Title: FUSED HETEROCYCLIC DERIVATIVES AS S1P MODULATORS

Field of the invention

This invention relates to new fused heterocyclic derivatives having affinity to S1P receptors, a pharmaceutical composition containing said compounds, as well as the use of said compounds for the preparation of a medicament for treating, alleviating or preventing diseases and conditions in which any S1P receptor is involved or in which modulation of the endogenous S1P signaling system via any S1P receptor is involved.

Background of the invention

Sphingosine-1-phosphate (S1P) is a bioactive sphingolipid that mediates a wide variety of cellular responses, such as proliferation, cytoskeletal organization and migration, adherence- and tight junction assembly, and morphogenesis. S1P can bind with members of the endothelial cell differentiation gene family (EDG receptors) of plasma membrane-localized G protein-coupled receptors. To date, five members of this family have been identified as S1P receptors in different cell types, S1P1 (EDG-1), S1P2 (EDG-5), S1P3 (EDG-3), S1P4 (EDG-6) and S1P5 (EDG-8). S1P can produce cytoskeletal re-arrangements in many cell types to regulate immune cell trafficking, vascular homeostasis and cell communication in the central nervous system (CNS) and in peripheral organ systems.

It is known that S1P is secreted by vascular endothelium and is present in blood at concentrations of 200-900 nanomolar and is bound by albumin and other plasma proteins. This provides both a stable reservoir in extracellular fluids and efficient delivery to high-affinity cell-surface receptors. S1P binds with low nanomolar affinity to the five receptors S1P1-5. In addition, platelets also contain S1P and may be locally released to cause e.g. vasoconstriction. The receptor subtypes S1P1, S1P2 and S1P3 are widely expressed and represent dominant receptors in the cardiovascular system. Further, S1P1 is also a receptor on lymphocytes. S1P4 receptors are almost exclusively in the haematopoietic and lymphoid system. S1P5 is primarily (though not exclusively) expressed in central nervous system. The expression of S1P5 appears to be restricted to

oligodendrocytes in mice, the myelinating cells of the brain, while in rat and man expression at the level of astrocytes and endothelial cells was found but not on oligodendrocytes.

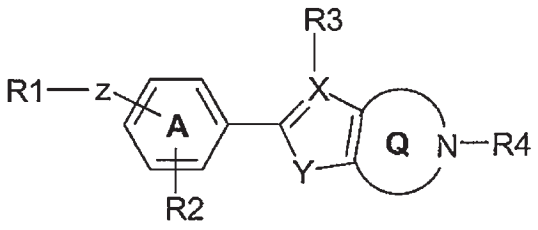
S1P receptor modulators are compounds which signal as (ant)agonists at one or more S1P receptors. The present invention relates to modulators of the S1P5 receptor, in particular agonists, and preferably to agonists with selectivity over S1P1 and/or S1P3 receptors, in view of unwanted cardiovascular and/or immunomodulatory effects. It has now been found that S1P5 agonists can be used in the treatment of cognitive disorders, in particular age-related cognitive decline.

Although research is ongoing to develop therapeutics that can be used to treat age related cognitive decline and dementia, this has not yet resulted in many successful candidates. Therefore, there is a need for new therapeutics with the desired properties.

Description of the invention

It has now been found that fused heterocyclic derivatives of the formula (I)

A fused heterocyclic derivative of the formula (I)



(I)

wherein
R1 is selected from

cyano,

(2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkyl, each optionally substituted with CN or one or more fluoro atoms,

(3-6C)cycloalkyl, (4-6C)cycloalkenyl or a (8-10C)bicyclic group, each optionally substituted with halogen or (1-4C)alkyl optionally substituted with one or more fluoro atoms,

phenyl, biphenyl, naphthyl, each optionally substituted with one or more substituents independently selected from halogen, cyano, (1-4C)alkyl

optionally substituted with one or more fluoro atoms, (1-4C)alkoxy optionally substituted with one or more fluoro atoms, amino, dimethylamino, and (3-6C)cycloalkyl optionally substituted with phenyl which may be substituted with (1-4C)alkyl or halogen, and phenyl substituted with phenoxy, benzyl, benzyloxy, phenylethyl or monocyclic heterocycle, each optionally substituted with (1-4C)alkyl,

Z is a linking group –W-(C_n-alkylene)-T- wherein

W is attached to R1 and selected from a bond, -O-, -CO-, -S-, -SO-, -SO_2-, -NH-, -CH=CH-, -$C(CF_3)$=CH-, -C≡C-, -CH_2-O-, -O-CO-, -CO-O-, -CO-NH-, -NH-CO- and trans-cyclopropylene;

n is an integer from 0 to 10; and

T is attached to the phenylene/pyridyl moiety and selected from a bond, -O-, -S-, -SO-, -SO_2-, -NH-, -CO-, -C=C-, -C≡C-, and trans-cyclopropylene;

R2 is H or one or more substituents independently selected from cyano, halogen, (1-4C)alkyl optionally substituted with one or more halogen atoms, or (1-4C)alkoxy optionally substituted with one or more halogen atoms;

ring structure **A** may contain one nitrogen atom;

X is selected from C or N; if X is C, R3 is selected from H and (1-4C)alkyl, otherwise R3 is not present;

Y is selected from NH, O and S;

structure **Q** is a 5-, 6- or 7- membered cyclic amine;

and

R4 is (1-4C)alkylene-R5 wherein one or more carbon atoms in the alkylene group may independently be substituted with one or more halogen atoms or with $(CH_2)_2$ to form a cyclopropyl moiety , or R4 is (3-6C)cycloalkylene-R5, -CH_2-(3-6C)cycloalkylene-R5, (3-6C)cycloalkylene-CH_2-R5 or -CO-CH_2-R5, wherein R5 is -OH, -PO_3H_2, -OPO_3H_2, -COOH, -COO(1-4C)alkyl or tetrazol-5-yl;

or a pharmaceutically acceptable salt, a solvate or hydrate thereof or one or more N-oxides thereof display affinity for S1P receptors. In particular, compounds of the invention show selective affinity for the S1P5 receptor over the S1P1 and/or S1P3 receptor(s).

In WO 2008/012010, some of the disclosed compounds have somewhat structural similarity to the compounds of the present invention; however, they are described as histamine H3-receptor ligands.

The compounds of the invention are modulators of the S1P receptor, in particular of the S1P5 receptor. More specifically, the compounds of the invention are S1P5 receptor agonists. The compounds of the invention are useful for treating, alleviating and preventing diseases and conditions in which (any) S1P receptor(s) - in particular S1P5 – is (are) involved or in which modulation of the endogenous S1P signaling system via any S1P receptor is involved. In particular, the compounds of the present invention may be used to treat, alleviate or prevent CNS (central nervous system) disorders, such as neurodegenerative disorders, in particular -but not limited to- cognitive disorders (in particular age-related cognitive decline) and related conditions, Alzheimer's disease, (vascular) dementia, Nieman's Pick disease, and cognitive deficits in schizophrenia, obsessive-compulsive behavior, major depression and autism, multiple sclerosis, pain, etc.. Preferably, the compounds of the present invention may be used to treat, alleviate or prevent cognitive disorders (in particular age-related cognitive decline) and related conditions.

In a preferred embodiment of the invention, the compounds have formula (I) wherein

R1 is selected from

(3-6C)cycloalkyl or a (8-10C)bicyclic group optionally substituted with halogen, (1-4C)alkyl, and

phenyl optionally substituted with one or more substituents independently selected from halogen, cyano, (1-4C)alkyl, (1-4C)alkoxy, trifluoromethyl and trifluoromethoxy;

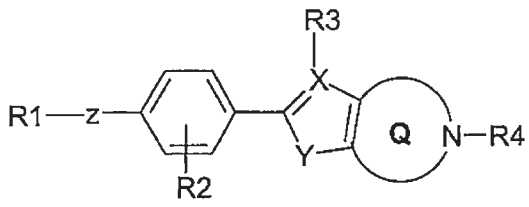
W is selected from a bond, -O-, -CO-, -S-, -SO-, -SO_2-, -NH-, -CH=CH-, -C≡C-, and trans-cyclopropylene; and

n is an integer from 0 to 4; and preferably, n is selected from 0, 1 and 2; and

R2 is H or one or more substituents independently selected from halogen, (1-4C)alkyl optionally substituted with one or more fluoro atoms or (1-4C)alkoxy optionally substituted with one or more fluoro atoms;

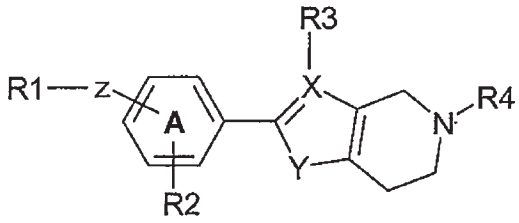
and wherein the definition of the other groups / symbols is as defined previously.

In another embodiment, the compound of the invention has the structure (**Ia**)



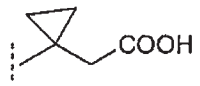
(**Ia**).

In an embodiment of the invention, ring structure **Q** is a 6-membered ring. In particular, the compound of the invention has the structure (**Ib**)



(**Ib**).

In a further embodiment of the invention, R4 is selected from -$(CH_2)_2$-OH, -CH_2-COOH, -$(CH_2)_2$-COOH, -$(CH_2)_3$-COOH, -CH_2-$CHCH_3$-COOH, -CH_2-$C(CH_3)_2$-COOH, -$CHCH_3$-CH_2-COOH, -CH_2-CF_2-COOH, -CO-CH_2-COOH,



, 1,3-cyclobutylene-COOH, -$(CH_2)_2$-PO_3H_2, -$(CH_2)_3$-PO_3H_2, -$(CH_2)_2$-OPO_3H_2, -$(CH_2)_3$-OPO_3H_2, -CH_2-tetrazol-5-yl, -$(CH_2)_2$-tetrazol-5-yl and -$(CH_2)_3$-tetrazol-5-yl. Preferred R4 groups are selected from -$(CH_2)_2$-COOH, -$(CH_2)_3$-COOH, -CH_2-$CHCH_3$-COOH, -CH_2-$C(CH_3)_2$-COOH, -$CHCH_3$-CH_2-COOH, -CH_2-CF_2-COOH and. Highly preferred are -$(CH_2)_2$-COOH, -$CHCH_3$-CH_2-COOH, -CH_2-$CHCH_3$-COOH and 1,3-cyclobutylene-COOH. In particular preferred is -CH_2-$CHCH_3$-COOH.

In another preferred embodiment, the compounds have formula (I) wherein Y is O.

Further, in a preferred embodiment of the invention, X is N.

In preferred embodiments of the invention, R1 is indanyl optionally substituted with halogen, (1-4C)alkyl, or -more preferred- R1 is optionally substituted phenyl, wherein the optional substituents are selected from any of the previously defined substituents, but in particular the optional substituents are one or more substituents independently selected from halogen, cyano, (1-4C)alkyl,

(1-4C)alkoxy, trifluoromethyl and trifluoromethoxy. In highly preferred embodiments, R1 is 4Cl-phenyl or 4CF_3-phenyl.

In an embodiment of the invention, R2 is H or one or more substituents independently selected from methyl, methoxy, chloro or fluoro. In a preferred embodiment, R2 is H or R2 represents one methyl, one methoxy, one chloro, one chloro, or one or two fluoro atoms.

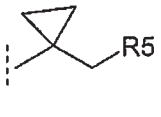
In embodiments of the invention, wherin X is CR3, R3 is preferably H or methyl and in particular, R3 is H.

Further, in an embodiment of the invention, Z is the linking group -W-$(CH_2)_n$-T-, the meaning of which is selected from a bond, -O-, -CO-, -S-, -SO_2-, -NH-, -CH_2-, -$(CH_2)_2$-, -CCH_3-O-, -CH=CH-, -C≡C-, -CH_2-O-, -O-CH_2-, -CH_2-S-, -S-CH_2-, -CH_2-SO_2-, -SO_2-CH_2-, -CH_2-NH-, -NH-CH_2-, and trans-cyclopropylene. In preferred embodiments, Z is -O-, -CH_2-O- or trans-cyclopropylene. In particular, Z is -CH_2-O-.

The term halogen refers to fluoro, chloro, bromo, or iodo. Preferred halogens are fluoro and chloro, and in particular chloro.

The term (1-4C)alkyl means a branched or unbranched alkyl group having 1-4 carbon atoms, for example methyl, ethyl, propyl, isopropyl and butyl. A preferred alkyl group is methyl.

The term (1-4C)alkoxy means an alkoxy group having 1-4 carbon atoms, wherein the alkyl moiety is as defined above. A preferred alkoxy group is methoxy.

The terms (1-4C)alkylene and (C_n-alkylene) mean a branched or unbranched alkylene group having 1-4 or n carbon atoms, respectively, for example methylene, -$CHCH_3$-, -$C(CH_3)_2$-, -$CHCH_3CH_2$-, and the like. In the definition of R4 which is (1-4C)alkylene-R5, one or more carbon atoms in the alkylene group may (amongst others) independently be substituted with $(CH_2)_2$ to form a cyclopropyl moiety, meaning to form a R4 group such as 

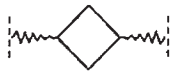
.

The term (2-4C)alkynyl means a branched or unbranched alkynyl group having 2-4 carbon atoms, wherein the triple bond may be present at different positions in the group, for example ethynyl, propargyl, 1-butynyl, 2-butynyl, etc.

The term (3-6C)cycloalkyl means a cyclic alkyl group having 3-6 carbon atoms, thus cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Preferred are cyclopentyl and cyclohexyl.

The term (4-6C)cycloalkenyl means a cyclic alkenyl group having 4-6 carbon atoms and comprising one or two double bonds, for example cyclohexenyl.

The term (3-6C)cycloalkylene means a cyclic alkyl group having two attachment points. Preferred is 1,3-cyclobutylene, having the structure



The term (8-10C)bicyclic group means a fused ring system of two groups selected from aromatic and non-aromatic ring structures having together 8-10 carbon atoms, for example the indane group.

With reference to substituents, the term "independently" means that the substituents may be the same or different from each other in the same molecule.

The compounds of the invention may suitably be prepared by methods available in the art, and as illustrated in the experimental section of this description.

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds. The independent syntheses of these diastereomers 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 which 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 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.

Compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, 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.

Isotopically-labeled compound of formula (I) or pharmaceutically acceptable salts thereof, including compounds of formula (I) isotopically-labeled to be detectable by PET or SPECT, also fall within the scope of the invention. The same applies to compounds of formula (I) labeled with [^{13}C]-, [^{14}C]-, [^{3}H]-, [^{18}F]-, [^{125}I]- or other isotopically enriched atoms, suitable for receptor binding or metabolism studies.

The term "pharmaceutically acceptable salt" refers to those salts that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well-known in the art. They can be prepared *in situ* when isolating and purifying the compounds of the invention, or separately by reacting them with pharmaceutically acceptable non-toxic bases or acids, including inorganic or organic bases and inorganic or organic acids.

The compounds of the invention may be administered enterally or parenterally. The exact dose and regimen of these compounds and compositions thereof will be dependent on the biological activity of the compound *per se*, the age, weight and sex of the patient, the needs of the individual subject to whom the medicament is administered, the degree of affliction or need and the judgment of the medical practitioner. In general, parenteral administration requires lower dosages than other methods of administration which are more dependent upon adsorption. However, the dosages for humans are preferably 0.001 – 10 mg per kg body weight. In general, enteral and parenteral dosages will be in the range of 0.1 to 1,000 mg per day of total active ingredients.

Mixed with pharmaceutically suitable auxiliaries, *e.g.* as described in the standard reference "Remington, The Science and Practice of Pharmacy" (21st

edition, Lippincott Williams & Wilkins, 2005, see especially Part 5: Pharmaceutical Manufacturing) the compounds may be compressed into solid dosage units, such as pills or tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the compounds can also be applied in the form of a solution, suspension or emulsion.

For making dosage units, *e.g.* tablets, the use of conventional additives such as fillers, colorants, polymeric binders and the like, is contemplated. In general, any pharmaceutically suitable additive which does not interfere with the function of the active compounds can be used.

Suitable carriers with which the compounds of the invention can be administered include for instance lactose, starch, cellulose derivatives and the like, or mixtures thereof, used in suitable amounts. Compositions for intravenous administration may for example be solutions of the compounds of the invention in sterile isotonic aqueous buffer. Where necessary, the intravenous compositions may include for instance solubilizing agents, stabilizing agents and/or a local anesthetic to ease the pain at the site of the injection.

Pharmaceutical compositions of the invention may be formulated for any route of administration and comprise at least one compound of the present invention and pharmaceutically acceptable salts thereof, with any pharmaceutically suitable ingredient, excipient, carrier, adjuvant or vehicle.

By "pharmaceutically suitable" it is meant that the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

In an embodiment of the invention, a pharmaceutical pack or kit is provided comprising one or more containers filled with one or more pharmaceutical compositions of the invention. Associated with such container(s) can be various written materials such as instructions for use, or a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals products, which notice reflects approval by the agency of manufacture, use, or sale for human or veterinary administration.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the

present invention, suitable methods and materials are described in this document.

LEGEND TO THE FIGURES

Figure 1 Percentage of alternation of young and old C57BL/6J male mice in the T-maze with either vehicle (control groups) or compound of the invention (dose in mg/kg; p.o.)

The following examples are intended to further illustrate the invention in more detail.

Any novel intermediate as disclosed herein is a further embodiment of the present invention.

EXAMPLES

§1. ANALYTICAL METHODS

Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR, APT) were determined in the indicated solvent using a Bruker ARX 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) at 300 K, unless indicated otherwise. ^{19}F NMR and ^{13}C NMR experiments were carried out on a Varian Inova 500 spectrometer operating at 11.74 T (499.9 MHz for ^{1}H; 125.7 MHz for ^{13}C; 50.7 Mhz, 470.4 MHz for ^{19}F) using a 5 mm SW probe. The spectra were determined in deuterated chloroform or DCM obtained from Cambridge Isotope Laboratories Ltd. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane (^{1}H, ^{13}C) or CCl_3F (^{19}F). Coupling constants J are given in Hz. Peak shapes in the NMR spectra are indicated with the symbols 'q' (quartet), 'dq' (double quartet), 't' (triplet), 'dt' (double triplet), 'd' (doublet), 'dd' (double doublet), 's' (singlet), 'bs' (bs) and 'm' (multiplet). NH and OH signals were identified after mixing the sample with a drop of D_2O.

Flash chromatography refers to purification using the indicated eluent and silica gel (either Acros: 0.030-0.075 mm or Merck silica gel 60: 0.040-0.063 mm).

Column chromatography was performed using silica gel 60 (0.063-0.200 mm, Merck).

Reactions were monitored by using **thin-layer chromatography** (TLC) on silica coated plastic sheets (Merck precoated silica gel 60 F254) with the indicated eluent. Spots were visualized by UV light (254 nm) or I_2.

Melting points were recorded on a Büchi B-545 melting point apparatus.

Liquid Chromatography- Mass Spectrometry (LC-MS):

- Method A.

The LC-MS system consists of a Waters 1525 µ-pump. The pump is connected to a Waters 2777 auto sampler.

The LC method is:

step	total time	flow (ul/min)	A(%)	B(%)
0	0.2	1600	90	10
1	2.5	1600	0	100
2	2.8	1600	0	100
3	2.9	1600	90	10
4	3.10	1600	90	10
5	3.11	500	90	10

A= 100% Water with 0.2% HCOOH

B= 100% ACN with 0.2% HCOOH

The auto sampler has a 10 ul injection loop; the injection volume is 10 µl. The auto sampler is connected to a Waters Sunfire C18 30*4.6 mm column with 2.5 um particles. The column is thermo stated at Room temperature +/- 23°C

The column is connected to a Waters 2996 PDA. The wavelength is scanned from 240 to 320 nm. The resolution is 1.2 nm and the sampling ate is 20 Hz. After the PDA the flow is split 1:1 and connected to a Waters 2424 ELSD.

The ELSD has the following parameters:

Gas pressure: 40 psi

Data rate 20 points/sec

Gain 500

Time constant 0.2 sec
Nebulizer mode cooling
Drift tube 50°C

The samples are also measured with a Waters ZQ mass detector.
The mass spectrometer has the following parameters:
Scan range: 117-900 Amu
Polarity: positive
Data format: centroid
Time per scan: 0.500 sec
Interscan time: 0.05 sec
Capillary 2.5 kV
Cone 25 V
Extractor 2 V
RF lens 0.5 V
Source Temp. 125°C
Desolvation Temp 400 °C
Cone gas 100 L/Hr
Desolvation Gas 800 L/Hr
LM 1 Resolution 15
HM 1 Resolution 15
Ion energy 0.5
Multiplier 500 V

The complete system is controlled by Masslynx 4.1.

- **Method B.**

The LC-MS system consists of 2 Perkin Elmer series 200 micro pumps. The pumps are connected to each other by a 50 ul tee mixer. The mixer is connected to the Gilson 215 auto sampler.

The LC method is:

step	total time	flow (ul/min)	A (%)	B (%)
0	0	1800	95	5
1	1.8	1800	0	100
2	2.6	1800	0	100
3	2.8	1800	95	5
4	3.0	1800	95	5

A= 100% Water with 0.1% HCOOH

B= 100% Acetonitril with 0.1% HCOOH

The auto sampler has a 2 ul injection loop. The auto sampler is connected to a Waters Sunfire C18 4.6x30 mm column with 2.5 □m particles. The column is thermo stated in a Perkin Elmer series 200 column oven at 23 °C. The column is connected to a Perkin Elmer 785 UV/VIS meter with a 2.7 ul flow cell. The wavelength is set to 254 nm. The UV meter is connected to a Sciex API 150EX mass spectrometer. The mass spectrometer has the following parameters:

Scan range: 100-900 Amu

Polarity: positive

Scan mode: profile

Resolution Q1: UNIT

Step size: 0.10 amu

Time per scan: 0.500 sec

NEB: 10

CUR: 10

IS: 5200

TEM: 325

DF: 30

FP: 225

EP: 10

The light scattering detector is connected to the Sciex API 150. The light scattering detector is a Polymer Labs PL-ELS 2100 operating at 70° C and 1.7 bar N_2 pressure.

The complete system is controlled by a Dell precision GX370 computer operating under Windows 2000.

The reported retention times in Table 1 (R_t) are for the peak in the Total Ion Current (TIC) chromatogram which showed the mass for $[M+H]^+$ within 0.5 amu accuracy of the calculated exact MW and had an associated peak in the Evaporative Light Scattering (ELS) chromatogram with a relative area% (purity) of >85%.

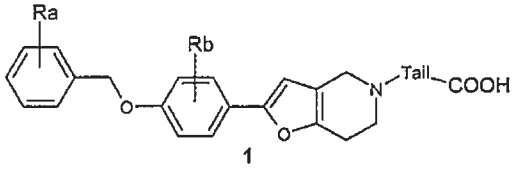
§2. ABBREVIATIONS

ACE-Cl	1-Chloroethyl chloroformate
9-BBN	9-borabicyclo[3.3.1]nonane dimer
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
CH_3CN	Acetonitrile
$CuBr_2$	Copper(II) bromide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIAD	Diisopropyl azodicarboxylate
DIPEA	*N,N*-Diisopropylethylamine
DMF	*N,N*-dimethylformamide
DMSO	Dimethyl sulfoxide
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOH	Ethanol
EtOAc	Ethyl acetate
HCl	Hydrogen chloride
K_2CO_3	Potassium carbonate
$KHCO_3$	Potassium bicarbonate
KI	Potassium iodide
KOH	Potassium hydroxide
KOtBu	Potassium *tert*-butoxide
MeOH	Methanol
$NaBH_4$	Sodium borohydride
$NaHCO_3$	Sodium bicarbonate
NaI	Sodium iodide
NaOH	Sodium hydroxide

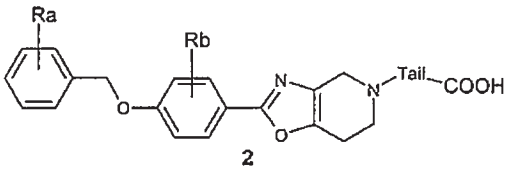
NaOtBu	Sodium *tert*-butoxide
Na_2SO_4	Sodium sulfate
NBS	*N*-Bromosuccinimide
iPr_2O	Diisopropyl ether
RT	Room Temperature
SiO_2	Silica gel
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMSCl	Chlorotrimethylsilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate

§3. GENERAL ASPECTS OF SYNTHESES

Suitable syntheses of claimed compounds are described below.



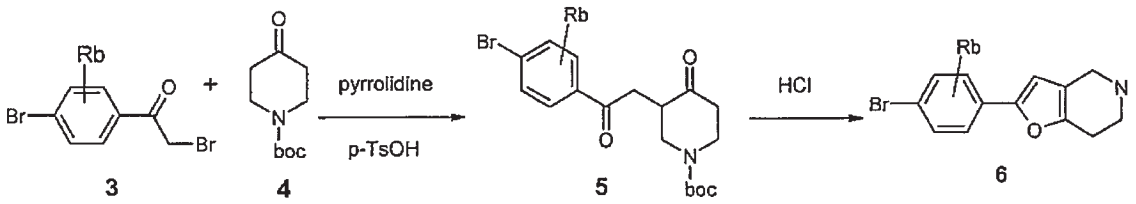
1



2

For the synthesis of compounds **1**, two routes are described in respectively Schemes 2 and 3. Both routes start with compound **6**, the synthesis of which is depicted in Scheme 1. Alpha alkylation of the pyrrolidine-enamine of **4** with alpha-bromo-acetophenones (**3**) -thereby introducing the Rb-group in the molecule- gives compound **5**. Subsequent ring-closure of **5** under acidic conditions yielded compound **6** in fair yields.

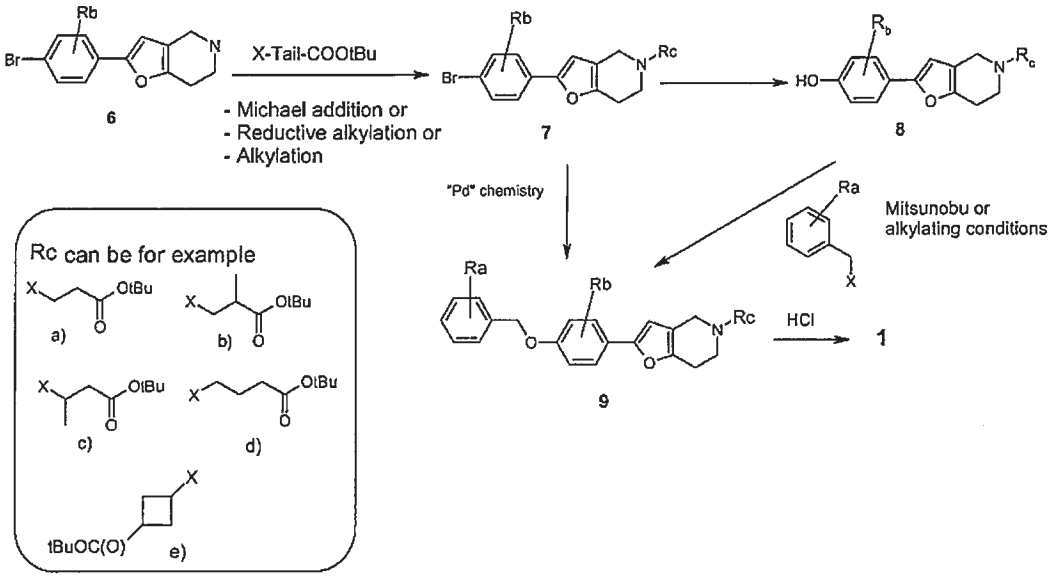
Scheme 1. Synthesis of key-intermediate 6.



3 4 5 6

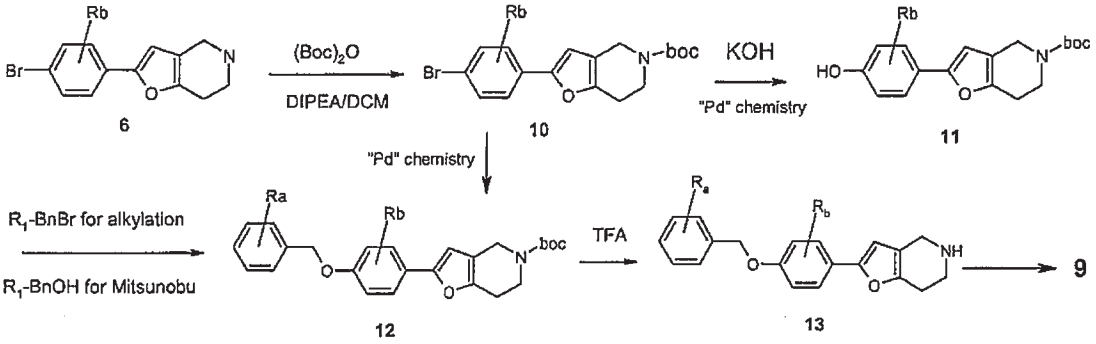
introduced in two ways. Firstly, the bromine in **7** could be converted directly to the benzyl ether derivative **9** by a palladium catalyzed reaction. Additionally, bromide **7** can be converted to the phenol derivative **8** derivative *via* a palladium mediated reaction. Compound **8** can be converted to the desired benzyl ether derivatives **9** under phase transfer conditions with benzyl bromides or *via* a Mitsunobu reaction with benzyl alcohols. Finally, compounds **9** could be deprotected to give the end-products **1**.

