Title: 2-OXO-3,4-DIHYDROPYRIDINE-5-CARBOXYLATES AND THEIR USE

Abstract: The present invention is directed to novel compounds of Formula (I), pharmaceutically acceptable salts or solvates thereof, and their use.

$$\text{Formula (I)}$$
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, S, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, Published: with international search report (Art. 21(3))
2-OXO-3,4-DIHYDROPYRIDINE-5-CARBOXYLATES AND THEIR USE

The present invention relates to novel compounds including their pharmaceutically acceptable salts and solvates, which are agonists of TGR5 (G protein-coupled bile acid receptor 1, also named Gpbar1 or M-BAR) and are useful as therapeutic compounds, particularly in the treatment and/or prevention of TGR5 related diseases, such as Type 2 diabetes (T2D) also known as diabetes mellitus and conditions that are often associated with this disease including, lipid disorders such as dyslipidemia, hypertension, obesity, atherosclerosis and its sequelae.

[BACKGROUND OF THE INVENTION]

Type 2 diabetes (T2D) also known as diabetes mellitus is a growing health problem. Recent estimates indicate there were 171 million people in the world with diabetes in the year 2000 and this is projected to increase to 366 million by 2030 (Wild S., Roglic G., Green A., Sicree R., King H. Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care. 2004, 27, 1047-1 053). The classical treatment for type 2 diabetes developed over the past 20 years has been based on 2 types of oral anti-hyperglycemic drugs; sulfonylureas that stimulate insulin secretion and the biguanides that have a broad spectrum of effects, but act primarily on hepatic insulin resistance. Then, alpha glucosidase inhibitors (i.e. acarbose) have been developed which decrease the intestinal absorption of glucose. A new category of molecules has appeared called thiazolidinediones (TZD). They act through binding and activation of the nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ). More recently, the recognition that hormones secreted by the gut play a role in maintaining blood glucose homoeostasis has led to emergence of several novel class of medications acting as analogs of the incretin glucagon-like peptide (GLP-1) or as inhibitors of its degrading enzyme dipeptidyl peptidase IV (DPP-IV inhibitors) stabilizing its half-life. GLP-1 is an incretin hormone causing enhanced post-prandial insulin secretion, but also known to have a range of additional effects including reduced gastric motility and appetite suppression, which indirectly impact on glucose metabolism in vivo (Drucker, D. J.; Sherman, S. I.; Bergenstal, R. M.; Buse, J. B., The safety of incretin-based therapies-review of the scientific evidence. J Clin Endocrinol Metab 201 1, 96, 2027-203 1. Baggio, L. L.; Drucker, D. J., Biology of Incretins: GLP-1 and GIP. Gastroenterology 2007, 132, 2131-2157). These new incretin-based medications offer the advantage of highly successful efficacy associated with an exceedingly favorable side effect profile and neutral effects on weight (Cefalu, W. T., Evolving treatment strategies for the management of type 2 diabetes. Am J Med Sci 2012, 343, 21-6. Gallwitz, B., Glucagon-like peptide-1 analogues for Type 2 diabetes mellitus: current and emerging agents. Drugs 2011, 71, 1675-88).

Despite the use of various hypoglycemic agents, current treatments often fail to
achieve sufficient lowering of serum glucose and/or are often associated with deficiencies including hypoglycemic episodes, gastrointestinal problems, weight gain, and loss of effectiveness over time (El-Kaisi, S.; Sherbeeni, S., Pharmacological management of type 2 diabetes mellitus: an update. Curr Diabetes Rev 201 1, 7, 392-405).


described recently.

However, safety concerns for some systemic TGR5 agonists were recently mentioned. Hyperplasia of the gall bladder which becomes enlarged due to delayed emptying, increased filling, or a combination of these effects was reported by investigators working with systemic TGR5 agonists in mouse models. Li, T.; Holmstrom, S. R.; Kir, S.; Umetani, M.; Schmidt, D. R.; Kliwer, S. A.; angelsdorf, D. J. The G protein-coupled bile acid receptor, TGR5, stimulates gallbladder filling. Mol. Endocrinol. 201 1, 25, 1066-1071 , Duan, H.; Ning, M.; Chen, X.; Zou, Q.; Zhang, L ; Feng, Y.; Zhang, L ; Leng, Y.; Shen, J., Design, Synthesis, and Antidiabetic Activity of 4-Phenoxycotinamide and 4-Phenoxypyrimidine-5-carboxamide Derivatives as Potent and Orally Efficacious TGR5 Agonists. Journal of Medicinal Chemistry 2012, 55, (23), 10475.

More recently, it was reported that TGR5 stimulation in skin by systemic agonists triggers intense pruritus, comparable to the effect of the naturally occurring bile acids during cholestasis (Ale mi, F.; Kwon, E.; Poole, D. P.; Lieu, T.; Lyo, V.; Cattaruzza, F.; Cevikbas, F.; Steinhoff, M.; Nassini, R.; Materazzi, S.; Guerrero-Alba, R.; Valdez-Morales, E.; Cottrell, G. S.; Schoonjans, K.; Geppetti, P.; Vanner, S. J.; Bunnett, N. W.; Corvera, C. U., The TGR5 receptor mediates bile acid-induced itch and analgesia. The Journal of Clinical Investigation 2013, 123, (4), 1513). Consequently, a much lower systemic exposure or even a non systemic exposure may be necessary for the development of a nontoxic TGR5 agonist.

International patent application WO 2011/071565 describes imidazole and triazole based TGR5 agonists having a quaternary ammonium moiety.

On this basis, there is still a need for new compounds that may be of therapeutic value in the treatment of TGR5 related diseases, such as T2D and conditions that are associated with this disease including, lipid disorders such as dyslipidemia, hypertension, obesity, atherosclerosis and its sequelae.

[SUMMARY OF THE INVENTION]

The invention thus encompasses compounds of general Formula I, their pharmaceutically acceptable salts and solvates as well as methods of use of such compounds or compositions comprising such compounds as agonists of TGR5 activity.

In a general aspect, the invention provides compounds of general Formula I:
or pharmaceutically acceptable salts or solvates thereof,

wherein

R₁ is C₁-C₆-alkyl, aryl or heteroaryl, wherein said aryl moiety is independently substituted by one or more groups selected from the group consisting of halo, cyano, C₁-C₂-alkyl, C₁-C₂-alkoxy, C₁-C₂-haloalkyl, and 5- or 6-membered aryl, and said heteroaryl moiety is optionally independently substituted by one or more groups selected from the group consisting of halo, cyano, C₁-C₂-alkyl, C₁-C₂-alkoxy, C₁-C₂-haloalkyl, and 5- or 6-membered aryl;

L₁ is a single bond or (CH₂)ₓ, wherein x is 1, 2 or 3;

R² is H, C₁-C₄ alkyl, alkenyl, alkiny, alkoxy, hydroxy, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxycarbonylamino, cyano, alkylsulfonyl, aralkyl, cycloalkyl, heterocyclyl, heteroaryl, wherein said heterocyclyl moiety is optionally substituted by one or more substituents independently selected from the group consisting of alkyl and alkoxy carbonyl, and said heteroaryl moiety is optionally substituted by one or more C₁-C₂ alkyl;

L² is a single bond or (CH₂)ₓ, wherein x is 1 or 2;

R³ is aryl, heteroaryl, cycloalkyl or aryl carbonyl wherein each of said moieties is optionally substituted by one or more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, aryl, cyano, alkoxy, haloalkoxy, alkoxycarbonyl, aminoalkoxy, alkylaminoalkoxy, dialkylaminoalkoxy, H₃S-alkoxy,

, wherein m is 1 to 500,
[N(R\textsuperscript{8})\textsubscript{3}-alkoxy\textsuperscript{+}] \textsuperscript{-} Q\textsuperscript{-}, wherein R\textsuperscript{8} is linear C1-C4-alkyl and Q\textsuperscript{-} is a counter anion, and a cyclic moiety selected from the group consisting of

![Chemical structures](image)

wherein R\textsuperscript{A} is H, OH, C0-C4-alkyl-COOH or C1-C6-alkyl, R\textsuperscript{B} is C1-C6-alkyl optionally substituted with -COOH, R\textsuperscript{C} is C1-C6-alkyl, and Q\textsuperscript{-} is a counter anion;

or wherein said cycloalkyl moiety is fused to an aryl, preferably phenyl, moiety;

R\textsuperscript{4} is H, C1-C2-alkyl or 5- or 6-membered aryl;

R\textsuperscript{5} is H, C1-C4-alkyl, 5- or 6-membered aryl, alkoxyalkyl; and

X is O or NR', wherein R' is H, C1-C2-alkyl or R' taken together with L\textsuperscript{2} and R\textsuperscript{3} form a 5- or 6-membered heterocyclic moiety which is optionally fused to an aryl moiety.

Suitable, generally pharmaceutically acceptable, counter anions Q\textsuperscript{-} are well known to those skilled in the art. Non-limiting examples of suitable counter anions Q\textsuperscript{-} include acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, halides such as fluoride, chloride,
bromide and iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate. Preferred counter anions $Q^-$ are halides such as fluoride, chloride, bromide and iodide, especially iodide. Unless otherwise specified, the above definition of $Q^-$ applies at all occurrences of $Q^-$ throughout the application.

