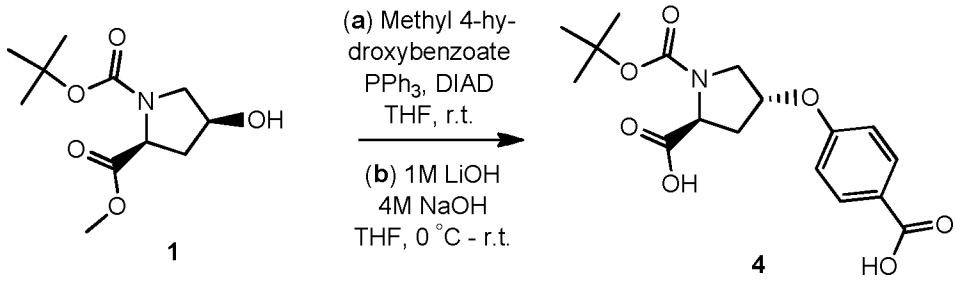
1 3

Proline analogue **1** (300 mg, 1.22 mmol, 1.00 equiv), methyl 3-hydroxybenzoate (230 mg, 1.51 mmol, 1.24 equiv) and PPh_3 (374 mg, 1.43 mmol, 1.17 equiv) were weight out in a dry flask, dissolved in dry THF (8 mL) and cooled to 0 °C. DIAD (290 □L, 1.47 mmol, 1.20 equiv) was drop wise added over the course of 15 min and the mixture was left to stir at room temperature for 18 h. The mixture was added Et_2O (20 mL) and washed with 2M NaOH (2 x 10 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The mixture was purified using DCVC (0 – 25 % EtOAc in toluene and 0 – 35 % EtOAc in heptanes).

The mixture was dissolved in THF (10 mL), cooled to 0 °C and drop wise added 2M NaOH (5 mL) over the course of 2 min. The mixture was left to stir at 0 °C for 15 min and at room temperature for 20 h. The mixture was added H_20 (20 mL) and the aqueous phase washed with Et_2O (2 x 20 mL). The aqueous phase was added conc. HCl (pH ≈ 1) and extracted with a mixture of Et_2O and THF (1 : 1, 3 x 20 mL). The combined organic phases was washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield diacid **3** (336 mg, 91 %) as a white foam. ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ 1.36 (9H, s), 2.10 – 2.30 (1H, m), 2.35 – 2.52 (1H, m), 3.50 – 3.70 (2H, m), 4.21 (1H, q, *J* = 8 Hz), 5.08 (1H, bs), 7.20 (1H, dd, *J* = 8, 2 Hz), 7.36 - 7.46 (2H, m), 7.54 (1H, d, *J* = 7 Hz); ^{13}C NMR (75 MHz,

$(CD_3)_2SO$): δ 27.9, 28.1, 35.0, 35.8, 51.6, 51.8, 57.4, 57.6, 74.8, 75.7, 79.3, 115.5, 115.8, 120.2, 120.3, 122.0, 122.1, 129.9, 132.2, 153.0, 153.4, 156.4, 166.8, 173.2, 173.6; LCMS: m/z $[M + H]^+$: calc: 352.1, found: 252.0 (-Boc); TLC: R_f: 0.18 (EtOAc : heptanes : AcOH (40 : 20 : 1)); OR: $[a]^{35}_D$: -23.33 (c = 0.45 g/100 mL; Abs. EtOH).

(2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(4-carboxyphenoxy)pyrrolidine-2-carboxylic acid (4):

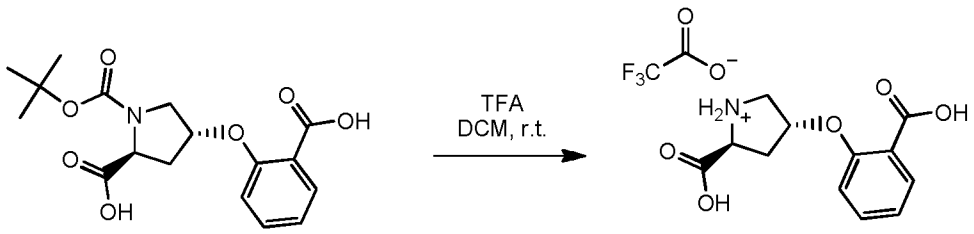


Proline analogue **1** (140 mg, 0.57 mmol, 1.00 equiv), methyl 2-hydroxybenzoate (108 mg, 0.71 mmol, 1.24 equiv), PPh_3 (140 mg, 0.69 mmol, 1.21 equiv) and DIAD (181 mg, 0.69 mmol, 1.21 equiv) were weight out in a dry flask and dissolved in dry THF (4 mL). The mixture was left to stir at room temperature for 18 h. The mixture was added a combination of Et_2O and THF (1 : 1, 20 mL) and washed with 2M NaOH (2 x 10 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The mixture was purified using DCVC (0 – 24 % EtOAc in toluene).

The mixture was dissolved in THF (6 mL), cooled to 0 °C and drop wise added 1M LiOH (6 mL) over the course of 2 min and subsequently 4M NaOH (1 mL) over the course of 2 min. The mixture was left to stir at 0 °C for 15 min and at room temperature for 20 h. The mixture was added H_20 (20 mL) and the aqueous phase washed with Et_2O (2 x 20 mL). The aqueous phase was added conc. HCl (pH ≈ 1) and extracted with a mixture of Et_2O and THF (1 : 1, 3 x 20 mL). The combined organic phases was washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* The mixture was purified using DCVC (0 – 100 % EtOAc in heptanes containing 2 % AcOH) to yield diacid **4** (106 mg, 53 %) as a clear, colorless oil. ^1H NMR (300 MHz, $((CD_3)_2SO$): δ 1.34/1.35 (9H, 2 x s), 2.15 – 2.30 (1H, m), 2.35 – 2.54 (1H, m), 3.54 (1H, d, *J* = 13 Hz), 3.64 (1H, td, *J* = 11, 3 Hz), 4.19 (1H, q, *J* = 8 Hz), 5.08 (1H, bs), 6.99 (2H, d, *J* = 9 Hz), 7.86 (2H, d, *J* = 9 Hz); ^{13}C NMR (75 MHz, $((CD_3)_2SO$): δ 27.9, 28.1, 35.1, 35.9, 51.7, 52.0, 57.4, 57.6, 74.9,

75.7, 79.3, 115.0, 123.3, 131.4, 153.0, 153.4, 160.1, 166.8, 173.2, 173.7; LCMS: m/z $[M + H]^+$: calc: 352.1, found: 252.1 (-Boc); HPLC: $purity_{254}$ = 100 %; TLC: R_f: 0.19 (EtOAc : heptanes : AcOH (40 : 20 : 1)); OR: $[a]^{35}_D$: -21.62 (c = 0.45 g/100 mL; Abs. EtOH).

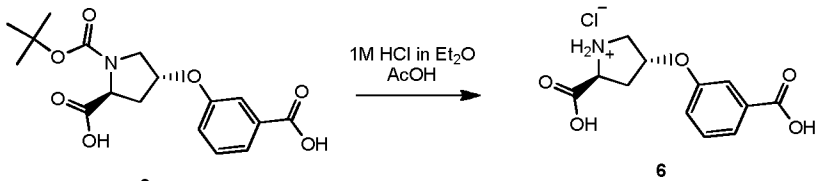
(2*S*,4*R*)-4-(2-carboxyphenoxy)pyrrolidine-2-carboxylic acid trifluoroacetic acid (5):



2 5

Protected proline analogue **2** (70 mg, 0.20 mmol, 1.00 equiv) was suspended in DCM (1.5 mL) and dissolved by addition of TFA (2 mL). The mixture was left to stir at room temperature under nitrogen for 18 h. The mixture was concentrated *in vacuo*, suspended in H_20 and freeze dried to yield proline salt **5** (65 mg, 89 %) as a white solid. ^{1}H NMR (300 MHz, D_2O): δ 2.33 (1H, ddd, *J* = 15, 11, 5 Hz), 2.62 (1H, dd, *J* = 15, 8 Hz), 3.63 (2H, m), 4.53 (1H, dd, *J* = 11, 8 Hz), 5.20 (1H, m), 6.97 – 7.05 (2H, m), 7.46 (1H, ddd, *J* = 8, 8, 2 Hz), 7.64 (1H, dd, *J* = 8, 2 Hz); ^{13}C NMR (75 MHz, D_2O): δ 35.2, 51.4, 59.7, 77.6, 115.7, 121.3, 122.6, 132.1, 134.8, 155.2, 170.4, 172.4; LCMS: m/z $[M + H]^+$: calc: 252.1, found: 252.2; OR: $[a]^{22}_D$: -6.70 (c = 0.37 g/100 mL; H_2O).