Scheme 2. Route A to compounds **1**



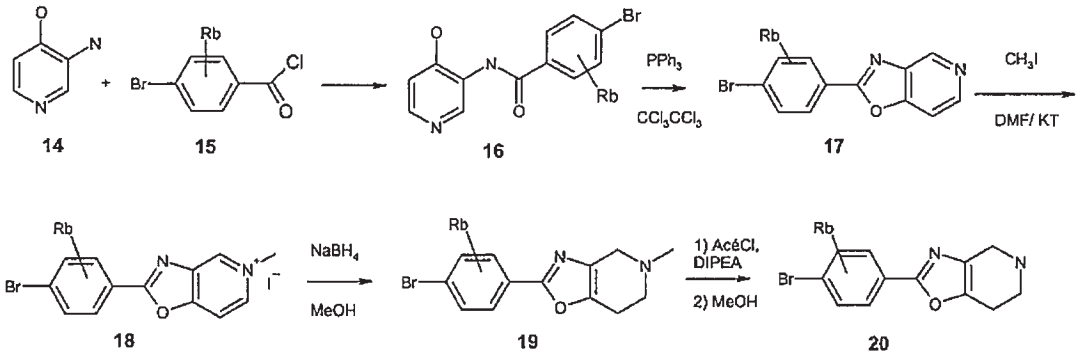
Alternatively, Route B (see Scheme 3) could be followed for the synthesis of compounds **1**. The piperidine in compound **6** was protected with a BOC group. Hereafter, first the benzyl ether moiety was introduced either *via* a direct palladium mediated reaction of the bromine in **10** to **12** or *via* transforming the bromine to the phenol derivative **11**, which could be converted to **12** under alkylation or Mitsunobu conditions. Finally, compound **12** could be converted to **9** by acidic removal of the BOC group and subsequent introduction of the protected carboxylic acid tails.

Scheme 3. Route B to compounds 1



For the synthesis of oxazolo-derivatives **2**, three routes were developed. The synthesis of key-intermediate **20** is depicted in Scheme 4. Acylation of commercially available **14** with a properly substituted benzoyl chloride (**15**) gave **16**, which was subsequently ring-closed to **17** by using triphenylphosphine and hexachloroethane. Methylation of the pyridine in **17** to the quaternary salt **18** and subsequent reduction of **18** with sodium borohydride yielded compound **19**. Compound **19** was demethylated with 1-chloroethyl chloroformate to furnish key-intermediate **20**.

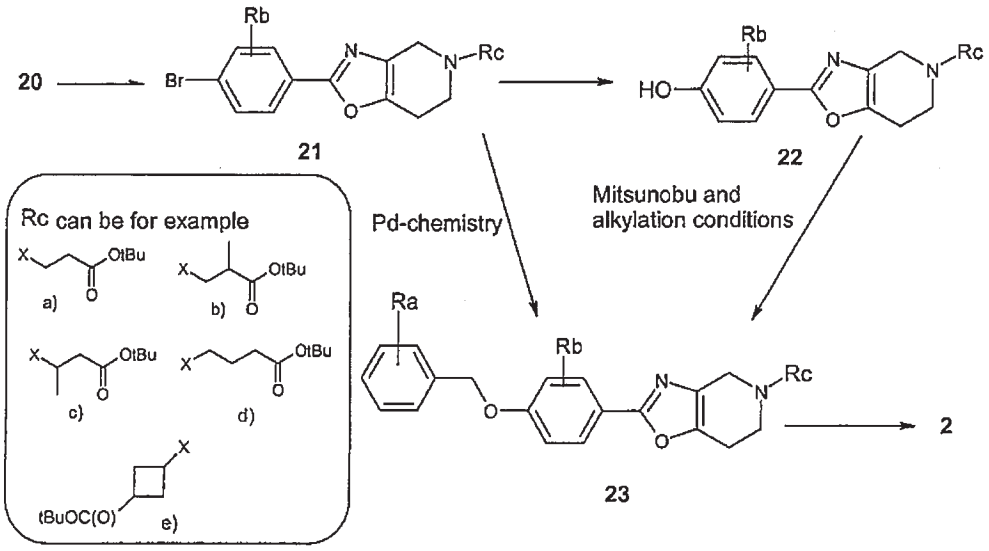
Scheme 4. Synthesis of compounds 20.



The first route (Route C) to compounds **2** is outlined in Scheme 5 and starts from compound **20**. In a similar fashion as described for the synthesis of compounds **7** in the furanyl series, the t-butyl protected carboxylic acid tails could be introduced in **20** to give **21**. Starting from **21**, the benzyl ether derivatives **23** could be prepared by either a direct palladium mediated coupling (**21** to **23**) with benzyl alcohols or by first transforming the bromide in **21** to phenol **22** and subsequent benzylation of **22** (to **23**) under phase transfer or Mitsunobu

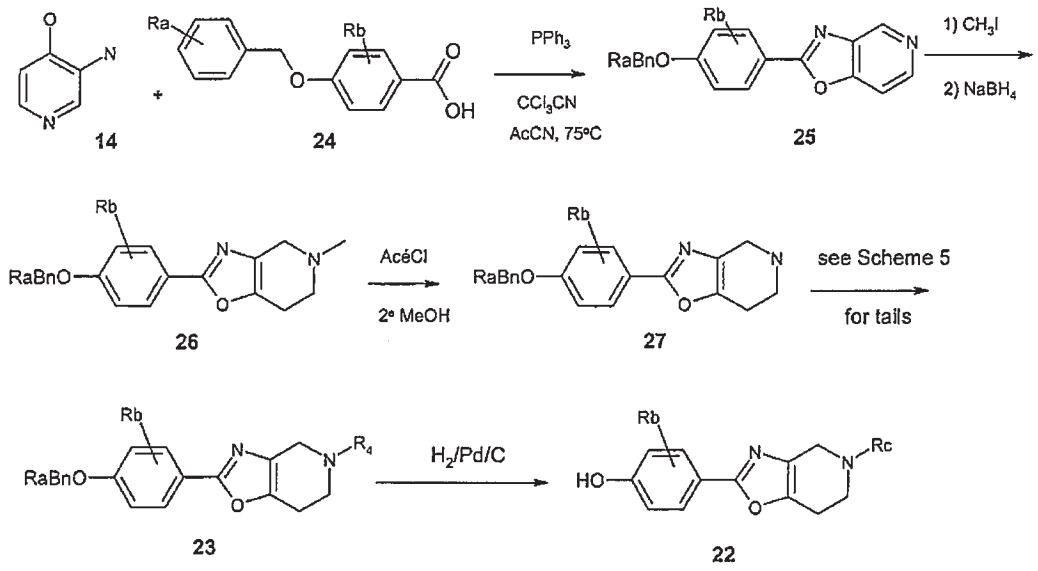
conditions. Finally, acidic deprotection of the carboxylic acid in **23** yielded compounds **2**.

Scheme 5. Route C to compounds **2**.



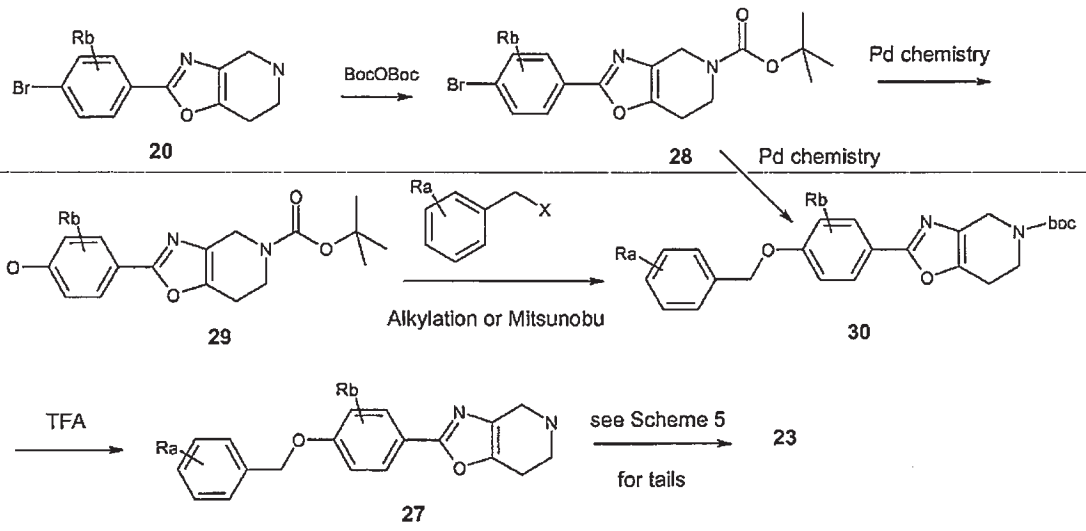
Alternatively, route D could be followed as depicted in Scheme 6. Compounds **25** could be prepared starting from **14** and a properly substituted 4-benzyloxy-benzoic acid derivative (**24**) under the influence of triphenylphosphine and trichloroacetonitril. Compound **25** could be converted to the benzyloxy-derivatives **23** in a similar fashion as described above in Schemes 4 and 5 for the synthesis of compounds **21**. Thus, methylation of **25** and subsequent reduction with $NaBH_4$ gave **26**, which was demethylated with ACE-Cl to give **27**. Finally, the tails were introduced in **27** to give compound **23**. From here, the t-butyl group in **23** could be removed under acidic conditions to give compound **2**. On the other hand, the benzyl in **23** can be removed by hydrogenation to give phenol derivatives **22**.

Scheme 6. Route D to compounds 2.

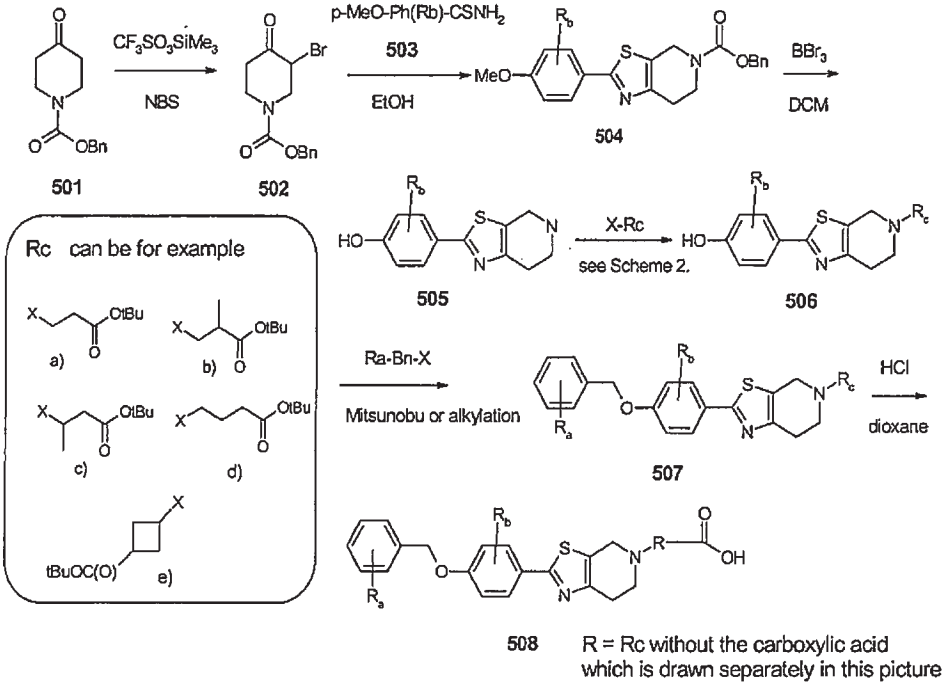


And finally, the third route (Route E) to compounds **2** is depicted in Scheme 7. Compound **20** was protected with a t-butyloxycarbonyl group to give **28**, which could be converted to the corresponding phenol (**29**) under standard palladium conditions. Alkylation of **29** under phase transfer or Mitsunobu conditions gave **30.** On the other hand, compound **30** could also be obtained directly from the bromide **28** under palladium chemistry conditions. Acidic removal of the BOC group in **30** resulted in the formation of compound **27**, which could be alkylated to **23** as described in Scheme 5.

Scheme 7. Route E for the synthesis of compounds 2

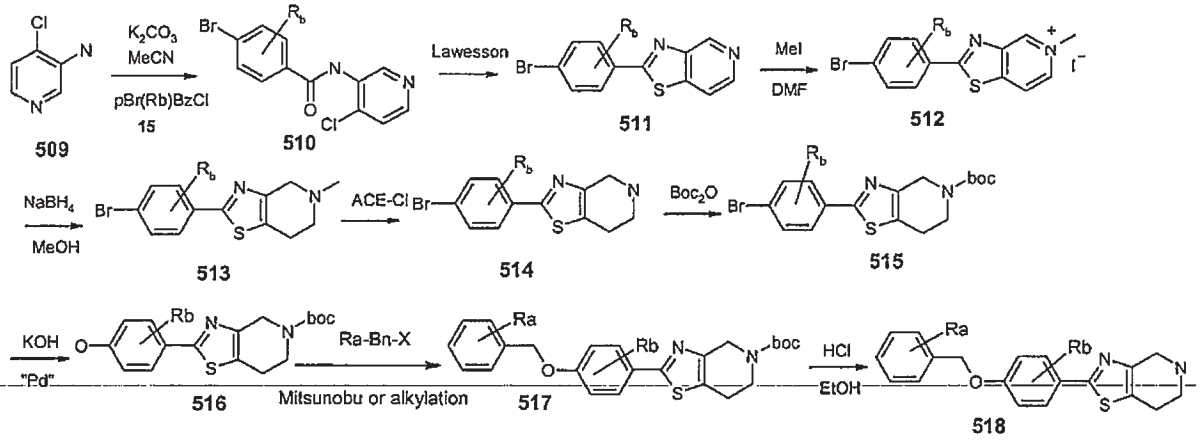


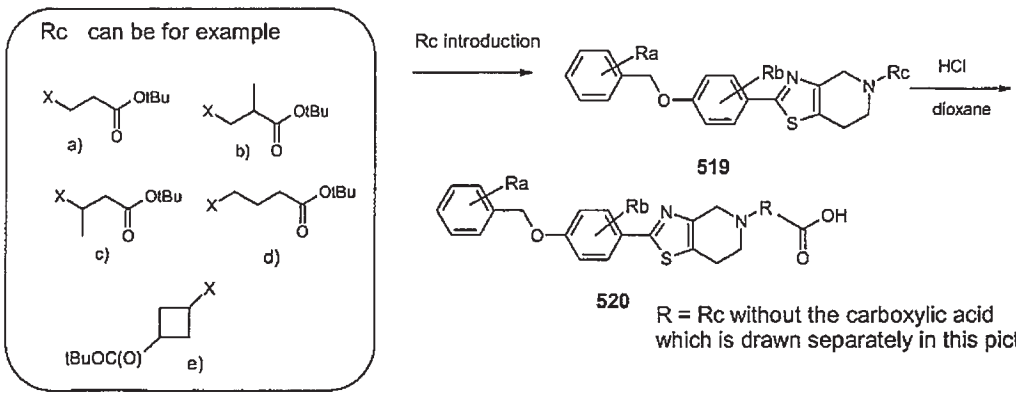
Scheme 8.



Thiazolo derivatives **508** and **520** were synthesized as described in Scheme 8 and 9. Adjustments of R-groups in the reagents leads to the introduction of Ra, Rb and Rc.

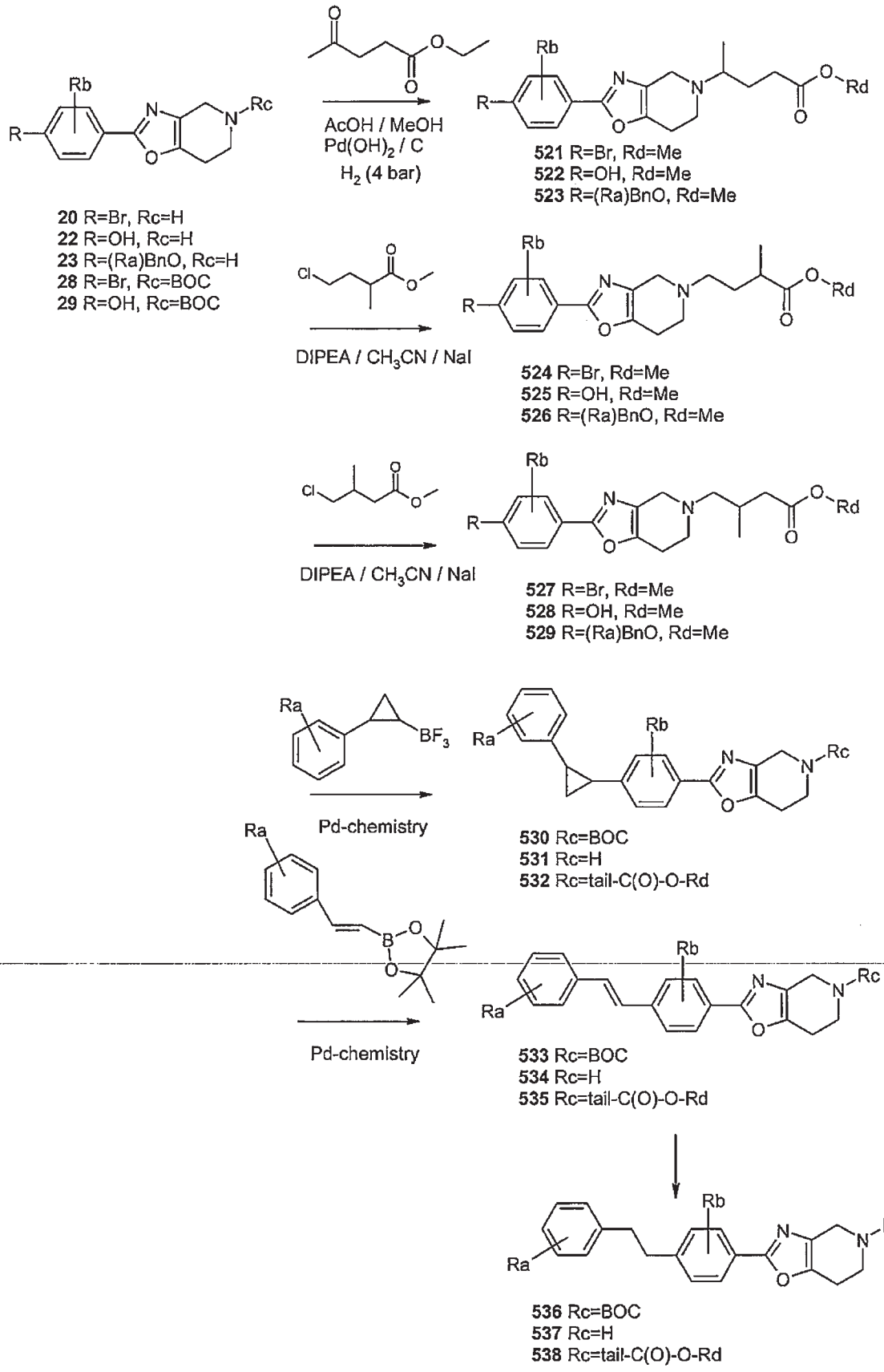
Scheme 9.





The synthetic route towards a number of alternative tails and linkers is depicted in Scheme 10.

Scheme 10.



20 R=Br, Rc=H
22 R=OH, Rc=H
23 R=(Ra)BnO, Rc=H
28 R=Br, Rc=BOC
29 R=OH, Rc=BOC

521 R=Br, Rd=Me
522 R=OH, Rd=Me
523 R=(Ra)BnO, Rd=Me

524 R=Br, Rd=Me
525 R=OH, Rd=Me
526 R=(Ra)BnO, Rd=Me

527 R=Br, Rd=Me
528 R=OH, Rd=Me
529 R=(Ra)BnO, Rd=Me

530 Rc=BOC
531 Rc=H
532 Rc=tail-C(O)-O-Rd

533 Rc=BOC
534 Rc=H
535 Rc=tail-C(O)-O-Rd

536 Rc=BOC
537 Rc=H
538 Rc=tail-C(O)-O-Rd

For those skilled in the art, it is clear that the choice for a certain route can be based on the availability of the reagents. In addition, the routes B, D and E are very suitable for the introduction of diversity in the Rc-tail part of compounds 1 and 2. Routes A and C have the introduction of the Ra-Bn moiety in the last part of the synthesis which makes it more suitable for exploring diversity in that part of the molecule.

§4. SYNTHESES OF INTERMEDIATES

General procedure for the synthesis of compounds 5. To a solution of 4-oxo-piperidine-1-carboxylic acid t-butyl ester in toluene (2ml/mmol) was added a catalytic amount of para-toluenesulphonic acid mono hydrate (0.1eq) and pyrrolidine (4eg). The mixture was heated to reflux under Dean Stark conditions for 18 hours. The mixture was concentrated under reduced pressure and the residue was redissolved in toluene. To this solution was added slowly (in 25 minutes) a solution of a properly substituted 2-bromo-1-(4-bromo-phenyl)-ethanone (1.05eq) in toluene/DCM (2ml/mmol, ½, v/v). The mixture was stirred overnight at room temperature and the resulting white slurry was poured out into water. The water layer was extracted with DCM (3 times) and the combined organic layers were dried ($MgSO_4$) and subsequently concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography giving compound **5** in a yield of 50-90%.

General procedure for the synthesis of compounds 6. Compound **5** was suspended in concentrated hydrochloric acid (10eq, 12N). The mixture was heated (in steps of 10°C per 30 minutes) to 80°C. The mixture starts to foam heavily, so allow enough volume in the starting reaction vessel. After 45 minutes, the mixture was cooled to 0°C and neutralized with 50wt% solution of NaOH (exothermic). After stirring overnight at room temperature, the resulting solid material was collected by filtration and washed with 0.1M NaOH. The light brown material was purified by Soxhlet extraction in EtOAc giving **6** as beige solid which was used in the next step without further purification.

General procedure for the introduction of the protected carboxylic acid tails (7).

a) introduction of the propionic acid t-butyl ester. Compound **6** was suspended in methanol (4ml/mmol) and DIPEA was added (1.05 eg). To the mixture was added t-butyl acrylate (1.2eq) and the mixture was refluxed for 16 hrs. Conversion was checked by TLC analysis. The solvents were evaporated and the residue was redissolved in EtOAc and extracted with a 5% solution of $NaHCO_3$.The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by silica gel column chromatography to give pure **7a**.

b) Introduction of the 2-methyl-propionic acid t-butyl ester. Compound **6** was suspended in DMF (6ml/mmol). To this suspension was added 1,8–diazabicyclo[5.4.0]undec-7-ene (3eg) and t-butyl methacrylate (2eq). The mixture was heated at 125°C for 16-100hrs. The solution was cooled and 5% $NaHCO_3$ was added (15ml/mmol) and extracted with EtOAc. The organic layer was washed with water (4x), dried on $MgSO_4$, concentrated *in vacuo* and the residue was purified by silica gel column chromatography to give pure **7b**.

c) Introduction of the 3-butyric acid t-butyl ester. Compound **6** was suspended in 1,2-dichloroethane (6ml/mmol). To this suspension was added t-butylacetoacetate (1eq) and sodium triacetoxy borohydride (1.4eq). The mixture was stirred at room temperature for 16hrs. If the reaction was not complete, another portion of t-butylacetoacetate (1eq) and sodium triacetoxy borohydride (1.4eq) was added. To the solution was added 5% $NaHCO_3$ (15ml/mmol) and the mixture was extracted with DCM. The combined organic layers were dried on Na_2SO_4, concentrated *in vacuo* and the residue was purified by silica gel column chromatography to furnish pure **7c**.

d)) Introduction of the 4-butyric acid t-butyl ester. Compound **6** was suspended in acetonitril (3ml/mmol). To this suspension was added potassium carbonate (2eq), t-butyl 4-bromo-butanoate (1.1eq) and potassium iodide (1.1 eq). The mixture was stirred at room temperature for 16hrs after which time TLC analysis revealed complete reaction. The mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc, washed with 5% NaHCO3 (15ml/mmol). The organic layer was dried on Na_2SO_4, concentrated *in vacuo* and the residue was purified by silica gel column chromatography to yield **7d**.

General procedure for the introduction of the benzyl ether moiety in 7 to compound 9. A solution of compound **7**, the properly substituted benzyl alcohol (1.1eq), palladium(II) acetate (0.02eq), 2-dit-butylphosphino-3,4,5,6-

tertamethyl-2',4',6'-triisopropyl-1,1'biphenyl (0.02eq), cesium carbonate (1.5eq) in degassed toluene (4ml/mmol) was heated at 75°C for 16 hrs. Conversion was checked by TLC analysis. The solution was cooled to room temperature, diluted with DCM, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give compound **9** in yields varying from 30-80%.

General procedure for the conversion of the bromine derivatives 7 to the phenol derivatives 8. Compound **7** was dissolved in toluene (8mml/mmol) and to the solution was added potassium hydroxide (2eq, 11.7N) and the solution was degassed. To the solution was added 2-dit-butylphosphino-2',4',6'-triisopropylbiphenyl (0.06eq) and tris-(dibenzylideneaceton)-dipalladium(0) (0.03eq). The mixture was stirred at 60°C for 1.25hrs. The mixture was allowed to reach room temperature, diluted with EtOAc and washed with 5% NaHCO3 solution (10ml/mmol). The organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give compound **8** in yields varying from 25-85%.

General procedure for the conversion of the phenol 8 to benzyl ethers 9. Method A) Compound **8** was dissolved in DCM/water, 2/1, v/v (4ml/mmol) and to this solution was added sodium hydroxide (2N, 3eq). To this mixture were added tetrabutylammonium bromide (0.1eq) and the properly substituted benzyl bromide (1.1eq). The mixture was stirred for 16hrs at room temperature after which time TLC analysis showed complete reaction. The mixture was diluted with DCM (15ml/mmol), the layers were separated and the water layer was extracted with DCM. The organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give compound pure **9** in yields varying from 80-90%.

Method B) Compound **8** was dissolved in N,N'-dimethylacetamide (4ml/mmol) and to this solution was added triphenylphosphine (1.25eq) and diisopropyl azodicarboxylate (1.25eq) and the properly substituted benzyl alcohol (1.2eq). The mixture was stirred at room temperature for 16hrs after which time TLC analysis showed complete reaction. The mixture was diluted with diethyl ether and washed with water (3x). The combined organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give compound **9** in yields varying from 70-90%.

General procedure for the acidic deprotection of compounds 9 to 1. Compound **9** was dissolved in a solution of HCl in 1,4-dioxan (4N, 45eq) and the mixture was stirred at room temperature for 24 hrs. Heating at 50°C was applied when needed to push the reaction to completion. The solvents were evaporated and diisopropyl ether was added to precipitate the product. The white solid material was filtered and dried *in vacuo* to give compound **1** in a yield varying from 80-100%.

General procedure for the synthesis of the BOC protected derivatives of 6. To a suspension of compound **6** in DCM (6ml/mmol) were added DIPEA (1eq), dimethylamino pyridine (DMAP, 0.05eq) and di-t-butyl dicarbonate (1.1eq). The mixture was stirred at room temperature for 16hrs after which time TLC analysis revealed complete reaction. The reaction mixture was washed with 5% ag. $NaHCO_3$ solution and the resulting water layers were extracted with DCM. The combined organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give compound **10** in yields varying from 70-90%.

General procedure for the synthesis of compounds 11. Compound **10** was dissolved in 1,4-dioxan/water, 1/1, v/v (2ml/mmol) and to the solution was added potassium hydroxide (4eq, 11.7N) and the solution was degassed. To the solution was added 2-dit-butylphosphino-2',4',6'-triisopropylbiphenyl (0.04eq) and tris-(dibenzylideneaceton)-dipalladium(0) (0.02eq). The mixture was stirred at 80°C for 16hrs. The mixture was cooled to room temperature, diluted with EtOAc, acidified to pH 6 with 0.1N HCl and extracted with EtOAc. The organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give pure compound **11** in yields varying from 60-95%.

General procedure for the synthesis of the benzyl ether derivatives 12. Method A) Compound **11** was dissolved in DCM/water, 2/1, v/v (4ml/mmol) and to this solution was added sodium hydroxide (2N, 3 eq). To this mixture were added tetrabutylammonium bromide (0.1eq) and the properly substituted benzyl bromide (1.1eq). The mixture was stirred for 16hrs at room temperature after

which time TLC analysis showed complete reaction. The mixture was diluted with DCM (15ml/mmol), the layers were separated and the water layer was extracted with DCM. The organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give compound **12** in yields varying from 80-90%.

Method B) Compound **11** was dissolved in N,N'-dimethylacetamide (4ml/mmol) and to this solution was added triphenylphosphine (1.25eq), diisopropyl azodicarboxylate (DIAD, 1.25eq) and a properly substituted benzyl alcohol (1.2eq). The mixture was stirred for 16hrs at room temperature after which time TLC analysis showed complete reaction. The mixture was diluted with diethyl ether and washed with water (3x). The combined organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give compound **12** in yields varying from 70-90%.

Method C) Compound **10** was dissolved in toluene (8mml/mmol) and to the solution was added potassium hydroxide (2eq, 11.7N) and the solution was degassed. To the solution was added properly substituted benzyl bromide (1.1eq), 2-di-t-butylphosphino-2',4',6'-triisopropylbiphenyl (0.06eq) and tris-(dibenzylideneaceton)-dipalladium(0) (0.03eq). The mixture was stirred at 60°C for 1.25hrs. The mixture was cooled to room temperature, diluted with EtOAc and washed with 5% $NaHCO_3$ solution (10ml/mmol). The organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give compound **12** in yields varying from 30-80%.

General procedure for the deprotection of compounds 12 to 13.