In another aspect, the present invention provides a pharmaceutical composition comprising at least one compound according to the invention or a pharmaceutically acceptable salt or solvate thereof.

The invention also relates to the use of the above compounds or their pharmaceutically acceptable salts and solvates as modulators of TGR5, preferably as agonists of TGR5 and more preferably as agonists of TGR5 exerting their action locally in the intestine with low or even without systemic exposure. In view of the drawbacks reported for systemic TGR5 agonists, the preferred agonists of the invention have the advantage of enhancing safety and the therapeutic index for potential chronic administration. The invention further provides the use of a compound according to the invention or a pharmaceutically acceptable salt or solvate thereof as a medicament. Preferably, the medicament is used for the treatment and/or prevention of TGR5 related diseases, such as metabolic and/or gastrointestinal diseases.

Metabolic diseases within the meaning of the present invention include, but are not limited to, type II diabetes, obesity, dyslipidemia such as mixed or diabetic dyslipidemia, hypercholesterolemia, low HDL cholesterol, high LDL cholesterol, hyperlipidemia, hypertriglyceridemia, hypoglycemia, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypertension, hyperlipoproteinemia, metabolic syndrome, syndrome X, thrombotic disorders, cardiovascular disease, atherosclerosis and its sequelae including angina, claudication, heart attack, stroke and others, kidney diseases, ketoacidosis, nephropathy, diabetic neuropathy, diabetic retinopathy, nonalcoholic fatty liver diseases such as steatosis or nonalcoholic steatohepatitis (NASH).

In a preferred embodiment, the metabolic disease is type II diabetes, a lipid disorder such as dyslipidemia, hypertension, obesity, or atherosclerosis and its sequelae, preferably the disease is type II diabetes.

Gastrointestinal diseases within the meaning of the present invention include, but are not limited to, Inflammatory Bowel Diseases (IBD) including but not limited to colitis, Ulcerative colitis (UC) and Crohn's Disease (CD), and Irritable Bowel Syndrome (IBS), intestinal injury disorders such as short-bowel syndrome, diseases involving intestinal barrier dysfunction such as proctitis and pouchitis, and gastrointestinal disorders characterized by
hypermotilenemia or gastrointestinal hypermotility, including but not limited to any type of diarrhea.

In a preferred embodiment the gastrointestinal disease is Inflammatory Bowel Diseases (IBD) including but not limited to colitis, Ulcerative colitis (UC) and Crohn's Disease (CD).

[DETAILED DESCRIPTION OF THE INVENTION]

As noted above, the invention relates to compounds of Formula I, as well as their pharmaceutically acceptable salts and solvates.

Preferred compounds of Formula I and pharmaceutically acceptable salts and solvates thereof are those wherein one or more of $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $L^1$, $L^2$ and $X$ are defined as follows:

$R^1$ is C1-C4 alkyl, 5- or 6-membered aryl or 5- to 9-membered heteroaryl, wherein said aryl moiety is independently substituted by one or more groups selected from the group consisting of halo, C1-C2-alkyl, C1-C2-alkoxy, C1-C2-haloalkyl, and 5- or 6-membered aryl, and said heteroaryl moiety is optionally independently substituted by one or more groups selected from the group consisting of halo, C1-C2-alkyl, C1-C2-alkoxy, C1-C2-haloalkyl, and 5- or 6-membered aryl, preferably $R^1$ is C2-C4-alkyl, phenyl, pyridinyl or benzothiadiazolyl, wherein said phenyl or pyridinyl moiety is independently substituted by one or more substituents selected from the group consisting of halo, C1-C2-alkyl, C1-C2-alkoxy, C1-C2-haloalkyl, and 5- or 6-membered aryl, more preferably $R^1$ is n-propyl, phenyl or pyridinyl, independently substituted by one or more substituents selected from the group consisting of halo, C1-C2-alkyl, C1-C2-haloalkyl, still more preferably $R^1$ is phenyl or pyridinyl, independently substituted by one or more substituents selected from the group consisting of chloro, cyano, and trifluoromethyl, even more preferably $R^1$ is phenyl substituted by one chloro;

$L^1$ is $(CH_2)_n$, wherein $n$ is 1, 2 or 3, preferably $L^1$ is CH$_2$;

$R^2$ is alkoxy, hydroxy, alkoxy carbonyl, cycloalkyl, heterocyclyl, or heteroaryl, said heteroaryl moiety being optionally substituted by one or more C1-C2 alkyl preferably methyl groups; preferably $R^2$ is C1-C2-alkoxy, hydroxy, C1-C2-alkoxy carbonyl, C3-C5-cycloalkyl, C5-C6-heterocyclyl comprising 1 or 2 oxygen atoms, C5-C6-heteroaryl comprising 1 oxygen atom and 0, 1 or 2 nitrogen atoms, said C5-C6-heteroaryl moiety being optionally substituted by one methyl group, more preferably $R^2$ is methoxy, hydroxy, methoxycarbonyl, cyclopropyl, cyclobutyl, furanyl, 3-methyl-1,2,4-oxadiazol-5-yl, tetrahydrofuran-5-yl, even more preferably $R^2$ is tetrahydrofuran-5-yl;
$L^2$ is a single bond;

$R^3$ is phenyl, substituted by one or more substituents independently selected from the group consisting of halo, C1-C2-alkyl, C1-C2-haloalkyl, phenyl, cyano, C1-C2-alkoxy, C1-C2-haloalkoxy, C1-C2-alkoxycarbonyl, aminoalkoxy, C1-C2-alkylaminoalkoxy, di-C1-C2-alkylaminoalkoxy, H0$_3$S-C2-C8-alkoxy,

![image]

, wherein $m$ is 1 to 500, preferably 1 to 50, and

$[N(R^8)\text{C2-C6-alkoxy}]^*Q^-$, wherein $R^8$ is C1-C2-alkyl and $Q^-$ is a counter anion,

preferably $R^3$ is phenyl, substituted by one or more substituents independently selected from the group consisting of halo, C1-C2-alkyl, C1-C2-haloalkyl, phenyl, cyano, C1-C2-alkoxy, C1-C2-haloalkoxy, C1-C2-alkoxycarbonyl, aminoalkoxy, C1-C2-alkylaminoalkoxy, di-C1-C2-alkylaminoalkoxy, H0$_3$S-C2-C6-alkoxy,

![image]

, wherein $m$ is 1 to 500, preferably 1 to 50, and

$[N(R^8)\text{C2-C6-alkoxy}]^*Q^-$, wherein $R^8$ is C1-C2-alkyl and $Q^-$ is a counter anion,

more preferably $R^3$ is phenyl, substituted by one or more substituents independently selected from the group consisting of halo, methyl, trifluoromethyl, phenyl, cyano, methoxy, trifluoromethoxy, methoxycarbonyl, di-methylaminoalkoxy, H0$_3$S-CH$_2$CH$_2$0-

![image]

, wherein $m$ is 1 to 500, preferably 1 to 50, and

$[N(R^8)\text{C2-C6-alkoxy}]^*Q^-$, wherein $R^8$ is methyl and $Q^-$ is a counter anion,

still more preferably $R^3$ is phenyl, substituted by one or more substituents independently selected from the group consisting of chloro, fluoro, methyl, trifluoromethyl, phenyl, cyano, methoxy, trifluoromethoxy, methoxycarbonyl, di-methylaminoalkoxy,

![image]

, wherein $m$ is 1 to 500, preferably 1 to 50, and
[N(R^8)_3\cdot C2-C6-alkoxy] \cdot Q^-, wherein R^8 is methyl and Q^- is a counter anion;

R^4 is H;

R^5 is methyl;

X is O.

Particularly preferred compounds of Formula I and pharmaceutically acceptable salts and solvates thereof are those wherein R^3 is aryl, heteroaryl, cycloalkyl or arylcarbonyl, preferably aryl or heteroaryl, more preferably phenyl or pyridinyl, even more preferably phenyl, wherein each of said moieties is substituted by one or more substituents independently selected from H0_{3-S}-alkoxy, preferably H0_{3-S-C2-C8-alkoxy}, more preferably H0_{3-S-C2-C6-alkoxy}, even more preferably H0_{3-S-CH2CH_2O}^-, in particular in form of one of its salts, such as ammonium salts, preferably its NH_4^+ salt,

\[ \text{[N(R^8)_3\cdot C2-C6-alkoxy] \cdot Q^-} \]

, wherein m is 1 to 500, preferably 1 to 50, and [N(R^8)_3\cdot C2-C6-alkoxy] \cdot Q^-, wherein R^8 is linear C1-C4-alkyl and Q^- is a counter anion, preferably [N(R^8)_3\cdot C2-C6-alkoxy] \cdot Q^-, wherein R^8 is C1-C2-alkyl and Q^- is a counter anion, more preferably [N(R^8)_3\cdot C2-C6-alkoxy] \cdot Q^-, wherein R^8 is methyl and Q^- is a counter anion. Indeed, without wanting to be bound to any theory, the present inventors believe that the H0_{3-S-alkoxy}, polyethyleneglycol, and [N(R^8)_3\cdot alkoxyl] \cdot Q^- moieties on the R^3 substituent as defined herein (in the case of the H0_{3-S-alkoxy moiety especially its pharmaceutically acceptable salts) particularly limit the absorption of the compound of the invention in the intestine and thus decrease their systemic action.