(2*S*,4*R*)-4-(3-carboxyphenoxy)pyrrolidine-2-carboxylic acid hydrochloride (6):

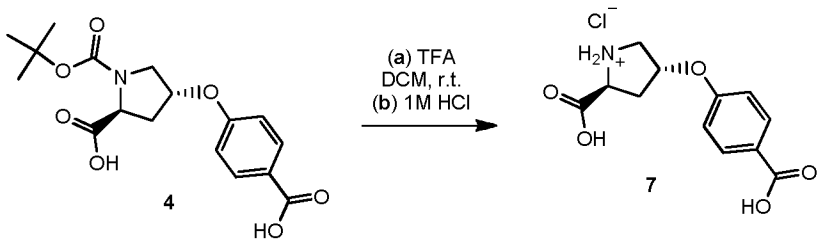


3 6

Protected proline analogue **3** (120 mg, 0.34 mmol, 1.00 equiv) was dissolved in AcOH (3 mL) and added 1M HCl in Et_2O (2 mL). The mixture was left to stir at room temperature under nitrogen for 18 h. The white precipitate formed was isolated by decantation of the solvents, washing with Et_2O, re-suspension in Et_2O and filtering. The solid was dried *in vacuo* to yield proline salt **6** (94 mg, 96 %) as a white solid. ^{1}H NMR (300 MHz, D_2O): δ 2.43 (1H,

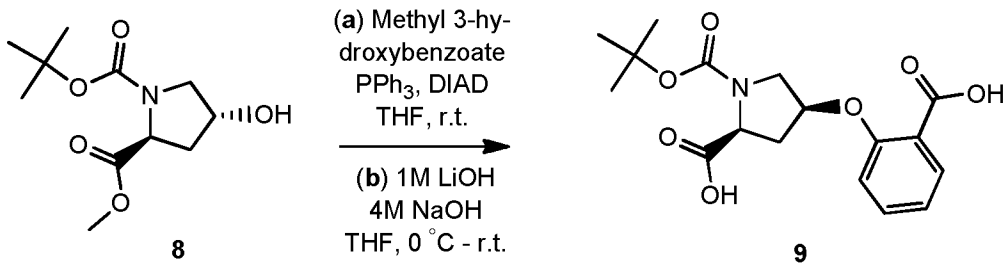
ddd, *J* = 14, 10, 5 Hz), 2.74 (1H, dd, *J* = 14, 8 Hz), 3.59 – 3.80 (2H, m), 4.61 (1H, dd, *J* = 11, 8 Hz), 5.31 (1H, bs), 7.22 (1H, dd, *J* = 8, 2 Hz), 7.44 (1H, t, *J* = 8 Hz), 7.51 (1H, bs), 7.64 (1H, d, *J* = 8 Hz); ^{13}C NMR (75 MHz, D_2O): δ 35.1, 51.6, 59.4, 76.6, 116.9, 121.9, 124.0, 130.7, 131.8, 156.2, 170.4, 172.4; LCMS: m/z $[M + H]^+$: calc: 252.1, found: 252.0; HPLC: purity$_{254}$ = 100 %; OR: $[a]^{35}_D$: -9.48 (c = 0.57 g/100 mL; Abs. EtOH).

(2*S*,4*R*)-4-(4-carboxyphenoxy)pyrrolidine-2-carboxylic acid hydrochloride (7):



Protected proline analogue **4** (89 mg, 0.25 mmol, 1.00 equiv) was suspended in DCM (4.5 mL) and added TFA (4.5 mL). The mixture was left to stir at room temperature under nitrogen for 18 h. The mixture was concentrated *in vacuo*, dissolved in H_2O (5 mL) and freeze dried. The salt was dissolved in 2M HCl (5 mL), concentrated *in vacuo*, redissolved in H_2O (3 x 5 mL) and concentrated *in vacuo* after each time. The salt was then dissolved in H_2O (5 mL) and freeze dried to yield proline salt **7** (65 mg, 90 %) as a reddish foam. ^{1}H NMR (300 MHz, D_2O): δ 1.36 (1H, m), 1.63 (1H, dd, *J* = 14, 8 Hz), 2.24 (1H, d, *J* = 13 Hz), 2.66 (1H, dd, *J* = 14, 5 Hz), 3.07 (1H, dd, *J* = 9, 8 Hz), 4.18 (1H, m), 6.23 (2H, dm, *J* = 9 Hz), 7.19 (2H, dm, *J* = 9 Hz); ^{13}C NMR (75 MHz, D_2O): δ 34.4, 48.6, 57.7, 75.5, 111.9, 125.7, 128.0, 156.0, 171.6, 178.3; LCMS: m/z $[M + H]^+$: calc: 252.1, found: 252.1; HPLC: purity$_{254}$ > 99 %; OR: $[a]^{22}_D$: -81.18 (c = 0.11 g/100 mL; 2M NaOH).

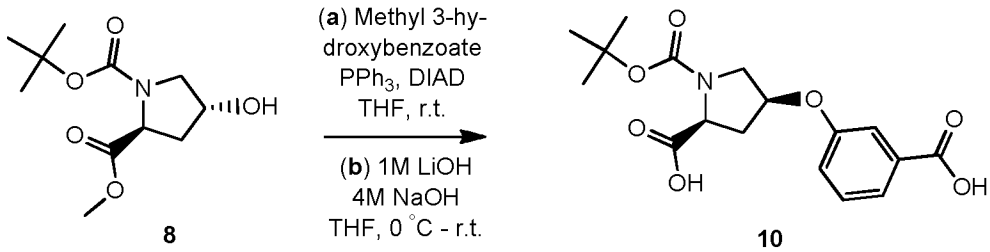
(2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(2-carboxyphenoxy)pyrrolidine-2-carboxylic acid (9):



Methyl ester **8** (303 mg, 1.24 mmol, 1.00 equiv), methyl 2-hydroxybenzoate (236 mg, 1.55 mmol, 1.26 equiv), PPh_3 (395 mg, 1.51 mmol, 1.22 equiv) and DIAD (325 mg, 1.61 mmol, 1.30 equiv) were weight out in a dry flask and dissolved in dry THF (6 mL). The mixture was left to stir at room temperature for 18 h. The mixture was added a combination of Et_2O and THF (1 : 1, 40 mL) and washed with 2M NaOH (2 x 20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The mixture was purified using DCVC (0 – 30 % EtOAc in toluene).

The mixture was dissolved in THF (6 mL), cooled to 0 °C and drop wise added 2M LiOH (12 mL) over the course of 5 min. The mixture was left to stir at 0 °C for 15 min and at room temperature for 20 h. The mixture was added H_20 (40 mL) and the aqueous phase washed with Et_2O (2 x 40 mL). The aqueous phase was added conc. HCl (pH ≈ 0) and extracted with a mixture of Et_2O and THF (1 : 1, 3 x 40 mL). The combined organic phases was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield diacid **9** (333 mg, 77 %) as a clear, colorless oil. ^1H NMR (300 MHz, $((CD_3)_2SO)$: δ 1.36/1.41 (9H, 2 x s), 2.10 – 2.18 (1H, m), 2.59 – 2.74 (1H, m), 3.38 (1H, dd, *J* = 11, 4 Hz), 3.79 – 3.87 (1H, m), 4.19-4.27 (1H, m), 4.93 – 5.01 (1H, m), 7.00 – 7.09 (2H, m), 7.44 – 7.50 (1H, m), 7.62 (1H, dd, *J* = 8, 2 Hz); ^{13}C NMR (75 MHz, $((CD_3)_2SO)$: δ 28.0, 28.2, 34.7, 35.5, 51.3, 51.7, 57.2, 57.4, 75.8, 76.7, 78.9, 79.1, 115.5, 121.0, 122.5, 130.9, 132.8, 152.7, 153.2, 155.7, 166.8, 172.7, 173,0; LCMS: m/z $[M + H]^+$: calc: 352.1, found: 252.1 (-Boc); HPLC: $purity_{254}$ > 99 %; TLC: R_f : 0.20 (EtOAc : heptanes : AcOH (40 : 20 : 1)); OR: $[a]^{35}_D$: (c = mL; Abs. EtOH).

(2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(3-carboxyphenoxy)pyrrolidine-2-carboxylic acid (10):



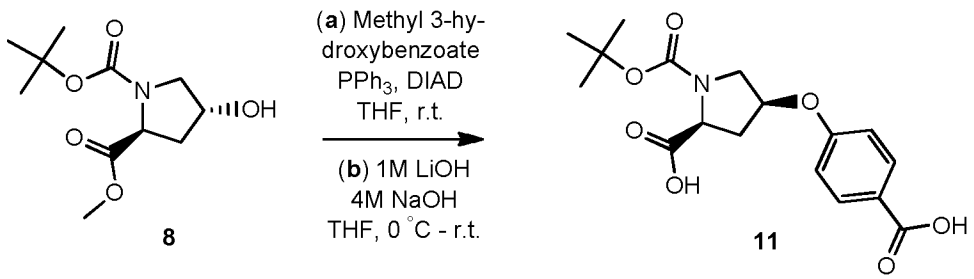
8 10

Methyl ester **8** (350 mg, 1.43 mmol, 1.00 equiv), methyl 3-hydroxybenzoate (270 mg, 1.77 mmol, 1.24 equiv), DIAD (351 mg, 1.74 mmol, 1.22 equiv) and PPh_3 (452 mg, 1.72 mmol, 1.20 equiv) were weight

out in a dry flask and dissolved in dry THF (8 mL) under nitrogen. The mixture was left to stir at room temperature for 18 h. The mixture was added a combination of Et_2O and THF (1 : 1, 40 mL) and washed with 2M NaOH (2 x 20 mL), brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The mixture was purified using DCVC (0 – 24 % EtOAc in toluene).