Compound **12** was dissolved in DCM (10ml/mmol) and trifluoroacetic acid (10eq) was added. The solution was refluxed for 16hrs after which time TLC analysis showed complete reaction. The mixture was neutralized with 5% aq. $NaHCO_3$. The mixture was extracted with DCM (3x) and the combined organic layers were washed with brine, dried on Na_2SO_4 and concentrated *in vacuo* to give compound **13** which was used in the next step without further purification.

General procedure for the introduction of the protected carboxylic acid tails (9) starting from compound 13.

a) introduction of the propionic acid t-butyl ester. Compound **13** was suspended in methanol (4ml/mmol) and DIPEA was added (1.05eg). To the mixture was added 1.2eg of t-butyl acrylate and the mixture was refluxed for 16 hrs. Conversion was checked by TLC analysis. The solvents were evaporated and the residue was redissolved in EtOAc and extracted with a 5% solution of $NaHCO_3$ .The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by silica gel column chromatography to give pure **9a**.

b) Introduction of the 2-methyl-propionic acid t-butyl ester. To a solution of compound **13** in DMF (6ml/mmol) in a pyrex bottle was added 1,8–diazabicyclo[5.4.0]undec-7-ene (3eg) and t-butyl-methacrylate (2eq). The mixture was heated at 125°C for 100hrs. The solution was cooled and 5% $NaHCO_3$ was added (15ml/mmol) and extracted with diethyl ether/EtOAc, 1/1, v/v. The organic layer was washed with water (4x), dried on $MgSO_4$, concentrated *in vacuo* and the residue was purified by silica gel column chromatography to give pure **9b**.

c) Introduction of the 3-butyric acid t-butyl ester. Compound **13** was suspended in 1,2-dichloroethane (6ml/mmol). To this suspension was added t-butylacetoacetate (1eq) and sodium triacetoxy borohydride (1.4eq). The mixture was stirred at room temperature for 16hrs. If the reaction was not complete, another portion of t-butylacetoacetate (1eq) and sodium triacetoxy borohydride (1.4eq) was added. After complete reaction, the solution was diluted with 5% $NaHCO_3$ (15ml/mmol) and the mixture was extracted with DCM. The combined organic layers were dried on Na_2SO_4, concentrated *in vacuo* and the residue was purified by silica gel column chromatography to furnish pure compound **9c**.

d)) Introduction of the 4-butyric acid t-butyl ester. Compound **13** was suspended in acetonitril (3ml/mmol). To this suspension were added potassium carbonate (2eq), t-butyl 4-bromo-butanoate (1.1eq) and potassium iodide (1.1eq). The mixture was heated at room temperature for 16hrs after which time TLC analysis revealed complete reaction. The mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc, washed with 5% $NaHCO_3$ (15ml/mmol). The organic layer was dried on Na_2SO_4, concentrated *in vacuo* and the residue was purified by silica gel column chromatography to yield compound **9d**.

General procedure for the synthesis of 2-(4-Bromo-phenyl)-oxazolo[4,5-c]pyridine 17. To a cooled (0°C) suspension of commercially available 4-hydroxy-3-amino-pyridine in DCM (**14**, 6ml/mmol) was added triethyl amine (1.25eq) and

a solution of properly substituted benzoyl chloride **15** (1eq, 0.3M in DCM). The reaction mixture was allowed to reach room temperature and the mixture was stirred for 16 to 64hrs after which time TLC analysis showed complete reaction. The mixture was filtered, washed with DCM and ether to furnish **16** as a solid material (50-80% yield) which was used in the next step without further purification. Hexachloroethane (2.5eq) was dissolved in DCM and triphenyl phosphine (3eq) and triethyl amine (8eq) was added. The mixture was stirred for 10 minutes at room temperature and compound **16** was added slowly in 5 equal portions. The mixture was stirred at room temperature for 64 hrs after which time TLC analysis (DCM/MeOH, 97/3, v/v) revealed complete reaction. The solution was concentrated and the residue was suspended in DCM. The mixture was filtered and the residue washed with DCM and diethyl ether to give **17** in a yield of 30-80%.

General procedure for the synthesis of compounds 19. To a solution of compound **17** in DMF was added iodomethane (4eg) and the mixture was stirred for 16hrs. The mixture was concentrated *in vacuo* and the residue was stirred in EtOAc to give **18** as a white solid. Compound **18** was dissolved in methanol (10ml/mmol) and the solution was cooled to 0°C. Sodium borohydride (2eg) was added and the mixture was stirred at 0°C for 2 hrs after which time it was allowed to reach room temperature and stirring was continued for 16 hrs. Water was added (1ml/mmol) and the mixture was stirred for 5 minutes. The mixture was co-evaporated with acetonitril and the residue was purified by silica gel column chromatography to yield compound **19** in 50-90%.

General procedure for the synthesis of compounds 20. To a cooled (0°C) solution of compound **19** in 1,2-dichloroethane (10ml/mmol) was added DIPEA (2eq). At 0°C 1-chloroethyl chloroformate (3eq) was added and the mixture was stirred for 10 minutes at 0°C after which time the temperature was raised to reflux temperature. After 2hrs, the mixture was concentrated *in vacuo* and the residue was dissolved in methanol (10ml/mmol). The solution was stirred for 48hrs at room temperature. Removal of the solvent resulted in the isolation of compound **20** in a yield of 70-90%.

General procedure for the synthesis of compounds 21.

a) introduction of the propionic acid t-butyl ester.

Compound **20** was suspended in methanol (10ml/mmol) and DIPEA was added (2.05 eg). To the mixture was added 1.2eg of t-butyl acrylate and the mixture was refluxed for 16 to 120hrs. Conversion was checked by TLC analysis and when needed additional reagents were added to push the reaction to completion. The solvents were evaporated and the residue was redissolved in EtOAc and extracted with a 5% solution of $NaHCO_3$.The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by silica gel column chromatography to give **21a** in yields varying from 50-90%

b) Introduction of the 2-methyl-propionic acid t-butyl ester.

To a solution of compound **20** in DMF (6ml/mmol) was added 1,8–diazabicyclo[5.4.0]undec-7-ene (DBU, 3eg) and t-butylmethacrylate (5eq). The mixture was heated at 125°C for 100hrs. The solution was cooled and 5% $NaHCO_3$ was added (15ml/mmol) and extracted with diethyl ether/EtOAc, 1/1, v/v. The organic layer was washed with water (4x), dried on $MgSO_4$, concentrated *in vacuo* and the residue was purified by silica gel column chromatography to give pure **21b**.

c) Introduction of the 3-butyric acid t-butyl ester.

Compound **20** was suspended in 1,2-dichloroethane (8ml/mmol). To this suspension were added t-butylacetoacetate (1.4eq), acetic acid (1eg) and sodium triacetoxy borohydride (1.8eq). The mixture was stirred at room temperature for 16hrs. If the reaction was not complete, another portion of t-butylacetoacetate (1eq) and sodium triacetoxy borohydride (1.4eq) was added. After complete reaction, the solution was diluted with 5% NaHCO3 (15ml/mmol) and the mixture was extracted with DCM. The combined organic layers were dried on Na_2SO_4, concentrated *in vacuo* and the residue was purified by silica gel column chromatography to furnish pure compound **21c**.

d)) Introduction of the 4-butyric acid t-butyl ester.

Compound **20** was suspended in DMF (5ml/mmol). To this suspension was added potassium carbonate (3eq) and t-butyl 4-bromobutanoate (3eq). The mixture was heated at 80°C for 16hrs after which time TLC analysis revealed complete reaction. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography to yield **21d**.

General procedure for the synthesis of compounds 22. Compound **21** was dissolved in acetonitril (25mml/mmol) and to the solution was added powdered potassium hydroxide (2eq) and the solution was degassed. To the solution was added 2-dit-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1-biphenyl (0.06eq) and tris-(dibenzylideneaceton)-dipalladium(0) (0.03eq). The mixture was stirred at 60°C for 4hrs. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in DCM and washed with 0.1M HCl and water. The water layers were extracted with DCM and the combined organic layers was dried on $MgSO_4$. Compound **22** was obtained after silica gel column chromatography in yields varying from 30-70%.

General procedure for the introduction of the benzyl ether moiety in 21 to compound 23. A solution of compound **21,** the properly substituted benzyl alcohol (2eq), palladium(II) acetate (0.02eq), 2-dit-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'biphenyl (0.02eq), cesium carbonate (1.5eq) in degassed toluene (3ml/mmol) was heated at 75°C for 16 hrs. Conversion was checked by TLC analysis. The solution was cooled to room temperature, diluted with DCM, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give compound pure **23** in yields varying from 30-80%.

General procedure for the conversion of the phenol 22 to benzyl ethers 23.

Method A) Compound **22** was dissolved in DCM/water, 2/1, v/v (4ml/mmol) and to this solution was added sodium hydroxide (2N, 3 eq). To this mixture were added tetrabutylammonium bromide (0.1eq) and a properly substituted benzyl bromide (1.1eq). The mixture was stirred for 16hrs at room temperature after which time TLC analysis showed complete reaction. The mixture was diluted with DCM (15ml/mmol), the layers were separated and the water layer was extracted with DCM. The organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give compound pure **23** in yields varying from 80-90%.

Method B) Compound **22** was dissolved in dry DCM (15ml/mmol) and to this solution were added triphenylphosphine (1.8eq) and the properly substituted

benzyl alcohol (1.8eq). To this mixture was added diisopropyl azodicarboxylate (1.8eq) and the mixture was stirred for 16hrs at room temperature after which time TLC analysis showed complete reaction. The mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give compound pure **23** in yields varying from 70-90%.

Method C) PS-TBD (3.7 eq.) resin was incubated with a solution of **22** (1.1eg) in 1 mL of acetonitril for 1.5h at 50 °C. Thereafter, the properly substituted benzyl bromide (1.10 eq.) in acetonitril was added. Subsequently, the reaction mixture was shaken and heated at 75 °C for 16hrs. Next, the solvent was removed by filtration and the resin was washed with 3 x 2.5 mL ACN. The combined organics were concentrated *in vacuo*, followed by flash column chromatography on silica to give compound **23** in yields varying from 60-95%.

General procedure for the deprotection of 23 to compounds 2. Compound **23** was dissolved in a solution of HCl in 1,4-dioxan (4N, 100eq) and the mixture was stirred for 16 hrs at room temperature. Heating at 50°C was applied when needed to push the reaction to completion. The solvents were evaporated and diisopropyl ether was added to precipitate the product. The white solid material was filtered and dried *in vacuo* to give compound **2** in a yield varying from 70-100%.

General procedure for the synthesis of compounds 25. To a cooled (0°C) suspension of commercially available 4-hydroxy-3-amino-pyridine (**14**) in acetonitril (15ml/mmol) was added a properly substituted 4-benzyloxy-benzoic acid (**24**, 1eq), triphenylphosphine (3eq) and trichloroacetonitril (3eq). The reaction mixture was allowed to reach room temperature and the mixture was stirred for 16 to 64hrs at 80°C. The mixture was concentrated *in vacuo* and the residues was dissolved in DCM and washed with 2N NaOH (3x). The combined water layers were extracted with DCM and the organic layers dried (Na2SO4) to give crude **25** as oil which was used in the next step without further purification.

General procedure for the synthesis of compounds 26. To a solution of compound **25** in DMF (5ml/mmol) was added iodomethane (4eg) and the mixture was stirred for 16hrs. The mixture was concentrated *in vacuo* and the residue was stirred in EtOAc to give the quaternary salt of **25** as a white solid. The crude

material was dissolved in methanol (10ml/mmol) and the solution was cooled to 0°C. Sodium borohydride (2.5eg) was added and the mixture was stirred at 0°C for 2 hrs after which time it was allowed to reach room temperature and stirring was continued for 16-64 hrs. Water was added (1ml/mmol) and the mixture was stirred for 5 minutes. The mixture was concentrated *in vacuo*, the residues suspended in 2 N NaOH (5ml/mmol) and extracted with DCM (3x). The combined organic layers were dried (Na2SO4) and concentrated to give crude **26** as a yellow solid which was used in the next step without further purification.

General procedure to compounds 27. To a cooled (0°C) solution of compound **26** in 1,2-dichloroethane (10ml/mmol) was added DIPEA (2eq) and 1-chloroethyl chloroformate (3eq) was added. The mixture was stirred for 10 minutes at 0°C after which time the temperature was raised to reflux temperature. After 4hrs, the mixture was allowed to reach room temperature and stirring was continued for 16hrs. The mixture was concentrated *in vacuo* and the residue was dissolved in methanol (10ml/mmol). The solution was stirred for 16-48hrs at room temperature. Removal of the solvent resulted in the isolation of crude **27** in an overall yield of 20-40% based on **25**.

General procedure for the introduction of the protected carboxylic acid tails (to 23) starting from compound 27.

a) introduction of the propionic acid t-butyl ester.

Compound **27** was suspended in methanol (4ml/mmol) and DIPEA was added (1.05 eg). To the mixture was added 1.2eg of t-butyl acrylate and the mixture was refluxed for 16 hrs. Conversion was checked by TLC analysis. The solvents were evaporated and the residue was redissolved in EtOAc and extracted with a 5% solution of $NaHCO_3$. The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by silica gel column chromatography to give pure **23a**.

b) Introduction of the 2-methyl-propionic acid t-butyl ester.

To a solution of compound **27** in DMF (6ml/mmol) was added 1,8–diazabicyclo[5.4.0]undec-7-ene (3eg) and t-butylmethacrylate (4eq). The mixture was heated at 125°C for 100hrs. The solution was cooled and 5% $NaHCO_3$ was added (15ml/mmol) and extracted with diethyl ether/EtOAc, 1/1, v/v. The organic

layer was washed with water (4x), dried on $MgSO_4$, concentrated *in vacuo* and the residue was purified by silica gel column chromatography to give pure **23b.**

c) Introduction of the 3-butyric acid t-butyl ester.

Compound **27** was suspended in 1,2-dichloroethane (6ml/mmol). To this suspension was added t-butylacetoacetate (1eq) and sodium triacetoxy borohydride (1.4eq). The mixture was stirred at room temperature for 16hrs. If the reaction was not complete, another portion of t-butylacetoacetate (1eq) and sodium triacetoxy borohydride (1.4eq) was added. After complete reaction, the solution was diluted with 5% $NaHCO_3$ (15ml/mmol) and the mixture was extracted with DCM. The combined organic layers were dried on Na_2SO_4, concentrated *in vacuo* and the residue was purified by silica gel column chromatography to furnish pure compound **23c**.

d)) Introduction of the 4-butyric acid t-butyl ester.

Compound **27** was suspended in acetonitril (3ml/mmol). To this suspension was added potassium carbonate (2eq), t-butyl 4-bromobutanoate (1.1eq) and potassium iodide (1.1 eq). The mixture was heated at room temperature for 16hrs after which time TLC analysis revealed complete reaction. The mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc, washed with 5% $NaHCO_3$ (15ml/mmol). The organic layer was dried on Na_2SO_4, concentrated *in vacuo* and the residue was purified by silica gel column chromatography to yield **23d**.

e)) Introduction of the 3-cyclobutanecarboxylic acid.

Compound **27** was suspended in 1,2-dichloroethane (20ml/mmol). To this suspension was added 3-oxocyclobutanecarboxylic acid (1.3eq) and sodium triacetoxy borohydride (1.6eq). The mixture was stirred at room temperature for 16hrs. If the reaction was not complete, another portion of 3-oxocyclobutanecarboxylic acid (1.3eq) and sodium triacetoxy borohydride (1.6eq) was added. After complete reaction, the solution was diluted with 5% $NaHCO_3$ (15ml/mmol) and the mixture was extracted with DCM. The combined organic layers were dried on Na_2SO_4, concentrated *in vacuo* and the residue was purified by silica gel column chromatography to furnish pure compound **2e**.

General procedure for the hydrogenation of 23 to compound 22. To a solution of compound **23** in ethanol (10ml/mmol) was added palladium hydroxide on carbon (20%, 0.22eg). Hydrogenation was started under atmospheric pressure

of hydrogen. Stirring was continued for 16hrs at room temperature. The mixture was filtered over Hyflo and the residue washed with ethanol. The filtrate was concentrated *in vacuo* to give compound **22**.

General procedure for the synthesis of compounds 28. To a suspension of compound **20** in DCM (6ml/mmol) were added DIPEA (1eq), dimethylamino pyridine (DMAP, 0.05eq) and di-t-butyl dicarbonate (1.1eq). The mixture was stirred at room temperature for 16hrs after which time TLC analysis revealed complete reaction. The mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give compound pure **28** in yields varying from 70-90%.

General procedure for the synthesis of compounds 29. Compound **28** was dissolved in 1,4-dioxan/water, 1/1, v/v (10ml/mmol) and to the solution was added potassium hydroxide (4eq, 11.7N) and the solution was degassed. To the solution was added 2-di-t-butylphosphino-2',4',6'-triisopropylbiphenyl (0.04eq) and tris-(dibenzylideneaceton)-dipalladium(0) (0.02eq). The mixture was stirred at 80°C for 16hrs. The mixture was cooled to room temperature, diluted with EtOAc, acidified to pH 6 with 0.1N HCl and extracted with EtOAc. The organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give compound pure **29** in yields varying from 60-95%.

General procedure for the synthesis of the benzyl ether derivatives 30.
Method A) Compound **29** was dissolved in DCM/water, 2/1, v/v (4ml/mmol) and to this solution was added sodium hydroxide (2N, 3 eq). To this mixture was added tetrabutylammonium bromide (0.1eq) and the properly substituted benzyl bromide (1.1eq). The mixture was stirred for 16hrs at room temperature after which time TLC analysis showed complete reaction. The mixture was diluted with DCM (15ml/mmol), the layers were separated and the water layer was extracted with DCM. The organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give compound pure **30** in yields varying from 80-90%.
Method B) Compound **29** was dissolved in N,N'-dimethylacetamide (4ml/mmol) and to this solution was added triphenylphosphine (1.25eq), diisopropyl

azodicarboxylate (1.25eq) and a properly substituted benzyl alcohol (1.2eq). The mixture was stirred for 16hrs at room temperature after which time TLC analysis showed complete reaction. The mixture was diluted with diethyl ether and washed with water (3x). The combined organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give compound pure **30** in yields varying from 70-90%.
Method C) Compound **28** was dissolved in toluene (8mml/mmol) and to the solution was added potassium hydroxide (2eq, 11.7N) and the solution was degassed. To the solution was added properly substituted benzyl bromide (1.1eq), 2-di-t-butylphosphino-2',4',6'-triisopropylbiphenyl (0.06eq) and tris-(dibenzylideneaceton)-dipalladium(0) (0.03eq). The mixture was stirred at 60°C for 1.25hrs. The mixture was cooled to room temperature, diluted with EtOAc and washed with 5% $NaHCO_3$ solution (10ml/mmol). The organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give compound pure **30** in yields varying from 30-80%.

<u>General procedure for the deprotection of compounds 30 to 27.</u>
Compound **30** was dissolved in DCM (10ml/mmol) and trifluoroacetic acid (6eq) was added. The solution was refluxed for 16hrs after which time TLC analysis showed complete reaction. The mixture was neutralized with 5% aq. $NaHCO_3$. The mixture was extracted with DCM (3x) and the combined organic layers were washed with brine, dried on Na_2SO_4 and concentrated *in vacuo* to give compound **27** which was used in the next step without further purification.

§5. SYNTHESES OF SPECIFIC COMPOUNDS

<u>(See Table 1)</u>

All furanyl derivatives from Table 1 could be prepared by following either route A or B appropriate reagents. The following compounds are typical examples.
All oxazolo derivatives from Table 1 could be prepared by following either route C, D or E by choosing the appropriate reagents. The following compounds are typical examples.

3-[2-(4-Bromo-phenyl)-2-oxo-ethyl]-4-oxo-piperidine-1-carboxylic acid t-butyl ester (5, Rb=H). To a solution of 4-oxo-piperidine-1-carboxylic acid t-butyl ester (4, 104.1g, 522 mmol) in toluene (800ml) was added a catalytic amount of para-toluenesulphonic acid mono hydrate (0.5g, 2.6 mmol) and pyrrolidine (172.8 ml, 2090mmol). The mixture was heated to reflux under Dean Stark conditions for 18 hours. The mixture was concentrated under reduced pressure and the residue was redissolved in toluene (600ml). To this solution was added slowly (in 25 minutes) a solution of 2-bromo-1-(4-bromo-phenyl)-ethanone (**3**, Rb=H, 145.2g, 522 mmol) in toluene/ DCM (900ml, ½, v/v). The mixture was stirred overnight at room temperature and the resulting white slurry was poured out in water (1.5L). The water layer was extracted with DCM (3x300ml) and the combined organic layers were dried ($MgSO_4$) and subsequently concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (diethyl ether/petroleum ether, 2/3, v/v to 100% diethyl ether) giving compound **5** (Rb=H, 166.6g, 87%) as a yellow solid. TLC analysis, Rf 0.3 in diethyl ether/petroleum ether, 1/1, v/v.

2-[4-Bromo-phenyl]-4,5,6,7-tetrahydro-furo[3,2-c]pyridine (6, Rb=H). Compound **5** (Rb=H, 166g, 456 mmol) was suspended in concentrated hydrochloric acid (500ml, 12N, 6mol). The mixture was heated with 10°C per 30 minutes to 80°C. The mixture starts to foam heavily, so allow enough volume in the starting reaction vessel. After 45 minutes, the mixture was cooled to 0°C and neutralized with 50 wt% solution of NaOH (exothermic). After stirring overnight at room temperature, the resulting solid material was collected by filtration and washed with 250 ml 0.1M NaOH. The light brown material was purified by Soxhlet extraction in EtOAc giving **6** (Rb=H, 51g, 38%) as a beige solid which was used in the next step without further purification. LC-MS (Method A): Rt 1.19, [M+H] 278.

3-[2-(4-Bromo-phenyl)-6,7-dihydro-4H-furo[3,2-c]pyridine-5-yl]-propionic acid t-butyl ester (7a, Rb=H). Compound **6** (Rb=H, 1.46g, 5mmol) was suspended in methanol (30ml) and DIPEA was added (0.91ml, 1.05 eg). To the mixture was added t-butyl acrylate (0.88ml, 1.2eq) and the mixture was refluxed for 16 hrs. Conversion was checked by TLC analysis (diethyl ether/petroleum ether, 1/1, v/v). The solvents were evaporated and the residue was redissolved in

EtOAc and extracted with a 5% solution of $NaHCO_3$ .The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by silica gel column chromatography (diethyl ether/petroleum ether, 2/3 to 1/1, v/v) to give pure **7a** (Rb=H, 1.75g, 86%) as a white solid. LC-MS (Method A): Rt 1.38, [M+H] 407.

3-[2-(4-Hydroxy-phenyl)-6,7-dihydro-4H-furo[3,2-c]pyridine-5-yl]-propionic acid t-butyl ester (8a, Rb=H). Compound **7a** (Rb=H, 3.85g, 9.5mmol) was dissolved in toluene (80ml) and to the solution was added potassium hydroxide (2eq, 11.7N) and the solution was degassed. To the solution was added 2-di-t-butylphosphino-2',4',6'-triisopropylbiphenyl (0.24g, 0.57mmol, 0.06eq) and tris-(dibenzylideneaceton)-dipalladium(0) (0.26g, 0.28mmol, 0.03eq). The mixture was stirred at 60°C for 1.25hrs. The mixture was cooled to room temperature, diluted with EtOAc and washed with 5% $NaHCO_3$ solution (10ml/mmol). The organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (diethyl ether/ petroleum ether, 1/1, v/v, Rf 0.1) to give pure compound **8a** (Rb=H, 1.86g, 57%) as a yellow solid. LC-MS (Method A): Rt 1.14, [M+H] 344.

3-{2-[4-(2-Fluoro-benzyloxy)-phenyl]-6,7-dihydro-4H-furo[3,2-c]pyridine-5-yl}-propionic acid t-butyl ester (9a, Ra=2F, Rb=H). Compound **8a** (Rb=H, 1.24g, 3.61mmol) was dissolved in N,N-dimethylacetamide (10ml) and to this solution was added triphenylphosphine (1.33g, 5.06mmol, 1.4eq), diisopropyl azodicarboxylate (1ml, 5.05mmol, 1.4eq) and 2-fluorobenzyl alcohol (0.46ml, 4.33mmol, 1.2eq). The mixture was stirred for 16hrs at room temperature after which time TLC analysis (diethyl ether, Rf 0.3) showed complete reaction. The mixture was diluted with diethyl ether and washed with water (3x). The combined organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (diethyl ether/petroleum ether, 1/1, v/v to 2/1, v/v) to give compound pure **9a** (Ra=2F, Rb=H, 1.38g, 84%) as an oil. LC-MS (Method A): Rt 1.46, [M+H] 452.

3-{2-[4-(2-Fluoro-benzyloxy)-phenyl]-6,7-dihydro-4H-furo[3,2-c]pyridine-5-yl}-propionic acid (33). Compound **9a** (Ra=2F, Rb=H, 1.38g, 3.1mmol) was dissolved in a solution of HCl in 1,4-dioxan (4N, 30ml) and the mixture was stirred for 2 hrs at 35°C. The solvents were evaporated and diisopropyl ether

(30ml) was added to precipitate the product as the hydrochloric acid salt. The white solid material was filtered and dried *in vacuo* to give compound **33** (0.75g, 54%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 2.93 (t, *J*=7.6 Hz, 2 H), 3.07 (bs, 2 H), 3.28 - 3.55 (bs, 2 H), 3.44 (t, *J*=7.6 Hz, 2 H), 3.60 – 3.90 (bs, 2 H), 4.06 – 4.56 (bs, 2 H), 5.17 (s, 2 H), 6.76 (s, 1 H), 7.10 (d, *J*=8.8 Hz, 2 H), 7.21 – 7.31 (m, 2 H), 7.39 - 7.48 (m, 1 H), 7.57 (t, *J*=7.5 Hz, 1 H), 7.63 (d, *J*=8.8 Hz, 2 H), 10.7 - 11.5 (bs, 1 H), 12.3 – 13.2 (bs, 1 H); LC-MS (Method A): Rt 1.39, [M+H] 396.

2-(4-Bromo-phenyl)-6,7-dihydro-4H-furo[3,2-c]pyridine-5-carboxylic acid t-butyl ester 10 (Rb=H). To a suspension of compound **6** (Rb=H, 5g, 17mmol) in DCM (100ml) were added DIPEA (2.92ml, 1eq), DMAP (0.1g, 0.05eq) and di-t-butyl dicarbonate (4.1g, 18.8mmol, 1.1eq). The mixture was stirred at room temperature for 16hrs after which time TLC analysis (DCM, Rf, 0.40) revealed complete reaction. The reaction mixture was washed with 5% ag. $NaHCO_3$ solution and the resulting water layers were extracted with DCM. The combined organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: 100% DCM) to give compound **10** (Rb=H, 5.99g, 92%) as an oil.

2-(4-Hydroxy-phenyl)-6,7-dihydro-4H-furo[3,2-c]pyridine-5-carboxylic acid t-butyl ester 11a (Rb=H). Compound **10** (Rb=H, 11.77g, 31mmol) was dissolved in 1,4-dioxan/water, 1/1, v/v (200ml) and to the solution was added potassium hydroxide (6,98g, 124.5mmol, 4eq) and the solution was degassed. To the solution was added 2-di-t-butylphosphino-2',4',6'-triisopropylbiphenyl (0.53g, 1.24mmol, 0.04eq) and tris-(dibenzylideneaceton)-dipalladium(0) (0.57g, 0.62mmol, 0.02eq). The mixture was stirred at 80°C for 16hrs. The mixture was cooled to room temperature, diluted with EtOAc, acidified to pH 6 with 0.1N HCl and extracted with EtOAc. The organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: DCM/MeOH, 1/0 to 99.5/0.5) to give compound **11** (Rb=H, 9g, 90%) as a white solid.

2-[4-(4-Chloro-benzyloxy)-phenyl]-6,7-dihydro-4H-furo[3,2-c]pyridine-5-carboxylic acid t-butyl ester (12, Ra=4Cl, Rb=H). Compound **11a** (Rb=H, 2.0g, 6.34mmol) was dissolved in DCM/water, 2/1, v/v (30ml) and to this solution

was added sodium hydroxide (2N, 10ml). To this mixture was added tetrabutylammonium bromide (0.2g, 0.63mmol, 0.1eq) and 4-chlorobenzyl bromide (1.43g, 6.98mmol, 1.1eg). The mixture was stirred for 16hrs at room temperature after which time TLC analysis (100% DCM, Rf 0.55) showed complete reaction. The mixture was diluted with DCM (15ml/mmol), the layers were separated and the water layer was extracted with DCM. The organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM/petroleum ether, 3/1 to 1/0, v/v) to give compound **12** (Ra=4Cl, Rb=H, 2.3g, 82%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.4 (s, 9 H); 2.75 (bs, 2 H); 3.75 (bs, 2 H); 4.35 (bs, 2 H); 5.05 (s, 2 H); 6.4 (s, 1H), 6.94 (d, 1 H); 7.30 – 755 (m, 7 H).

2-[4-(4-Chloro-benzyloxy)-phenyl]-6,7-dihydro-4H-furo[3,2-c]pyridine (13, Ra= 4Cl, Rb=H). Compound **12** (Ra=4Cl, Rb=H, 2.3g, 5.2mmol) was dissolved in DCM (50ml) and trifluoroacetic acid (4ml, 10eq) was added. The solution was refluxed for 16hrs after which time TLC analysis (100% DCM, Rf 0.05) showed complete reaction. The mixture was neutralized with 5% aq. $NaHCO_3$. The mixture was extracted with DCM (3x) and the combined organic layers were washed with brine, dried on Na_2SO_4 and concentrated *in vacuo* to give crude **13** (Ra=4Cl, Rb=H, 1.79g) which was used in the next step without further purification. LC-MS (Method A): Rt 1.49, [M+H] 340.