Further preferred compounds of Formula I and pharmaceutically acceptable salts and solvates thereof are those wherein L^1 and R^2 are taken together to form a moiety selected from the group consisting of cycloalkylmethyl, heterocyclylmethyl, heteroarylalkyl, 2-alkoxyethyl-1-yl, 3-alkoxyprop-1-yl, alkoxy carbonylmethyl, said heteroarylalkyl moiety being optionally substituted by one or more C1-C2 alkyl groups on its heteroaryl part, preferably L^1 and R^2 are taken together to form a moiety selected from the group consisting of C3-C5-cycloalkylmethyl, C5-C6-heterocyclylmethyl, C5-C6-heteroarylalkyl, 2-C1-C2-alkoxyethyl-1-yl, 3-C1-C2-alkoxyprop-1-yl, C1-C2-alkoxycarbonylmethyl, said C5-C6-heteroarylalkyl moiety being optionally substituted by one or more methyl groups on its heteroaryl part more preferably L^1 and R^2 are taken together to form a moiety selected from the group consisting of C3-C4-cycloalkyl meth yl, C5-heterocyclylmethyl, C5-heteroarylalkyl, 2-methoxyethyl-1-yl, 3-
methoxyprop-1-yl, methoxycarbonylmethyl, said C5-heteroarylmethyl moiety being optionally substituted by one methyl group on its heteroaryl part, even more preferably L¹ and R² are taken together to form a moiety selected from the group consisting of C3-C4-cycloalkylmethyl, furanylethyl, 3-methyl-1,2,4-oxadiazol-5-ylmethyl, tetrahydrofuranylmethyl or 1,3-dioxolanylmethyl, 2-methoxyeth-1-yl, 3-methoxyprop-1-yl, methoxycarbonylmethyl, still more preferably L¹ and R² are taken together to form 2-methoxyeth-1-yl or tetrahydrofuranylmethyl, and still more preferably L¹ and R² are taken together to form tetrahydrofuranylmethyl.

In one embodiment of the invention, the compounds of Formula I are those of Formula II

![Chemical structure](image)

and pharmaceutically acceptable salts and solvates thereof, wherein R¹, R², R³, R⁵, and L¹ are as defined above with respect to Formula I.

Preferred compounds of Formula II and pharmaceutically acceptable salts and solvates thereof are those wherein L¹ and R² are taken together to form a moiety selected from the group consisting of cycloalkylmethyl, heterocyclylmethyl, heteroarylmethyl, 2-alkoxyeth-1-yl, 3-alkoxyprop-1-yl, alkoxy carbonylmethyl, said heteroarylmethyl moiety being optionally substituted by one or more C1-C2 alkyl groups on its heteroaryl part, preferably L¹ and R² are taken together to form a moiety selected from the group consisting of C3-C5-cycloalkylmethyl, C5-C6-heterocyclylmethyl, C5-C6-heteroarylmethyl, 2-C1-C2-alkoxyeth-1-yl, 3-C1-C2-alkoxyprop-1-yl, C1-C2-alkoxy carbonylmethyl, said C5-C6-heteroarylmethyl moiety being optionally substituted by one or more methyl groups on its heteroaryl part, more preferably L¹ and R² are taken together to form a moiety selected from the group consisting of C3-C4-cycloalkylmethyl, C5-heterocyclylmethyl, C5-heteroarylmethyl, 2-methoxyeth-1-yl, 3-methoxyprop-1-yl, methoxycarbonylmethyl, said C-5-heteroarylmethyl moiety being optionally substituted by one methyl group on its heteroaryl part, even more preferably L¹ and R² are
taken together to form a moiety selected from the group consisting of C3-C4-cycloalkylmethyl, furanylmethyl, 3-methyl-1,2,4-oxadizol-5-ylmethyl, tetrahydrofuranylmethyl or 1,3-dioxolanylmethyl, 2-methoxyeth-1-yl, 3-methoxyprop-1-yl, methoxycarbonylmethyl, still more preferably L¹ and R² are taken together to form 2-methoxyeth-1-yl or tetrahydrofuranylmethyl, and still more preferably L¹ and R² are taken together to form tetrahydrofuranylmethyl.

In one embodiment, preferred compounds of Formula II are those of Formula IIa

\[
\begin{align*}
\text{Il} & \text{a} \\
\end{align*}
\]

![Chemical Structure](image)

and pharmaceutically acceptable salts and solvates thereof, wherein

1 R¹, R², R⁵ and L¹ are as defined above with respect to Formula II, and

2 R⁶ is halo, alkyl, haloalkyl, aryl, cyano, alkoxy, haloalkoxy, alkoxy carbonyl, aminoalkoxy, alkylaminoalkoxy, dialkylaminoalkoxy, H₂O₃S-alkoxy,

3 \[\text{N(R⁸)₃-alkoxy}\]₂⁺ Q⁻, wherein R⁸ is linear C1-C4-alkyl and Q⁻ is a counter anion, or

4 a cyclic moiety selected from the group consisting of
wherein $R^A$ is $\text{H, OH, C0-C4-alkyl-COOH}$ or $\text{C1-C6-alkyl}$, $R^B$ is $\text{C1-C6-alkyl}$ optionally substituted with $\text{-COOH}$, $R^C$ is $\text{C1-C6-alkyl}$, and $Q^-$ is a counter anion;

preferably $R^6$ is halo, $\text{C1-C2-alkyl}$, $\text{C1-C2-haloalkyl}$, phenyl, cyano, $\text{C1-C2-alkoxy}$, $\text{C1-C2-haloalkoxy}$, $\text{C1-C2-alkoxycarbonyl}$, aminoalkoxy, $\text{C1-C2-alkylaminoalkoxy}$, $\text{di-C1-C2-alkylaminoalkoxy}$, $\text{H0}_3\text{S-C2-C6-alkoxy}$,

\[
\begin{align*}
&\text{[N(R^8)_3-C2-C6-alkoxy]}^+Q^- , \text{wherein } R^8 \text{ is } \text{C1-C2-alkyl and } Q^- \text{ is a counter anion,} \\
&\text{more preferably } R^6 \text{ is halo, } \text{C1-C2-alkyl, } \text{C1-C2-haloalkyl, } \text{phenyl, cyano, } \text{C1-C2-alkoxy, } \text{C1-C2-haloalkoxy, } \text{C1-C2-alkoxycarbonyl, } \text{aminoalkoxy, } \text{C1-C2-alkylaminoalkoxy, } \text{di-C1-C2-alkylaminoalkoxy, } \text{H0}_3\text{S-C2-C6-alkoxy},
\end{align*}
\]

\[
\begin{align*}
&, \text{wherein } m \text{ is } 1 \text{ to } 500, \text{ preferably } 1 \text{ to } 50, \text{ or}
\end{align*}
\]
[N(R^8)_3-C2-C6-alkoxy] \text{+ Q}^-, \text{wherein R}^8 \text{ is C1-C2-alkyl and Q}^- \text{ is a counter anion,}

still more preferably R^6 is halo, methyl, trifluoromethyl, phenyl, cyano, methoxy, trifluoromethoxy, methoxycarbonyl, di-methylaminoalkoxy, H$_2$S-CH2CH$_2$O-, or

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} \quad \text{H}
\end{align*}
\]

, wherein m is 1 to 500, preferably 1 to 50, or

5 [N(R^8)_3-C2-C6-alkoxy] \text{+ Q}^-, \text{wherein R}^8 \text{ is methyl and Q}^- \text{ is a counter anion,}

even more preferably R^6 is chloro, fluoro, methyl, trifluoromethyl, phenyl, cyano, methoxy, trifluoromethoxy, methoxycarbonyl, di-methylaminoalkoxy, H$_3$S-C2CH20-,

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} \quad \text{H}
\end{align*}
\]

, wherein m is 1 to 500, preferably 1 to 50, or

[N(R^8)_3-C2-C6-alkoxy] \text{+ Q}^-, \text{wherein R}^8 \text{ is methyl and Q}^- \text{ is a counter anion.}

Particularly interesting compounds of Formula Ila and pharmaceutically acceptable salts and solvates thereof are those, wherein R^6 is H$_0$S-alkoxy, preferably H$_0$S-C2-C6-alkoxy, more preferably H$_0$S-C2-C6-alkoxy, still more preferably H$_0$S-C2CH$_2$0-, in particular in form of one of its salts, such as ammonium salts, wherein m is 1 to 500 preferably 1 to 50, or [N(R^6)_3-C2-C6-alkoxy]^+Q^-, wherein R^8 is linear C1-C4-alkyl and Q^- is a counter anion, preferably [N(R^8)_3-C2-C6-alkoxy]^+Q^-, wherein R^8 is C1-C2-alkyl and Q^- is a counter anion, more preferably [N(R^8)_3-C2-C6-alkoxy]^+Q^-, wherein R^8 is methyl and Q^- is a counter anion.