The mixture was dissolved in THF (12 mL), cooled to 0 °C and drop wise added 1M LiOH (12 mL) over the course of 2 min and subsequently 4M NaOH (2 mL) over the course of 4 min. The mixture was left to stir at 0 °C for 15 min and at room temperature for 20 h. The mixture was added H_20 (40 mL) and the aqueous phase washed with Et_2O (2 x 40 mL). The aqueous phase was added conc. HCl (pH ≈ 1) and extracted with a mixture of Et_2O and THF (1 : 1, 3 x 40 mL). The pooled organic phases was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* The mixture was purified using DCVC (0 – 100 % EtOAc in heptanes containing 2 % AcOH) to yield diacid **10** (343 mg, 68 %) as a clear, colorless oil. ^{1}H NMR (300 MHz, $((CD_3)_2SO)$: δ 1.36/1.40 (9H, 2 x s), 2.15 – 2.26 (1H, m), 2.50 – 2.65 (1H, m), 3.41 (1H, dd, *J* = 12, 6 Hz), 3.65 – 3.77 (1H, m), 4.28 (1H, m), 5.05 – 5.15 (1H, m), 7.07 – 7.14 (1H, m), 7.32 – 7.35 (1H, m), 7.40 (1H, t, *J* = 8 Hz), 7.52 (1H, dm, *J* = 8 Hz); ^{13}C NMR (75 MHz, $((CD_3)_2SO)$: δ 28.0, 28.2, 34.7, 35.5, 51.4, 51.8, 57.2, 57.4, 74.5, 75.6, 78.8, 79.0, 116.0, 119.8, 121.8, 129.8, 132.2, 153.1, 153.2, 156.3, 166.8, 172.7, 172.9 LCMS: m/z $[M + H]^+$: calc: 352.1, found: 252.1 (-Boc); HPLC: purity$_{254}$ = 100 %; TLC: R_f: 0.27 (EtOAc : heptanes : AcOH (40 : 20 : 1)); OR: $[a]^{35}_D$: -17.03 (c = 0.49 g/100 mL; Abs. EtOH).

(2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(4-carboxyphenoxy)pyrrolidine-2-carboxylic acid (11):



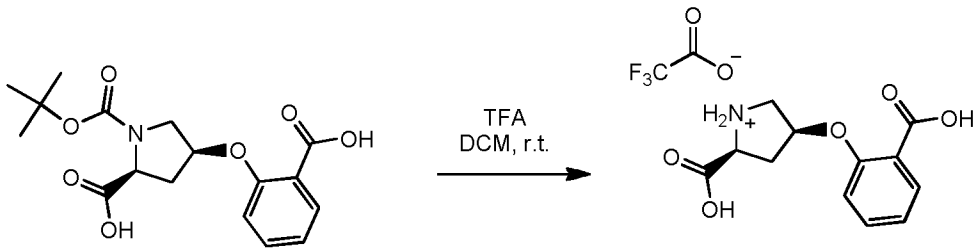
8 11

Methyl ester **8** (305 mg, 1.24 mmol, 1.00 equiv), methyl 4-hydroxybenzoate (246 mg, 1.62 mmol, 1.30 equiv), PPh_3 (395 mg, 1.51 mmol, 1.21 equiv) and DIAD (317 mg, 1.57 mmol, 1.26 equiv) were weight

out in a dry flask and dissolved in dry THF (6 mL). The mixture was left to stir at room temperature for 18 h. The mixture was added a combination of Et_2O and THF (1 : 1, 40 mL) and washed with 2M NaOH (2 x 20 mL), brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The mixture was purified using DCVC (0 – 30 % EtOAc in toluene).

The mixture was dissolved in THF (6 mL), cooled to 0 °C and drop wise added 2M LiOH (12 mL) over the course of 5 min. The mixture was left to stir at 0 °C for 15 min and at room temperature for 20 h. The mixture was added H_20 (40 mL) and the aqueous phase washed with Et_2O (2 x 40 mL). The aqueous phase was added conc. HCl (pH = 0) and extracted with a mixture of Et_2O and THF (1 : 1, 3 x 40 mL). The combined organic phases was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield diacid **11** (311 mg, 71 %) as a clear, colorless oil. ^{1}H NMR (300 MHz, $((CD_3)_2SO)$: δ 1.36/1.40 (9H, 2 x s), 2.17 – 2.22 (2H, m), 2.51 – 2.66 (1H, m), 3.41 (1H, dd, *J* = 12, 6 Hz), 3.69-3.78 (1H, m), 4.24-4.32 (1H, m), 5.08-5.11 (1H, m), 6.92 (2H, dd, *J* = 9, 3 Hz), 7.86 (2H, d, *J* = 9 Hz); ^{13}C NMR (75 MHz, $((CD_3)_2SO)$: δ 28.0, 28.2, 30.5, 34.7, 35.5, 51.5, 51.8, 57.2, 57.4, 74.6, 75.7, 78.9, 79.0, 115.0, 123.2, 131.3, 153.0, 153.1, 166.8, 172.6, 172.9; LCMS: m/z $[M + H]^+$: calc: 352.1, found: 252.1 (-Boc); HPLC: $purity_{254}$ = 100%; TLC: R_f: 0.23 (EtOAc : heptanes : AcOH (40 : 20 : 1); OR: $[a]^{35}_D$: (c = 0. g/100 mL; Abs. EtOH).

(2*S*,4*S*)-4-(1-carboxyphenoxy)pyrrolidine-2-carboxylic acid trifluoroacetic acid (12):

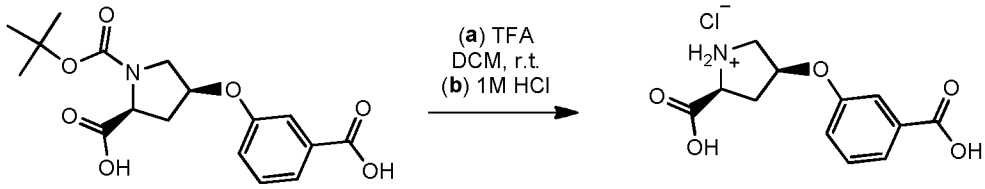


9 **12**

Protected proline **9** (288 mg, 0.82 mmol, 1.00 equiv) was suspended in DCM (5 mL) and dissolved by addition of TFA (5 mL). The mixture was left to stir at room temperature under nitrogen for 18 h. The mixture was concentrated *in vacuo*, dissolved in H_2O (5 mL) and freeze dried to yield proline salt **12** (260 mg, 87 %) as a brownish foam. ^{1}H NMR (300 MHz, D_2O): δ

2.46-2.62 (2H, m), 3.47 (1H, dd, *J* = 13, 4 Hz), 3.69 (1H, d, *J* = 13 Hz), 4.29 (1H, dd, *J* = 10, 4 Hz), 5.14 (1H, m), 6.95 – 7.03 (2H, m), 7.40-7.46 (1H, m), 7.61 (1H, dd, *J* = 8, 2 Hz); ^{13}C NMR (400 MHz, D_2O): δ 34.3, 51.1, 59.5, 76.6, 115.2, 121.3, 122.2, 131.5, 134.2, 154.5, 170.4, 172.7; LCMS: m/z [M + H]$^+$: calc: 252.1, found: 252.1; HPLC: purity$_{254}$ = 100 %; OR: [a]$^{22}_D$: -7.54 (c = 0.31 g/100 mL; H_2O and 1% TFA).

(2*S*,4*S*)-4-(3-carboxyphenoxy)pyrrolidine-2-carboxylic acid hydrochloride (13):

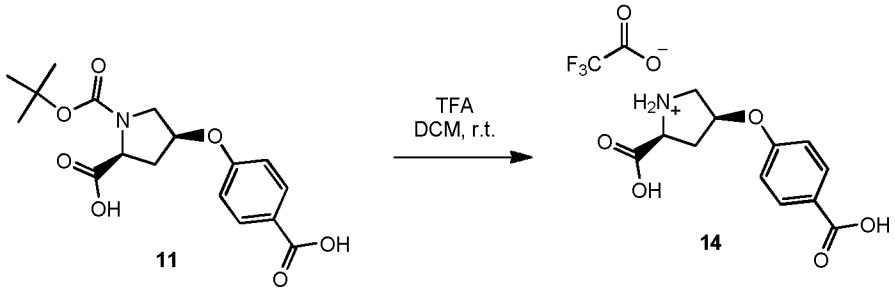


10 13

Protected proline **10** (204 mg, 0.58 mmol, 1.00 equiv) was suspended in DCM (5 mL) and dissolved by addition of TFA (5 mL). The mixture was left to stir at room temperature under nitrogen for 18 h. The mixture was concentrated *in vacuo*, dissolved in H_2O (5 mL) and freeze dried.