3-{2-[4-(4-Chloro-benzyloxy)-phenyl]-6,7-dihydro-4H-furo[3,2-c]pyridine-5-yl}-2-methyl-propionic acid t-butyl ester (9b, Ra=4Cl, Rb=H). To a solution of compound **13a** (0.25g, 0.74mmol) in DMF (5ml) in a 25ml pyrex bottle were added 1,8–diazabicyclo[5.4.0]undec-7-ene (0.33ml, 2.21mmol) and t-butylmethacrylate (0.24ml, 1.47mmol). The mixture was heated at 140°C for 16hrs. The solution was cooled and 5% $NaHCO_3$ was added (10ml) and extracted with diethyl ether/EtOAc, 1/1, v/v. The organic layer was washed with water (4x20ml), dried on $MgSO_4$, concentrated *in vacuo* and the residue was purified by silica gel column chromatography (diethyl ether/petroleum ether, 9/1 to 4/1, v/v, Rf 0.65) to give pure **9b** (Ra=4Cl, Rb=H, 0.1g, 28%) as a colorless oil. LC-MS (Method A): Rt 1.88, [M+H] 482.

3-{2-[4-(4-Chloro-benzyloxy)-phenyl]-6,7-dihydro-4H-furo[3,2-c]pyridine-5-yl}-2-methyl-propionic acid (77). Compound **9b** (Ra=4Cl, Rb=H, 0.12g, 0.25mmol) was dissolved in a solution of HCl in 1,4-dioxan (4N, 2.8ml) and the mixture was stirred for 16 hrs at room temperature. The solvent was evaporated and diisopropyl ether (30ml) was added to precipitate the product as the hydrochloric acid salt. The white solid material was filtered and dried *in vacuo* to give compound **77** (0.09g, 74%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 1.29 (d, J=7.2 Hz, 3 H), 3.05 - 3.17 (m, 3 H), 3.23 (dd, J= 5.4, 13.3 Hz, 1 H), 3.51 - 3.68 (m, 3 H), 4.24 (br. s., 2 H), 5.16 (s, 2 H), 6.73 (s, 1 H), 7.08 (d, J=8.9 Hz, 2 H), 7.42 - 7.53 (m, 4 H), 7.61 (d, J=8.9 Hz, 2 H), 10.4 – 13.1 (bs, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ ppm 16.42 (q, 1 C), 20.36 (t, 1 C), 35.17 (d, 1 C), 48.74 (t, 1 C), 49.57 (t, 1 C), 56.96 (t, 1 C), 68.60 (t, 1 C), 102.92 (d, 1 C), 113.06 (s, 1 C), 115.41 (d, 1 C), 123.20 (s, 1 C), 124.87 (d, 1 C), 128.41 (d, 1 C), 129.42 (d, 1 C), 132.46 (s, 1 C), 136.01 (s, 1 C), 145.10 (s, 1 C), 152.99 (s, 1 C), 157.85 (s, 1 C), 174.95 (s, 1 C). LC-MS (Method A): Rt 1.56, [M+H] 426.

2-[4-(Benzyloxy)-phenyl]-6,7-dihydro-4H-furo[3,2-c]pyridine-5-carboxylic acid t-butyl ester 12 (Ra=Rb=H). Compound **11** (Rb=H, 0.84g, 2.66mmol) was dissolved in DCM/water, 2/1, v/v (30ml) and to this solution was added sodium hydroxide (2N, 4.2ml). To this mixture was added tetrabutyl-ammonium bromide (0.09g, 0.27mmol, 0.1eq) and benzyl bromide (0.35ml, 2.93 mmol, 1.1eg). The mixture was stirred for 16hrs at room temperature after which time TLC analysis (DCM/MeOH, 98/2, v/v, Rf 0.8) showed complete reaction. The mixture was diluted with DCM (100ml), the layers were separated and the water layer was extracted with DCM. The organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM/petroleum ether, 3/1 to 1/0, v/v) to give compound **12** (Ra=Rb=H, 1.03g, 95%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.4 (s, 9 H); 2.75 (bs, 2 H); 3.75 (bs, 2 H); 4.35 (bs, 2 H); 5.05 (s, 2 H); 6.35 (s, 1H); 6.98 (d, 2 H); 7.30 – 7.55 (m, 7 H).

2-[4-Benzyloxy-phenyl]-6,7-dihydro-4H-furo[3,2-c]pyridine (13, Ra=Rb=H). Compound **12** (Ra=Rb=H, 1.03g, 2.54mmol) was dissolved in DCM (20ml) and trifluoroacetic acid (1.5ml) was added. The solution was refluxed for 16hrs after which time TLC analysis (100% DCM, Rf 0.05) showed complete

reaction. The mixture was neutralized with 5% aq. $NaHCO_3$ (40ml) and extracted with DCM (3x50ml) and the combined organic layers were washed with brine, dried on Na_2SO_4 and concentrated *in vacuo* to give compound **13** (Ra=Rb=H, 0.67g, 86%) which was used in the next step without further purification. LC-MS (Method A): Rt 1.50, [M+H] 306.

3-{2-[4-Benzyloxy-phenyl]-6,7-dihydro-4H-furo[3,2-c]pyridine-5-yl}-butyric acid t-butyl ester (9c, Ra=Rb=H). Compound **13** (Ra=Rb=H, 0.16g, 0.52mmol) was suspended in 1,2-dichloroethane (3.2ml). To this suspension was added t-butylacetoacetate (0.09ml, 0.52mmol) and sodium triacetoxy borohydride (0.16g, 0.73mmol). The mixture was stirred at room temperature for 16hrs, after which time another portion of t-butylacetoacetate (1eq) and sodium triacetoxy borohydride (1.4eq) were added together with a drop of acetic acid. After stirring for another 60 hrs, again a portion of t-butylacetoacetate (1eq) and sodium triacetoxy borohydride (1.4eq) were added and stirring was continued for 36hrs. The solution was diluted with 5% $NaHCO_3$ (10ml) and the mixture was extracted with DCM (3x100ml). The combined organic layers were dried on Na_2SO_4, concentrated *in vacuo* and the residue was purified by silica gel column chromatography (diethyl ether/petroleum ether, 9/1 to 4/1, v/v) to furnish pure compound **9c** (Ra=Rb=H, 0.06g, 25%) as a white solid. LC-MS (Method A): Rt 1.68, [M+H] 448.

3-{2-[4-Benzyloxy-phenyl]-6,7-dihydro-4H-furo[3,2-c]pyridine-5-yl}-butyric acid (76). Compound **9c** (Ra=Rb=H, 0.08g, 0.18mmol) was dissolved in a solution of HCl in 1,4-dioxan (4ml, 2N) and the mixture was stirred for 16 hrs at room temperature. The solvents were evaporated and the residue was co-evaporated with cyclohexane. Diisopropyl ether (30ml) was added to precipitate the product as the hydrochloric acid salt, the white solid material was filtered and dried *in vacuo* to give compound **76** (0.06g, 80%). ^1H NMR (400 MHz, DMSO-d_6), δ ppm: 1.38 (d, *J*=6.6 Hz, 3 H), 2.58 - 2.75 (m, 1 H), 2.90 - 3.18 (m, 3 H), 3.39 - 3.54 (m, 1 H), 3.61 - 3.78 (m, 1 H), 3.80 - 3.93 (m, 1 H), 4.13 - 4.32 (m, 2 H), 5.14 (s, 2 H), 6.76 (s, 1 H), 7.07 (d, *J*=8.8 Hz, 2 H), 7.30 - 7.36 (m, 1 H), 7.40 (s, 2 H), 7.45 (s, 2 H), 7.62 (d, *J*=8.8 Hz, 2 H), 10.15 - 10.80 (m, 1 H), 12.54 - 13.10 (m, 1 H);). LC-MS (Method A): Rt 1.46, [M+H] 392.

4-[2-(4-Bromo-phenyl)-6,7-dihydro-4H-furo[3,2-c]pyridine-5-yl]-butyric acid t-butyl ester (7d). Compound **6** (Rb=H, 4.55g, 16.3mmol) was suspended in acetonitril (55ml). To this suspension were added potassium carbonate (4.52g, 32.7 mmol), t-butyl 4-bromobutanoate (4.38g, 19.6mmol, 1.2eq) and potassium iodide (3.2g, 19.6mmol, 1.2eq). The mixture was heated to reflux for 16hrs after which time TLC analysis (diethyl ether/petroleum ether, 1/1, v/v, Rf 0.1) revealed complete reaction. The mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc and washed with 5% $NaHCO_3$ (2x60ml). The organic layer was dried on Na_2SO_4, concentrated *in vacuo* and the residue was purified by silica gel column chromatography (diethyl ether/petroleum ether, 1/1, v/v) to yield **7d** (Rb=H, 4.94g, 71%) as a yellow solid. LC-MS (Method A): Rt 1.37, [M+H] 420.

4-[2-(4-Hydroxy-phenyl)-6,7-dihydro-4H-furo[3,2-c]pyridine-5-yl]-butyric acid t-butyl ester (8d). Compound **7d** (Rb=H, 4.91g, 11.68mmol) was dissolved in toluene (100ml) and to the solution was added potassium hydroxide (2ml, 11.7N) and the solution was degassed. To the solution was added 2-di-t-butylphosphino-2',4',6'-triisopropylbiphenyl (0.27g, 0.64mmol, 0.06eq) and tris-(dibenzylideneaceton)-dipalladium(0) (0.29g, 0.32mmol, 0.03eq). The mixture was stirred at 60°C for 1.25hrs. The mixture was cooled to room temperature, diluted with EtOAc and washed with 5% $NaHCO_3$ solution (100ml). The organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (diethyl ether/ petroleum ether, 1/1 to 1/0, v/v, Rf 0.1) to give pure compound **8d** (Rb=H, 4.0g) as a yellow solid. LC-MS (Method A): Rt 1.21, [M+H] 358.

4-{2-[4-(2-Fluoro-benzyloxy)-phenyl]-6,7-dihydro-4H-furo[3,2-c]pyridine-5-yl}-butyric acid t-butyl ester (9d). Compound **8d** (Rb=H, 0.43g, 1.2mmol) was dissolved in DCM/water, 2/1, v/v (5ml) and to this solution was added sodium hydroxide (1.8ml, 2N, 3eq). To this mixture was added tetrabutylammonium bromide (0.1eq) and 2F-benzyl bromide (1.32mmol, 250mg). The mixture was stirred for 16hrs at room temperature after which time TLC analysis (diethyl ether, Rf 0.5) showed complete reaction. The mixture was diluted with DCM (15ml), the layers were separated and the water layer was extracted with DCM. The organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (diethyl

ether/petroleum ether, 1/1 to 1/0, v/v to give compound **9d** (Ra=2F, Rb=H) in a yield of 80%. LC-MS (Method A): Rt 1.49, [M+H] 466.

4-{2-[4-(2-Fluoro-benzyloxy)-phenyl]-6,7-dihydro-4H-furo[3,2-c]pyridine-5-yl}-butyric acid (35). Compound **9d** (Ra=2F, Rb=H, 0.3g, 0.64mmol) was dissolved in a solution of HCl in 1,4-dioxan (4N, 2.8ml) and the mixture was stirred for 16 hrs at room temperature. The solvents were evaporated and diisopropyl ether (30ml) was added to precipitate the product as the hydrochloric acid salt. The white solid material was filtered and dried *in vacuo* to give compound **35** (0.32g, 95%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ PPM: 1.69 - 1.83 (m, 2 H), 2.18 (t, *J*=7.2 Hz, 2 H), 2.81-2.91 (m, 2 H), 3.02 - 3.13 (m, 2 H), 3.23 - 3.36 (bs, 1 H), 3.50 - 3.68 (bs, 1 H), 3.89 – 4.05 (m, 1 H), 4.15 – 4.29 (m, 1 H), 4.98 (s, 2 H), 6.58 (s, 1 H), 6.91 (d, *J*=8.7 Hz, 2 H), 7.02 - 7.12 (m, 2 H), 7.21 - 7.29 (m, 1H), 7.38 (dt, *J*=7.7, 1.5 Hz, 1 H), 7.44 (d, *J*=8.7 Hz, 2 H), 9.80 (br.s., 1 H), 11.37 - 13.06 (bs, 1 H); LC-MS (Method A): Rt 1.37, [M+H] 410.

4-{2-[4-(2-Fluoro-benzyloxy)-2-fluoro-phenyl]-6,7-dihydro-4H-furo[3,2-c]-pyri-dine-5-yl}-butyric acid (73). Compound **73** was prepared in a similar fashion as described for **35** starting from 2-bromo-1-(4-bromo-2-fluoro-phenyl)-ethanone. Compound **73:** ^{1}H NMR (400 MHz, DMSO-d_6), δ PPM: 1.92 – 2.04 (m, 2 H), 2.38 (t, *J*=7.1 Hz, 2 H), 3.02 – 3.13 (m, 2 H), 3.17 – 3.28 (m, 2 H), 3.44 – 3.92 (bs, 2 H), 3.98 - 4.54 (bs, 2 H), 5.21 (s, 2 H), 6.70 (d, *J*=2.8 Hz, 1 H), 7.00 (dd, *J*=8.9, 1.9 Hz, 1 H), 7.12 (dd, J=13.4, 1.9 Hz, 1 H) 7.23 – 7.32 (m, 2 H) 7.41 - 7.50 (m, 1 H) 7.56 – 7.63 (m, 1 H) 7.69 (t, *J*=9.0 Hz, 1 H), 10.06 - 10.93 (bs, 1 H), 12.07 - 12.85 (bs, 1 H); LC-MS (Method A): Rt 1.35, [M+H] 428.

2-(4-Bromo-phenyl)-oxazolo[4,5-c]pyridine (17, Rb=H). To a cooled (0°C) suspension of commercially available 4-hydroxy-3-amino-pyridine **14** (4g, 36mmol) in DCM (200ml) were added triethyl amine (6.3ml, 1.25eq) and a solution of 4-bromo-benzoyl chloride (**15**, Rb=H, 8g, 36mmol, 1eq, 0.3M in DCM). The reaction mixture was allowed to reach room temperature and the mixture was stirred for 16hrs. The mixture was filtered, washed with DCM and ether to furnish crude **16** (Rb=H) as a solid material which was used in the next step without further purification. Hexachloroethane (10.2g, 43mmol, 2.5eq) was dissolved in DCM (150ml) and triphenyl phosphine (13.56g, 51,69mmol, 3eq) and

triethyl amine (19.2ml, 137.8mmol, 8eq) was added. The mixture was stirred for 10 minutes at room temperature and crude compound **16** (Rb=H) was added slowly in 5 equal portions. The mixture was stirred at room temperature for 64 hrs after which time TLC analysis (DCM/MeOH, 97/3, v/v, Rf 0.3) revealed complete reaction. The solution was concentrated and the residue was suspended in DCM. The mixture was filtered and the residue washed with DCM and diethyl ether to give crude **17** (Rb=H) which was used in the next step without further purification.

2-(4-Bromo-phenyl)-5-methyl-4,5,6,7-tetrahydro-oxazolo[4,5-c]pyridine (19, Rb=H). To a solution of compound **17** (Rb=H, 11.4mmol) in DMF (95ml) was added iodomethane (2.84ml, 45.58mmol, 4eg) and the mixture was stirred for 16hrs. The mixture was concentrated *in vacuo* and the residue was stirred in EtOAc to give crude **18** (Rb=H, 3.3g, 69%) as a white solid. Compound **18** (Rb=H, 2.3g, 5.5mmol) was dissolved in methanol (55ml) and the solution was cooled to 0°C. Sodium borohydride (0.42g, 11mmol, 2eg) was added and the mixture was stirred at 0°C for 2 hrs after which time it was allowed to reach room temperature and stirring was continued for 16 hrs. Water was added (4ml) and the mixture was stirred for 5 minutes. The mixture was co-evaporated with acetonitril and the residue was purified by silica gel column chromatography (DMA 0.5) to yield compound **19** (Rb=H) in a yield of 61%.

2-(4-Bromo-phenyl)-4,5,6,7-tetrahydro-oxazolo[4,5-c]pyridine (20, Rb=H). To a cooled (0°C) solution of compound **19** (Rb=H, 0.95g, 3.2mmol) in 1,2-dichloroethane (32ml) was added DIPEA (1.1ml, 6.4mmol, 2eq). At 0°C, 1-chloroethylchloroformate (1,05ml, 9.72mmol, 3eq) was added and the mixture was stirred for 10 minutes at 0°C after which time the temperature was raised to reflux temperature. After 2hrs, the mixture was concentrated *in vacuo* and the residue was dissolved in methanol (35ml). The solution was stirred for 48hrs at room temperature. The precipitate was filtered, the solid product was washed with diethyl ether to give compound **20** (Rb=H, 0.9g, 88%). LC-MS (Method A): Rt 1.1, [M+H] 280.

3-[2-(4-Bromo-phenyl)-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl]-propionic acid t-butyl ester (21, Rb=H). Compound **20** (Rb=H, 8g, 22.8mmol)

was suspended in methanol (200ml) and DIPEA was added (8.15ml, 46.8mmol, 2.05eg). To the mixture was added t-butyl acrylate (3.97ml, 27.4mmol, 1.2eq) and the mixture was refluxed for 120rs. Conversion was checked by TLC analysis and after 16 and 64hrs additional t-butyl acrylate (3.97ml, 27.4mmol, 1.2eq) was added to push the reaction to completion. The solvents were evaporated and the residue was redissolved in EtOAc and extracted with a 5% solution of $NaHCO_3$ .The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by silica gel column chromatography (eluent: diethyl ether/petroleum ether, 1/1, v/v) to give **21a** (Rb=H, 8.8g, 93%). LC-MS (Method A): Rt 1.38, [M+H] 408.

3-{2-[4-(Benzyloxy)-phenyl)]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-propionic acid t-butyl ester (23a, Ra=Rb=H). Compound **21a** (Rb=H, 0.9g, 2.21mmol) was dissolved in degassed toluene (7ml) and to the solution was added cesium carbonate (1.08g, 3.3mmol), benzyl alcohol (0.46ml, 4.42mmol, 2eq), 2-di-t-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1-biphenyl (25.5mg, 0.05 mmol, 0.02eq) and palladium(II) acetate (9.92mg, 0.04mmol, 0.02eq). The mixture was stirred at 70°C for 16hrs. The mixture was cooled to room temperature, concentrated *in vacuo* and the residue was purified by silica gel column chromatography (diethyl ether/petroleum ether, 3/1, v/v) to give pure **23a** (Ra=Rb=H, 0.71g, 74%) as a white solid. LC-MS (Method A): Rt 1.46, [M+H] 435.

3-{2-[4-(Benzyloxy)-phenyl)]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-propionic acid (47). Compound **23a** (Ra=Rb=H, 0.71g, 1.63mmol) was dissolved in a solution of HCl in 1,4-dioxan (4N, 12ml, 30eq) and the mixture was stirred for 16 hrs at 50°C. The solvents were evaporated and diethyl ether was added to precipitate the product. The white solid material was filtered and dried *in vacuo* to give compound **47** (0.67g, 93%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm, 2.92 (t, *J*= 7.1 Hz, 2 H), 3.06 - 3.31 (bs, 2 H), 3.57 (t, *J*= 7.1 Hz, 2 H), 3.50 - 3.61 (bs, 1 H), 3.79 - 4.04 (bs, 1 H), 4.21 - 4.42 (bs, 1 H), 4.42 - 4.60 (bs, 1 H), 5.20 (s, 2 H), 7.16 (d, *J*=8.6 Hz, 2 H), 7.35 (t, *J*= 7.5 Hz, 1 H), 7.41 (t, *J*= 7.5 Hz, 2 H), 7.49 (d, *J*= 7.5 Hz, 2 H), 7.93 (d, *J*=8.6 Hz, 2 H), 10.31 - 10.84 (bs, 1 H). LC-MS (Method A): Rt 1.32, [M+H] 379.

4-[2-(4-Bromo-phenyl)-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl]-butyric acid t-butyl ester (21d, Rb=H). Compound **20** (Rb=H, 2.5g, 7.92mmol) was suspended in DMF (40ml). To this suspension was added potassium carbonate (3.8g, 27.7mmol, 3.5eq) and t-butyl 4-bromobutanoate (5.3g, 23.7mmol, 3eq). The mixture was heated at 80°C for 16hrs after which time TLC analysis revealed complete reaction. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (eluent: diethyl ether/petroleum ether, 1/1, v/v to 100% diethyl ether) to yield **21d** (Rb=H, 3.15g, 94%) as a white solid.

4-{2-[4-(2,3-Difluoro-benzyloxy)-phenyl)]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-butyric acid t-butyl ester (23d, Ra=2,3-diF, Rb=H). Compound **21d** (Rb=H, 0.6g, 1.42mmol) was dissolved in degassed toluene (5ml) and to the solution was added cesium carbonate (0.7g, 2.14mmol), 2,3-difluoro-benzyl alcohol (0.32ml, 2.85mmol, 2eq), 2-di-t-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1-biphenyl (16.43mg, 0.03mmol, 0.02eq) and palladium(II) acetate (6.39mg, 0.03mmol, 0.02eq). The mixture was stirred at 70°C for 16hrs. The mixture was cooled to room temperature, concentrated *in vacuo* and the residue was purified by silica gel column chromatography (diethyl ether/petroleum ether, 2/1, v/v to 100% diethyl ether) to give pure **23d** (Ra=2,3-diF, Rb=H, 0.48g, 70%) as an oil.

4-{2-[4-(2,3-Difluoro-benzyloxy)-phenyl)]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-butyric acid (57). Compound **23d** (Ra=2,3-diF, Rb=H, 0.46g, 0.95mmol) was dissolved in a solution of HCl in 1,4-dioxan (4N, 14ml, 60eq) and the mixture was stirred for 16 hrs at room temperature. The solvents were evaporated and diethyl ether was added to precipitate the product. The white solid material was filtered and dried *in vacuo* to give compound **57** (0.45g, 99%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 2.08 (m., 2 H), 2.41 (t, J= 7.0 Hz, 2 H), 3.00 - 3.29 (m, 2 H), 3.31 – 3.40 (m, 2 H), 3.48 - 3.70 (bs, 1 H), 3.70 - 3.96 (bs, 1 H), 4.18 - 4.38 (m, 1 H), 4.38 - 4.61 (m, 1 H), 5.26 (s, 2 H), 7.16 (d, J= 8.8 Hz, 2 H), 7.19 - 7.25 (m, 1 H), 7.28 – 7.39 (m, 2 H), 7.94 (d, J= 8.8 Hz, 2 H), 10.37 - 10.88 (bs, 1 H); LC-MS (Method A): Rt 1.16, [M+H] 429.

4-{2-[4-Benzyloxy-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-butyric acid (53). Compound **53** was prepared in a similar fashion as described for the synthesis of **57** starting from **23d** (Ra=Rb=H). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 2.01 - 2.17 (m, 2 H), 2.42 (t, J= 6.9 Hz 2 H), 3.00 - 3.30 (m, 2 H), 3.32 - 3.41 (m, 2 H), 3.50 - 3.69 (m, 1 H), 3.78 - 3.96 (m, 1 H), 4.18 - 4.37 (m, 1 H), 4.43 - 4.59 (m, 1 H), 5.18 (s, 2 H), 7.14 (d, *J*= 8.8 Hz, 2 H), 7.34 (t, *J*= 7.9 Hz, 1 H), 7.40 (t, *J*= 7.9 Hz, 2 H), 7.47 (d, *J*= 7.9 Hz, 2 H), 7.93 (d, *J*= 8.8 Hz, 2 H), 10.45 - 10.89 (bs, 1 H); LC-MS (Method A): Rt 1.17, [M+H] 393.

4-{2-[4-(4-Trifluoromethyl-benzyloxy)-2-fluoro-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-butyric acid (85). Compound **85** was prepared following route C starting from 2-fluoro-4-bromo-benzoyl chloride. ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm: 1.98 – 2.11 (m, 2 H), 2.40 (t, *J*=7.1 Hz, 2 H), 3.10 - 3.24 (m, 2 H), 3.30 - 3.42 (m, 2 H), 3.51 - 3.66 (bs, 1 H), 3.79 - 3.97 (bs, 1 H), 4.25 - 4.39 (m, 1 H), 4.49 - 4.65 (m, 1 H), 5.32 (s, 2 H), 6.98 - 7.13 (m, 2 H), 7.66 - 7.78 (m, 4 H), 7.93 (t, *J*=8.6 Hz, 1 H), 9.91 - 10.46 (bs, 1 H); LC-MS (Method A): Rt 1.77, [M+H] 479.

4-{2-[4-(2-Fluoro-benzyloxy)-2-methyl-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-butyric acid (89). Compound **89** was prepared following route C starting from 2-methyl-4-bromo-benzoyl chloride. ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm: 2.00 - 2.12 (m, 2 H), 2.41 (t, *J*=7.1 Hz, 2 H), 2.64 (s, 3 H), 3.05 - 3.26 (m, 2 H), 3.32 - 3.42 (m, 2 H), 3.50 - 3.70 (bs, 1 H), 3.79 - 3.95 (bs, 1 H), 4.22 - 4.39 (m, 1 H), 4.48 - 4.65 (m, 1 H), 5.21 (s, 2 H), 6.97 - 7.04 (m, 2 H), 7.17 - 7.27 (m, 2 H), 7.37 - 7.46 (m, 1 H), 7.56 (dt, *J*=7.4, 1.4 Hz, 1 H), 7.89 (d, *J*=8.5 Hz, 1 H), 9.97 - 10.46 (bs, 1 H); LC-MS (Method A): Rt 1.61, [M+H] 425.

4-{2-[4-(3,4-Dichloro-benzyloxy)-2-fluoro-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-butyric acid (227). Compound **227** was prepared following route C starting from 2-fluoro-4-bromo-benzoyl chloride. ^{1}H NMR (600 MHz, DMSO-d_6), δ ppm:1.74 (q, *J*=7.1 Hz, 2 H), 2.26 (t, *J*=7.1 Hz, 2 H), 2.55 (t, *J*=7.1 Hz, 2 H), 2.73 - 2.78 (m, 2 H), 2.81 (t, *J*=5.3 Hz, 2 H), 3.43 (br.s, 2 H), 5.21 (s, 2 H), 7.00 (dd, *J*=8.8, 2.5 Hz, 1 H), 7.11 (dd, *J*=13.0, 2.5 Hz, 1 H), 7.47 (dd, *J*=8.4 , 2.0 Hz, 1 H), 7.69 (d, *J*=8.3 Hz, 1 H), 7.76 (d, *J*=1.9 Hz, 1 H), 7.89 (t, *J*=8.3 Hz, 1 H), 11.30 - 12.80 (bs, 1 H); LC-MS (Method A): Rt 1.42, [M+H] 479.

4-{2-[4-(2-Fluoro-benzyloxy)-3-chloro-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-butyric acid (283). Compound **283** was prepared following route C starting from 3-chloro-4-bromo-benzoyl chloride. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 1.69 - 1.801.74 (m, , 2 H), 2.27 (t, *J*=7.2 Hz, 2 H), 2.55 (t, *J*=7.0 Hz, 2 H), 2.73 – 2.79 (m, , 2 H), 2.81 (t, *J*=4.6 Hz, 2 H), 3.43 (s, 2 H), 5.32 (s, 2 H), 7.25 - 7.33 (m, 2 H), 7.42 – 7.50 (m, 2 H), 7.58 – 7.65 (m, 1 H), 7.88 (dd, *J*=8.7, 2.1 Hz, 1 H), 7.93 (d, *J*=2.1 Hz, 1 H), 11.0 – 13.0 (bs, 1 H); LC-MS (Method B): Rt 1.99*, [M+H] 445.

4-{2-[4-(4-Chloro-benzyloxy)-3-fluoro-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-butyric acid (211). Compound **211** was prepared following route C starting from 3-fluoro-4-bromo-benzoyl chloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.95 - 2.06 (m, 2 H), 2.38 (t, *J*=7.2 Hz, 2 H), 3.09 - 3.20 (m, 2 H), 3.23 – 3.32 (m., 2 H), 3.44 - 3.53 (m, 1 H), 3.76 - 3.86 (m, 1 H), 4.20 - 4.32 (m, 1 H), 4.43 - 4.52 (m, 1 H), 5.28 (s, 2 H), 7.43 (t, *J*=8.6 Hz, 1 H), 7.51 (m, 4 H), 7.76 (m, 2 H),10.65 - 11.02 (bs, 1 H), 12.03 - 12.77 (bs, 1 H); LC-MS (Method B): Rt 2.03*, [M+H] 445.

2-(4-Benzyloxy-phenyl)-oxazolo[4,5-c]pyridine (25, Ra=Rb=H). To a cooled (0°C) suspension of commercially available 4-hydroxy-3-amino-pyridine (**14**, 19.3g, 175mmol) in acetonitril (1500ml) was added 4-benzyloxy-benzoic acid (**24**, Ra=Rb=H, 40g, 175mmol), triphenylphosphine (142.5g, 543mmol, 3.1eq) and trichloroactonitril (54.5ml, 543mmol, 3.1eq). The reaction mixture was allowed to reach room temperature and the mixture was stirred for 16hrs at 80°C. The mixture was concentrated *in vacuo* and the residues was dissolved in DCM and washed with 2N NaOH (3x). The combined water layers were extracted with DCM and the organic layers dried (Na_2SO_4) to give crude **25** (Ra=Rb=H) as oil which was used in the next step without further purification.