In one embodiment, the compounds of Formula Ila are selected from the group consisting of Formulae Ila-1, Ila-2, and Ila-3:
wherein $R^1$, $R^2$, $R^5$, $L^1$, and $R^6$ are as defined above with respect to Formula IIa.

Particularly preferred compounds of Formulae II, IIa, IIa-1, IIa-2, IIa-3 and lib and pharmaceutically acceptable salts and solvates thereof are those wherein $R^5$ is methyl.

In another embodiment, preferred compounds of Formula I are those of Formula III.
III

and pharmaceutically acceptable salts and solvates thereof, wherein

\[ R^2, R^3, R^4, R^5, L \text{ and } L^2 \text{ are as defined above with respect to Formula I; and} \]

\[ R^7 \text{ and } R^8 \text{ are independently selected from the group consisting of } H, \text{ halo, haloalkyl, and cyano, with the proviso that at least one of } R^7 \text{ and } R^8 \text{ is not } H; \text{ preferably } R^7 \text{ and } R^8 \text{ are independently selected from the group consisting of } H, \text{ chloro, trifluoromethyl, and cyano, with the proviso that at least one of } R^7 \text{ and } R^8 \text{ is not } H. \]

Preferred compounds of Formula III and pharmaceutically acceptable salts and solvates thereof are those wherein \( L^1 \) and \( R^2 \) are taken together to form a moiety selected from the group consisting of cycloalkylmethyl, heterocyclylmethyl, heteroarylmethyl, 2-alkoxyeth-1-yl, 3-alkoxyprop-1-yl, alkoxy carbonylmethyl, said heteroarylmethyl moiety being optionally substituted by one or more C1-C2 alkyl groups on its heteroaryl part, preferably \( L^1 \) and \( R^2 \) are taken together to form a moiety selected from the group consisting of C3-C5-cycloalkylmethyl, C5-C6-heterocyclylmethyl, C5-C6-heteroarylmethyl, 2-C1-C2-alkoxyeth-1-yl, 3-C1-C2-alkoxyprop-1-yl, alkoxy carbonylmethyl, said heteroarylmethyl moiety being optionally substituted by one or more methyl groups on its heteroaryl part, more preferably \( L^1 \) and \( R^2 \) are taken together to form a moiety selected from the group consisting of C3-C4 cycloalkylmethyl, C5-heterocyclylmethyl, C5-heteroarylmethyl, 2-methoxyeth-1-yl, 3-methoxyprop-1-yl, methoxycarbonylmethyl, said C5-heteroarylmethyl moiety being optionally substituted by one methyl group on its heteroaryl part, even more preferably \( L^1 \) and \( R^2 \) are taken together to form a moiety selected from the group consisting of C3-C4 cycloalkylmethyl, furanylmethyl, 3-methyl-1,2,4-oxadiazol-5-ylmethyl, tetrahydrofuranylmethyl or 1,3-dioxolanylmethyl, 2-methoxyeth-1-yl, 3-methoxyprop-1-yl, methoxycarbonylmethyl, still more
preferably \( L^1 \) and \( R^2 \) are taken together to form 2-methoxyeth-1-yl or tetrahydrofuranylmethyl, and still more preferably \( L^1 \) and \( R^2 \) are taken together to form tetrahydrofuranylmethyl.

In one embodiment, preferred compounds of Formula III are those of Formula Ilia

\[
\begin{align*}
\text{IIIa} & \\
\end{align*}
\]

and pharmaceutically acceptable salts and solvates thereof, wherein \( R^2, R^3, R^4, R^5, R^7, R^8 \), and \( L^1 \) are as defined above with respect to Formula III.

Particularly preferred compounds of Formula Ilia are those of Formula llb
and pharmaceutically acceptable salts and solvates thereof, wherein

R², R³, R⁴, R⁶, R⁷, R⁸, and L¹ are as defined above with respect to Formula Ilia; and

R⁶ is halo, alkyl, haloalkyl, aryl, cyano, alkoxy, haloalkoxy, alkoxy carbonyl, aminoalkoxy, alkylaminoalkoxy, dialkylaminoalkoxy, H₂O₃S-alkoxy,

![Chemical Structure](image)

wherein m is 1 to 500, preferably 1 to 50,

[N(R⁸)₃-alkoxy]⁺ Q⁻, wherein R⁸ is linear C₁-C₄-alkyl and Q⁻ is a counter anion, or

a cyclic moiety selected from the group consisting of
wherein $R^A$ is H, OH, C0-C4-alkyl-COOH or C1-C6-alkyl, $R^B$ is C1-C6-alkyl optionally substituted with -COOH, $R^C$ is C1-C6-alkyl, and $Q^-$ is a counter anion;

preferably $R^6$ is halo, C1-C2-alkyl, C1-C2-haloalkyl, phenyl, cyano, C1-C2-alkoxy, C1-C2-haloalkoxy, C1-C2-alkoxycarbonyl, aminoalkoxy, C1-C2-alkylaminoalkoxy, di-C1-C2-alkylaminoalkoxy, H0$_3$S-C2-C8-alkoxy,

\[
\begin{align*}
\text{wherein } m \text{ is 1 to 500, preferably 1 to 50, or}
\end{align*}
\]

$[N(R^8)_3\text{-C2-C6-alkoxyl}]^+Q^-$, wherein $R^8$ is C1-C2-alkyl and $Q^-$ is a counter anion,

more preferably $R^6$ is halo, C1-C2-alkyl, C1-C2-haloalkyl, phenyl, cyano, C1-C2-alkoxy, C1-C2-haloalkoxy, C1-C2-alkoxycarbonyl, aminoalkoxy, C1-C2-alkylaminoalkoxy, di-C1-C2-alkylaminoalkoxy, H0$_3$S-C2-C6-alkoxy,
[\text{N(R}^8\text{)}_3\text{-C2-C6-alkoxy}]^+ \text{Q}^-, \text{wherein } R^8 \text{ is C1-C2-alkyl and } Q^- \text{ is a counter anion,}

\begin{center}
\includegraphics[width=0.2\textwidth]{formula}
\end{center}

\text{still more preferably } R^6 \text{ is halo, methyl, trifluoromethyl, phenyl, cyano, methoxy, trifluoromethoxy, methoxycarbonyl, di-methylaminoalkoxy, HO}_3\text{S-CH2CH2O}-,\text{ wherein } m \text{ is 1 to 500, preferably 1 to 50, or}

\begin{center}
\includegraphics[width=0.2\textwidth]{formula}
\end{center}

\text{[N(R}^8\text{)}_3\text{-C2-C6-alkoxy}]^+ \text{Q}^-, \text{wherein } R^8 \text{ is methyl and } Q^- \text{ is a counter anion,}

\begin{center}
\includegraphics[width=0.2\textwidth]{formula}
\end{center}

\text{even more preferably } R^6 \text{ is chloro, fluoro, methyl, trifluoromethyl, phenyl, cyano, methoxy, trifluoromethoxy, methoxycarbonyl, di-methylaminoalkoxy, HO}_3\text{S-CH2CH2O}-, \text{ wherein } m \text{ is 1 to 500, preferably 1 to 50, or}

\begin{center}
\includegraphics[width=0.2\textwidth]{formula}
\end{center}

\text{[N(R}^8\text{)}_3\text{-C2-C6-alkoxy}]^+ \text{Q}^-, \text{wherein } R^8 \text{ is methyl and } Q^- \text{ is a counter anion.}

\text{Particularly interesting compounds of Formula } 1\text{Mb and pharmaceutically acceptable salts and solvates thereof are those, wherein } R^6 \text{ is HO}_3\text{S-alkoxy, preferably HO}_3\text{S-C2-C8-alkoxy, more preferably HO}_3\text{S-C2-C6-alkoxy, still more preferably HO}_3\text{S-CH}_2\text{CH}_2\text{O}-, \text{ in particular in form of one of its salts, such as ammonium salts, or}

\begin{center}
\includegraphics[width=0.2\textwidth]{formula}
\end{center}

\text{[N(R}^8\text{)}_3\text{-alkoxy]}^+\text{Q}^-, \text{wherein } R^8 \text{ is linear C1-C4-alkyl and } Q^- \text{ is a counter anion, preferably [N(R}^8\text{)}_3\text{-C2-C6-alkoxy]}^+\text{Q}^-, \text{wherein } R^8 \text{ is C1-C2-alkyl and } Q^- \text{ is a counter anion, more preferably [N(R}^8\text{)}_3\text{-C2-C6-alkoxy]}^+\text{Q}^-, \text{wherein } R^8 \text{ is methyl and } Q^- \text{ is a counter anion.}

\text{In one embodiment, the compounds of Formula } 1\text{Mb are selected from the group consisting of Formulae lllb-1, lllb-2, and lllb-3:}
IIIb-1

, and

IIIb-2
and pharmaceutically acceptable salts and solvates thereof,

wherein $R^2$, $R^3$, $R^4$, $R^5$, $R^7$, $R^8$, $L^1$, and $R^6$ are as defined above with respect to Formula IIIb.