The salt was dissolved in 2M HCl (3 mL), concentrated *in vacuo*, redissolved in H_2O (3 x 5 mL) and concentrated *in vacuo* after each time. The salt was then dissolved in H_2O (5 mL) and freeze dried to yield proline salt **13** (156 mg, 93 %) as a reddish foam. ^{1}H NMR (300 MHz, D_2O): δ 2.50 – 2.67 (2H, m), 3.59 (1H, dd, *J* = 13, 4 Hz), 3.70 (1H, d, *J* = 13 Hz), 4.59 (1H, t, *J* = 6 Hz), 5.14 (1H, m), 7.03 (1H, ddm, *J* = 8, 3 Hz), 7.25 - 7.34 (2H, m), 7.47 (1H, dm, *J* = 8 Hz); ^{13}C NMR (75 MHz, D_2O): δ 34.3, 51.4, 58.8, 75.2, 116.3, 121.3, 123.4, 130.1, 131.0, 155.1, 169.6, 171.7; LCMS: m/z [M + H]$^+$: calc: 252.1, found: 252.1; HPLC: purity$_{254}$ = 100 %; OR: [a]$^{22}_D$: 8.04 (c = 0.56 g/100 mL; H_2O).

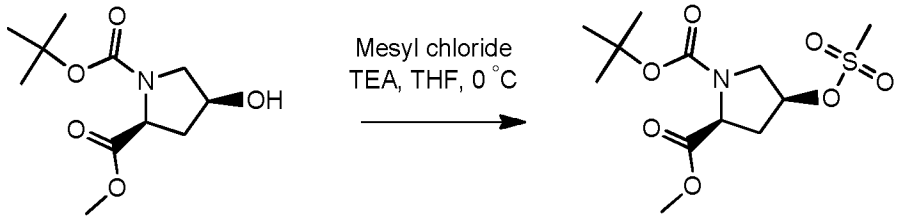
(2*S*,4*S*)-4-(1-carboxyphenoxy)pyrrolidine-2-carboxylic acid trifluoroacetic acid (14):



11 14

Protected proline **11** (262 mg, 0.75 mmol, 1.00 equiv) was suspended in DCM (5 mL) and added TFA (5 mL). The mixture was left to stir at room temperature under nitrogen for 18 h. The mixture was concentrated *in vacuo*, dissolved in H_2O (5 mL) and freeze dried to yield proline salt **14** (231 mg, 85 %) as a brownish foam. ^{1}H NMR (300 MHz, D_2O): δ 2.51 – 2.66 (2H, m), 3.57 (1H, dd, *J* = 13, 4 Hz), 3.70 (1H, d, *J* = 13 Hz), 4.53 (1H, dd, *J* = 9, 4Hz), 5.25 (1H, m), 6.87-6.92 (2H, m) , 7.84 - 7.90 (2H, m); ^{13}C NMR (400 MHz, $((CD_3)_2SO$): δ 34.3, 50.7, 57.8, 75.0, 113,7, 115.2, 123.9, 131.4, 158.5, 166.8, 170.2; LCMS: m/z $[M + H]^+$: calc: 252.1, found: 252.0; HPLC: purity$_{254}$ > 98 %; OR: $[a]^{22}_D$: 28.16 (c = 0.25 g/100 mL; H_2O and 1% TFA).

(2*S*,4*S*)-1-*tert*-butyl 2-methyl 4-((methylsulfonyl)oxy)pyrrolidine-1,2-dicarboxylate (15):

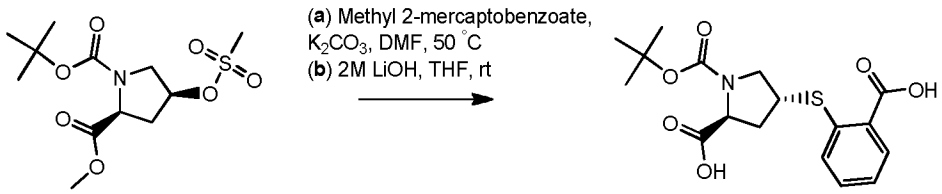


1 15

Alcohol **1** (550 mg, 2.24 mmol, 1.00 equiv) was dissolved in dry THF (5 mL) and added TEA (1.70 mL, 3.95 mmol, 1.76 equiv) under nitrogen. The mixture was cooled to 0 °C, drop wise added mesyl chloride (0.30 mL, 3.88 mmol, 1.73 equiv) over the course of 10 min and the mixture was stirred at 0 °C for an additional 5 h. The mixture was added H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases was washed with 1M HCl (10 mL), sat. $NaHCO_3$ (15 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield mesylate **15** (714 mg, 98 %) as a slightly, white solid. ^{1}H NMR (300 MHz, $(CDCl_3)$: δ 1.44, 1.49 (9H, 2 x s), 2.46 – 2.58 (2H, m), 3.02 (3H, s), 3.75 – 3.84 (2H, m), 3.76 (3H, s), 4.42 (0.53H, dd, *J*

= 8, 3 Hz), 4.53 (0.46H, dd, *J* = 7, 5 Hz), 5.24 (1H, m). Characterisation is consistent which existing literature.

(2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-((2-carboxyphenyl)thio)pyrrolidine-2-carboxylic acid (16):



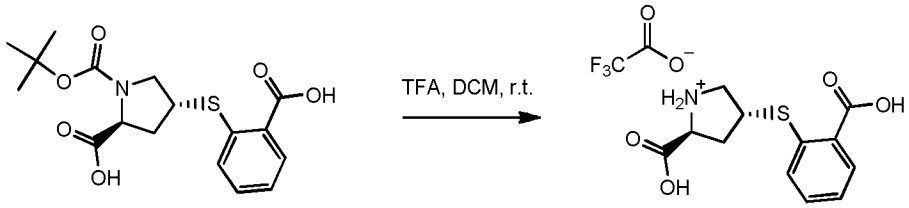
15 16

Methyl 2-mercaptobenzoate (307 mg, 183 mmol, 1.63 equiv) was dissolved in DMF (7 mL) and added K_2CO_3 (265 mg, 1.92 mmol, 1.71 equiv). Mesylate **15** (345 mg, 1.12 mmol, 1.00 equiv) was drop wise added to the mixture over the course of 5 min, which was subsequently heated to 50 °C and stir under nitrogen for 18 h. The mixture was added 10 % brine (75 mL) and extracted with Et_2O (2 x 75 mL). The combined organic phases was washed with 0.5 M NaOH (2 x 50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*.

The crude oil was dissolved in THF (7.5 mL), cooled to 0 °C and drop wise added 2M LiOH (20 mL) over the course of 5 min. After additional 15 min at 0 °C the mixture was left to stir for 18 h at room temperature. The mixture was added H_2O (75 mL) and was washed with Et_2O (2 x 50 mL). The aqueous phase was acidified (pH ≈ 1) using conc. HCl and extracted with a combination of Et_2O and THF (1 : 1) (3 x 70 mL). The combined organic phases was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified using DCVC (0 – 75 % EtOAc in toluene and 2 % AcOH) yielding thioether **16** (304 mg, 78 %) as a clear, colorless oil. ^{1}H NMR (300 MHz, ($CDCl_3$): δ 1.43/1.47 (9H, 2 x s), 2.26 – 2.68 (2H, m), 3.40-3.56 (1H, m), 3.96 – 4.06 (1.5H, m), 4.17 (0.5H, dd, *J* = 11, 7 Hz), 4.46 (0.5H, dd, *J* = 8, 5 Hz), 4.57 (0.5H, dd, *J* = 8, 3 Hz), 7.13-7.25 (1H, m), 7.33 (1H, t, *J* = 10 Hz), 7.48 (1H, q, *J* = 8 Hz), 8.07 (1H, dd, *J* = 8, 3 Hz), 12.0 (2H, bs); ^{13}C NMR (75 MHz, ($CDCl_3$): δ 28.4, 28.5, 35.5, 36.5, 40.5, 41.0, 52.4, 52.5, 58.4, 58.5, 81.3, 81.7, 124.7, 124.8, 126.6, 126.8, 126.9, 132.5, 133.5, 140.7, 140.8, 153.5, 155.0, 171.3, 176.5, 178.4; LCMS: m/z $[M + H]^+$: calc: 368.1, found: 268.1 (-Boc); HPLC: $purity_{254}$ =

100 %; TLC: R_f: 0.19 (EtOAc : heptanes : AcOH (40 : 20 : 1)); OR: $[a]^{22}_D$: -22.53 (c = 0.49 g/100 mL; abs EtOH).

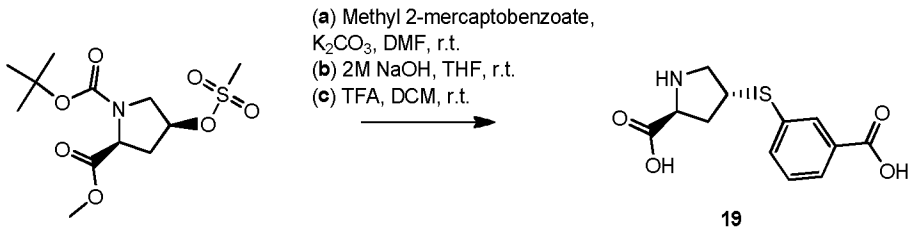
(2*S*,4*R*)-4-((2-carboxyphenyl)thio)pyrrolidine-2-carboxylic acid trifluoroacetic acid (18).