2-(4-Benzyloxy-phenyl)-5-methyl-4,5,6,7-tetrahydro-oxazolo[4,5-c]pyridine (26, Ra=Rb=H). To a solution of crude **25** (Ra=Rb=H, 117mmol) in DMF (540ml) was added iodomethane (29.35ml, 471mmol, 4eg) and the mixture was stirred for 16hrs. The mixture was concentrated *in vacuo* and the residue was stirred in EtOAc to give the quaternary salt of **25** a white solid, which

dissolved in methanol (950ml) and the solution was cooled to 0°C. Sodium borohydride (10.2g, 268mmol, 2.5eg) was added and the mixture was stirred at 0-°C for 2 hrs after which time it was allowed to reach room temperature and stirring was continued for 64 hrs. Water was added (117ml) and the mixture was stirred for 5 minutes. The mixture was concentrated *in vacuo*, the residues suspended in 2N NaOH (5ml/mmol) and extracted with DCM (3x). The combined organic layers were dried (Na_2SO_4) and concentrated to give crude **26** (Ra=Rb=H) as a yellow solid which was used in the next step without further purification.

2-(4-Benzyloxy-phenyl)-4,5,6,7-tetrahydro-oxazolo[4,5-c]pyridine (27, Ra=Rb= H). To a cooled (0°C) solution of compound **26** (Ra=Rb=H, 35.2g, 109.8mmol) in 1,2-dichloroethane (880ml) was added DIPEA (37.61ml, 219.7mmol, 2eq) and 1-chloroethyl chloroformate (35,56ml, 329.6mmol, 3eq) was added. The mixture was stirred for 10 minutes at 0°C after which time the temperature was raised to reflux temperature. After 4hrs, the mixture was allowed to reach room temperature and stirring was continued for 16hrs. The mixture was concentrated *in vacuo* and the residue was dissolved in methanol (880ml). The solution was stirred for 16hrs at room temperature after which time TLC analysis revealed the reaction to be complete. Removal of the solvent resulted in the isolation of crude **27** (Ra=Rb=H) in an overall yield of 20% based on **25** (Ra=Rb=H).

3-[2-(4-Benzyloxy-phenyl)-4,5,6,7-tetrahydro-oxazolo[4,5-c]pyridine]-2-methyl-propionic acid t-butyl ester (28b). To a solution of compound **27** (Ra=Rb=H, 13.45g, 43.9mmol) in DMF (270ml) was added 1,8–diazabicyclo[5.4.0]undec-7-ene (3eg) and t-butylmethacrylate (28.54ml, 175.6mmol, 4eq). The mixture was heated at 125°C for 100hrs. The solution was cooled and 5% $NaHCO_3$ was added (15ml/mmol) and extracted with diethyl ether/EtOAc, 1/1, v/v. The organic layer was washed with water (4x), dried on $MgSO_4$, concentrated *in vacuo* and the residue was purified by silica gel column chromatography (eluent: diethyl ether/petroleum ether, 1/2 to 3/1, v/v) to give **23b** (Ra=Rb=H, 14.58g, 74%) as an oil.

3-[2-(4-Benzyloxy-phenyl)-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl]-2-methyl-propionic acid (146). Compound **23b** (Ra=Rb=H, 0.45g, 1mmol) was

dissolved in a solution of HCl in 1,4-dioxan (4N, 14ml, 60eq) and the mixture was stirred for 16 hrs at room temperature. The solvents were evaporated and diethyl ether was added to precipitate the product. The white solid material was filtered and dried *in vacuo* to give compound **146** (0.43g, 99%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm:1.28 (d, J=7.3 Hz, 3 H), 3.07 - 3.20 (m, 3 H), 3.26 (dd, J=13.2, 4.9 Hz, 1 H), 3.60 (dd, J=13.2, 7.9 Hz, 1 H), 3.66 (bs, 2 H), 4.34 (br. s., 2 H), 5.18 (s, 2 H), 7.11 - 7.17 (m, 2 H), 7.31 - 7.37 (m, 1 H), 7.37 - 7.43 (m, 2 H), 7.44 - 7.49 (m, 2 H), 7.85 - 7.93 (m, 2 H), 10.17 - 12.85 (bs, 1 H); LC-MS (Method A): Rt 1.48, [M+H] 393.

3-{2-[4-(4-Trifluoromethyl-benzyloxy)-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-2-methyl-propionic acid (156). Compound **156** was prepared following Route C. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 1.29 (d, J=7.2 Hz, 3 H), 3.09 - 3.21 (bs, 3 H), 3.27 (dd, J=13.1, 5.3 Hz, 1 H), 3.57 - 3.72 (dd, J=13.1, 7.3 Hz, 1 H), 3.65 - 3.72 (bs, 2 H), 4.34 (br. s., 2 H), 5.33 (s, 2 H), 7.21 (d, J=8.8 Hz, 2 H), 7.68 - 7.74 (m, 2 H), 7.75 - 7.81 (m, 2 H), 7.93 (d, J=8.8 Hz, 2 H), 10.50 - 12.32 (bs, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6), δ PPM: 16.35 (q, 1 C), 19.25 (t, 1 C), 35.14 (d, 1 C), 49.04 (br. t., 1 C), 49.76 (br. t., 1 C), 57.23 (t, 1 C), 68.66 (t, 1 C), 115.60 (d, 2 C), 119.65 (s, 1 C), 124.21 (s, ^1JCF=272.5 Hz, 1 C), 125.34 (d, ^3JCF=3.6 Hz, 2 C), 127.63 (d, 2 C), 128.05 (d, 2 C), 128.51 (s, ^2JCF=31.7 Hz, 1 C), 128.63 (s, 1 C), 141.51 (s, 1 C), 142.86 (s, 1 C), 160.11 (s, 1 C), 160.76 (s, 1 C), 174.95 (s, 1 C); LC-MS (Method A): Rt 1.82, [M+H] 461.

3-{2-[4-(4-Chloro-benzyloxy)-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-2-methyl-propionic acid (157). Compound **157** was prepared following route C. ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm: 1.19 (d, J=7.4 Hz, 3 H), 3.00 - 3.12 (m, 3 H), 3.18 (dd, J=13.2, 5.3 Hz, 1 H), 3.52 (dd, J=13.2, 7.1 Hz, 1 H), 3.56 - 3.66 (bs, 2 H), 4.24 (br. s., 2 H), 5.11 (s, 2 H), 7.08 (d, J=9.0 Hz, 2 H), 7.35 - 7.43 (m, 4 H), 7.81 (d, J=9.0 Hz, 2 H), 10.57 - 11.92 (bs, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6), δ PPM: 16.44 (q, 1 C), 19.19 (t, 1 C), 35.09 (d, 1 C), 49.1 (br. t., 1 C), 49.6 (br. t., 1 C), 57.17 (t, 1 C), 68.72 (t, 1 C), 115.59 (d, 2 C), 119.50 (s, 1 C), 127.60 (d, 2 C), 128.45 (d, 2 C), 128.52 (s, 1 C), 129.51 (d, 2 C), 132.58 (s, 1 C), 135.69 (s, 1 C), 142.79 (s, 1 C), 160.22 (s, 1 C), 160.80 (s, 1 C), 174.92 (s, 1 C); LC-MS (Method A): Rt 1.72, [M+H] 427.

3-{2-[4-(4-(2,3-Difluoro-benzyloxy)-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-butyric acid (175). Compound **175** was prepared following route C. ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm: 1.27 (d, J=6.6 Hz, 3 H), 2.5 - 2.6 (m, 1 H), 2.8 - 3.1 (m, 3 H), 3.1 - 3.5 (bs, 2 H), 3.6 - 3.7 (bs, 1 H), 3.9 – 4.1 (bs, 2 H), 5.28 (s, 2 H), 7.0 – 7.2 (m, 2 H), 7.2 - 7.3 (m, 1 H), 7.4 - 7.5 (m, 2 H), 7.9 – 8.0 (m, 2 H), 12.16(br. s., 1 H); LC-MS (Method A): Rt 1.3, [M+H] 429.

3-{2-[4-(4-Trifluoromethyl-benzyloxy)-2-fluoro-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-2-methyl-propionic acid (271). Compound **271** was prepared following route C. ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm: 1.29 (d, J=7.2 Hz, 3 H), 3.06 - 3.36 (m, 4 H), 3.51 - 3.68 (m, 2 H), 3.70 – 3.90 (bs, 1 H), 4.18 - 458 (bs, 2 H), 5.33 (s, 2 H), 7.03 (dd, J=8.7, 2.2 Hz, 1 H), 7.10 (dd, J=12.9, 2.2 Hz, 1 H), 7.65 - 7.71 (m, 2 H), 7.73 - 7.77 (m, 2 H), 7.92 (t, J=8.7 Hz, 1 H), 11.01 (br. s., 1 H); LC-MS (Method A): Rt 1.56, [M+H] 479.

2-(4-Bromo-phenyl)-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-carboxylic acid t-butyl ester (28, Rb=H). To a suspension of compound **20** (Rb=H, 14.3g, 48.2mmol) in DCM (300ml) were added DIPEA (1eq) and di-t-butyl dicarbonate (11.59g, 53mmol, 1.1eq). The mixture was stirred at room temperature for 16hrs after which time TLC analysis revealed complete reaction. The mixture was concentrated *in vacuo* to give crude compound pure **28** (Rb=H) which was used in the next step without further purification.

2-(4-Hydroxy-phenyl)-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-carboxylic acid t-butyl ester (29, Rb=H). Compound **28** (Rb=H, 9g, 20.4mmol) was dissolved in 1,4-dioxan (90ml) and to the solution was added potassium hydroxide (4.58g, 81mmol, in 90 ml water) and the solution was degassed. To the solution was added 2-di-t-butylphosphino-2',4',6'-triisopropylbiphenyl (346mg, 0.82mmol, 0.04eq) and tris-(dibenzylideneaceton)-dipalladium(0) (373.5mg, 0.41mmol, 0.02eq). The mixture was stirred at 80°C for 16hrs after which time LC-MS analysis showed that the conversion was complete. The mixture was cooled to room temperature, diluted with EtOAc, acidified to pH 6 with 0.1N HCl and extracted with EtOAc. The organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column

chromatography (DCM/MeOH, 97/3, v/v) to give compound pure **29** (Rb=H, 6g, 83%).

2-[4-(4-Trifluoromethyl-benzyloxy)-phenyl)-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-carboxylic acid t-butyl ester (30, Ra=4CF$_3$, Rb=H). Compound **29** (Rb=H, 6g, 17mmol) was dissolved in DCM/water, 2/1, v/v (78ml/mmol) and to this solution was added sodium hydroxide (27ml, 2N, 3 eq). To this mixture was added tetrabutylammonium bromide (549mg, 0.1eq) and 4-trifluoromethyl-benzyl bromide (4.48g, 18.75mmol, 1.1eq). The mixture was stirred for 16hrs at room temperature after which time LC-MS analysis showed complete reaction. The mixture was diluted with DCM (200ml), the layers were separated and the water layer was extracted with DCM. The organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: EtOAc/petroleum ether, 1/3) to give compound pure **30** (Rb=H, 9.0g, 96%) as a colorless foam.

2-[4-(4-Trifluoromethyl-benzyloxy)-phenyl)-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine(30, Ra=4CF$_3$, Rb=H). Compound **30** (9.6g, 18.5mmol) was dissolved in DCM (150ml) and trifluoroacetic acid (8.5ml, 111mmol, 6eq) was added. The solution was refluxed for 16hrs after which time TLC analysis showed complete reaction. The mixture was neutralized with 5% aq. $NaHCO_3$. The mixture was extracted with DCM (3x) and the combined organic layers were washed with brine, dried on Na_2SO_4 and concentrated *in vacuo* to give compound **27** (Ra=4CF$_3$, Rb=H) which was used in the next step without further purification.

3-{2-[4-(4-Trifluoromethoxybenzyloxy)-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-cyclobutane carboxylic acid (306). Compound **27** (Ra=4CF$_3$, Rb=H 0.71g, 1.8mmol) was suspended in 1,2-dichloroethane (40ml). To this suspension was added 3-oxocyclobutanecarboxylic acid (0.27g, 2.34mmol, 1.3eq) and sodium triacetoxy borohydride (0.61g, 2.88mmol, 1.6eq). The mixture was stirred at room temperature for 16hrs after which time TLC analysis revealed complete reaction. The solution was diluted with 5% NaHCO3 (15ml/mmol) and the mixture was extracted with DCM. The combined organic layers were dried on Na_2SO_4, concentrated *in vacuo* and the residue was purified by silica gel column chromatography to furnish a mixture of cis and trans

stereoisomers in a ratio of 2 to 1. A second silica gel column chromatography purification (DCM/MeOH, 9/1, v/v) resulted in the isolation of two enriched stereoisomer fractions. Compound **307-cis** (Rf, 0.2, 0.46g, 51%, cis/trans = 95/5) and **306-trans** (Rf 0.25, 0.21g, 25%, cis/trans = 5/95). **307-cis:** ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 1.92 - 2.05 (m, 2 H); 2.26 - 2.37 (m, 2 H); 2.68 (t, J=4.5 Hz, 2 H); 2.70 - 2.79 (m, 3 H); 2.89 - 3.00 (m, 1 H); 3.30 – 3.41 (bs, 2 H); 5.21 (s, 2 H) 7.14 (d, J=8.8 Hz, 2 H); 7.41 (d, J=8.5 Hz, 2 H); 7.61 (d, J=8.5 Hz, 2 H); 7.87 (d, J=8.8 Hz, 2 H); 12.15 (br. s., 1 H); **306-trans:** ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.10 - 2.21 (m, 2 H); 2.22 - 2.34 (m, 2 H); 2.67 (t, J=4.8 Hz, 2 H); 2.71 - 278 (m., 2 H); 2.84 – 2.95 (m, J=9.6 Hz, 1 H); 3.17 (quin, J=7.4 Hz, 1 H); 3.31 – 3.40 (bs, 2 H); 5.21 (s, 2 H); 7.14 (d, J=8.8 Hz, 2 H); 7.41 (d, J=8.5 Hz, 2 H); 7.61 (d, J=8.5 Hz, 2 H); 7.87 (d, J=8.8 Hz, 2 H); 12.20 (br. s., 1 H). LC-MS Rt 1.41, [M+H] = 489.

3-{2-[4-(3,4-Difluorobenzyloxy)-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-cyclobutane carboxylic acid (277). Compounds **278-cis** and **277-trans** were prepared as described for **306**. **278-cis:** ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 1.93 - 2.04 (m, 2 H) 2.26 - 2.36 (m, 2 H) 2.68 (t, J=4.8 Hz, 2 H) 2.70 - 2.80 (m, 3 H) 2.88 - 3.00 (m, 1 H) 3.33 - 3.40 (bs, 2 H) 5.16 (s, 2 H) 7.14 (d, J=8.8 Hz, 2 H) 7.29 - 7.38 (m, 1 H) 7.47 (dt, J=10.7, 8.4 Hz, 1 H) 7.56 (ddd, J=11.5, 8.0, 2.0 Hz, 1 H) 7.87 (d, J=8.8 Hz, 2 H) 12.15 (br. s., 1 H); LC-MS (method A): Rt 1.33, [M+H] = 441; **277-trans:** ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 2.09 - 2.20 (m, 2 H) 2.23 - 2.31 (m, 2 H) 2.67 (t, J=4.5 Hz, 2 H) 2.70 – 2.77 (m, 2 H) 2.84 - 2.93 (m, 1 H) 3.12 - 3.22 (m, 1 H) 3.32 – 3.39 (bs, 2 H) 5.16 (s, 2 H) 7.14 (d, J=8.8 Hz, 2 H) 7.30 - 7.37 (m, 1 H) 7.47 (dt, J=10.8, 8.4 Hz, 1 H) 7.56 (ddd, J=11.4, 8.0, 1.9 Hz, 1 H) 7.87 (d, J=8.8 Hz, 2 H) 12.20 (br. s., 1 H);); LC-MS (method A): Rt 1.31, [M+H] = 441.

3-Bromo-N-benzyloxycarbonyl-4-piperidone (502). To a cooled (0°C) solution of N-benzyloxycarbonyl-4-piperidone (**501**, 27.3g 117 mmol) in DCM (3ml/mmol) was added DIPEA (25.5ml, 146.2mmol, 1.25eg) and trimethylsilyl trifluoromethane sulfonate (25.4ml, 141 mmol, 1.2eg). The mixture was stirred for 30 minutes at 0°C. Next, N-bromosuccinimide (21.2g, 119.3mml, 1.02eg) was added and stirring was continued for 16hrs at room temperature. The reaction mixture was washed with 5% $NaHCO_3$ and the organic layer was dried ($MgSO_4$)

and subsequently concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (diethyl ether/ petroleum ether, 1/1 to 1/0, v/v, Rf 0.1) giving **502** in a yield of 90% as a yellow oil.

2-(4-Methoxy-phenyl)-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid benzyl ester (504). Compound **502** (2.0g, 6.5mmol) was dissolved in ethanol (20ml). To the solution was added 4-methoxythiobenzamide (**503**, 1.09g, 6.5 mmol, 1eq) and the yellow mixture was refluxed for 17 hrs after which time TLC analysis showed full conversion of **502.** The reaction mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc, washed with 5% Na_2SO_4 and the organic layer was dried ($MgSO_4$) and subsequently concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (diethyl ether, Rf 0.3) giving compound **504** in a yield of 49% as a colorless oil. Compounds having a Rb substitute can be prepared by choosing a properly substituted (Rb)- 4-methoxythiobenzamide (**503**).

4-(4,5,6,7-Tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-phenol 505. Compound **504** (18.0g, 47.3mmol) was dissolved in ethanol (300ml). To the cooled (-78 °C) solution was added boron tribromide (5eg, 236mmol) dropwise. After one hour cooling was removed and the mixture was stirred 16hrs at room temperature. The reaction was quenched with MeOH, the mixture was concentrated *in vacuo* to give compound **505** as an oil which was used in the next step without further purification.

General procedure for the synthesis of compounds 508. Compounds **508** are prepared starting from compounds **505** in a similar fashion as described for the synthesis of compounds 7 and 21 (see schemes 1-4). As a typical example we describe the synthesis of compound **508** (Ra=F, Rb=H, Rc=C2).

3-[2-(4-(Hydroxy-phenyl)-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-yl]-propionic acid t-butyl ester (506, Rb=H, Rc=C2). To a suspension of **505** (Rb=H, 5.8g, 25.1mmol) in MeOH (100ml) and DIPEA (5.1ml, 30.1mmol, 1.2eq) was added t-butyl acrylate (4.4ml, 30.1mmol, 1.2eq) and the mixture was refluxed for 16hrs after which time TLC analysis (diethyl ether, Rf 0.2) showed full conversion of **505.** The reaction mixture was concentrated *in vacuo* and the

resdue was dissolved in EtOAc, washed with 5% NaHCO3 and the organic layer was dried (Na_2SO_4) and subsequently concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (diethyl ether) giving compound **506** (Rb=H, Rc=C2) in a yield of 79% as a white solid material.

3-[2-(4-(2-Fluoro-benzyloxy)-phenyl)-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-yl]-propionic acid t-butyl ester (507, Ra= 2F, Rb=H, Rc=C2). To a suspension of **506** (Rb=H, Rc=C2, 0.5g, 1.4mmol) in DMA (4ml) was added triphenyl phosphine (0.45g, 1.7mmol, 1.25eg), diisopropyl azodicarboxylate (0.33ml, 1.7mmol, 1.25eq) and 2-fluoro benzyl alcohol (0.17ml, 1.56mmol, 1.15eg) and the mixture was stirred at room temperature for 16hrs. The reaction mixture was diethyl ether (150ml) and washed with 3x50ml water. The combined organic layers were dried (Na_2SO_4) and subsequently concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (diethyl ether/petroleum ether, 2/1, v/v) giving compound **507** (Ra=2F, Rb=H, Rc=C2) in a yield of 67% as a white solid material.

3-[2-(4-(2-Fluoro-benzyloxy)-phenyl)-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-yl]-propionic acid (38, Ra= 2F, Rb=H, Rc=C2). Compound **507**, Ra=2F, Rb=H, Rc=C2, 0.43g, 0.9mmol) was dissolved in 4N HCl in dioxane (10ml). The mixture was stirred for 16hrs at room temperature. The mixture was concentrated *in vacuo* and the resulting solid was washed with diisopropyl ether to give **38** as a white solid (Ra= 2F, Rb=H, Rc=C2, 0.42g, 97%). Compound **38:** ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 2.88-3.03 (m, 2H), 3.06 - 3.14 (m, 1 H), 3.20 (m, 1 H), 3.48 (broad signal, 3 H), 3.73 - 3.87 (m, 1 H), 4.44 (bd, *J*=15.9, 6.0 Hz,1 H), 4.72 (b, *J*=15.9 Hz, 1 H), 5.22 (s, 2 H), 7.16 (d, *J*=8.6 Hz, 2 H), 7.23 - 7.32 (m, 2 H), 7.41 - 7.49 (m, 1 H), 7.59 (dt, *J*=7.6, 1.5 Hz, 1 H), 7.87 (d, *J*=8.6 Hz, 2 H), 11.63 (br. s., 1 H); LC-MS (Method A): Rt 1.3, [M+H] 473.

4-Bromo-N-(4-chloro-pyridin-3-yl)-benzamide (510). A mixture of 4-amino-3-chloropyridine (**509**, 5.9g, 46,2 mmol), 4-bromobenzoyl chloride (**15**, **11**.15g, 50.8mmol) and potassium carbonate (22.4g, 161.7 mmol) in acetonitril (150ml) was refluxed for 24hrs. The reaction mixture was concentrated *in vacuo*, redissolved in DCM and the solution was washed with water. The organic layer was dried ($MgSO_4$), concentrated and the resulting oil was purified by silica gel

column chromatography (DCM/MeOH, 99/1, v/v, Rf 0.2) to give pure **510** (10.4g, 72%) as an oil. When a substituted compound **15** is used, the Rb in compound **510** is introduced.

2-(4-Bromo-phenyl)-thiazolo-[4,5c]-pyridine (511). Compound **510** (10.4g, 33.4mmol) was suspended in toluene (400ml) and Lawesson's reagent (9.4g, 23.4mmol, 0.7eq) was added and the mixture was refluxed for 24 hrs after which time TLC analysis (DCM/MeOH, 97/3, v/v, Rf 0.7) revealed the reaction to be complete. The mixture was concentrated *in vacuo* and to the oil was added $NaHCO_3$ (5% solution, 200ml) and the suspension was extracted with DCM (3x200ml). The combined organic layers was dried over $MgSO_4$, concentrated and the oil was purified by silica gel column chromatography (DCM/MeOH, 99/1 to 97/3, v/v) to give pure **511** (8.7g, 89%) as an oil.

2-(4-Benzyloxy-phenyl)-4,5,6,7-tetrahydro-thiazolo-[4,5c]-pyridine (518). Compounds **518** were obtained starting from **511** in a similar fashion as described for the synthesis of compounds **27** in schemes 4 and 7. The appropriate tails Rc could be linked to **518** in a similar fashion as described for compounds **27**.

4-{2-[4-(3,5-Difluoro-benzyloxy)-phenyl]-6,7-dihydro-4H-thiazolo-[4,5c]-pyridin-5-yl}-butyric acid (446, Ra=3,5-F, Rb=H, Rc=C3). Compound **519** (Ra=3,5-F, Rb=H, Rc=C3, 0.79g, 1.58mmol) was dissolved in 4N HCl in dioxan (25ml) was stirred for 18hrs at 50°C and for 70hrs at room temperature. The mixture was concentrated *in vacuo* and the resulting oil was stirred in diethyl ether to yield **446** as a white solid (0.72g, 94%). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.03 - 2.15 (m, 2 H), 2.40 (t, *J*=7.3 Hz, 2 H), 3.12 - 3.22 (m, 1 H), 3.32 (broad signal, 3 H), 3.40 – 3.51 (m, 1 H), 3.75 – 3.90 (m, 1 H), 4.36 (dd, *J*=15.2, 6.8 Hz, 1 H), 4.59 (d, *J*=15.2 Hz, 1 H), 5.21 (s, 2 H), 7.05 (tt, *J*=9.0, 2.3 Hz, 1 H), 7.09 - 7.18 (m, 4 H), 7.84 (d, *J*=8.9 Hz, 2 H), 11.17 (br. s., 1 H); Rt 1.33, [M+H] 502.

2-{2-[4-(3,5-Difluoro-benzyloxy)-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-acetic acid (463). 2-[4-(3,5-difluoro-benzyloxy)-phenyl]-4,5,6,7-tetrahydro-oxazolo[4,5-c]pyridine (**27**, Ra=3,5-diF, Rb= H) was synthesized following route C as described above. Compound **27** (Ra=3,5diF, Rb=

H, 0.4g, 1.17mmol) was dissolved in acetonitril (20ml). To the solution was added DIPEA (0.51ml, 2.9mmol, 2,5eq) and t-butyl bromoacetate (0.19ml, 1.29mmol, 1.1eq). The mixture was refluxed for 6 hrs after which time LCMS analysis showed the reaction to be complete. The mixture was concentrated *in vacuo*, water was added and the suspension was extracted with DCM (3x200ml). The combined organic layers was dried over $MgSO_4$, concentrated and the oil was purified by silica gel column chromatography (diethyl ether/petroleum ether, 3/1, v/v). The resulting oil was suspended in 4N HCl in dioxan (20ml). The mixture was stirred at 45°C for 5 hrs and at room temperature for 16hrs. The mixture was concentrated *in vacuo* to give a white solid. The solid material was washed 3 times with diethyl ether to give **463** (0.39g, 91%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 3.10 – 3.20 (m., 2 H), 3.70 – 3.80 (m., 2 H), 4.31 (s, 2 H), 4.44 (s, 2 H), 5.22 (s, 2 H), 7.02 - 7.10 (m, 1 H), 7.13 – 7.20 (m, 4 H), 7.92 (d, *J*=8.8 Hz, 2 H), 9.53 - 12.44 (br.s., 1 H); Rt 1.51; [M+H] 401.

2-{2-[4-(3,5-Difluoro-benzyloxy)-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-propionic acid (464). Compound **27** (Ra=3,5diF, Rb= H, 0.4g, 1.17mmol) was dissolved in acetonitril (20ml). To the solution was added DIPEA (0.51ml, 2.9mmol, 2,5eq) and t-butyl 2-bromo-propionic ester (0.27gl, 1.29mmol, 1.1eq). The mixture was refluxed for 24 hrs after which time LCMS analysis showed the reaction to be complete. The mixture was concentrated *in vacuo*, water was added and the suspension was extracted with DCM (3x200ml). The combined organic layers were dried on $MgSO_4$, concentrated and the oil was purified by silica gel column chromatography (diethyl ether/petroleum ether, 3/2, v/v, Rf 0.3). The resulting oil was suspended in 4N HCl in dioxan (20ml). The mixture was stirred at 45°C for 5 hrs and at room temperature for 16hrs. The mixture was concentrated *in vacuo* to give a white solid. The solid material was washed 3 times with diethyl ether to give **464** (0.41g, 89%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm, 1.66 (d, *J*=7.1 Hz, 3 H), 3.17 (br. s., 2 H), 3.74 (br. s., 2 H), 4.33 - 4.52 (m, 4 H), 5.22 (s, 2 H), 7.02 - 7.11 (m, 1 H), 7.13 – 7.25 (m, 4 H), 7.92 (d, *J*=8.8 Hz, 2 H); Rt 1.53, [M+H] 415.

3-{2-[4-(3,5-Difluoro-benzyloxy)-phenyl]-6,7-dihydro-4H-oxazolo[4,5-c]-pyridin-5-yl}-cyclopentane carboxylic acid (465, 1/1 cis-trans mixture). Compound **27** (Ra=3,5diF, Rb= H, 0.1g, 0.29mmol) was dissolved in 1,2-

dichloroethane (5ml). To the solution was added 3-oxo-cyclopentane-carboxylic acid (0.05g, 0.41mmol, 1.4eq), sodium triacetoxy borohydride (0.11g, 0.53mmol, 1,8eq) and AcOH (0.03ml, 0.58mmol, 2eq). The mixture was stirred for 16 hrs after which time LCMS analysis showed the reaction to be complete. To the mixture was added a saturated solution of NH_4Cl and the mixture was extracted with DCM. The combined organic layers was concentrated *in vacuo* and the oil was purified by silica gel column chromatography (DCM/MeOH, 9/1, v/v) to give compound **465** as a cis/trans mixture in a ratio of 1/1.

Rt 1.27, [M+H] 455.