Particularly preferred compounds of Formulae III, IIIa, IIIb, IIIb-1, IIIb-2 and IIIb-3 and pharmaceutically acceptable salts and solvates thereof are those wherein $R^5$ is methyl.

In another embodiment, preferred compounds of Formula I are those of Formula IV

![IV](image)
and pharmaceutically acceptable salts and solvates thereof, wherein

R², R³, R⁴, R⁵, L¹ and L² are as defined above with respect to Formula I; and

R⁹ and R¹⁰ are independently selected from the group consisting of H, halo, haloalkyl, and cyano, with the proviso that at least one of of R⁹ and R¹⁰ is not H, preferably R⁹ and R¹⁰ are independently selected from the group consisting of H, chloro, trifluoromethyl, and cyano, with the proviso that at least one of of R⁹ and R¹⁰ is not H, more preferably R⁹ and R¹⁰ are independently selected from the group consisting of H, chloro, and trifluoromethyl, with the proviso that at least one of of R⁹ and R¹⁰ is not H.

Preferred compounds of Formula IV and pharmaceutically acceptable salts and solvates thereof are those wherein L¹ and R² are taken together to form a moiety selected from the group consisting of cycloalkylmethyl, heterocyclylmethyl, heteroarylmethyl, 2-alkoxyeth-1-yl, 3-alkoxyprop-1-yl, alkoxy carbonylmethyl, said heteroarylmethyl moiety being optionally substituted by one or more C1-C2 alkyl groups on its heteroaryl part, preferably L¹ and R² are taken together to form a moiety selected from the group consisting of C3-C5-cycloalkylmethyl, C5-C6-heterocyclylmethyl, C5-C6-heteroarylmethyl, 2-C1-C2-alkoxyeth-1-yl, 3-C1-C2-alkoxyprop-1-yl, C1-C2-alkoxycarbonylmethyl, said C5-C6-heteroarylmethyl moiety being optionally substituted by one or more methyl groups on its heteroaryl part, more preferably L¹ and R² are taken together to form a moiety selected from the group consisting of C3-C4-cycloalkylmethyl, C5-heterocyclylmethyl, C5-heteroarylmethyl, 2-methoxyeth-1-yl, 3-methoxyprop-1-yl, methoxycarbonylmethyl, said C5-heteroarylmethyl moiety being optionally substituted by one methyl group on its heteroaryl part, even more preferably L¹ and R² are taken together to form a moiety selected from the group consisting of C3-C4-cycloalkylmethyl, furanylmethyl, 3-methyl-1,2,4-oxadiazol-5-ylmethyl, tetrahydrofuran ylmethyl or 1,3-dioxolan ylmethyl, 2-methoxyeth-1-yl, 3-methoxyprop-1-yl, methoxycarbonylmethyl, still more preferably L¹ and R² are taken together to form 2-methoxyeth-1-yl or tetrahydrofuranylmethyl, and still more preferably L¹ and R² are taken together to form tetrahydrofuranylmethyl.

In one embodiment, preferred compounds of Formula IV are those of Formula IVa.
and pharmaceutically acceptable salts and solvates thereof, wherein

$R^2, R^3, R^5, R^9, R^{10},$ and $L^1$ are as defined above with respect to Formula IV.

Particularly preferred compounds of Formula IVa and pharmaceutically acceptable salts and solvates thereof are those of Formula IVb.
and pharmaceutically acceptable salts, and solvates thereof, wherein

\( R^2, R^5, R^9, R^{10}, \) and \( L^1 \) are as defined above with respect to Formula IVa; and

\( R^6 \) is halo, alkyl, haloalkyl, aryl, cyano, alkoxy, haloalkoxy, alkoxycarbonyl, aminoalkoxy, alkylaminoalkoxy, dialkylaminoalkoxy, \( H_0^3 S \)-alkoxy, or

\[
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\]

\( \text{m} \) wherein \( m \) is 1 to 500, preferably 1 to 50,

\([N(R^8)_{3}-\text{alkoxy}]^+ Q^-\), wherein \( R^8 \) is linear C1-C4-alkyl and \( Q^- \) is a counter anion; or

a cyclic moiety selected from the group consisting of

\[
\begin{align*}
\text{N}^+ & \text{R}^6 \\
\text{N}^- & \text{R}^6 \\
\text{N}^+ & \text{R}^6
\end{align*}
\]

\( \text{N}^+ \) is H, OH, C0-C4-alkyl-COOH or C1-C6-alkyl, \( R^6 \) is C1-C6-alkyl optionally substituted with -COOH, \( R^6 \) is C1-C6-alkyl, and \( Q^- \) is a counter anion;

preferably \( R^6 \) is halo, C1-C2-alkyl, C1-C2-haloalkyl, phenyl, cyano, C1-C2-alkoxy, C1-C2-haloalkoxy, C1-C2-alkoxycarbonyl, aminoalkoxy, C1-C2-alkylaminoalkoxy, di-C1-C2-alkylaminoalkoxy, \( H_0^3 S \)-C2-C8-alkoxy,
[\text{N}(\text{R}^{8})_{3}-\text{C}2-\text{C}6-\text{alkoxy}]^{+} \text{Q}^{-}, \text{wherein } \text{R}^{8} \text{ is } \text{C}1-\text{C}2-\text{alkyl} \text{ and } \text{Q}^{-} \text{ is a counter anion,}

more preferably \text{R}^{6} \text{ is halo, } \text{C}1-\text{C}2-\text{alkyl, } \text{phenyl, cyano, } \text{C}1-\text{C}2-\text{alkoxy, } \text{C}1-\text{C}2-\text{haloalkoxy, } \text{C}1-\text{C}2-\text{alkoxycarbonyl, } \text{C}1-\text{C}2-\text{alkylaminoalkoxy, } \text{di-C}1-\text{C}2-\text{alkylaminoalkoxy, } \text{H}0_{3}\text{S-C}2-\text{C}6-\text{alkoxy},

\begin{equation}
\begin{array}{c}
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\end{array}
\end{equation}

\text{m, wherein m is 1 to 500, preferably 1 to 50, or}

[\text{N}(\text{R}^{8})_{3}-\text{C}2-\text{C}6-\text{alkoxy}]^{+} \text{Q}^{-}, \text{wherein } \text{R}^{8} \text{ is } \text{C}1-\text{C}2-\text{alkyl} \text{ and } \text{Q}^{-} \text{ is a counter anion,}

\text{still more preferably } \text{R}^{6} \text{ is halo, methyl, trifluoromethyl, phenyl, cyano, methoxy,}
\text{trifluoromethoxy, methoxycarbonyl, di-methylaminoalkoxy, } \text{H}0_{3}\text{S-CH}2\text{CH}2\text{0-}, \text{or}

\begin{equation}
\begin{array}{c}
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\end{array}
\end{equation}

\text{m, wherein m is 1 to 500, preferably 1 to 50, or}

[\text{N}(\text{R}^{8})_{3}-\text{C}2-\text{C}6-\text{alkoxy}]^{+} \text{Q}^{-}, \text{wherein } \text{R}^{8} \text{ is } \text{C}1-\text{C}2-\text{alkyl} \text{ and } \text{Q}^{-} \text{ is a counter anion,}

\text{even more preferably } \text{R}^{6} \text{ is chloro, fluoro, methyl, trifluoromethyl, phenyl, cyano, methoxy,}
\text{trifluoromethoxy, methoxycarbonyl, di-methylaminoalkoxy, } \text{HO}_{3}\text{S-CH}2\text{CH}2\text{0-}, \text{or}

\begin{equation}
\begin{array}{c}
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\end{array}
\end{equation}

\text{m, wherein m is 1 to 500, preferably 1 to 50, or}

\text{Particularly interesting compounds of Formula IVb and pharmaceutically}
\text{acceptable salts and solvates thereof are those, wherein } \text{R}^{6} \text{ is } \text{H}0_{3}\text{S-alkoxy, preferably } \text{HO}_{3}\text{S-C}2-\text{C}8-\text{alkoxy, more preferably } \text{H}0_{3}\text{S-C}2-\text{C}6-\text{alkoxy, still more preferably } \text{H}0_{3}\text{S-CH}2\text{CH}2\text{0-, in particular in form of one of its salts, such as ammonium salts, or}

\begin{equation}
\begin{array}{c}
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\end{array}
\end{equation}

\text{m, wherein m is 1 to 500 preferably 1 to 50, or } \text{[N}(\text{R}^{8})_{3}-\text{C}2-\text{C}6-\text{alkoxy}]^{+} \text{Q}^{-}, \text{wherein } \text{R}^{8} \text{ is } \text{methyl and } \text{Q}^{-} \text{ is a counter anion.}
alkoxy]$^+Q^-$, wherein $R^8$ is linear C1-C4-alkyl and $Q^-$ is a counter anion, preferably $[N(R^8)_3-C2-C6-alkoxy]$^+Q^-$, wherein $R^8$ is C1-C2-alkyl and $Q^-$ is a counter anion, more preferably $[N(R^8)_3-C2-C6-alkoxy]$^+Q^-$, wherein $R^8$ is methyl and $Q^-$ is a counter anion.