16 18

Protected proline **16** (196 mg, 0.53 mmol) was dissolved in DCM (5 mL) and added TFA (4 mL). The mixture was stirred at room temperature for 18 h under nitrogen and subsequently concentrated in vacuo. The product was dissolved in 15 H_2O and freeze dried to yield proline salt **18** (191 mg, 94 %) as a pale, brown solid. ^{1}H NMR (400 MHz, D_2O): δ 2.41-2.48 (1H, m), 2.60-2.68 (1H, m), 3.37 (1H, dd, *J* = 12, 4 Hz), 3.87 (1H, dd, *J* = 12, 4 Hz), 4.25 (1H, s), 4.63 (1H, dd, *J* = 12, 8 Hz), 7.34 (1H, t, *J* = 8 Hz), 7.45 (1H, d, *J* = 8 Hz), 7.54 (1H, t, *J* = 8, Hz), 7.88 (1H, d, *J* = 8 Hz); ^{13}C NMR (400 MHz, D_2O): δ 34.3, 41.9, 50.8, 59.0, 126.7, 129.3, 130.4, 131.1, 133.2, 135.3, 163.0, 171.2; LCMS: m/z $[M + H]^+$: calc: 268.1, found: 268.1; HPLC: purity$_{254}$ > 99 %; OR: $[a]^{22}_D$: -11.78 (c = 0.44 g/100 mL; H_2O and 2% TFA).

(2*S*,4*R*)-4-((3-carboxyphenyl)thio)pyrrolidine-2-carboxylic acid (19):



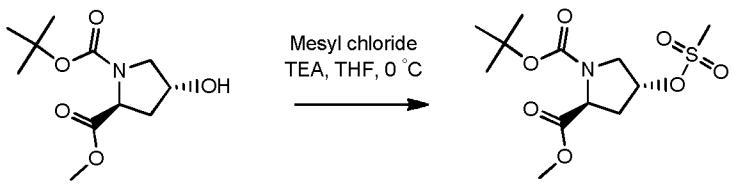
15 19

Methyl 3-mercaptobenzoate (286 mg, 1.70 mmol, 1.44 equiv) was dissolved in DMF (12 mL) and added K_2CO_3 (243 mg, 1.76 mmol, 1.49 equiv). Mesylate **15** (365 mg, 1.18 mmol, 1.00 equiv) was added to the mixture, which was subsequently left to stir at room temperature under nitrogen for 18 h. The mixture was added 10 % brine (100 mL) and extracted with Et_2O (3 x 60 mL). The combined organic phases was washed with 0.5 M NaOH (2 x 80 mL), brine (60 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*.

The crude oil was dissolved in THF (10 mL), cooled to 0 °C and drop wise added 2M NaOH (5 mL) over the course of 5 min. After additional 15 min at 0 °C the mixture was left to stir at room temperature for 19 h. The mixture was added H_2O (20 mL) and washed with Et_2O (2 x 20 mL). The aqueous phase was acidified (pH ≈ 1) using conc. HCl, extracted with a combination of Et_2O and THF (3 : 4) (20 mL) and concentrated *in vacuo*.

The crude product was suspended in DCM (2 mL) and dissolved by addition of TFA (2 mL). The mixture was left to stir at room temperature under nitrogen for 22 h. The mixture was concentrated *in vacuo*, dissolved in H_2O (30 mL) and washed with DCM (3 × 30 mL). The water phase was freeze dried to yield thioether **19** (121 mg, 40 %) as an off-white solid. ^{1}H NMR (400 MHz, D_2O): δ 2.33-2.40 (1H, m), 2.49-2.57 (1H, m), 3.32 (1H, dd, *J* = 12, 4 Hz), 3.77 (1H, dd, *J* = 12, 4 Hz), 4.07 (1H, pentet, *J* = 4 Hz), 4.60 (1H, t, *J* = 8 Hz), 7.37 (1H, t, *J* = 8 Hz), 7.56 (1H, d, *J* = 8 Hz), 7.78 (1H, d, *J* = 8 Hz), 7.85 (1H, s); ^{13}C NMR (400 MHz, D_2O): δ 34.4, 43.5, 50.7, 58.9, 129.1, 129.66, 130.7, 132.4, 133.0, 136.4, 169.2, 171.4; LCMS: m/z $[M + H]^+$: calc: 268.1, found: 268.1; HPLC: $purity_{254}$ > 98 %; OR: $[a]^{22}_D$: -6.55 (c = 0.29 g/100 mL; H_2O).

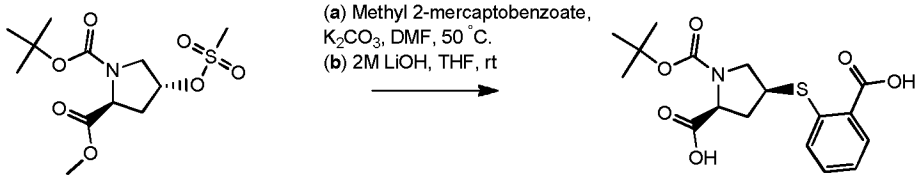
(2*S*,4*R*)-1-*tert*-butyl 2-methyl 4-((methylsulfonyl)oxy)pyrrolidine-1,2-dicarboxylate (20):



8 20

Alcohol **8** (2.11 g, 8.60 mmol, 1.00 equiv) was dissolved in dry THF (15 mL) and added TEA (1.70 mL, 12.2 mmol, 1.42 equiv) under nitrogen. The mixture was cooled to 0 °C and drop wise added mesyl chloride (1.00 mL, 12.9 mmol, 1.50 equiv) over the course of 15 min and the mixture was stirred for an additional 5 h. The mixture was added H_2O (30 mL) and extracted with EtOAc (3 x 25 mL). The combined organic phases was washed with 1M HCl (30 mL), sat. $NaHCO_3$ (40 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield mesylate **20** (2.50 g, 90 %) as a white solid. ^{1}H NMR (300 MHz, ($CDCl_3$): 1.43, 1.47 (9H, 2 x s), 2.25 (0.40H, dd, *J* = 14, 5 Hz), 2.28 (0.60, dd, *J* = 14, 5 Hz), 2.58 (0.40, ddd, *J* = 14, 8, 3

Hz), 2.67 (0.60, tdd, *J* = 14, 8, 2 Hz) 3.06 (3H, s), 3.72 – 3.89 (5H, m), 4.40 (0.60H, t, *J* = 8 Hz), 4.46 (0.40H, t, *J* = 8 Hz), 5.26 (1H, m). Characterisation is consistent which existing literature.



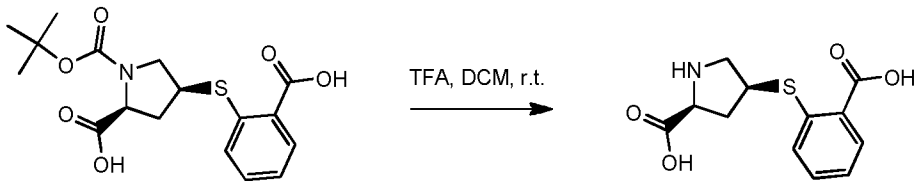
20 21

(2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-((2-carboxyphenyl)thio)pyrrolidine-2-carboxylic acid (21): Methyl 2-mercaptobenzoate (180 mg, 1.07 mmol, 1.66 equiv) was dissolved in DMF (4 mL) and added K_2CO_3 (149 mg, 1.08 mmol, 1.67 equiv). Mesylate **20** (200 mg, 0.65 mmol, 1.00 equiv) was drop wise added to the mixture, which was subsequently heated to 50 °C and stired under nitrogen for 18 h. The mixture was added 10 % brine (40 mL) and extracted with Et_2O (2 x 50 mL). The combined organic phases was washed with 0.5 M NaOH (2 x 30 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The oil was purified using DCVC (0 – 22 % EtOAc in toluene)

The oil was dissolved in THF (5 mL), cooled to 0 °C and drop wise added 2M LiOH (10 mL) over the course of 5 min. After additional 15 min at 0 °C the mixture was left to stir for 18 h at room temperature. The mixture was added H_2O (50 mL) and was washed with Et_2O (2 x 25 mL). The aqueous phase was acidified (pH ≈ 1) using conc. HCl and extracted with a combination of Et_2O and THF (1 : 1) (3 x 25 mL). The combined organic phases was washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified using DCVC (0 – 75 % EtOAc in toluene and 2 % AcOH) yielding thioether **21** (153 mg, 67 %) as a white solid. ^{1}H NMR (300 MHz, ($CDCl_3$): δ 1.47/1.54 (9H, 2 x s), 2.44 – 2.66 (2H, m), 3.60-3.78 (1H, m), 3.89 – 4.03 (1H, m), 4.09-4.16 (1H, m), 4.44 (0.5H, d, *J* = 8 Hz), 4.55 (0.5H, d, *J* = 8 Hz), 7.20 (1H, d, *J* = 8 Hz), 7.33 (1H, d, *J* = 8 Hz), 7.48 (2H, t, *J* = 8 Hz); ^{13}C NMR (400 MHz, ($CDCl_3$): δ 28.3, 28.5, 34.9, 36.0, 42.0, 50.9, 57.8, 58.0, 80.7, 81.0, 124.7, 124.8, 126.9, 127.1, 128.3, 128.5, 132.5, 132.6, 132.9, 133.1, 135.8, 140.3, 140.8, 153.9, 154.7, 171.7, 179.1, 179.7; LCMS: m/z $[M + H]^+$: calc: 368.1, found: 268.1 (-Boc);

HPLC: purity$_{254}$ = 100 %; TLC: R_f: 0.18 (EtOAc : heptanes : AcOH (40 : 20 : 1)); OR: $[a]^{22}_D$: -28.30 (c = 0.29 g/100 mL; abs EtOH).