4-{2-[4-(2,3-Difluoro-benzyloxy)-2-methyl-phenyl]-6,7-dihydro-4H-oxazolo-[4,5c]-pyridin-5-yl}-pentanoic acid (393). Compound **22** (Rb=2Me, Rc=H) was prepared by stirring **29** (Rb=2Me) in a mixture of TFA and DCM for 16hrs. The solvents were evaporated to give crude **22** (Rb=2Me, Rc=H) as an oil which was used in the next step without further purification. A SCX-2 column was used to make the free base of compound **22** (Rb=2Me, Rc=H, 1g, 4.3mmol), which was dissolved in MeOH. To this solution was added ethyl levulinate (2.46ml, 17.4mmol, 4eq), AcOH (0.5ml, 8.7mmol, 2eq) and palladium hydroxide on carbon. The reaction mixture was shaken at a pressure of 4atm of hydrogen. After 16hrs, ELSD showed that the reaction was not yet complete. Another portion of ethyl levulinate (2.46ml, 17.4mmol, 4eq) and palladium hydroxide on carbon was added and hydrogenation at 4 atm was continued for 72hrs. The mixture was degassed, filtered over Hyflo and the residue was washed with MeOH. The filtrate was concentrated *in vacuo* and the resulting oil was purified by silica gel column chromatography to give **522** (Rb=2Me, Rc=x$CH_2(CH_3)CH_2CH_2C(=O)OEt$) in an yield of 41%. Subsequent benzylation of **522** with 2,3-di-fluoro-benzyl bromide was performed in a similar fashion as described for the compounds of Schemes 1-5 giving compound **523**. Finally, the latter was dissolved in a solution of sodium hydroxide in ethanol (18ml, 0.3M) and the solution was stirred at 50°C for 16hrs. The mixture was concentrated *in vacuo* and the residue was stirred in diethyl ether to give **393** as a white solid (Ra=2,3-diF, Rb=2Me, Rc=$CH_2(CH_3)CH_2CH_2C(=O)OH$). ^1H NMR (400 MHz, DMSO-d_6): δ ppm 1.40 (d, J=5.9 Hz, 3 H), 1.74 - 1.93 (m, 1 H), 2.15 – 2.30 (m, 1 H), 2.31 - 2.50 (m, 3 H), 2.63 (s, 3 H), 3.04 – 3.15 (m, 1 H), 3.22 - 3.35 (m, 1 H), 3.45 - 3.69 (m, 2 H), 3.72 – 3.85 (m, 1 H), 4.22-4.46 (m, 2 H), 5.25 (s, 2 H), 6.98-7.07 (m, 2 H), 7.20-7.29 (m, 1 H), 7.34-7.45 (m, 2

H), 7.87 (d, *J*=8.6 Hz, 1 H), 10.49 - 10.69 (br.band, 1 H), 11.47 - 13.29 (br.band, 1 H). Rt 1.37, [M+H] 457.

4-{2-[4-(2,3-Difluoro-benzyloxy)-2-methyl-phenyl]-6,7-dihydro-4H-oxazolo[4,5-c]-pyridin-5-yl}-2-methyl-butyric acid (394). Compound **22** (Rb=2Me, 1g, 3.8mmol) was dissolved in acetonitril (10ml) and to the solution was added DIPEA (1.93 ml, 11.25mmol), sodium iodide (0.56g, 3.75mmol) and 4-chloro-2-methylbutyric acid methyl ester (0.85g, 5.6mmol). The mixture was stirred at 60°C for 16hrs, after which time again added DIPEA (1.93 ml, 11.25mmol), sodium iodide (0.56g, 3.75mmol) and 4-chloro-2-methylbutyric acid methyl ester (0.85g, 5.6mmol) were added and stirring was continued for 30hrs at 60°C. The mixture was concentrated *in vacuo* and purified by silica gel column chromatography (DCM/MeOH, 95/5 to 9/1, v/v) to give **525** (Rb=2Me; Rd=Me) as an oil. Compound **525** (Rb=2Me; Rd=Me) was benzylated at Mitsunobu conditions in a similar fashion as described above for the synthesis of **23**. The resulting compounds **526** (0.5mmol) were dissolved in ethanol (20ml) and 2N NaOH solution was added (4ml) and the mixture was stirred for 2hrs at 50°C. The solution was neutralized with 1M HCl, extracted with DCM (3x20ml) and the organic layers were dried on $MgSO_4$. Evaporation of the solvent resulted in the isolation of pure compound **394.** ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 1.09 (d, *J*=7.1 Hz, 3 H), 1.51 – 1.61 (m, 1 H), 1.80 - 1.92 (m, 1 H), 2.36 - 2.46 (m, 1 H), 2.56 (t, *J*=7.1 Hz, 2 H), 2.60 (s, 3 H), 2.72 – 2.78 (m, 2 H), 2.79 – 2.85 (m, 2 H), 3.39 - 3.47 (m, 2 H), 5.24 (s, 2 H), 6.95 - 7.04 (m, 2 H), 7.20 - 7.29 (m, 1 H), 7.35 - 7.47 (m, 2 H), 7.82 (d, *J*=8.6 Hz, 1 H), 10.85 - 13.06 (br.band, 1 H). LC-MS: Rt 1.38, [M+H] 457.

4-{2-[4-(2,3-Difluoro-benzyloxy)-2-methyl-phenyl]-6,7-dihydro-4H-oxazolo-[4,5c]-pyridin-5-yl}-3-methyl-butyric acid (437).

Synthesis of 4-Chloro-3-methyl-butyric acid methyl ester.

4-Methyl-dihydro-furan-2-one (4g, 39.95mmol) was dissolved in MeOH (10ml) and the solution was cooled to -10°C. Thionyl chloride (3.6ml, 49.9mmol) was added dropwise. The mixture was stirred at -10 °C for 2hrs and hereafter for 16hrs at room temperature. The mixture was concentrated *in vacuo* to give crude 4-Chloro-3-methyl-butyric acid methyl ester (4g, 87%) which was used in the next step without further purification.

Compound **22** (Rb=2Me, Rd=Me) was selectively alkylated at the nitrogen position with 4-chloro-3-methyl-butyric acid methyl ester to give **528.** Subsequent benzylation of **528** under previously described Mitsunobu conditions gave **529.** Compound **529** was demethylated in a similar fashion as described above for the synthesis of compound **394** to give compound **437** (Ra=2,3-diF, Rb=2Me, Rd=H) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 1.12 (d, J=6.6 Hz, 3 H), 2.26 (dd, J=16.3, 7.3 Hz, 1 H), 2.44 - 2.57 (m, 2 H), 2.63 (s, 3 H), 2.99 - 3.96 (m, 6 H), 4.10 – 4.65 (br. b., 2 H), 5.24 (s, 2 H), 6.96 - 7.08 (m, 2 H), 7.18 - 7.27 (m, 1 H), 7.31 - 7.43 (m, 2 H), 7.88 (d, J=8.6 Hz, 1 H), 10.17 - 11.21 (br.band, 1 H), 11.46 - 13.30 (br.band, 1 H). LC-MS: Rt 1.44, [M+H] 457.

3-{2-[4-(2-phenyl-cyclopropyl)-3-fluoro-phenyl]-6,7-dihydro-4H-oxazolo-[4,5-c]-pyridin-5-yl}-cyclobutane carboxylic acid (459 trans).

2-Phenyl-cyclopropyl-trifluoroborane. 4,4,5,5-Tetramethyl-2-(2-phenyl-cyclopropyl)-[1,3,2]dioxaborolane (3.1g, 12.7mmol) in MeOH (48ml) and water (12ml) was cooled to 0°C. Potassium bifluoride (6.96g, 88.9mmol, 7eq) was added and the mixture was stirred for 16hrs at room temperature. The mixture was concentrated *in vacuo* and the residue was co-evaporated with acetonitril (3x40ml). The residue was washed with warm acetonitril (3x40ml) and the combined actonitril washings were concentrated to give 2-phenyl-cyclopropyl-trifluoroborane (2g, 71%). This trifluoroborane derivative (1.8g, 8.2mmol,1.3mmol) was dissolved in degassed toluene/water (137.5ml, 10/1, v/v) and potassium phosphate tribasic (5.2g, 24.7mmol, 3.9eq) was added. The mixture was stirred for 15 minutes and to this solution was added compound **28** (Rb=3F, 2.5g, 6.3mmol), palladium(II) acetate (71.2mg, 0.3mmol, 0.05eq) and 2-dicyclohexylphosphino-2,6-di-isopropoxy-1,1-biphenyl (296mg, 0.6mmol, 0.1eq, RuPhos). The mixture was stirred at 115°C for 3 hrs after which time TLC analysis (Et_2O/PA, 3/7, v/v) revealed the reaction to be complete. The mixture was allowed to reach room temperature and was diluted with EtOAc (300ml) and the solution was washed with water. The organic layer was dried on $MgSO_4$ and concentrated *in vacuo* to give an oil which was purified by silica gel column chromatography (Et_2O/PA, 3/7, v/v) to give pure **530** (2.54g, 92%) as a white solid. The BOC in **530** was removed under acidic conditions to give **531**, which was transformed to **532** under conditions for introducing the Rc-tail as described above. Compound **532** (pure trans, 0.45g, 0.94mmol) was dissolved in 20ml 4M

HCl in dioxan. The solution was stirred for 16hrs at room temperature. The mixture was concentrated *in vacuo* and stirred in diethyl ether. The resulting solid was filtered to give compound **459** (trans, 0.36g, 83%). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 1.27 (d, J=7.3 Hz, 3 H), 1.51 - 1.70 (m, 2 H), 2.26 - 2.40 (m, 2 H), 3.05 - 3.23 (m, 3 H), 3.27 (dd, J=13.1, 4.8 Hz, 2 H), 3.55 - 3.84 (m, 3 H), 4.37 (br. s., 2 H), 7.14 - 7.23 (m, 3 H), 7.26 - 7.35 (m, 3 H), 7.64 (d, J=11.1, Hz, 1 H), 7.74 (d, J=8.3 Hz, 1 H), 10.00 - 11.79 (br.band, 1 H), 11.93 - 13.53 (br.band, 1 H). LC-MS: Rt 1.36, [M+H] 433.

4-(2-{4-[2-(3,5-Difluoro-phenyl)-vinyl]-phenyl}-6,7-dihydro-4H-oxazolo-[4,5c]-pyridin-5-yl)-butyric acid (451). A solution of compound **28** (Rb=H, 4.3g, 11.1mmol), trans-2-(3,5-difluorophenyl)vinyl boronic acid pinacol ester (4.09ml, 16.7mmol, 1.5eq) in toluene (100ml) was degassed. To this solution was added chloro (2-dicyclohexylphosphino-2,4,6-tri-isopropopyl-1,1-biphenyl)[2-(2-aminoethyl)pentyl]palladium(II) methyl-tbutyl ether adduct (183.8mg, 0.22mmol, 0.02eq) and potassium phosphate tribasic (7.08g, 33.3mmol, 3.0eq) was added. The mixture was stirred for 24hrs at 115°C after which time LC-MS analysis revealed the reaction to be complete. The mixture was allowed to reach room temperature and was diluted with EtOAc (300ml) and the solution was washed with a 5% NaHCO3 solution. The organic layer was dried on $MgSO_4$ and concentrated *in vacuo* to give an oil which was purified by silica gel column chromatography (DCM/MeOH, 99.5/0.5, v/v) to give pure **533** (3.4g, 69%) as a white solid. The BOC in **533** was removed under acidic conditions to give **534**, which was transformed to **535** under conditions for introducing the Rc-tail as described above. Compound **535** (0.45g, 0.94mmol) was dissolved in 20ml 4M HCl in dioxan. The solution was stirred for 16hrs at 55°C. The mixture was concentrated *in vacuo* and stirred in diethyl ether. The resulting solid was filtered to give compound **451** (0.426g, 95%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.02 - 2.14 (m, 2 H) 2.40 (t, J=7.1 Hz, 2 H) 3.07 - 3.18 (m, 1 H) 3.23 - 3.38 (m, 3 H) 3.65 - 3.72 (m, 1H) 3.78 - 3.89 (m, 1 H) 4.23 – 4.35 (m, 1 H) 4.41 - 4.54 (m, 1 H) 6.96 - 7.05 (m, 1 H) 7.28 - 7.37 (m, 3 H) 7.41 (d, J=16.4 Hz, 1 H) 7.74 (d, J=8.3 Hz, 2 H) 7.98 (d, J=8.3 Hz, 2 H) 11.25 (br. s., 1 H). LC-MS: Rt 1.39, [M+H] 425.

4-(2-{4-[2-(3,5-Difluoro-phenyl)-ethyl]-phenyl}-6,7-dihydro-4H-oxazolo[4,5c] pyridin-5-yl)-butyric acid (452). Compound **533** (1.5g, 3.4mmol) was dissolved in MeOH (250ml). To the suspension was added palladium hydroxide on carbon (20%, 0.2g, 1,42mmol, 0.42eq). The mixture was placed under a blanket of hydrogen at room temperature and 1 atmosphere. After 24 hrs, LC-MS analysis revealed the reaction to be complete (TLC analysis: DCM/MeOH, 99/1, v/v). The mixture was filtered over Hyflo and the filtrate was concentrated *in vacuo* to give **536** (1.43g, 95%) as an oil. Compound **536** was converted to the corresponding tail derivative **538** as described above. The tBu or methyl esters were deprotected in a similar fashion as described above. Compound **452**: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.99 - 2.13 (m, 2 H) 2.39 (t, *J*=7.2 Hz, 2 H) 2.96 (s, 4 H) 3.18 (broad band, 2 H) 3.25 - 3.33 (m, 2 H) 3.51 - 3.95 (broad band, 2 H) 4.34 (br. s., 2 H) 6.85 - 6.98 (m, 3 H) 7.37 (d, *J*=8.3 Hz, 2 H) 7.88 (d, *J*=8.3 Hz, 2 H) 10.67 - 11.61 (broad band, 1 H) 11.86 - 12.71 (broad band, 1 H). LC-MS: Rt 1.36, [M+H] 427.

Preparation of the pure enantiomers of chiral compounds 1 and 2. Compounds having for example a methyl substitution in the Rc-tail give mixtures of enantiomers as the testcompound. Separation of this mixture in the pure enantiomers can be performed by chiral HPLC techniques from the moment that the chiral tail is introduced in the core, *i.e.* of for example compounds **1, 2, 7, 8, 9, 21, 22, 23.** For those skilled in the art, it is obvious that small changes in the core can lead to a different behavior in the chiral separation process. Therefore, each compound has been screened using a broad set of conditions such as chiral column material and eluents. In that way, for each compound was determined in which stage and under which chiral separation conditions the separation would be most succesfull. The separated endproducts were named as Rel1 and Rel2 as the absolute configuration was not yet determined. This process is illustrated by the following typical examples.

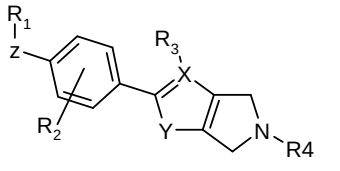
3-[2-(4-Hydroxy-phenyl)-4,5,6,7-tetrahydro-oxazolo[4,5-c]pyridine]-2-methyl-propionic acid t-butyl ester (+) and (-) enantiomers of 22b (Rb=H). Compound **22b** was made as an enantiomeric mixture as described in Scheme 5. Enantiomeric mixture was separated by chiral HPLC using the following chiral HPLC system. Stationary phase: Chiralcel OD-H (5micron);

mobile phase : n-heptane/2-propanol (90/10, v/v) +0.1%TFA; flowrate 1ml/min; detection by UV at 280nm. Compound **22b-rel1**: $[\alpha]^{25}$= +37.1; ^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm 1.14 (d, *J*=6.8 Hz, 3 H) 1.43 (s, 9 H) 2.54 (dd, *J*=12.1, 6.2 Hz, 1 H) 2.60 - 2.70 (m, 1 H) 2.73 – 2.77 (m, 2 H) 2.80 - 2.97 (m, 3 H) 3.49 (d, *J*=14.1 Hz, 1 H) 3.60 (d, *J*=14.1 Hz, 1 H) 6.71 - 6.96 (br.band, 1 H) 6.84 (d, *J*=8.6 Hz, 2 H) 7.82 (d, *J*=8.6 Hz, 2 H). Compound **22-rel2**: $[\alpha]^{25}$= -35.9; ^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm 1.14 (d, *J*=6.8 Hz, 3 H) 1.42 (s, 9 H) 2.53 (dd, *J*=12.4, 6.2 Hz, 1 H) 2.60 - 2.70 (m, 1 H) 2.72 - 2.79 (m, 2 H) 2.80 - 2.96 (m, 3 H) 3.49 (d, *J*=14.1 Hz, 1 H) 3.59 (d, *J*=14.1 Hz, 1 H) 6.83 (d, *J*=8.6 Hz, 2 H) 7.45 - 7.75 (br.band, 1 H) 7.79 (d, *J*=8.6 Hz, 2 H).

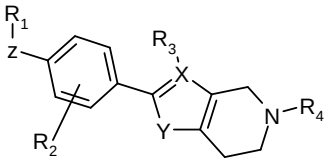
3-[2-(4-hydroxy-3-F-phenyl)-4,5,6,7-tetrahydro-oxazolo[4,5-c]pyridine]-2-methyl-propionic acid t-butyl ester (+) and (-) enantiomers of 22b (Rb=3F). Compound **22b** (Rb=H) was made as an enantiomeric mixture as described in Scheme 5. Enantiomeric mixture was separated by chiral HPLC using the following chiral HPLC system. Stationary phase: Chiralcel OD-H (5micron); mobile phase : n-heptane/2-propanol (90/10, v/v) +0.1%TFA; flowrate 1ml/min; detection by UV at 280nm. Compound **22b-rel1**: $[\alpha]^{25}$= -36.4 (MeOH). Compound **22-rel2**: $[\alpha]^{25}$= +34.8; ^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm 1.15 (d, *J*=6.8 Hz, 3 H) 1.43 (s, 9 H) 2.54 (dd, *J*=11.9, 6.2 Hz, 1 H) 2.60 - 2.71 (m, 1 H) 2.73 – 2.79 (m, 2 H) 2.81 - 2.96 (m, 3 H) 3.49 (d, *J*=14.1 Hz, 1 H) 3.59 (d, *J*=14.1 Hz, 1 H) 4.88 - 6.89 (br.band, 1 H) 7.02 (t, *J*=8.5 Hz, 1 H) 7.61 - 7.73 (m, 2 H).

3-{2-[4-(4-2,3-diF-benzyloxy)-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-butyric acid rel 1 and rel 2 of compound 175. The tbutylprotected derivative of **175** was separated in its pure enantiomers by chiral HPLC. Stationary phase: Chiralpak IC (5μ); column code no.: WJH022830; dimensions: 250x4.6 mm; Mobile phase: n-Heptane/DCM/ethanol (50/50/1) + 0.1% DEA; flowrate: 1 ml/min; Injection: 5 μl; Detection: UV(290 nm). Deprotection of thus obtained pure enantiomers resulted in the isolation of the testcompounds **426** and **425.** Compound **426**, rel1: $[\alpha]^{25}$= -22 (MeOH), Rt 1.3, [M+H] 429. Compound **425** rel2: $[\alpha]^{25}$= +19.9 (MeOH); Rt 1.3, [M+H] 429.

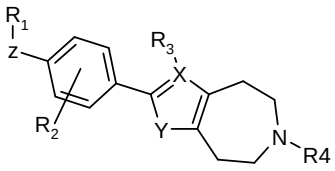
Table 1



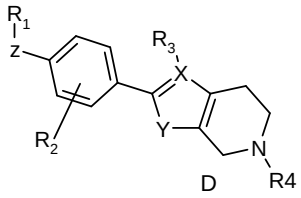
A



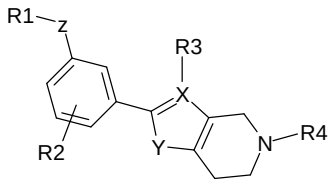
B



C



D



E

No.	R1	Z	R2	X	Y	R3	Structure	R4	Rt (min) LC-MS
31	4Cl-phenyl	CH_2N	H	C	O	H	B	$-(CH_2)_2$-COOH	1,37
32	cyclohexyl	CH_2O	H	C	O	H	B	$-(CH_2)_3$-COOH	1,46
33	2F-phenyl	CH_2O	H	C	O	H	B	$-(CH_2)_2$-COOH	1,39
34	2,6diCl-phenyl	CH_2O	H	C	O	H	B	$-(CH_2)_3$-COOH	1,4
35	2F-phenyl	CH_2O	H	C	O	H	B	$-(CH_2)_3$-COOH	1.37
**36	2F-3pyridyl	CH_2O	H	C	O	H	B	$-(CH_2)_2$-COOH	1,21
37	phenyl	CH_2	H	C	O	H	B	$-(CH_2)_2$-COOH	1,38
38	2F-phenyl	CH_2O	H	N	S		D	$-(CH_2)_2$-COOH	1,3
39	phenyl	N	H	C	O	H	B	$-(CH_2)_2$-COOH	1,31
40	2,6diCl-phenyl	CH_2O	H	N	S		D	$-(CH_2)_3$-COOH	1,35
41	phenyl	C=C	H	C	O	H	B	$-(CH_2)_2$-COOH	1,42
42	phenyl	$(CH_2)_2$	H	C	O	H	B	$-(CH_2)_2$-COOH	1,45
43	phenyl	SO_2	H	C	O	H	B	$-(CH_2)_2$-COOH	#

44	**phenyl**	**S**	**H**	**C**	**O**	**H**	**B**	**-$(CH_2)_2$-COOH**	**1,43**
45	**benzyl**	**S**	**H**	**C**	**O**	**H**	**B**	**-$(CH_2)_2$-COOH**	**1,41**
46	**phenyl**	**O**	**H**	**C**	**O**	**H**	**B**	**-$(CH_2)_2$-COOH**	**1,37**
47	**phenyl**	**CH_2O**	**H**	**N**	**O**		**B**	**-$(CH_2)_2$-COOH**	**1,32**
48	**2F-phenyl**	**CH_2O**	**2Cl**	**C**	**O**	**H**	**B**	**-$(CH_2)_2$-COOH**	**1,43**
49	**phenyl**	**CH_2SO_2**	**H**	**C**	**O**	**H**	**B**	**-$(CH_2)_2$-COOH**	**1,16**
****50**	**phenyl**	**CH_2O**	**3-pyr**	**C**	**O**	**H**	**B**	**-$(CH_2)_2$-COOH**	**1,27**
51	**2F-phenyl**	**CH_2O**	**3F**	**C**	**O**	**H**	**B**	**-$(CH_2)_2$-COOH**	**1,34**
52	**phenyl**	**C=O**	**H**	**C**	**O**	**H**	**B**	**-$(CH_2)_2$-COOH**	**1,23**
53	**phenyl**	**CH_2O**	**H**	**N**	**O**		**B**	**-$(CH_2)_3$-COOH**	**1,17**
54	**2F-phenyl**	**CH_2O**	**H**	**N**	**O**		**B**	**-$(CH_2)_2$-COOH**	**1,18**
55	**2,3-diF-phenyl**	**CH_2O**	**H**	**N**	**O**		**B**	**-$(CH_2)_2$-COOH**	**1,19**
56	**2F-phenyl**	**CH_2O**	**H**	**N**	**O**		**B**	**-$(CH_2)_3$-COOH**	**1,15**
57	**2,3-diF-phenyl**	**CH_2O**	**H**	**N**	**O**		**B**	**-$(CH_2)_3$-COOH**	**1,16**
58	**4Cl-phenyl**	**CH_2O**	**H**	**N**	**O**		**B**	**-$(CH_2)_2$-COOH**	**1,37**
59	**2F-phenyl**	**CH(Me)-O**	**H**	**C**	**O**	**H**	**B**	**-$(CH_2)_3$-COOH**	**#**
60	**2,6-diCl-phenyl**	**CH_2O**	**H**	**N**	**O**		**B**	**-$(CH_2)_3$-COOH**	**1,32**
61	**4Cl-phenyl**	**CH_2O**	**H**	**N**	**O**		**B**	**-$(CH_2)_3$-COOH**	**1,29**
62	**2,6-diCl-phenyl**	**CH_2O**	**H**	**N**	**O**		**B**	**-$(CH_2)_2$-COOH**	**1,36**
63	**2F-phenyl**	**NH**	**H**	**C**	**O**	**H**	**E**	**-$(CH_2)_2$-COOH**	**1,33**
64	**2F-phenyl**	**CH_2O**	**H**	**C**	**N**	**H**	**A**	**-$(CH_2)_2$-COOH**	**1,32**
65	**2F-phenyl**	**bond**	**H**	**C**	**O**	**H**	**E**	**-$(CH_2)_2$-COOH**	**1,33**
66	**2F-phenyl**	**O**	**H**	**C**	**O**	**H**	**E**	**-$(CH_2)_2$-COOH**	**1,34**
67	**2F-phenyl**	**CH_2O**	**H**	**C**	**O**	**H**	**E**	**-$(CH_2)_2$-COOH**	**1,36**
68	**2F-phenyl**	**CH_2N**	**H**	**C**	**O**	**H**	**E**	**-$(CH_2)_2$-COOH**	**1,29**
69	**2F-phenyl**	**CH_2O**	**H**	**C**	**O**	**CH_3**	**B**	**-$(CH_2)_2$-COOH**	**1,38**

70	2F-phenyl	CH_2O	H	C	O	H	C	$-(CH_2)_3$-COOH	1,35
71	2F-phenyl	CH_2O	H	C	O	H	A	$-(CH_2)_2$-COOH	1,32
72	2F-phenyl	CH_2O	H	C	O	H	D	$-(CH_2)_2$-COOH	1,36
73	2F-phenyl	CH_2O	2F	C	O	H	B	$-(CH_2)_3$-COOH	1.35
74	$4CF_3$-phenyl	CH_2O	H	C	O	H	B	$-(CH_2)_2$-COOH	#
75	phenyl	CH_2O	H	C	O	H	B	$-CH_2-CH(CH_3)$-COOH	1,46
76	phenyl	CH_2O	H	C	O	H	B	$-CH(CH_3)-CH_2$-COOH	1,46
77	4Cl-phenyl	CH_2O	H	C	O	H	B	$-CH_2-CH(CH_3)$-COOH	1,56
78	4Cl-phenyl	CH_2O	H	C	O	H	B	$-CH_2-C(CH_3)_2$-COOH	1,76
79	2F-phenyl	cyclo-propyl	H	C	O	H	B	$-(CH_2)_2$-COOH	1,46
80	2F-phenyl	OCH_2	H	C	O	H	B	$-(CH_2)_2$-COOH	1,39
81	phenyl	CH_2O	2F	N	O		B	$-(CH_2)_3$-COOH	1,54
82	phenyl	C≡C	H	C	O	H	E	$-(CH_2)_2$-COOH	1,63
83	2F-phenyl	C≡C	H	C	O	H	E	$-(CH_2)_2$-COOH	1,65
84	3F,5Cl-phenyl	CH_2O	H	C	O	H	B	$-(CH_2)_2$-COOH	1,8
85	$4CF_3$-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_3$-COOH	1,77
86	4Cl-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_3$-COOH	1,65
87	2F-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_3$-COOH	1,58
88	2,3-diF-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_3$-COOH	1,59
89	2F-phenyl	CH_2O	$2CH_3$	N	O		B	$-(CH_2)_3$-COOH	1,61
90	phenyl	CH_2O	$2CH_3$	N	O		B	$-(CH_2)_3$-COOH	1,69
91	4Cl-phenyl	CH_2O	$2CH_3$	N	O		B	$-(CH_2)_3$-COOH	1,75
92	2,3-diF-phenyl	O	$2CH_3$	N	O		B	$-(CH_2)_3$-COOH	1,77
93	3,4-diF-phenyl	O	$2CH_3$	N	O		B	$-(CH_2)_3$-COOH	1,8

94	4CF_3-phenyl	O	2CH_3	N	O		B	-$(CH_2)_3$-COOH	1,98
95	2CH_3-phenyl	O	H	N	O		B	-$(CH_2)_2$-COOH	2,09*
96	4CH_3-phenyl	CH_2O	H	N	O		B	-$(CH_2)_2$-COOH	1,97*
97	4CH_3O-phenyl	CH_2O	H	N	O		B	-$(CH_2)_2$-COOH	1,93*
98	4CF_3-phenyl	CH_2O	H	N	O		B	-$(CH_2)_2$-COOH	2,1*
99	4CF_3O-phenyl	CH_2O	H	N	O		B	-$(CH_2)_2$-COOH	2,08*
100	4F-phenyl	CH_2O	H	N	O		B	-$(CH_2)_2$-COOH	1,98*
101	3CH_3O-phenyl	CH_2O	H	N	O		B	-$(CH_2)_2$-COOH	1,86*
102	3F-phenyl	CH_2O	H	N	O		B	-$(CH_2)_2$-COOH	1,87*
103	3CF_3O-phenyl	CH_2O	H	N	O		B	-$(CH_2)_2$-COOH	2*
104	3CF_3-phenyl	CH_2O	H	N	O		B	-$(CH_2)_2$-COOH	2,04*
105	2,6diF-phenyl	CH_2O	H	N	O		B	-$(CH_2)_2$-COOH	1,82*
106	2,5diF-phenyl	CH_2O	H	N	O		B	-$(CH_2)_2$-COOH	1,83*
107	2F,6Cl-phenyl	CH_2O	H	N	O		B	-$(CH_2)_2$-COOH	1,84*
108	2,3,6triF-phenyl	CH_2O	H	N	O		B	-$(CH_2)_2$-COOH	1,82*
109	3,4diF-phenyl	CH_2O	H	N	O		B	-$(CH_2)_2$-COOH	1,84*
110	2,4diF-phenyl	CH_2O	H	N	O		B	-$(CH_2)_2$-COOH	1,84*
111	3CH_3-phenyl	CH_2O	H	N	O		B	-$(CH_2)_2$-COOH	1,86*
112	3,5diF-phenyl	CH_2O	H	N	O		B	-$(CH_2)_2$-COOH	1,85*
113	2CF3-phenyl	CH_2O	H	N	O		B	-$(CH_2)_2$-COOH	1,88*
114	3,4diF-phenyl	CH_2O	2F	N	O		B	-$(CH_2)_3$-COOH	1,68
115	2F-phenyl	CH_2O	2CH_3	N	O		B	-$(CH_2)_2$-COOH	1,53
116	phenyl	CH_2O	2CH_3	N	O		B	-$(CH_2)_2$-COOH	1,53
117	4Cl-phenyl	CH_2O	2CH_3	N	O		B	-$(CH_2)_2$-COOH	1,59
118	2,3diF-phenyl	CH_2O	2CH_3	N	O		B	-$(CH_2)_2$-COOH	1,52
119	3,4diF-phenyl	CH_2O	2CH_3	N	O		B	-$(CH_2)_2$-COOH	1,74