In one embodiment, the compounds of Formula IVb are selected from the group consisting of Formulae IVb-1, IVb-2, and IVb-3:

\[
\text{IVb-1,}
\]
and pharmaceutically acceptable salts and solvates thereof,

wherein $R^2$, $R^5$, $R^8$, $R^{10}$, $L^1$, and $R^6$ are as defined above with respect to Formula IVb.

Particularly preferred compounds of Formulae IV, IVa, IVb, IVb-1, IVb-2, and IVb-3, and pharmaceutically acceptable salts and solvates thereof are those wherein $R^5$ is methyl.
In another embodiment, preferred compounds of Formula I are those of Formula V and pharmaceutically acceptable salts, and solvates thereof, wherein

\[ \text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}', \text{L}, \text{and} \text{L}^2 \text{ are as defined above with respect to Formula I.} \]

Preferred compounds of Formula V and pharmaceutically acceptable salts and solvates thereof are those wherein \( \text{R}' \) is H, methyl or \( \text{R}' \) taken together with \( \text{L}^2 \) and \( \text{R}^3 \) form a 5- or 6-membered heterocycyl moiety which is optionally fused to an aryl moiety, preferably \( \text{R}' \) is H, methyl or \( \text{R}' \) taken together with \( \text{L}^2 \) and \( \text{R}^3 \) form a 5-membered heterocycyl moiety which is optionally fused to a phenyl moiety, more preferably \( \text{R}' \) is H, methyl or \( \text{R}' \) taken together with \( \text{L}^2 \) and \( \text{R}^3 \) form a piperazinyl moiety which is optionally fused to a phenyl moiety, even more preferably \( \text{R}' \) is H, methyl or \( \text{R}' \) taken together with \( \text{L}^2 \) and \( \text{R}^3 \) form a piperazinyl moiety which is fused to a phenyl moiety; and/or \( \text{L}^1 \) and \( \text{R}^2 \) are taken together to form a moiety selected from the group consisting of cycloalkylmethyl, heterocyclylmethyl, heteroarylmethyl, 2-alkoxyeth-1-yl, 3-alkoxyprop-1-yl, alkoxycarbonylmethyl, said heteroarylmethyl moiety being optionally substituted by one or more C1-C2 alkyl groups on its heteroaryl part, preferably \( \text{L}^1 \) and \( \text{R}^2 \) are taken together to form a moiety selected from the group consisting of C3-C5-cycloalkylmethyl, C5-C6-heterocyclylmethyl, C5-C6-heteroarylmethyl, 2-C1-C2-alkoxyeth-1-yl, 3-C1-C2-alkoxyprop-1-yl, C1-C2-alkoxycarbonylmethyl, said C5-C6-heteroarylmethyl moiety being optionally substituted by one or more methyl groups on its heteroaryl part, more preferably \( \text{L}^1 \) and \( \text{R}^2 \) are taken together to form a moiety selected from the group consisting of C3-C4-cycloalkylmethyl, C5-heterocyclylmethyl, C5-heteroarylmethyl, 2-methoxyeth-1-yl, 3-methoxyprop-1-yl, methoxycarbonylmethyl, said C5-heteroarylmethyl moiety being optionally substituted by one methyl group on its heteroaryl part, even more preferably \( \text{L}^1 \) and \( \text{R}^2 \) are taken together to form a moiety selected from the group consisting of C3-C4-cycloalkylmethyl, furanylmethyl, 3-methyl-1,2,4-oxadiazol-5-ylmethyl, tetrahydrofuranylmethyl or 1,3-dioxolanylmethyl, 2-methoxyeth-1-yl,
3-methoxyprop-1-yl, methoxycarbonylmethyl, still more preferably $L^1$ and $R^2$ are taken together to form 2-methoxyeth-1-yl or tetrahydrofuranylmethyl, and still more preferably $L^1$ and $R^2$ are taken together to form tetrahydrofuranylmethyl.

Preferred compounds of Formula V are those of Formula Va

![Formula Va](image)

and pharmaceutically acceptable salts and solvates thereof, wherein

$R^1$, $R^2$, $R^3$, $R^5$, $R'$ and $L^1$ are as defined above with respect to Formula V.

In one embodiment, preferred compounds of Formula Va are those of Formula Vb

![Formula Vb](image)

and pharmaceutically acceptable salts and solvates thereof, wherein $R^1$, $R^2$, $R^5$, $R'$, and $L^1$ are as defined above with respect to Formula Va; and

$R^6$ is halo, alkyl, haloalkyl, aryl, cyano, alkoxy, haloalkoxy, alkoxy carbonyl, aminoalkoxy,
alkylaminoalkoxy, dialkylaminoalkoxy, $H_0^3S$-alkoxy,

wherein $m$ is 1 to 500, preferably 1 to 50,

$[N(R^8)_3$-alkoxy]$^+Q^-$, wherein $R^8$ is linear C1-C4-alkyl and $Q^-$ is a counter anion, or

a cyclic moiety selected from the group consisting of

![Chemical structures]

wherein $R^A$ is H, OH, C0-C4-alkyl-COOH or C1-C6-alkyl, $R^B$ is C1-C6-alkyl optionally substituted with -COOH, $R^C$ is C1-C6-alkyl, and $Q^-$ is a counter anion,

preferably $R^8$ is halo, C1-C2-alkyl, C1-C2-haloalkyl, phenyl, cyano, C1-C2-alkoxy, C1-C2-haloalkoxy, C1-C2-alkoxycarbonyl, aminoalkoxy, C1-C2-alkylaminoalkoxy, di-C1-C2-alkylaminoalkoxy, $H_0^3S$-C2-C8-alkoxy,

wherein $m$ is 1 to 500, preferably 1 to 50, or

$[N(R^8)_3$-C2-C6alkoxy]$^+Q^-$, wherein $R^8$ is C1-C2-alkyl and $Q^-$ is a counter anion,
more preferably $R^6$ is halo, C1-C2-alkyl, C1-C2-haloalkyl, phenyl, cyano, C1-C2-alkoxy, C1-C2-haloalkoxy, C1-C2-alkoxycarbonyl, aminoalkoxy, C1-C2-alkylaminoalkoxy, di-C1-C2-alkylaminoalkoxy, $\text{HO}_3\text{S-C2-C6-alkoxy}$,

\[ \begin{array}{c}
\text{O} \\
\text{m}
\end{array} \]

wherein $m$ is 1 to 500, preferably 1 to 50, or

$[N(R^8)_3\text{-C2-C6-alkoxy}]^+Q^-$, wherein $R^8$ is C1-C2-alkyl and $Q^-$ is a counter anion,

still more preferably $R^6$ is halo, methyl, trifluoromethyl, phenyl, cyano, methoxy, trifluoromethoxy, methoxycarbonyl, di-methylaminoalkoxy, $\text{HO}_3\text{S-CH2CH2O-}$, or

\[ \begin{array}{c}
\text{O} \\
\text{m}
\end{array} \]

wherein $m$ is 1 to 500, preferably 1 to 50,

$[N(R^8)_3\text{-C2-C6-alkoxy}]^+Q^-$, wherein $R^8$ is methyl and $Q^-$ is a counter anion.

Particularly interesting compounds of Formula Vb and pharmaceutically acceptable salts and solvates thereof are those, wherein $R^6$ is $\text{HO}_3\text{S-alkoxy}$, preferably $\text{HO}_3\text{S-C2-C8-alkoxy}$, more preferably $\text{HO}_3\text{S-C2-C6-alkoxy}$, still more preferably $\text{HO}_3\text{S-CH2CH2O-}$, in particular in form of one of its salts, such as ammonium salts, or

\[ \begin{array}{c}
\text{O} \\
\text{m}
\end{array} \]

wherein $m$ is 1 to 500 preferably 1 to 50, or $[N(R^8)_3\text{-alkoxy}]^+Q^-$, wherein $R^8$ is linear C1-C4-alkyl and $Q^-$ is a counter anion, preferably $[N(R^8)_3\text{-C2-C6-alkoxy}]^+Q^-$, wherein $R^8$ is C1-C2-alkyl and $Q^-$ is a counter anion, more preferably $[N(R^8)_3\text{-C2-C6-alkoxy}]^+Q^-$, wherein $R^8$ is methyl and $Q^-$ is a counter anion.