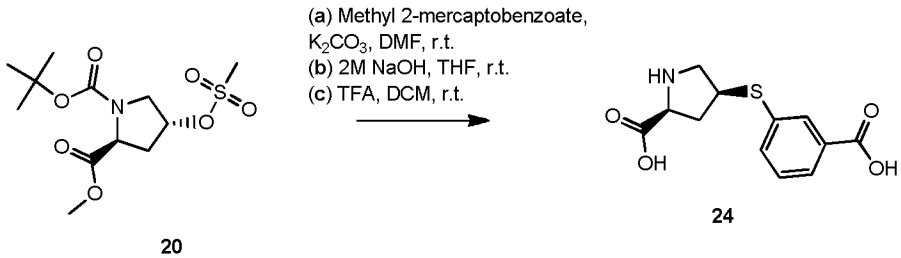
(2*S*,4*S*)-4-((2-carboxyphenyl)thio)pyrrolidine-2-carboxylic acid (23):



21 23

Protected proline **21** (100 mg, 0.27 mmol) was suspended in DCM (1 mL) and dissolved by addition of TFA (1 mL). The mixture was left to stir at room temperature under nitrogen for 1 h. The mixture was concentrated *in vacuo*, dissolved in H_2O (30 mL) and washed with DCM (3 × 20 mL). The aqueous phase was freeze dried to yield proline **23** (54 mg, 74 %) as an off-white solid. ^{1}H NMR (400 MHz, D_2O): δ 2.18-2.25 (1H, m), 2.77-285 (1H, m), 3.34 (0.5H, d, *J* = 4 Hz), 3.39 (0.5H, d, *J* = 4 Hz), 3.76 (1H, dd, *J* = 12, 8 Hz), 4.15 (1H, m), 4.50 (1H, dd, *J* = 8, 4 Hz), 7.26 (1H, t, *J* = 8 Hz), 7.35 (1H, t, *J* = 8 Hz), 7.47 (2H, t, *J* = 8 Hz); ^{13}C NMR (400 MHz, D_2O): δ 34.0, 41.6, 50.8, 58.9, 126.6, 129.5, 130.4, 131.0, 133.1, 135.3, 162.8, 170.9; LCMS: m/z $[M + H]^+$: calc: 268.1, found: 268.1; HPLC: purity$_{254}$ = 100 %; OR: $[a]^{22}_D$: -4.67 (c = 0.19 g/100 mL; H_2O and 5% TFA).

(2*S*,4*S*)-4-((3-carboxyphenyl)thio)pyrrolidine-2-carboxylic acid (24):



20 24

Methyl 3-mercaptobenzoate (473 mg, 2.81 mmol, 1.51 equiv) was dissolved in DMF (22 mL) and added K_2CO_3 (397 mg, 2.87 mmol, 1.54 equiv). Mesylate **20** (604 mg, 1.87 mmol, 1.00 equiv) was drop wise added to the mixture, which was subsequently left to stir at room temperature under nitrogen for 18 h. The mixture was added 1 % brine (400 mL) and extracted with Et_2O (3 x 100 mL). The combined organic phases was washed with 0.5 M

NaOH (2 x 100 mL), brine (80 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*.

The oil was dissolved in THF (10 mL), cooled to 0 °C and drop wise added 2M NaOH (5 mL) over the course of 5 min. After additional 15 min at 0 °C the mixture was left to stir at room temperature for 20 h. The mixture was added H_2O (30 mL) and washed with Et_2O (2 x 30 mL). The aqueous phase was acidified (pH ≈ 1) using conc. HCl, extracted with a combination of Et_2O and THF (3 : 4) (40 mL) and concentrated *in vacuo*.

The crude product was suspended in DCM (4 mL) and dissolved by addition of TFA (4 mL). The mixture was left to stir at room temperature under nitrogen for 21 h. The mixture was concentrated *in vacuo*, dissolved in H_2O (30 mL) and washed with DCM (3 × 30 mL). The aqueous phase was freeze dried to yield proline **24** (188 mg, 38 %) as an off-white solid. ^{1}H NMR (400 MHz, D_2O): δ 2.25-2.32 (1H, m), 2.79-2.87 (1H, m), 3.48 (1H, dd, *J* = 12, 4 Hz), 3.76 (1H, dd, *J* = 12, 4 Hz), 4.20 (1H, pentet, *J* = 4 Hz), 4.44 (1H, dd, *J* = 12, 8 Hz), 7.55 (1H, t, *J* = 8 Hz), 7.76 (1H, d, *J* = 8 Hz), 7.78 (1H, dd, *J* = 8, 4 Hz), 8.01 (1H, s); ^{13}C NMR (400 MHz, D_2O): δ 34.3, 43.7, 50.7, 59.8, 129.3, 129.7, 130.9, 132.9, 133.2, 137.0, 169.7, 171.8; LCMS: m/z $[M + H]^+$: calc: 268.1, found: 268.1; HPLC: $purity_{254}$ > 99 %; OR: $[a]^{22}_D$: -18.19 (c = 0.24 g/100 mL; H_2O).

The protected compounds produced above may be deprotected by methods, which are well-known by the skilled person.

The following compounds, compounds 25 to 33, were prepared following corresponding procedures as described above.

(2S,4R)-4-(2-(carboxymethyl)phenoxy)pyrrolidine-2-carboxylic acid, **(25)**,

(2S,4R)-4-(3-(carboxymethyl)phenoxy)pyrrolidine-2-carboxylic acid, **(26)**,

(2S,4R)-4-((3-carboxynaphthalen-2-yl)oxy)pyrrolidine-2-carboxylic acid, **(27)**,

(2S,4R)-4-((2-carboxynaphthalen-1-yl)oxy)pyrrolidine-2-carboxylic acid, **(28)**,

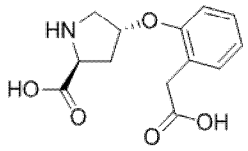
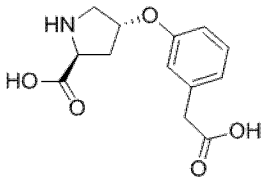
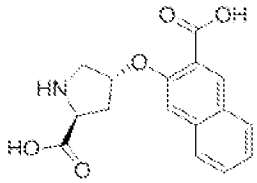
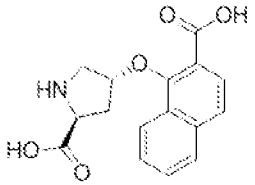
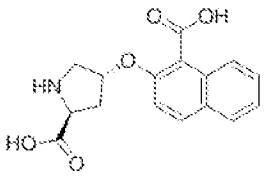
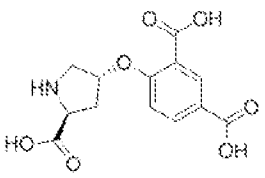
(2S,4R)-4-((1-carboxynaphthalen-2-yl)oxy)pyrrolidine-2-carboxylic acid, **(29)**,

(2S,4R)-4-(2,4-dicarboxyphenoxy)pyrrolidine-2-carboxylic acid, **(30)**,

(2S,4R)-4-(2-carboxy-4-methylphenoxy)pyrrolidine-2-carboxylic acid, **(31)**,

(2S,4R)-4-(4-acetyl-2-carboxyphenoxy)pyrrolidine-2-carboxylic acid, **(32)**,

(2S,4R)-4-(2-carboxy-6-methylphenoxy)pyrrolidine-2-carboxylic acid, (**33**).

Compound #	CNG code	Chemical structure
25	**10-211**	
26	**10-212**	
27	**10-213**	
28	**10-214**	
29	**10-215**	
30	**10-216**	

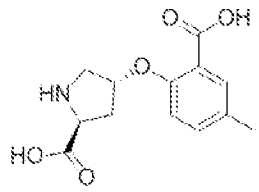
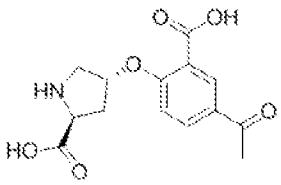
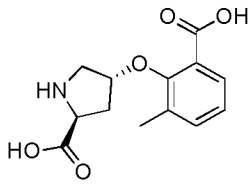
31	**10-217**	
32	**10-218**	
33	**10-219**	

Table 2. prepared compounds, 25 to 33.