120	4CF3-phenyl	CH_2O	$2CH_3$	N	O		B	$-(CH_2)_2$-COOH	1,8
121	$4CH_3$-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,86*
122	$4CF_3$-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,89*
123	$4CF_3O$-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,93*
124	4F-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,83*
125	$3CH_3O$-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,82*
126	3F-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,82*
127	4Cl-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,88*
128	$3CF_3O$-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,91*
129	2F-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,82*
130	$3CF_3$-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,9*
131	$2CH_3$-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,85*
132	2,6diF-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,8*
133	2,5diF-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,84*
134	2F,6Cl-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,89*
135	2,3,6triF-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,84*
136	2,6diCl-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,87*
137	2,3diF-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,84*
138	3,4diF-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,86*
139	2,4diF-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,86*
140	2,5diCl-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,91*
141	$3CH_3$-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,86*
142	3,5diF-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,84*
143	2Cl-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,9*
144	$2CF_3$-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,89*
145	3,4diCl-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,95*

146	phenyl	CH_2O	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	1,48
147	phenyl	CH_2O	H	N	O		D	$-(CH_2)_2-COOH$	1,28
148	3,4diF-phenyl	CH_2O	3Me	C	O		B	$-(CH_2)_3-COOH$	1,68
149	$4CF_3$-phenyl	CH_2O	H	N	O		B	$-(CH_2)_3-COOH$	1,63
150	$2CH_3$-phenyl	CH_2O	H	N	O		B	$-(CH_2)_3-COOH$	1,48
151	3,4diF-phenyl	CH_2O	H	N	O		B	$-(CH_2)_3-COOH$	1,56
152	4F-phenyl	CH_2O	H	N	O		B	$-(CH_2)_3-COOH$	1,55
153	3,5diF-phenyl	CH_2O	H	N	O		B	$-(CH_2)_3-COOH$	1,48
154	2,3diF-phenyl	CH_2O	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	1,32
155	3,4diF-phenyl	CH_2O	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	1,63
156	$4CF_3$-phenyl	CH_2O	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	1,82
157	4Cl-phenyl	CH_2O	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	1,72
158	2F-phenyl	CH_2O	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	1,44
159	phenyl	CH_2O	H	N	O		B	$-CH(CH_3)-CH_2-COOH$	1,87*
160	$4CF_3$-phenyl	CH_2O	H	N	O		B	$-CH(CH_3)-CH_2-COOH$	2,03*
161	$4CF_3O$-phenyl	CH_2O	H	N	O		B	$-CH(CH_3)-CH_2-COOH$	2,03*
162	4F-phenyl	CH_2O	H	N	O		B	$-CH(CH_3)-CH_2-COOH$	1,89*
163	$3CH_3O$-phenyl	CH_2O	H	N	O		B	$-CH(CH_3)-CH_2-COOH$	1,85*
164	3F-phenyl	CH_2O	H	N	O		B	$-CH(CH_3)-CH_2-COOH$	1,89*
165	4Cl-phenyl	CH_2O	H	N	O		B	$-CH(CH_3)-CH_2-COOH$	1,94*
166	$3CF_3O$-phenyl	CH_2O	H	N	O		B	$-CH(CH_3)-CH_2-COOH$	1,97*
167	2F-phenyl	CH_2O	H	N	O		B	$-CH(CH_3)-CH_2-COOH$	1.92*
168	$3CF_3$-phenyl	CH_2O	H	N	O		B	$-CH(CH_3)-CH_2-COOH$	2*

169	**3Cl-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1,95***
170	**2CH3-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1,91***
171	**4CH3-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1,92***
172	**2,6-diF-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1,89***
173	**2F,6Cl-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1,92***
174	**2,6diCl-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1,97***
175	**2,3-diF-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1,3**
176	**3,4-diF-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1,89***
177	**2,4-diF-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1,89***
178	**2,5-diCl-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1,99***
179	**3CH3-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1,93***
180	**3,5-diF-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1,9***
181	**2CF3-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1,96***
182	**4-CH3O-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**2.0***
183	**3,4-diCl-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1,6**
****184**	**4pyridinyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1,51***
185	**2F,4Cl-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1,95***
186	**2F,4CH3-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1,95***
187	**4CN-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1,84***
188	**2,3,6-triF-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1,89***
189	**2,5-diF-phenyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**1.89***
190	**chexyl**	**CH2O**	**H**	**N**	**O**		**B**	**-CH(CH3)-CH2-COOH**	**2,05***
191	**2Cl,4F-phenyl**	**CH2O**	**H**	**C**	**O**	**H**	**B**	**-(CH2)3-COOH**	**1,43**
192	**2,3-diCl-phenyl**	**CH_2O**	**H**	**C**	**O**	**H**	**B**	**-$(CH_2)_3$-COOH**	**1,48**
193	**phenyl**	**CH_2O**	**H**	**N**	**O**		**B**	**-$(CH_2)_3$-COOH**	**1,24**

194	2F-phenyl	CH_2O	H	N	O		B	-C[$(CH_2)_2$]-CH_2-COOH	1,87
195	4CF_3O-phenyl	CH_2O	2F	N	O		B	-$(CH_2)_3$-COOH	1,47
196	4F-phenyl	CH_2O	2F	N	O		B	-$(CH_2)_3$-COOH	1,35
197	phenyl	CH_2O	3CH_3O	N	O		B	-$(CH_2)_2$-COOH	1,3
198	4Cl-phenyl	CH_2O	3CH_3O	N	O		B	-$(CH_2)_2$-COOH	1,37
199	2,4diF-phenyl	CH_2O	2F	N	O		B	-$(CH_2)_3$-COOH	1,36
200	4Me-phenyl	CH_2O	2F	N	O		B	-$(CH_2)_3$-COOH	1,39
201	3,4diF-phenyl	CH_2O	3CH_3O	N	O		B	-$(CH_2)_2$-COOH	1,35
202	3,5diF-phenyl	CH_2O	3CH_3O	N	O		B	-$(CH_2)_2$-COOH	1,35
203	4CF3-phenyl	CH_2O	3CH_3O	N	O		B	-$(CH_2)_2$-COOH	1,41
204	2F-phenyl	CH_2O	3CH_3O	N	O		B	-$(CH_2)_2$-COOH	1,28
205	2,3diF-phenyl	CH_2O	3CH_3O	N	O		B	-$(CH_2)_2$-COOH	1,32
206	4CF_3-phenyl	CH_2O	3F	N	O		B	-$(CH_2)_3$-COOH	2,05*
207	4F-phenyl	CH_2O	3F	N	O		B	-$(CH_2)_3$-COOH	1,97*
208	3CH_3O-phenyl	CH_2O	3F	N	O		B	-$(CH_2)_3$-COOH	1,25*
209	3F-phenyl	CH_2O	3F	N	O		B	-$(CH_2)_3$-COOH	2,1*
210	3CF_3O-phenyl	CH_2O	3F	N	O		B	-$(CH_2)_3$-COOH	2,06*
211	4Cl-phenyl	CH_2O	3F	N	O		B	-$(CH_2)_3$-COOH	2,03*
212	2F-phenyl	CH_2O	3F	N	O		B	-$(CH_2)_3$-COOH	1,96*
213	3Cl-phenyl	CH_2O	3F	N	O		B	-$(CH_2)_3$-COOH	2*
214	4CH_3-phenyl	CH_2O	3F	N	O		B	-$(CH_2)_3$-COOH	2,02*
215	2,6diF-phenyl	CH_2O	3F	N	O		B	-$(CH_2)_3$-COOH	1,94*
216	2,3,6triF-phenyl	CH_2O	3F	N	O		B	-$(CH_2)_3$-COOH	1,98*
217	2,6diCl-phenyl	CH_2O	3F	N	O		B	-$(CH_2)_3$-COOH	2,03*
218	2,3diF-phenyl	CH_2O	3F	N	O		B	-$(CH_2)_3$-COOH	2,03*
219	2,5diCl-phenyl	CH_2O	3F	N	O		B	-$(CH_2)_3$-COOH	2,06*

220	3,4diF-phenyl	CH_2O	3F	N	O		B	$-(CH_2)_3$-COOH	2*
221	3,4diF-phenyl	CH_2O	3F	N	O		B	$-(CH_2)_3$-COOH	1,98*
222	$3CH_3$-phenyl	CH_2O	3F	N	O		B	$-(CH_2)_3$-COOH	2,03*
223	$2CF_3$-phenyl	CH_2O	3F	N	O		B	$-(CH_2)_3$-COOH	2,03*
224	$4CH_3O$-phenyl	CH_2O	3F	N	O		B	$-(CH_2)_3$-COOH	1,96*
225	3,5diF-phenyl	CH_2O	3F	N	O		B	$-(CH_2)_3$-COOH	1,99*
226	2,4diF-phenyl	CH_2O	3F	N	O		B	$-(CH_2)_3$-COOH	1,98*
227	3,4diCl-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_3$-COOH	1,42
228	$2F,4CH_3$-phenyl	CH_2O	3F	N	O		B	$-(CH_2)_3$-COOH	1.86*
229	3,4diCl-phenyl	CH_2O	3F	N	O		B	$-(CH_2)_3$-COOH	2,07*
230	3,5diF-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_3$-COOH	1,33
231	$2CH_3$-phenyl	CH_2O	3F	N	O		B	$-(CH_2)_3$-COOH	1,99*
232	2Cl-phenyl	CH_2O	3F	N	O		B	$-(CH_2)_3$-COOH	2,01*
233	4F-phenyl	CH_2O	$2CH_3$	N	O		B	$-(CH_2)_2$-COOH	1,38
234	2,4diF-phenyl	CH_2O	$2CH_3$	N	O		B	$-(CH_2)_2$-COOH	1,38
235	$3CF_3$-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_3$-COOH	1,39
236	$4CF_3O$-phenyl	CH_2O	$3CH_3O$	N	O		B	$-(CH_2)_2$-COOH	1,44
237	2F-phenyl	CH_2O	$3CH_3O$	N	O		B	$-(CH_2)_3$-COOH	1,26
238	$3CF_3$-phenyl	CH_2O	3F	N	O		B	$-(CH_2)_3$-COOH	2,06*
239	2F, 6Cl-phenyl	CH_2O	3F	N	O		B	$-(CH_2)_3$-COOH	1,99*
240	2,3diF-phenyl	CH_2O	$3CH_3O$	N	O		B	$-(CH_2)_3$-COOH	1,26
241	$3CF_3O$-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_3$-COOH	1,42
242	2F-phenyl	CH_2O	H	N	O		B	$-CH_2-CF_2$-COOH	2,16
243	$4CH_3$-phenyl	CH_2O	$2CH_3$	N	O		B	$-(CH_2)_3$-COOH	1,37
244	4F-phenyl	CH_2O	$2CH_3$	N	O		B	$-(CH_2)_3$-COOH	1,33
245	2,4diF-phenyl	CH_2O	$2CH_3$	N	O		B	$-(CH_2)_3$-COOH	1,33

246	3,4diF-phenyl	CH_2O	$3CH_3O$	N	O		B	$-(CH_2)_3$-COOH	1,3
247	3,5diF-phenyl	CH_2O	$3CH_3O$	N	O		B	$-(CH_2)_3$-COOH	1,3
248	4Cl-phenyl	CH_2O	$3CH_3O$	N	O		B	$-(CH_2)_3$-COOH	1,32
249	$4CF_3$-phenyl	CH_2O	$3CH_3O$	N	O		B	$-(CH_2)_3$-COOH	1,38
250	$4CF_3O$-phenyl	CH_2O	$3CH_3O$	N	O		B	$-(CH_2)_3$-COOH	1,38
251	$3CF_3$-phenyl	CH_2O	$2CH_3$	N	O		B	$-(CH_2)_3$-COOH	1,4
252	3,4diCl-phenyl	CH_2O	$2CH_3$	N	O		B	$-(CH_2)_3$-COOH	1,45
253	$3CF_3O$-phenyl	CH_2O	$2CH_3$	N	O		B	$-(CH_2)_3$-COOH	1,48
254	4Cl-phenyl	CH_2O	2Cl	N	O		B	$-(CH_2)_3$-COOH	1,38
255	3,4diF-phenyl	CH_2O	2Cl	N	O		B	$-(CH_2)_3$-COOH	1,36
256	3,5diF-phenyl	CH_2O	2Cl	N	O		B	$-(CH_2)_3$-COOH	1,39
257	$4CF_3$-phenyl	CH_2O	2Cl	N	O		B	$-(CH_2)_3$-COOH	1,42
258	2F-phenyl	CH_2O	3F	N	O		B	$-(CH_2)_2$-COOH	1,35
259	4CF3-phenyl	CH_2O	3F	N	O		B	$-(CH_2)_2$-COOH	3,02
260	3,5diF-phenyl	CH_2O	3F	N	O		B	$-(CH_2)_2$-COOH	2,98
261	2F-phenyl	CH_2O	2Cl	N	O		B	$-(CH_2)_3$-COOH	2,94
262	3,5diF-phenyl	CH_2O	$2CH_3$	N	O		B	$-(CH_2)_3$-COOH	1,66
263	2,3diF-phenyl	CH_2O	2Cl	N	O		B	$-(CH_2)_3$-COOH	1,33
264	$4CF_3O$-phenyl	CH_2O	2Cl	N	O		B	$-(CH_2)_3$-COOH	1,46
265	3,5diCl-phenyl	CH_2O	2Cl	N	O		B	$-(CH_2)_3$-COOH	1,49
266	3,5diF-Phenyl	CH_2O	2Cl	N	O		B	$-(CH_2)_2$-COOH	1,42
267	$4CF_3$-phenyl	CH_2O	2Cl	N	O		B	$-(CH_2)_2$-COOH	1,5
268	2F-phenyl	CH_2O	2Cl	N	O		B	$-(CH_2)_2$-COOH	1,36
269	2,6diCH3-phenyl	CH_2O	2F	N	O		B	$-(CH_2)_2$-COOH	1,36
270	2,3diF-phenyl	CH_2O	H	N	O		B	$-CH_2-C[(CH_2)_2]$-COOH	1,56

271	4CF_3-phenyl	CH_2O	2F	N	O		B	-CH_2-CH(CH_3)-COOH	1,56
272	2,6diCH_3-phenyl	CH_2O	2CH_3	N	O		B	-(CH_2)$_2$-COOH	1,46
273	3,4diF-phenyl	CH_2O	2CH_3O	N	O		B	-CH(CH_3)-CH_2-COOH	1,42
274	4CF_3-phenyl	CH_2O	2CH_3O	N	O		B	-CH(CH_3)-CH_2-COOH	1,51
275	2F-phenyl	CH_2O	2CH_3O	N	O		B	-CH(CH_3)-CH_2-COOH	1,37
276	3,5diF-phenyl	CH_2O	2CH_3O	N	O		B	-CH(CH_3)-CH_2-COOH	1,42
277	3,4diF-phenyl	CH_2O	H	N	O		B	-cyclobutyl-COOH	1,31
278	3,4diF-phenyl	CH_2O	H	N	O		B	-cyclobutyl-COOH	1,33
279	4Cl-phenyl	CH_2O	H	N	O		B	-cyclobutyl-COOH	1,36
280	4Cl-phenyl	CH_2O	H	N	O		B	-cyclobutyl-COOH	1,37
281	4F-phenyl	CH_2O	3Cl	N	O		B	-(CH_2)$_3$-COOH	2,03*
282	4CF_3-phenyl	CH_2O	3Cl	N	O		B	-(CH_2)$_3$-COOH	2,11*
283	2F-phenyl	CH_2O	3Cl	N	O		B	-(CH_2)$_3$-COOH	1,99*
284	4CF_3O-phenyl	CH_2O	3Cl	N	O		B	-(CH_2)$_3$-COOH	2,1*
285	4Cl-phenyl	CH_2O	3Cl	N	O		B	-(CH_2)$_3$-COOH	2,07*
286	3CF_3O-phenyl	CH_2O	3Cl	N	O		B	-(CH_2)$_3$-COOH	2,14*
287	3,4diF-phenyl	CH_2O	3Cl	N	O		B	-(CH_2)$_3$-COOH	2,03*
288	2,4diF-phenyl	CH_2O	3Cl	N	O		B	-(CH_2)$_3$-COOH	2,02*
289	3,4diCl-phenyl	CH_2O	3Cl	N	O		B	-(CH_2)$_3$-COOH	2,16*
290	3,5diF-phenyl	CH_2O	3Cl	N	O		B	-(CH_2)$_3$-COOH	2,03*
291	2Cl-phenyl	CH_2O	3Cl	N	O		B	-(CH_2)$_3$-COOH	2,05*
292	2F,4Cl-phenyl	CH_2O	3Cl	N	O		B	-(CH_2)$_3$-COOH	2,06*
293	3CF_3-phenyl	CH_2O	3Cl	N	O		B	-(CH_2)$_3$-COOH	2,09*
294	2,5diF-phenyl	CH_2O	3Cl	N	O		B	-(CH_2)$_3$-COOH	2,02*
295	4CF_3-phenyl	CH_2O	2F	N	O		B	-CH(CH_3)-CH_2-COOH	1,56

296	4CF_3O-phenyl	CH_2O	2CH_3O	N	O		B	-$CH(CH_3)$-CH_2-COOH	1,54
297	3,4diF-phenyl	CH_2O	2F	N	O		B	-CH_2-$CH(CH_3)$-COOH	1,47
298	3,4diF-phenyl	CH_2O	3Cl	N	O		B	-$(CH_2)_2$-COOH	1,44
299	2,3diF-phenyl	CH_2O	3Cl	N	O		B	-$(CH_2)_3$-COOH	2,01*
300	2,3diF-phenyl	CH_2O	H	N	NH		B	-CH_2-$CH(CH_3)$-COOH	1,1
301	2F-phenyl	CH_2O	H	N	O		B	-$(CH_2)_2$-COOH	1,38
302	2F-phenyl	CH_2O	H	N	O		B	-cyclobutyl-COOH	1,29
303	2F-phenyl	CH_2O	H	N	O		B	-cyclobutyl-COOH	1,3
304	4-fluoro-indan-2-yl	O	H	N	O		B	-$(CH_2)_2$-COOH	1,39
305	indan-2-yl	O	H	N	O		B	-$(CH_2)_2$-COOH	1,37
306	4CF_3O-phenyl	CH_2O	H	N	O		B	-cyclobutyl-COOH	1,41
307	4CF_3O-phenyl	CH_2O	H	N	O		B	-cyclobutyl-COOH	1,43
308	indan-1-yl	O	H	N	O		B	-$(CH_2)_2$-COOH	1,39
309	4-fluoro-indan-1-yl	O	H	N	O		B	-$(CH_2)_2$-COOH	1,4
310	4Cl-phenyl	CH_2O	3Cl	N	O		B	-$(CH_2)_2$-COOH	1,48
311	3,4diF-phenyl	CH_2O	2F	N	O		B	-$CH(CH_3)$-CH_2-COOH	1,45
312	4F-phenyl	CH_2O	H	N	O		B	-cyclobutyl-COOH	1,28
313	4F-phenyl	CH_2O	H	N	O		B	-cyclobutyl-COOH	1,3
314	4CF_3-phenyl	CH_2O	H	N	O		B	-cyclobutyl-COOH	1,41
315	4CF_3-phenyl	CH_2O	H	N	O		B	-cyclobutyl-COOH	1,42
316	3F,4Cl-phenyl	CH_2O	H	N	O		B	-$CH(CH_3)$-CH_2-COOH	1,52
317	2,4,6-triF-phenyl	CH_2O	H	N	O		B	-$CH(CH_3)$-CH_2-COOH	1,43
318	2Cl,4F-phenyl	CH_2O	H	N	O		B	-$CH(CH_3)$-CH_2-COOH	1,5

319	2F,3Cl-phenyl	CH_2O	H	N	O		B	-CH(CH_3)-CH_2-COOH	1,49
320	3F,5Cl-phenyl	CH_2O	H	N	O		B	-CH(CH_3)-CH_2-COOH	1,54
321	2,6-diF,4Cl-phenyl	CH_2O	H	N	O		B	-CH(CH_3)-CH_2-COOH	1,52
322	2,3diCl-phenyl	CH_2O	H	N	O		B	-CH(CH_3)-CH_2-COOH	1,59
323	2Cl-phenyl	CH_2O	H	N	O		B	-CH(CH_3)-CH_2-COOH	1,48
324	2,4diCl-phenyl	CH_2O	H	N	O		B	-CH(CH_3)-CH_2-COOH	1,6
325	3,5diCl-phenyl	CH_2O	H	N	O		B	-CH(CH_3)-CH_2-COOH	1,63
326	3,5diF-phenyl	CH_2O	H	N	O		B	-cyclobutyl-COOH (*trans*)	1,34
327	3,5diF-phenyl	CH_2O	H	N	O		B	-cyclobutyl-COOH(*cis*)	1,34
328	3,4diCl-phenyl	CH_2O	H	N	O		B	-cyclobutyl-COOH (*trans*	1,45
329	3,4diCl-phenyl	CH_2O	H	N	O		B	-cyclobutyl-COOH(*cis*)	1,46
330	4Cl-phenyl	CH_2O	H	N	NH		B	-CH(CH_3)-CH_2-COOH	1,16
331	3,4diF-phenyl	CH_2O	H	N	NH		B	-CH(CH_3)-CH_2-COOH	1,11
332	3,5diCl-phenyl	CH_2O	H	N	NH		B	-CH(CH_3)-CH_2-COOH	1,11
333	3F-phenyl	CH_2O	H	N	O		B	-CH_2-CH(CH_3)-COOH	1,57
334	3,5diF-phenyl	CH_2O	H	N	O		B	-CH_2-CH(CH_3)-COOH	1,65
335	2,5diF-phenyl	CH_2O	H	N	O		B	-CH_2-CH(CH_3)-COOH	1,61
336	2F,6Cl-phenyl	CH_2O	H	N	O		B	-CH_2-CH(CH_3)-COOH	1,62
337	2,4diF-phenyl	CH_2O	H	N	O		B	-CH_2-CH(CH_3)-COOH	1,59
338	4F-phenyl	CH_2O	H	N	O		B	-CH_2-CH(CH_3)-COOH	1,55
339	2F,3Cl-phenyl	CH_2O	H	N	O		B	-CH_2-CH(CH_3)-COOH	1,7

340	2,4,6triF-phenyl	CH_2O	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	1,6
341	2,6diF,4Cl-phenyl	CH_2O	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	#
342	2,3diCl-phenyl	CH_2O	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	#
343	2Cl-phenyl	CH_2O	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	#
344	2F,4Cl-phenyl	CH_2O	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	#
345	2Cl, 4F-phenyl	CH_2O	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	#
346	3F,4Cl-phenyl	CH_2O	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	#
347	2,6diCl-phenyl	CH_2O	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	1,71
348	3Cl,5F-phenyl	CH_2O	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	1,76
349	4Cl-phenyl	CH_2O	H	C	S	H	B	$-(CH_2)_2-COOH$	#)
350	$4CF_3$-phenyl	CH_2O	H	C	S	H	B	$-(CH_2)_2-COOH$	1.57
351	phenyl	CH_2O	3 CF_3	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.59
352	3,5-diCl-phenyl	CH_2O	H	C	S	H	B	$-(CH_2)_2-COOH$	1.6
353	3,5-diCl-phenyl	CH_2O	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	#
354	3,5-diF-phenyl	CH_2O	H	C	S	H	B	$-(CH_2)_2-COOH$	1.46
355	3,4-diCl-phenyl	CH_2O	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	#)
356	2,4-diCl-phenyl	CH_2O	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	#
357	3,4-diCl-phenyl	CH_2O	3Cl	N	O		B	$-(CH_2)_2-COOH$	1.56
358	3,4-diF-phenyl	CH_2O	3Cl	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.58

359	4-Cl-phenyl	CH_2O	3Cl	N	O		B	$-CH(CH_3)-CH_2-COOH$	1.73
360	3,4-diCl-phenyl	CH_2O	3Cl	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.73
361	4- CF_3-phenyl	O	H	N	O		B	$-(CH_2)_2-COOH$	1.45
362	2,4,6-triF-phenyl	CH_2O	H	N	O		B	$-(CH_2)_2-COOH$	1.36
363	2F, 3Cl-phenyl	CH_2O	H	N	O		B	$-(CH_2)_2-COOH$	1.4
364	2F, 4Cl-phenyl	CH_2O	H	N	O		B	$-(CH_2)_2-COOH$	1.44
365	2Cl, 4F-phenyl	CH_2O	H	N	O		B	$-(CH_2)_2-COOH$	1.44
366	3Cl, 5F-phenyl	CH_2O	H	N	O		B	$-(CH_2)_2-COOH$	1.44
367	3F,4Cl-phenyl	CH_2O	H	N	O		B	$-(CH_2)_2-COOH$	1.45
368	2,6-diF, 4Cl-phenyl	CH_2O	H	N	O		B	$-(CH_2)_2-COOH$	1.45
369	2,3-diCl-phenyl	CH_2O	H	N	O		B	$-(CH_2)_2-COOH$	1.5
370	2Cl-phenyl	CH_2O	H	N	O		B	$-(CH_2)_2-COOH$	1.4
371	4-Cl-phenyl	CH_2O	3CF_3	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.67
372	3,4-diCl-phenyl	CH_2O	3CF_3	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.78
373	3,4-diF-phenyl	CH_2O	3CF_3	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.61
374	3,4-diF-phenyl	CH_2O	2CF_3	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.61
375	4Cl-phenyl	CH_2O	2CF_3	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.68
376	3,5-diF-phenyl	CH_2O	2CF_3	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.61
377	4 CF_3-phenyl	CH_2O	2CF_3	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.72
378	4 CF_3-phenyl	CH_2O	3CF_3	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.72

379	3,4-diCl-phenyl	CH_2O	H	N	O		B	$-(CH_2)_2-COOH$	1.5
380	3,5-diCl-phenyl	CH_2O	H	N	O		B	$-(CH_2)_2-COOH$	1.53
381	2,4-diCl-phenyl	CH_2O	H	N	O		B	$-(CH_2)_2-COOH$	1.52
382	3,4-diF-phenyl	CH_2O	2Me	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.5
383	3,5-diF-phenyl	CH_2O	2Me	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.52
384	$4CF_3$-phenyl	CH_2O	2Me	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.62
385	2,3-diF-phenyl	CH_2O	2Me	N	O		B	$-CH_2-CHCH_3-COOH$	1.48
386	3,4-diCl-phenyl	CH_2O	2Me	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.66
387	4Cl-phenyl	CH_2O	2Me	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.57
388	3,5-diF-phenyl	CH_2O	$3CF_3$	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.62
389	2,3-diF-phenyl	CH_2O	$3CF_3$	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.57
390	3,4-diF-phenyl	CH_2O	3Cl	N	O		B	$-CH(CH_3)-CH_2-COOH$	1.56
391	4Cl-phenyl	CH_2O	3Cl	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.6
392	3,4-diCl-phenyl	CH_2O	3Cl	N	O		B	$-CH(CH_3)-CH_2-COOH$	1.67
393	2,3-diF-phenyl	CH_2O	2Me	N	O		B	$-CH(CH_3)-(CH_2)_2-COOH$	1.37
394	2,3-diF-phenyl	CH_2O	2Me	N	O		B	$-(CH_2)_2-CH(CH_3)-COOH$	1.38
395	4-Cl-phenyl	CH_2O	2Me	N	O		B	$-(CH_2)_2-CH(CH_3)-COOH$	1.43
396	4-CF_3-phenyl	CH_2O	2Me	N	O		B	$-(CH_2)_2-CH(CH_3)-COOH$	1.47
397	3,4-diF-phenyl	CH_2O	2Me	N	O		B	$-(CH_2)_2-CH(CH_3)-COOH$	1.39

398	3,5-diF-phenyl	CH_2O	2,6-dF	N	O		B	$-(CH_2)_3$-COOH	1.34
399	$4CF_3$-phenyl	CH_2O	2,6-dF	N	O		B	$-(CH_2)_3$-COOH	1.42
400	2,3-diF-phenyl	CH_2O	H	N	O		B	$-(CH_2)_2$-$CH(CH_3)$-COOH	#
401	Me	O	H	N	O		B	$-(CH_2)_2$-COOH	#)
402	Me	O	H	N	O		B	$-(CH_2)_3$-COOH	#
403	3,4-diF-phenyl	CH_2O	H	N	O		B	$-CH(CH_3)-(CH_2)_2$-COOH	#
404	4Cl-phenyl	CH_2O	2Me	N	O		B	$-CH(CH_3)-(CH_2)_2$-COOH	1.42
405	$4CF_3$-phenyl	CH_2O	2Me	N	O		B	$-CH(CH_3)-(CH_2)_2$-COOH	1.45
406	4Cl-phenyl	CH_2O	2,3diF	N	O		B	$-(CH_2)_3$-COOH	1.37
407	3,5-diF-phenyl	CH_2O	2,3diF	N	O		B	$-(CH_2)_3$-COOH	1.35
408	4Cl-phenyl	CH_2O	2,3diF	N	O		B	$-CH(CH_3)-CH_2$-COOH	1.53
409	3,5-diF-phenyl	CH_2O	2,3diF	N	O		B	$-CH(CH_3)-CH_2$-COOH	1.48
410	4Cl-phenyl	CH_2O	2,3diF	N	O		B	trans cyclobutyl-COOH	1.41
411	3,5-diF-phenyl	CH_2O	2,3diF	N	O		B	cis-cyclobutyl-COOH	1.41
412	3,5-diF-phenyl	CH_2O	2,3diF	N	O		B	trans cyclobutyl-COOH	1.36
413	3,5-diF-phenyl	CH_2O	2,3diF	N	O		B	cis-cyclobutyl-COOH	1.35
414	3,4-diF-phenyl	CH_2O	2Me	N	O		B	cis-cyclobutyl-COOH	#
415	3,4-diF-phenyl	CH_2O	2Me	N	O		B	trans cyclobutyl-COOH	#
416	2,3-diF-phenyl	CH_2O	3F	N	O		B	$-CH(CH_3)-CH_2$-COOH	#
417	2,3-diF-phenyl	CH_2O	3F	N	O		B	$-CH_2-CH(CH_3)$-COOH	#