In one embodiment, the compounds of Formula Vb are selected from the group consisting of Formulae Vb-1, Vb-2, and Vb-3:
and pharmaceutically acceptable salts and solvates thereof,

wherein $R^1$, $R^2$, $R^5$, $R'$, $L$, and $R^6$ are as defined above with respect to Formula Vb.
In one embodiment, preferred compounds of Formula Vb are those of Formula Vc:

\[
\begin{align*}
\text{Vc} & = \text{R}^7, \text{R}^5, \text{R}^6, \text{R}^8, \text{R}^9 \text{ and L}^1 \text{ are as defined above with respect to Formula Vb; and} \\
\text{R}^7 \text{ and } \text{R}^8 \text{ are independently selected from the group consisting of H, halo, haloalkyl, and cyano, with the proviso that at least one of } \text{R}^7 \text{ and } \text{R}^8 \text{ is not H; preferably } \text{R}^7 \text{ and } \text{R}^8 \text{ are independently selected from the group consisting of H, chloro, trifluoromethyl, and cyano, with the proviso that at least one of } \text{R}^7 \text{ and } \text{R}^8 \text{ is not H, more preferably } \text{R}^7 \text{ is H and } \text{R}^8 \text{ is chloro.}
\end{align*}
\]

In one embodiment, the compounds of Formula Vc are selected from the group consisting of Formulae Vc-1, Vc-2, and Vc-3:
Vc-1,

Vc-2, and
Vc-3,

and pharmaceutically acceptable salts and solvates thereof,

wherein $R_2$, $R_5$, $R_6$, $R_7$, $R_8$, $R'$, and $L^1$ are as defined above with respect to Formula Vc.

Particularly preferred compounds of Formulae V, Va, Vb, Vb-1, Vb-2, Vb-3, Vc, Vc-1, Vc-2, Vc-3 and pharmaceutically acceptable salts and solvates thereof are those wherein $R_5$ is methyl.

In a particularly preferred embodiment, the compounds of Formula I, any of its subformulae, and their pharmaceutically acceptable salts and solvates as described herein are those wherein $R_2$ is tetrahydrofuranyl, preferably $L^1$ is $C_2H_2$ and $R_2$ is tetrahydrofuranyl, more preferably they have Formula VI.

\[ \text{VI} \]
wherein $R^1$, $R^3$, $R^4$, $R^5$, $X$, and $L^2$ are as defined above with respect to Formula I or any of its subformulae and corresponding embodiments.

Particularly preferred compounds of the invention are those listed in Table 1 hereafter:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
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The compounds of the invention and their pharmaceutically acceptable salts and solvates can be prepared by different ways with reactions known by the person skilled in the art. Reaction schemes as described in the example section illustrate by way of example different possible approaches.

The invention further provides the use of the compounds of the invention or pharmaceutically acceptable salts, and/or solvates thereof as agonists of TGR5, in particular agonists of TGR5 having low or no systemic activity.

Accordingly, in a particularly preferred embodiment, the invention relates to the use of compounds of Formula I and subformulae in particular those of Table 1 above, or pharmaceutically acceptable salts and solvates thereof, as TGR5 agonists, in particular agonists of TGR5 having low or no systemic activity.

**[APPLICATIONS]**

The compounds of the invention are therefore useful in the prevention and/or the treatment of TGR5 related diseases, such as metabolic and/or gastrointestinal diseases.

The invention thus also relates to the use of a compound of the invention or a
pharmaceutically acceptable salt and/or solvate thereof for use in treating and/or preventing a TGR5 related disease, in particular a metabolic and/or a gastrointestinal disease. Or in other terms, the invention also relates to a method of treating and/or preventing a TGR5 related disease, in particular a metabolic and/or a gastrointestinal disease comprising the administration of a therapeutically effective amount of a compound or pharmaceutically acceptable salt or solvate of the invention, to a patient in need thereof. Preferably the patient is a warm-blooded animal, more preferably a human.

Metabolic diseases within the meaning of the present invention include, but are not limited to, type II diabetes, obesity, dyslipidemia such as mixed or diabetic dyslipidemia, hypercholesterolemia, low HDL cholesterol, high LDL cholesterol, hyperlipidemia, hypertriglyceridemia, hypoglycemia, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia hypertension, hyperlipoproteinemia, metabolic syndrome, syndrome X, thrombotic disorders, cardiovascular disease, atherosclerosis and its sequelae including angina, claudication, heart attack, stroke and others, kidney diseases, ketoacidosis, nephropathy, diabetic neuropathy, diabetic retinopathy, nonalcoholic fatty liver diseases such as steatosis or nonalcoholic steatohepatitis (NASH).

In a preferred embodiment, the metabolic disease is type II diabetes, a lipid disorder such as dyslipidemia, hypertension, obesity, or atherosclerosis and its sequelae.

In a particularly preferred embodiment the diseases are type II diabetes and a lipid disorder such as dyslipidemia, preferably type II diabetes.

Gastrointestinal diseases within the meaning of the present invention include, but are not limited to, Inflammatory Bowel Diseases (IBD) including but not limited to colitis, Ulcerative colitis (UC) and Crohn's Disease (CD), and Irritable Bowel Syndrome (IBS), intestinal injury disorders such as short-bowel syndrome, diseases involving intestinal barrier dysfunction such as proctitis and pouchitis, and gastrointestinal disorders characterized by hypermotilinemia or gastrointestinal hypermotility, including but not limited to any type of diarrhea.

In a preferred embodiment, the gastrointestinal disease is Inflammatory Bowel Diseases (IBD) including but not limited to colitis, Ulcerative colitis (UC) and Crohn's Disease (CD).

The invention also provides for a compound of the invention or a pharmaceutically acceptable salt and/or solvate thereof for use in delaying the onset of a TGR5 related disease, such as a metabolic and/or a gastrointestinal disease. Or in other terms, the
invention also provides for a method for delaying in patient the onset of a TGR5 related
diseases, such as a metabolic and/or a gastrointestinal disease comprising the administration of
a therapeutically effective amount of a compound or pharmaceutically acceptable salt or solvate
of the invention, to a patient in need thereof. Preferably the patient is a warm-blooded animal,
more preferably a human. The metabolic and/or gastrointestinal diseases are preferably those
defined above.

The invention further provides the use of a compound of the invention or a
pharmaceutically acceptable salt and/or solvate thereof for the manufacture of a medicament
for use in treating and/or preventing TGR5 related diseases, in particular metabolic and/or
gastrointestinal diseases. Preferably, the metabolic and/or gastrointestinal diseases are those
defined above.

According to a further feature of the present invention, there is provided the use
of a compound of the invention or a pharmaceutically acceptable salt and/or solvate for
modulating TGR5 receptor activity, in a patient, in need of such treatment, comprising
administering to said patient an effective amount of a compound of the present invention, or a
pharmaceutically acceptable salt and/or solvate thereof. In other terms, the invention also
provides a a method for modulating TGR5 receptor activity, in a patient, in need of such
treatment, which comprises administering to said patient an effective amount of a compound of
the present invention, or a pharmaceutically acceptable salt and/or solvate thereof. Preferably,
the patient is a warm blooded animal, and even more preferably a human.

According to one embodiment, the compounds of the invention, their
pharmaceutical acceptable salts and/or solvates may be administered as part of a combination
therapy. Thus, are included within the scope of the present invention embodiments comprising
coadministration of, and compositions and medicaments which contain, in addition to a
compound of the present invention, a pharmaceutically acceptable salt and/or solvate thereof as
active ingredient, additional therapeutic agents and/or active ingredients. Such multiple drug
regimens, often referred to as combination therapy, may be used in the treatment and/or
prevention of any of the diseases or conditions related to with TGR5 receptor modulation,
particularly type II diabetes, obesity, dyslipidemia such as mixed or diabetic dyslipidemia,
hypercholesterolemia, low HDL cholesterol, high LDL cholesterol, hyperlipidemia,
hypertriglyceridemia, hypoglycemia, hyperglycemia, glucose intolerance, insulin resistance,
hyperinsulinemia, hypertension, hyperlipoproteinemia, metabolic syndrome, syndrome X,
thrombotic disorders, cardiovascular disease, atherosclerosis and its sequelae including angina,
claudication, heart attack, stroke and others, kidney diseases, ketoacidosis, nephropathy,
diabetic neuropathy, diabetic retinopathy, nonalcoholic fatty liver diseases such as steatosis or
nonalcoholic steatohepatitis (NASH). The use of such combinations of therapeutic agents is especially pertinent with respect to the treatment of the above-mentioned list of diseases within a patient in need of treatment or one at risk of becoming such a patient.

In addition to the requirement of therapeutic efficacy, which may necessitate the use of active agents in addition to the TGR5 agonist compounds of the invention or their pharmaceutical acceptable salts and/or solvates thereof, there may be additional rationales which compel or highly recommend the use of combinations of drugs involving active ingredients which represent adjunct therapy, i.e., which complement and supplement the function performed by the TGR5 receptor agonist compounds of the present invention. Suitable supplementary therapeutic agents used for the purpose of auxiliary treatment include drugs which, instead of directly treating or preventing a disease or condition related to TGR5 receptor modulation, treat diseases or conditions which directly result from or indirectly accompany the basic or underlying TGR5 receptor related disease or condition.

Thus, the methods of treatment and pharmaceutical compositions of the present invention may employ the compounds of the invention or their pharmaceutical acceptable salts and/or solvates thereof in the form of monotherapy, but said methods and compositions may also be used in the form of multiple therapy in which one or more compounds of the invention or their pharmaceutically acceptable salts and/or solvates are coadministered in combination with one or more other therapeutic agents.