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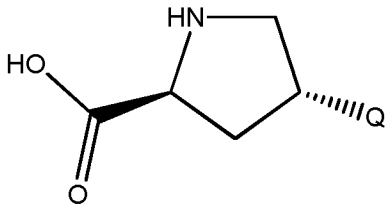
P A T E N T C L A I M S

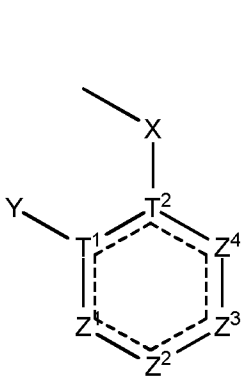
1. A compound of Formula (I)



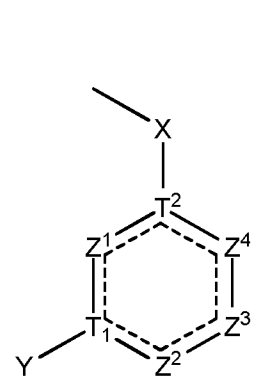
(I),

and pharmaceutically acceptable derivatives, the tautomers and stereoisomers, and protected compounds tereof, wherein

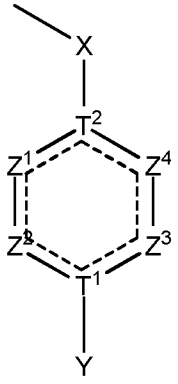
Q represents compounds of Formula (Ia), (Ib), (Ic), (Id), or (Ie);



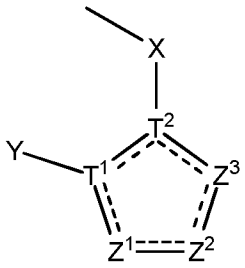
(Ia),



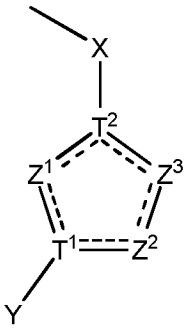
(Ib),



(1c),



(Id), or



(Ie)

---- in each case may represent if appropriate the presence of at least one double bond between two adjacent ringatoms forming the ring system consisting of T^1, T^2, Z^1, Z^2, Z^3 and optionally Z^4,

X is C, NH, O or S,

T^1 is C, or CH,

T^2 is C, or CH,

Y is COR^1, substituted or unsubstituted C_1-C_6-alkyleneCOR^1, $PO(OR^1)_2$, substituted or unsubstituted C_1-C_6-alkylene$PO(OR_1)_2$, SO_2OR_1, substituted or unsubstituted C_1-C_6-alkyleneSO_2OR^1, $SO_2N(R^1)_2$, or C_1-C_6-

alkylene$SO_2N(R^1)_2$, wherein one or more -CH_2- groups forming the alkylene group may optionally be replaced by –CH=CH- or –C≡C-,

Z^1 is CR^2, $C(R^2)_2$, N, S, O, or NR^3,

Z^2 is CR^2, $C(R^2)_2$, N, S, O, or NR^3,

Z^3 is CR^2, $C(R^2)_2$, N, S, O, or NR^3,

Z^4 is absent, CR^2, $C(R^2)_2$, N, S, O, or NR^3,

wherein if appropriate the residues Z^1, Z^2, Z^3 and Z^4, cannot represent adjacent O or S,

R^1 is independently selected from the group comprising H, OR^4, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, $COOR^4$, N(OH)H, or NHR^4,

R^2 is independently selected from the group comprising R^4, O, OR^4, C_1-C_6-alkyl OR^4, halogen, N(OH)H, N(OH)R^4, NHR^4, COR^4, C_1-C_6-alkyl COR^4, $COOR^4$, C_1-C_6-alkyl $COOR^4$, $CONHR^4$, C_1-C_6-alkyl $CONHR^4$, or SO_2NHR^4,

R^3 is independently selected from the group comprising R^4, O, OR^4, or halogen,

R^4 is independently selected from the group comprising H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, phenyl, C_1-C_6-alkylphenyl, or saturated or unsaturated C_5- or C_6-cycloalkyl, saturated or unsaturated C_5- or C_6-heterocyclyl, or saturated or unsaturated C_1-C_6-alkyl C_5- or C_6-heterocyclyl, wherein C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, phenyl, C_1-C_6-alkylphenyl, or saturated or unsaturated C_5- or C_6-cycloalkyl, saturated or unsaturated C_5- or C_6-heterocyclyl, or saturated or unsaturated C_1-C_6-alkyl C_5- or C_6-heterocyclyl may be substituted with one or more substituents selected from the group comprising C_1-C_6-alkyl, C_1-C_6-alkoxy, aryl, halogen, O, and amine,

R^1 may together with Z^1, Z^2, or Z^3 or

Z^2 may together with Z^1 or Z^3, or

Z^3 may together with Z^4,

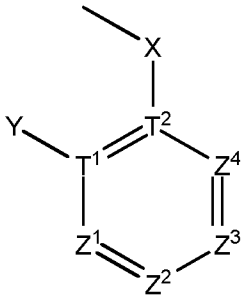
optionally form if appropriate a saturated or unsaturated C_5- or C_6-cycloalkyl or a 5- or 6-membered heterocyclyl, wherein the saturated or unsaturated C_5- or C_6-cycloalkyl or the 5- or 6-membered heterocyclyl may be substituted with one or more substituents selected from the group comprising R_2, OR_4 or R_4,

halogen represents Cl, Br, or I, and

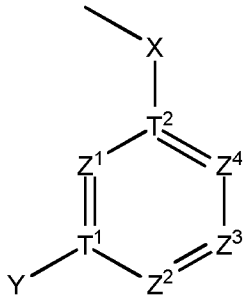
with the proviso that Z^1, Z^2, Z^3 and Z^4 are not all CH, and with the proviso that T^1 and T^2 are not both C, when R^1 is OH.

2. A compound according to claim 1 comprising Formula (I), wherein

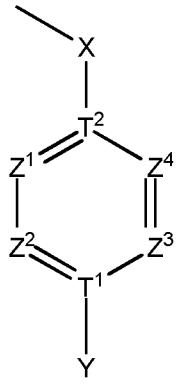
Q represents compounds of Formula (Ia2), (Ib2), (Ic2), (Id2), or (Ie2),



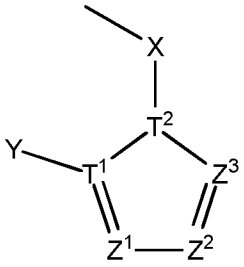
(Ia2),



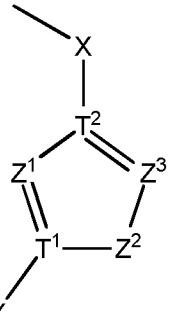
(Ib2),



(1c2),



(Id2), or



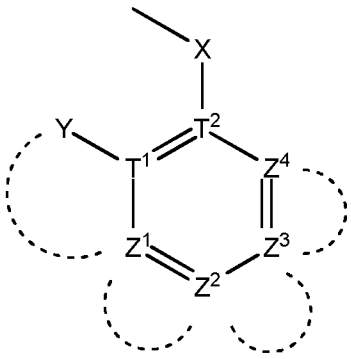
(Ie2),

wherein

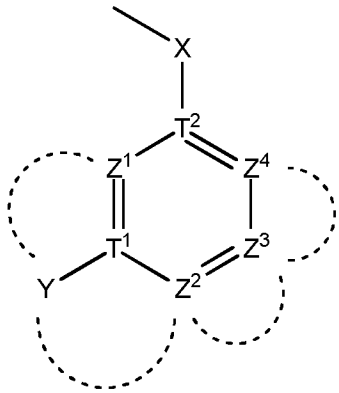
X, T^1, T^2, Y, Z^1, Z^2, Z^3, Z^4, R^1, R^2, R^3, R^4 and halogen have the same meaning as defined in claim 1.