418	2,3-diF-phenyl	CH_2O	3F	N	O		B	cis-cyclobutyl-COOH	#
419	3,5-diF-phenyl	CH_2O	3Me	N	O		B	$-(CH_2)_3$-COOH	1.38
420	3,5-diF-phenyl	CH_2O	3Me	N	O		B	$-CH_2-CH(CH_3)$-COOH	1.66
421	3,5-diF-phenyl	CH_2O	3Me	N	O		B	$-CH(CH_3)-CH_2$-COOH	1.63
422	$4CF_3$-phenyl	CH2S	H	N	O		B	$-(CH_2)_3$-COOH	1.12
423	3,4-diF-phenyl	CH2S	H	N	O		B	$-(CH_2)_3$-COOH	1.09
424	2,3-diF-phenyl	CH_2O	3F	N	O		B	trans cyclobutyl-COOH	#
425	2,3-diF-phenyl	CH_2O	H	N	O		B	$-CH(CH_3)-CH_2$-COOH *chiral2*	1.11
426	2,3-diF-phenyl	CH_2O	H	N	O		B	$-CH(CH_3)-CH_2$-COOH *chiral1*	1.2
427	3,5-diF-phenyl	CH_2O	3Me	N	O		B	trans cyclobutyl-COOH	1.37
428	3,5-diF-phenyl	CH_2O	3Me	N	O		B	cis cyclobutyl-COOH	1.39
429	2,3-diF-phenyl	CH_2O	3Me	N	O		B	trans cyclobutyl-COOH	1.35
430	2,3-diF-phenyl	CH_2O	3Me	N	O		B	cis cyclobutyl-COOH	1.36
431	3,5-diF-phenyl	CH_2O	2Me	N	O		B	$-CH(CH_3)-CH_2$-COOH	1.5
432	3,5-diF-phenyl	CH_2O	2Me	N	O		B	trans cyclobutyl-COOH	1.35
433	3,5-diF-phenyl	CH_2O	2Me	N	O		B	cis cyclobutyl-COOH	1.35
434	2,3-diF-phenyl	CH_2O	2Me	N	O		B	$-CH(CH_3)-CH_2$-COOH	1.47
435	4-Cl-phenyl	CH_2O	2Me	N	O		B	$-CH_2-CH(CH_3)-CH_2$-COOH	1.49
436	4-CF_3-phenyl	CH_2O	2Me	N	O		B	$-CH_2-CH(CH_3)-CH_2$-COOH	1.53

437	2,3-diF-phenyl	CH_2O	2Me	N	O		B	$-CH_2-CH(CH_3)-CH_2-COOH$	1.42
438	3,4-diF-phenyl	CH_2O	2Me	N	O		B	$-CH_2-CH(CH_3)-CH_2-COOH$	1.44
439	2,3-diF-phenyl	CH_2O	3Me	N	O		B	$-CHCH_3-CH_2-COOH$	1.49
440	2,3-diF-phenyl	CH_2O	3Me	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.5
441	4-Cl-phenyl	CH_2S	H	N	O		B	$-(CH_2)_3-COOH$	1.38
442	2,3-diF-phenyl	CH_2S	H	N	O		B	$-(CH_2)_3-COOH$	1.33
443	3,5-diF-phenyl	CH_2S	H	N	O		B	$-(CH_2)_3-COOH$	1.34
444	3,4-diCl-phenyl	CH_2S	H	N	O		B	$-(CH_2)_3-COOH$	1.44
445	4-Cl-phenyl	CH_2O	H	N	S		B	$-(CH_2)_3-COOH$	1.36
446	3,5-diF-phenyl	CH_2O	H	N	S		B	$-(CH_2)_3-COOH$	1.33
447	4-Cl-phenyl	CH_2O	H	N	S		B	$-CH(CH_3)-CH_2-COOH$	1.53
448	3,5-diF-phenyl	CH_2O	H	N	S		B	$-CH(CH_3)-CH_2-COOH$	1.48
449	4-Cl-phenyl	CH_2O	H	N	S		B	$-CH_2-CH(CH_3)-COOH$	1.52
450	3,5-diF-phenyl	CH_2O	H	N	S		B	$-CH_2-CH(CH_3)-COOH$	1.48
451	3,5-diF-phenyl	C=C	H	N	O		B	$-(CH_2)_3-COOH$	1.39
452	3,5-diF-phenyl	$(CH_2)_2$	H	N	O		B	$-(CH_2)_3-COOH$	1.36
453	3,5-diF-phenyl	C=C	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.59
454	3,5-diF-phenyl	$(CH_2)_2$	H	N	O		B	$-CH_2-CH(CH_3)-COOH$	1.53
455	phenyl	cyclo-propyl	3F	N	O		B	trans cyclobutyl-COOH	1.36
456	phenyl	cyclo-propyl	3F	N	O		B	cis-cyclobutyl-COOH	1.39
457	phenyl	cyclo-propyl	3F	N	O		B	$-CH(CH_3)-CH_2-COOH$	1.55

458	**phenyl**	**cyclo-propyl**	**3F**	**N**	**O**		**B**	**-CH_2-CH(CH_3)-COOH**	**1.55**
459	**phenyl**	**cyclo-propyl**	**3F**	**N**	**O**		**B**	**trans cyclobutyl-COOH**	**1.36**
460	**phenyl**	**cyclo-propyl**	**3F**	**N**	**O**		**B**	**cis-cyclobutyl-COOH**	**1.39**
461	**phenyl**	**cyclo-propyl**	**3F**	**N**	**O**		**B**	**-CH(CH_3)-CH_2-COOH**	**1.55**
462	**phenyl**	**cyclo-propyl**	**3F**	**N**	**O**		**B**	**-CH_2-CH(CH_3)-COOH**	**1.55**
463	**3,5-diF-phenyl**	**CH_2O**	**H**	**N**	**O**		**B**	**-CH_2COOH**	**1.51**
464	**3,5-diF-phenyl**	**CH_2O**	**H**	**N**	**O**		**B**	**-CH(CH_3)-COOH**	**1.53**
465	**3,5-diF-phenyl**	**CH_2O**	**H**	**N**	**O**		**B**	**1,3-cyclopentyl-COOH**	**1.27**

*** = determined with LC-MS method B**
**** = reference compound not according to the invention**
 # = NMR in accordance with proposed structure

§6. PHARMACOLOGICAL TESTS & DATA

***In vitro* functional activity (agonism) on human S1P5 receptors**

The CHO-human-S1P5-Aeqorin assay was bought from Euroscreen, Brussels (Euroscreen, Technical dossier, Human Lysophospholid S1P5 (Edg8) receptor, DNA clone and CHO AequoScreen™ recombinant cell-line, catalog n°: ES-593-A, September 2006). Human-S1P5-Aequorin cells express mitochondrial targeted apo-Aequorin. Cells have to be loaded with coelanterazine, in order to reconstitute active Aequorin. After binding of agonists to the human S1P5 receptor the intracellular calcium concentration increases and binding of calcium to the apo-Aequorin/coelenterazine complex leads to an oxidation reaction of coelenterazine, which results in the production of apo-Aequorin, coelenteramide, CO_2 and light (λ_{max} 469nm). This luminescent response is dependent on the agonist concentration. Luminescence is measured using the MicroBeta Jet (Perkin Elmer). Agonistic effects of compounds are expressed as pEC_{50}. Compounds were tested at a 10 points half log concentration range, and 3 independent experiments were performed in single point's measurements.

***In vitro* functional activity (agonism) on human S1P3 receptors**

The CHO-human-S1P3- Aeqorin assay (CHO/Gα16/AEQ/h-$S1P_3$) was established at Solvay Pharmaceuticals. The plasmid DNA coding for the S1P3 receptor (accession number in GenBank NM_005226 was purchased from UMR cDNA resource Centre (Rolla, MO). The pcDNA3.1/hS1P3 construct carrying the mitochondrially targeted apo-Aeqorin and Gα16 protein was transfected in CHO K1 cell-line.

Human-S1P3-Aequorin cells express mitochondrial targeted apo-Aequorin. Cells have to be loaded with coelanterazine, in order to reconstitute active Aequorin. After binding of agonists to the human S1P3 receptor the intracellular calcium concentration increases and binding of calcium to the apo-Aequorin/coelenterazine complex leads to an oxidation reaction of coelenterazine, which results in the production of apo-Aequorin, coelenteramide, CO_2 and light (λ_{max} 469nm). This luminescent response is dependent on the agonist concentration. Luminescence is measured using the MicroBeta Jet (Perkin Elmer). Agonistic effects of compounds are expressed as pEC_{50}. Compounds were tested at a 10 points half log concentration

range, and 3 independent experiments were performed in single point's measurements.

***In vitro* functional activity (agonism) on human S1P1 receptors (method A)**

The CHO-K1-human-S1P1-Aeqorin assay was bought from Euroscreen *Fast*, Brussels (Euroscreen, Technical dossier, Human S1P1 (Edg1) receptor, DNA clone and CHO-K1 AequoScreen™ recombinant cell-line, catalog n°: FAST-0197L, February 2010). Human-S1P1-Aequorin cells express mitochondrial targeted apo-Aequorin. Cells have to be loaded with coelanterazine, in order to reconstitute active Aequorin. After binding of agonists to the human S1P1 receptor the intracellular calcium concentration increases and binding of calcium to the apo-Aequorin/coelenterazine complex leads to an oxidation reaction of coelenterazine, which results in the production of apo-Aequorin, coelenteramide, CO_2 and light (λ_{max} 469nm). This luminescent response is dependent on the agonist concentration. Luminescence is measured using the MicroBeta Jet (Perkin Elmer). Agonistic effects of compounds are expressed as pEC_{50}. Compounds were tested at a 10 points half log concentration range, and 2 independent experiments were performed in single point's measurements.

***In vitro* functional activity (agonism) on human S1P1 receptors (method B)**

The CHO-K1-Human S1P1-c-AMP assay was performed at Euroscreen*fast,* Brussels (Euroscreen, Human S1P1 coupling $G_{i/0}$, (Edg1) receptor, catalog n°: FAST-0197C, December 2009).

Recombinant CHO-K1 cells expressing human S1P1, grown to mid-log Phase in culture media without antibiotics, detached, centrifuged and re-suspended. For agonist testing cells are mixed with compound and Forskolin and incubated at room temperature. Cells are lyses and cAMP concentration are estimated, according to the manufacturer specification, With the HTRF kit from CIS-BIO International (cat n°62AM2PEB).

Agonistic effects of compounds are expressed as a percentage of the activity of the reference compound at its EC_{100} concentration, EC_{50} is calculated and results are reported as pEC_{50}. Compounds were tested at a 10 points half log concentration range duplicated in 1 experiment.

Pharmacological data (receptor agonism) for selected compounds:

Compound	S1P5 pEC_{50}	$S1P1^A$ pEC_{50}	$S1P1^B$ pEC_{50}	S1P3 pEC_{50}
33	7.8		7.0	5.5
35	8.3		6.6	5.3
47	8.0		<5.5	<5
53	7.9	<4.5		<5
57	8.0		<5.5	<5
73	8.2		8.0	6.3
76	8.1		6.6	<5
77	8.4		7.5	6.1
85	8.6		<5.5	6.3
89	8.2		5.9	<5.0
146	7.8		<5.5	<5.0
156	8.4		6.2	5.5
157	8.1		6.2	5.3
175	8.3		<5.5	5.8
211	8.3		6.1	<5.0
227	8.5		6.0	<6.0
271	8.0		6.2	5.4
277 (trans)	8.5	5.2		<5.0
278 (cis)	7.4	<5		<5
283	7.7	<4.5		<5
306 (trans)	8.1	<5		<5.0
307 (cis)	7.3	<5		<5.0

$S1P1^A$: determined using method A

$S1P1^B$: determined using method B

In vivo therapeutic model; T-maze

Age-related memory deficits occur in humans and rodents. Spontaneous alternation is the innate tendency of rodents to alternate free choices in a T-maze over a series of

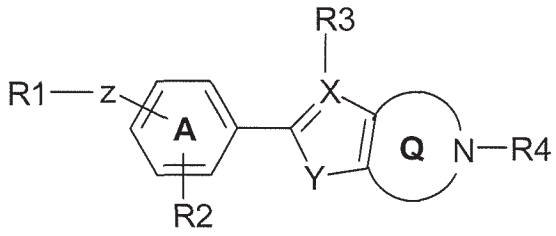
successive runs. This sequential procedure relies on working memory and is sensitive to various pharmacological manipulations affecting memory processes *(Aging and the physiology of spatial memory.* Barnes C.A. *Neurobiol. Aging* **1988***:563-8;* Dember WN, Fowler H. *Spontaneous alternation behavior. Psychol. Bull.* **1958**, *55(6):412–427;* Gerlai R. *A new continuous alternation task in T-maze detects hippocampal dysfunction in mice. A strain comparison and lesion study. Behav Brain Res* **1998** *95(1):91-101).*

For this study, male C57BL/6J mice of 2 months or 12 months old were used in the spontaneous alternation task in the T-maze. In short, mice were subjected to 1 session containing 15 trials, consisting of 1 "forced-choice" trial, followed by 14 "free-choice" trials. The animal was considered as entering one of the arms of the maze when all four paws are placed within this arm. A session is terminated and the animal is removed from the maze as soon as 14 free-choice trials have been performed or 15 min have elapsed, whatever event occurs first. The percentage of alternation over the 14 free-choice trials was determined for each mouse and was used as an index of working memory performance. A compound of the invention was administrated p.o. for 21 days prior the T-maze assay and on the day of the T-maze at t = -30 min. It was found that compounds of the invention at doses ranging from of 0.01 – 15 mg/kg/day reverse the age-related cognitive decline in the 12-month old C57BL6J mice with up to 100%. Thus, treated 12 month old mice were identical in their performance as 2 months old vehicle-treated mice. (See Figure 1)

Conclusion: compounds of the present invention have a positive effect on age-related cognitive decline.

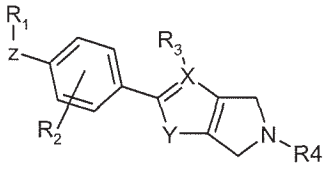
claims

1. A fused heterocyclic derivative of the formula (**I**)

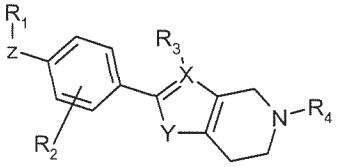


(**I**)

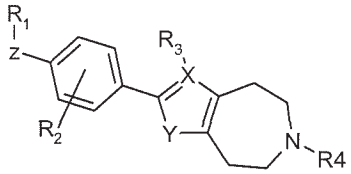
wherein formula (I) is selected from the formula's A, B, C, D and E:



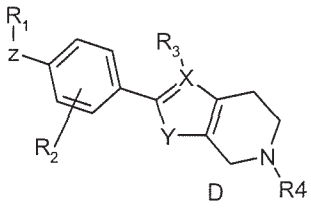
A



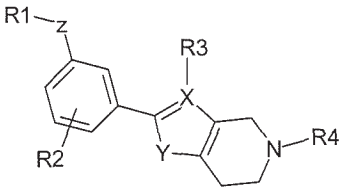
B



C



D



E

wherein
R1 is selected from

cyano,

(2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkyl, each optionally substituted with CN or one or more fluoro atoms,

(3-6C)cycloalkyl, (4-6C)cycloalkenyl or a (8-10C)bicyclic group, each optionally substituted with halogen or (1-4C)alkyl optionally substituted with one or more fluoro atoms,

phenyl, biphenyl, naphthyl, each optionally substituted with one or more substituents independently selected from halogen, cyano, (1-4C)alkyl

optionally substituted with one or more fluoro atoms, (1-4C)alkoxy optionally substituted with one or more fluoro atoms, amino, dimethylamino, and (3-6C)cycloalkyl optionally substituted with phenyl which may be substituted with (1-4C)alkyl or halogen, and

phenyl substituted with phenoxy, benzyl, benzyloxy, phenylethyl or monocyclic heterocycle, each optionally substituted with (1-4C)alkyl,

Z is a linking group –W-(C_n-alkylene)-T- wherein

W is attached to R1 and selected from a bond, -O-, -CO-, -S-, -SO-, -SO_2-, -NH-, -CH=CH-, -C(CF_3)=CH-, -C≡C-, -CH_2-O-, -O-CO-, -CO-O-, -CO-NH-, -NH-CO- and trans-cyclopropylene;

n is an integer from 0 to 10; and

T is attached to the phenylene moiety and selected from a bond, -O-, -S-, -SO-, -SO_2-, -NH-, -CO-, -C=C-, -C≡C-, and trans-cyclopropylene;

R2 is H or one or more substituents independently selected from cyano, halogen, (1-4C)alkyl optionally substituted with one or more halogen atoms, or (1-4C)alkoxy optionally substituted with one or more halogen atoms;

X is selected from C or N; if X is C, R3 is selected from H and (1-4C)alkyl, otherwise R3 is not present;

Y is selected from NH, O and S;

and

R4 is (1-4C)alkylene-R5 wherein one or more carbon atoms in the alkylene group may independently be substituted with one or more halogen atoms or with $(CH_2)_2$ to form a cyclopropyl moiety , or R4 is (3-6C)cycloalkylene-R5, -CH_2-(3-6C)cycloalkylene-R5, (3-6C)cycloalkylene-CH_2-R5 or -CO-CH_2-R5, wherein R5 is -OH, -PO_3H_2, -OPO_3H_2, -COOH, -COO(1-4C)alkyl or tetrazol-5-yl;

or a pharmaceutically acceptable salt, or one or more N-oxides thereof.

2. The compound of claim 1, wherein

R1 is selected from

(3-6C)cycloalkyl or a (8-10C)bicyclic group optionally substituted with halogen, (1-4C)alkyl, and

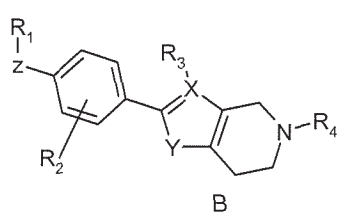
phenyl optionally substituted with one or more substituents independently selected from halogen, cyano, (1-4C)alkyl, (1-4C)alkoxy, trifluoromethyl and trifluoromethoxy;

W is selected from a bond, -O-, -CO-, -S-, -SO-, -SO_2-, -NH-, -CH=CH-, -C≡C-, and trans-cyclopropylene; and

n is an integer from 0 to 4; and

R2 is H or one or more substituents independently selected from halogen, (1-4C)alkyl optionally substituted with one or more fluoro atoms or (1-4C)alkoxy optionally substituted with one or more fluoro atoms.

3. The compound of claim 1 or 2, wherein the compound has the structure of formula B or E



B or E .

4. The compound of any one of claims 1-3, wherein Y is O.

5. The compound of any one of claims 1-4, wherein R4 is selected from -$(CH_2)_2$-COOH, -$(CH_2)_3$-COOH, -CH_2-$CHCH_3$-COOH, -CH_2-$C(CH_3)_2$-COOH, -$CHCH_3$-CH_2-COOH, -CH_2-CF_2-COOH and 1,3-cyclobutylene-COOH.

6. The compound of any one of claims 1-5, wherein R1 is phenyl optionally substituted with one or more substituents independently selected from halogen, cyano, (1-4C)alkyl optionally substituted with one or more fluoro atoms, (1-4C)alkoxy optionally substituted with one or more fluoro atoms, amino, dimethylamino, and (3-6C)cycloalkyl optionally substituted with phenyl which may be substituted with (1-4C)alkyl or halogen.

7. The compound of claim 6, wherein the optional substituents are one or more substituents independently selected from halogen, cyano, (1-4C)alkyl, (1-4C)alkoxy, trifluoromethyl and trifluoromethoxy.

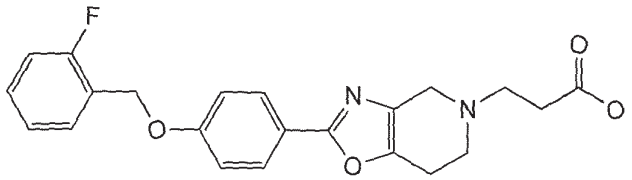
8. The compound of any one of claims 1-7, wherein Z is -CH_2O-.

9. The compound of any one of claims 1-8, wherein X is N.

10. The compound of claim 1, selected from
3-{2-[4-(2-Fluoro-benzyloxy)-phenyl]-6,7-dihydro-4H-furo[3,2-c]pyridine-5-yl}-propionic acid,
3-{2-[4-(4-Chloro-benzyloxy)-phenyl]-6,7-dihydro-4H-furo[3,2-c]pyridine-5-yl}-2-methyl-propionic acid,
3-{2-[4-Benzyloxy-phenyl]-6,7-dihydro-4H-furo[3,2-c]pyridine-5-yl}-butyric acid,
4-{2-[4-(2-Fluoro-benzyloxy)-phenyl]-6,7-dihydro-4H-furo[3,2-c]pyridine-5-yl}-butyric acid,
4-{2-[4-(2-Fluoro-benzyloxy)-2-fluoro-phenyl]-6,7-dihydro-4H-furo[3,2-c]pyridine-5-yl}-butyric acid,
3-{2-[4-(Benzyloxy)-phenyl)]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-propionic acid,
4-{2-[4-(2,3-Difluoro-benzyloxy)-phenyl)]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-butyric acid,
4-{2-[4-Benzyloxy-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-butyric acid,
4-{2-[4-(4-Trifluoromethyl-benzyloxy)-2-fluoro-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-butyric acid,
4-{2-[4-(2-Fluoro-benzyloxy)-2-methyl-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-butyric acid,
4-{2-[4-(3,4-Dichloro-benzyloxy)-2-fluoro-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-butyric acid,
4-{2-[4-(2-Fluoro-benzyloxy)-3-chloro-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-butyric acid,
4-{2-[4-(4-Chloro-benzyloxy)-3-fluoro-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-butyric acid,
3-[2-(4-Benzyloxy-phenyl)-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl]-2-methyl-propionic acid,
3-{2-[4-(4-Trifluoromethyl-benzyloxy)-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-2-methyl-propionic acid,
3-{2-[4-(4-Chloro-benzyloxy)-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-2-methyl-propionic acid,
3-{2-[4-(2,3-Difluoro-benzyloxy)-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-

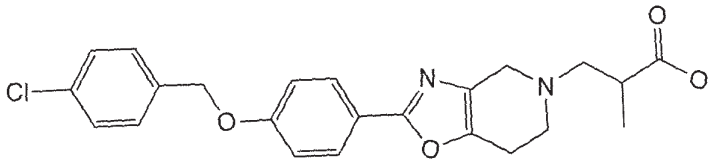
butyric acid,
3-{2-[4-(4-Trifluoromethyl-benzyloxy)-2-fluoro-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-2-methyl-propionic acid,
Cis and trans 3-{2-[4-(4-Trifluoromethoxybenzyloxy)-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-cyclobutane carboxylic acid,
Cis and trans 3-{2-[4-(3,4-Difluorobenzyloxy)-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-cyclobutane carboxylic acid,
3-[2-(4-(2-Fluoro-benzyloxy)-phenyl)-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-yl]-propionic acid,
4-{2-[4-(3,5-Difluoro-benzyloxy)-phenyl]-6,7-dihydro-4H-thiazolo-[4,5c]-pyridin-5-yl}–butyric acid,
2-{2-[4-(3,5-Difluoro-benzyloxy)-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-acetic acid,
2-{2-[4-(3,5-Difluoro-benzyloxy)-phenyl]-6,7-dihydro-*H*-oxazolo[4,5-c]pyridine-5-yl}-propionic acid,
3-{2-[4-(3,5-Difluoro-benzyloxy)-phenyl]-6,7-dihydro-4H-oxazolo[4,5-c]-pyridin-5-yl}-cyclopentane carboxylic acid,
4-{2-[4-(2,3-Difluoro-benzyloxy)-2-methyl-phenyl]-6,7-dihydro-4H-oxazolo-[4,5c]-pyridin-5-yl}-pentanoic acid,
4-{2-[4-(2,3-Difluoro-benzyloxy)-2-methyl-phenyl]-6,7-dihydro-4H-oxazolo[4,5-c]-pyridin-5-yl}-2-methyl-butyric acid,
4-{2-[4-(2,3-Difluoro-benzyloxy)-2-methyl-phenyl]-6,7-dihydro-4H-oxazolo-[4,5c]-pyridin-5-yl}-3-methyl-butyric acid,
3-{2-[4-(2-phenyl-cyclopropyl)-3-fluoro-phenyl]-6,7-dihydro-4H-oxazolo-[4,5-c]-pyridin-5-yl}-cyclobutane carboxylic acid,
4-(2-{4-[2-(3,5-Difluoro-phenyl)-vinyl]-phenyl}-6,7-dihydro-4H-oxazolo-[4,5c]-pyridin-5-yl)-butyric acid,
4-(2-{4-[2-(3,5-Difluoro-phenyl)-ethyl]-phenyl}-6,7-dihydro-4H-oxazolo[4,5c] pyridin-5-yl)-butyric acid,
or a pharmaceutically acceptable salt, a solvate or hydrate thereof or one or more N-oxides thereof.

11. A compound of formula



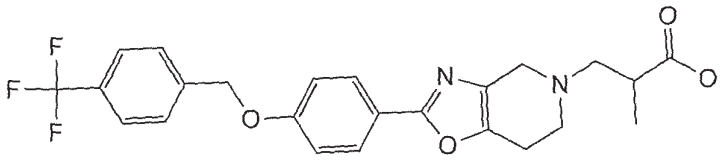
or a pharmaceutically acceptable salt thereof.

12. A compound of formula



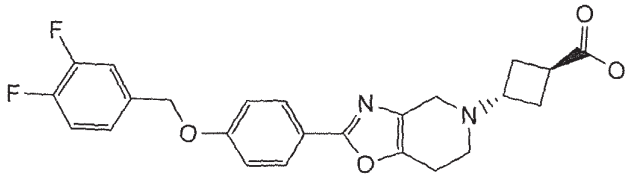
or a pharmaceutically acceptable salt thereof.

13. A compound of formula



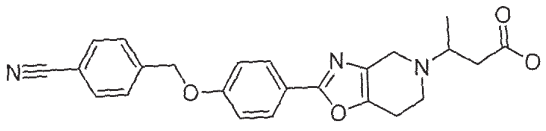
or a pharmaceutically acceptable salt thereof.

14. A compound of formula



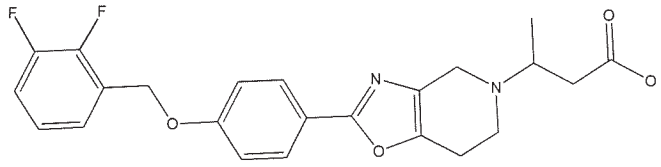
or a pharmaceutically acceptable salt thereof.

15. A compound of formula



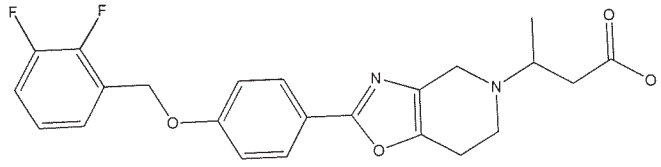
or a pharmaceutically acceptable salt thereof.

16. A compound of formula



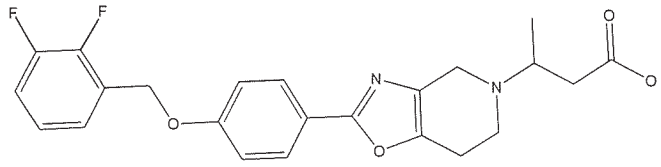
or a pharmaceutically acceptable salt thereof.

17. A compound which is the plus (+) enantiomer of formula



or a pharmaceutically acceptable salt thereof.

18. A compound which is the minus (-) enantiomer of formula



or a pharmaceutically acceptable salt thereof.

19. The compound of any one of claims 1 to 18 for use in therapy.

20. The compound of any one of claims 1 to 18 for use in the treatment, alleviation or prevention of a CNS disorder, such as a neurodegenerative disorder, in particular selected from a cognitive disorder, Alzheimer's disease, (vascular) dementia, Nieman's Pick disease, and cognitive deficits in schizophrenia, obsessive-compulsive behavior, major depression, autism, multiple sclerosis and pain, and specifically a cognitive disorder, such as age-related cognitive decline.

21. A pharmaceutical composition comprising the compound of any one of claims 1 to 18 and at least one pharmaceutically acceptable auxiliary.

22. Use of the compound of any one of claims 1 to 18 for the manufacture of a medicament for the treatment, alleviation or prevention of a CNS disorder, such as a neurodegenerative disorder, in particular selected from a cognitive disorder, Alzheimer's disease, (vascular) dementia, Nieman's Pick disease, and cognitive

deficits in schizophrenia, obsessive-compulsive behavior, major depression, autism, multiple sclerosis and pain, and specifically a cognitive disorder, such as age-related cognitive decline.