3. A compound according to any of the claims 1 to 2, comprising Formula (I), wherein

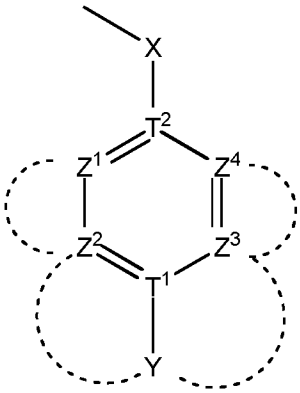
Q represents compounds of Formula (Ia3), (Ib3), (Ic3), (Id3), or (Ie3), wherein



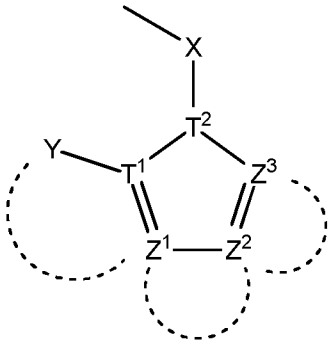
(Ia3),



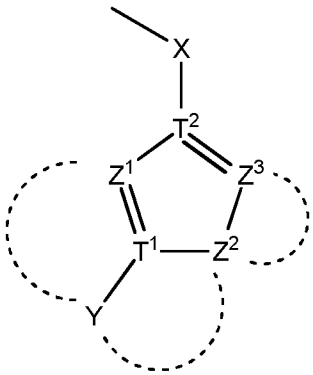
(Ib3),



(1c3),



(Id3), or



(Ie3),

wherein

R^1 and (Z^1, Z^2, or Z^3),

Z^2 and Z^1 or Z^3), or

Z^3 and Z^4,

form if appropriate a saturated or unsaturated C_5- or C_6-cycloalkyl or a 5- or 6-membered heterocyclyl ring, the heterocyclyl ring containing one, two, three or four heteroatoms selected from the group comprising sulfur, oxygen and nitrogen, and the saturated or unsaturated C_5- or C_6-cycloalkyl or the 5- or 6-membered heterocyclyl ring may be substituted with one or more substituents selected from the group comprising OR_4 or R_4,

X, T^1, T^2, Y, Z^1, Z^2, Z^3, Z^4, R^1, R^2, R^3, R^4 and halogen have the same meaning as defined in claim 1.

4. A compound of Formula (I) according to any of the claims 1 to 3, wherein the 5- or 6-membered ring is selected from the group consisting of pyrrolidine, pyrrole, tetrahydrofuran, furan, thiolane, thiophene, imidazolidine, pyrazolidine, imidazole, pyrazole, oxazolidine, isoxazolidine, oxazole, isoxazole, thiazolidine, isothiazolidine, thiazole, isothiazole, dioxolane, dithiolane, triazoles, furazan, oxadiazole, thiadiazole, dithiazole, tetrazole, piperidine, pyridine, oxane, pyran, thiane thiopyran, piperazine, diazines, morpholine, oxazine, thiomorpholine, thiazine, dioxane, dioxine, dithiane, dithiine, triazine, trioxane, or tetrazine, and wherein the 5- or 6-membered heterocyclic ring may be substituted with 1 to 3 substituents.

5. A compound according to any of the claims 1 to 4 comprising Formula (I), wherein

X is O or S,

T^1 is C,

T^2 is C,

Y is COOH,

Z^1 is CH,

Z^2 is CH,

Z^3 is CH,

Z^4 is absent or CH,

6. A compound according to any of the claims 1 to 5 selected from the group consisting of

(2) (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(2-carboxyphenoxy)pyrrolidine-2-carboxylic acid,

(3) (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(3-carboxyphenoxy)pyrrolidine-2-carboxylic acid,

(4) (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(4-carboxyphenoxy)pyrrolidine-2-carboxylic acid,

(5) (2*S*,4*R*)-4-(2-carboxyphenoxy)pyrrolidine-2-carboxylic acid trifluoroacetic acid,

(6) (2*S*,4*R*)-4-(3-carboxyphenoxy)pyrrolidine-2-carboxylic acid hydrochloride,

(7) (2*S*,4*R*)-4-(4-carboxyphenoxy)pyrrolidine-2-carboxylic acid hydrochlo-

ride,

(16) (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-((2-carboxyphenyl)thio)pyrrolidine-2-carboxylic acid,

(18) (2*S*,4*R*)-4-((2-carboxyphenyl)thio)pyrrolidine-2-carboxylic acid trifluoroacetic acid,

(19) (2*S*,4*R*)-4-((3-carboxyphenyl)thio)pyrrolidine-2-carboxylic acid,

(20) (2*S*,4*R*)-1-*tert*-butyl 2-methyl 4-((methylsulfonyl)oxy)pyrrolidine-1,2-dicarboxylate,

(25) (2S,4R)-4-(2-(carboxymethyl)phenoxy)pyrrolidine-2-carboxylic acid,

(26) (2S,4R)-4-(3-(carboxymethyl)phenoxy)pyrrolidine-2-carboxylic acid,

(27) (2S,4R)-4-((3-carboxynaphthalen-2-yl)oxy)pyrrolidine-2-carboxylic acid,

(28) (2S,4R)-4-((2-carboxynaphthalen-1-yl)oxy)pyrrolidine-2-carboxylic acid,

(29) (2S,4R)-4-((1-carboxynaphthalen-2-yl)oxy)pyrrolidine-2-carboxylic acid,

(30) (2S,4R)-4-(2,4-dicarboxyphenoxy)pyrrolidine-2-carboxylic acid,

(31) (2S,4R)-4-(2-carboxy-4-methylphenoxy)pyrrolidine-2-carboxylic acid,

(32) (2S,4R)-4-(4-acetyl-2-carboxyphenoxy)pyrrolidine-2-carboxylic acid, and (33) (2S,4R)-4-(2-carboxy-6-methylphenoxy)pyrrolidine-2-carboxylic acid.

7. A compound according to any one of the preceding claims for use as a medicament.

8. A pharmaceutical composition comprising a compound according to any one of claims 1 to 7 in combination with one or more therapeutically acceptable diluents or carriers.

9. A compound according to any one of claims 1 to 6 or a pharmaceutical composition according to claim 8 for use in treatment of disorders of the central nervous system, neuro-physiological processes such as memory, cognition; as well as neuronal plasticity and development, psychiatric diseases or neurological disorders such as depression, anxiety, addiction, pain, migraine, and schizophrenia, and neurodegenerative diseases; such as Alzheimer, Huntington disease, amyotrophic lateral sclerosis (ALS), cerebral stroke, and epilepsy; and diseases including aching, ADHD, Autism, Diabetes, Huntington's disease, ischemia, multiple sclerosis, Parkinson's disease (Parkinsonism), Rasmussen's encephalitis, seizures, AIDS dementia complex, amyotrophic lateral sclerosis, combined systems disease (vitamin B12 defi-

ciency), drug addiction, drug tolerance, drug dependency, glaucoma, hepatic encephalopathy, hydroxybutyric aminoaciduria, hyperhomocysteinemia and homocysteinuria, hyperprolinemia, lead encephalopathy, leber's disease, MELAS syndrome, MERRF, mitochondrial abnormalities (and other inherited or acquired biochemical disorders), neuropathic pain syndromes (e.g. causalgia or painful peripheral neuropathies), nonketotic hyperglycinemia, olivopontocerebellar atrophy, essential tremor, Rett syndrome, sulfite oxidase deficiency, Wernicke's encephalopathy or cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/DK2014/050218

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D207/12 C07D207/16 A61K31/401 A61P25/00
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 A61K A61P

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, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MALENE R. JØRGENSEN ET AL: "The Effects of Conformational Constraints and Steric Bulk in the Amino Acid Moiety of Philanthotoxins on AMPAR Antagonism", JOURNAL OF MEDICINAL CHEMISTRY, vol. 48, no. 1, 1 January 2005 (2005-01-01), pages 56-70, XP055139473, ISSN: 0022-2623, DOI: 10.1021/jm049906w page 59; compound 19d -----	1-9
X	WO 2004/039367 A1 (PFIZER LTD [GB]; RAWSON DAVID JAMES [GB]; PFIZER [US]) 13 May 2004 (2004-05-13) page 7, line 11 - line 12 page 93; claim 1 -----	1-9
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[X] Further documents are listed in the continuation of Box C.

[X] 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
24 September 2014	02/10/2014

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	Jeanjean, Fabien

INTERNATIONAL SEARCH REPORT

International application No
PCT/DK2014/050218

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 2 305 660 A1 (ALMIRALL SA [ES]) 6 April 2011 (2011-04-06) page 84; example 75	1-9
A	WO 2005/102390 A2 (PFIZER JAPAN INC [JP]; HIZUE MASANORI [JP]; IMAI AKI [JP]; TOIDE KATSU) 3 November 2005 (2005-11-03) page 58; claims 7-8	1-9
A	US 4 316 906 A (ONDETTI MIGUEL A ET AL) 23 February 1982 (1982-02-23) column 42; example 63(a)	1-9
A	EP 2 058 301 A1 (UNIV GIFU [JP]; UNIV KANSAI MEDICAL [JP]; OSAKA MEDICAL COLLEGE [JP]) 13 May 2009 (2009-05-13) page 11, paragraph 29; compound (IV) page 25 - page 28; examples 9-12; compounds (IIa)-(IId) page 48; claim 4; compound (II)	1-9
A	DAVID J RAWSON ET AL: "Part 2: Design, synthesis and evaluation of hydroxyproline-derivedligands", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 21, no. 12, 20 April 2011 (2011-04-20), pages 3767-3770, XP028387844, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2011.04.056 [retrieved on 2011-04-20] page 3768; table 2; compounds 11, 18, 23-29, 31-32	1-9
A	WO 2013/078468 A1 (PORTOLA PHARM INC [US]) 30 May 2013 (2013-05-30) page 187, paragraph 849 - page 188, paragraph 850; example 217	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/DK2014/050218

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Information on patent family members

International application No
PCT/DK2014/050218

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WO 2013078468 A1	30-05-2013	CA 2856306 A1	30-05-2013
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