The invention also provides pharmaceutical compositions comprising a compound of the invention or a pharmaceutically acceptable salt and/or solvate thereof and at least one pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant. As indicated above, the invention also covers pharmaceutical compositions which contain, in addition to a compound of the present invention, a pharmaceutically acceptable salt and/or solvate thereof as active ingredient, additional therapeutic agents and/or active ingredients.

Another object of this invention is a medicament comprising at least one compound of the invention, or a pharmaceutically acceptable salt and/or solvate thereof, as active ingredient.

Generally, for pharmaceutical use, the compounds of the invention or a pharmaceutically acceptable salt and/or solvate thereof may be formulated as a pharmaceutical preparation comprising at least one compound of the invention or a pharmaceutically acceptable salt and/or solvate thereof and at least one pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant, and optionally one or more further pharmaceutically active compounds.
By means of non-limiting examples, such a formulation may be in a form suitable for oral administration, for parenteral administration (such as by intravenous, intramuscular or subcutaneous injection or intravenous infusion), for topical administration (including ocular), for administration by inhalation, by a skin patch, by an implant, by a suppository, etc. Such suitable administration forms - which may be solid, semi-solid or liquid, depending on the manner of administration - as well as methods and carriers, diluents and excipients for use in the preparation thereof, will be clear to the skilled person; reference is made to the latest edition of Remington's Pharmaceutical Sciences.

[DEFINITIONS]

The definitions and explanations below are for the terms as used throughout the entire application, including both the specification and the claims.

Unless otherwise stated any reference to compounds of the invention herein, means the compounds as such as well as there pharmaceutically acceptable salts and/or solvates.

When describing the compounds of the invention, the terms used are to be construed in accordance with the following definitions, unless indicated otherwise.

The term "halo" or "halogen" means fluoro, chloro, bromo, or iodo. Preferred halo groups are fluoro and chloro, fluoro being particularly preferred.

The term "alkyl" by itself or as part of another substituent refers to a hydrocarbyl radical of Formula C\(_n\)H\(_{2n+1}\) wherein \(n\) is a number greater than or equal to 1. Suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl and i-butyl.

The term "haloalkyl" alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen as defined above. Non-limiting examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like. A preferred haloalkyl radical is trifluoromethyl.

The terms "heterocyclic", "heterocycloalkyl" or "heterocyclyl" as used herein by itself or as part of another group refer to non-aromatic, fully saturated or partially unsaturated cyclic groups (for example, 3 to 7 member monocyclic, 7 to 11 member bicyclic, or containing a total of 3 to 10 ring atoms) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen, oxygen and/or sulfur atoms, where the nitrogen and
sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. Any of the carbon atoms of the heterocyclic group may be substituted by oxo (for example piperidone, pyrrolidinone). The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system, where valence allows. The rings of multi-ring heterocycles may be fused, bridged and/or joined through one or more spiro atoms. Non limiting exemplary heterocyclic groups include oxetanyl, piperidinyl, azetidinyl, 2-imidazolinyl, pyrazolidinyl imidazolidinyl, isoaxazolyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, piperidinyl, 3H-indolyl, indoliny, isoindoliny, 2-oxopiperazinyl, piperazinyl, homopiperazinyl, 2-pyrazolinyl, 3-pyrazoliny, tetrahydro-2H-pyranyl, 2H-pyranyl, 4H-pyranyl, 3,4-dihydro-2H-pyranyl, 3-dioxolanyl, 1,4-dioxany, 2,5-dioximidazolidinyl, 2-oxopiperidinyl, 2-oxopyrroolidinyl, indoliny, tetrahydropyranyl, tetrahydrofurany, tetrahydroquinoliny, tetrahydroisquinoliny-1-yl, tetrahydroisquinolin-2-yl, tetrahydroisquinolin-3-yl, tetrahydroisquinoliny-4-yl, thiomorpholin-4-yl, thiomorpholin-4-ylsulfoxide, thiomorpholin-4-ylsulfone, 1,3-dioxolany, 1,4-oxath iany, 1H-pyrrol iziny, tetrahydro-1,1-dioxothiophenyl, N-formylpiperazinyl, and morpholin-4-yl.

The term "aryl" as used herein refers to a polyunsaturated, aromatic hydrocarbyl group having a single ring (i.e. phenyl) or multiple aromatic rings fused together (e.g. naphtyl), typically containing 5 to 12 atoms; preferably 6 to 10, wherein at least one ring is aromatic. The aromatic ring may optionally include one to two additional rings (either cycloalky, heterocyclyl or heteroaryl) fused thereto. Non-limiting examples of aryl comprise phenyl, biphenyl, biphenylenyl, 5- to 6-tetralinyl, napthalen-1- or -2-y1, 4-, 5-, 6 or 7-indenyl, 1-2-, 3-, 4- or 5-acenaphtylenyl, 3-, 4- or 5-acenaphtenyl, 1- or 2-pentaleny, 4- or 5-indany, 5-, 6-, 7- or 8-tetrahydro-1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl, 1-,2-, 3-, 4- or 5-pyrenyl.

The term "heteroaryl" as used herein by itself or as part of another group refers but is not limited to 5 to 12 carbon-atom aromatic rings or ring systems containing 1 to 2 rings which are fused together, typically containing 5 to 6 atoms; at least one of which is aromatic, in which one or more carbon atoms in one or more of these rings is replaced by oxygen, nitrogen and/or sulfur atoms where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. Such rings may be fused to an aryl, cycloalky, heteroaryl or heterocyclyl ring. Non-limiting examples of such heteroaryl, include: furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, oxatriazolyl, thiatriazolyl, pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl, oxazinyl, dioxinyl, thiazinyl, triazinyl, imidazo[2,1-b][1,3]thiazolyl, thieno[3,2-b]furany, thieno[3,2-b]thiophenyl, thieno[2,3-d][1,3]thiazolyl, thieno[2,3-d]imidazolyl, tetrazol[1,5-a]pyridinyl, indolyl, indolizinyl, isoindolyl, benzofurananyl, isobenzofurananyl, benzothiophenyl, isobenzothiophenyl, indazolyl, benzimidazolyl, 1,3-benzoaxazolyl, 1,2-
benzisoxazolyl, 2,1-benzisoxazolyl, 1,3-benzothiazolyl, 1,2-benzoisothiazolyl, 2,1-
benzoisothiazolyl, benzotriazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzoxadiazolyl, 1,2,3-
benzothiadiazolyl, 2,1,3-benzothiadiazolyl, thienopyridinyl, purinyl, imidazo[1,2-a]pyridinyl, 6-
oxo-pyridazin-1 (6H)-yl, 2-oxopyridin-1 (2H)-yl, 6-oxo-pyridazin-1 (6H)-yl, 2-oxopyridin-1 (2H)-yl,
1,3-benzodioxolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl.

The compounds of Formula I and subformulae thereof may contain at least one
asymmetric center and thus may exist as different stereoisomeric forms. Accordingly, the
present invention includes all possible stereoisomers and includes not only racemic compounds
but the individual enantiomers and their non racemic mixtures as well. When a compound is
desired as a single enantiomer, such may be obtained by stereospecific synthesis, by resolution
of the final product or any convenient intermediate, or by chiral chromatographic methods as
each are known in the art. Resolution of the final product, an intermediate, or a starting material
may be carried out by any suitable method known in the art. See, for example, Stereochemistry
incorporated by reference with regard to stereochemistry.

The bonds from an asymmetric carbon in compounds of the present invention
may be depicted herein using a solid line (—), a zigzag line (— — — —), a solid wedge (—), or
a dotted wedge (-- ). The use of a solid line to depict bonds from an asymmetric carbon atom
is meant to indicate that all possible stereoisomers are meant to be included, unless it is clear
from the context that a specific stereoisomer is intended. The use of either a solid or dotted
wedge to depict bonds from an asymmetric carbon atom is meant to indicate that only the
stereoisomer shown is meant to be included.

The compounds of the invention may also contain more than one asymmetric
carbon atom. In those compounds, the use of a solid line to depict bonds from asymmetric
carbon atoms is meant to indicate that all possible stereoisomers are meant to be included,
unless it is clear from the context that a specific stereoisomer is intended.

The compounds of the invention containing a basic functional group and/or an
acidic functional group may be in the form of pharmaceutically acceptable salts. Pharmaceutically
acceptable salts of the compounds of the invention containing one or more
basic functional group include in particular the acid addition salts thereof. Suitable acid addition
salts are formed from acids which form non-toxic salts. Examples include the acetate, adipate,
aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camyslate,
citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate,
hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide,
hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts. Compounds containing one or more acidic functional groups may be capable of forming pharmaceutically acceptable salts with a pharmaceutically acceptable base, for example and without limitation, inorganic bases based on alkaline metals or alkaline earth metals or organic bases such as ammonia (NH₃) and primary amine compounds, secondary amine compounds, tertiary amine compounds, cyclic amines or basic ion exchange resins. Compounds containing one or more basic functional groups may be capable of forming pharmaceutically acceptable salts, e.g. amine groups may be transformed into ammonium groups by reacting the amine group with an inorganic or organic base or an alkylating agent such as e.g. an alkylhalide (e.g. methyliodide). When the compounds of the invention contain an acidic group as well as a basic group the compounds of the invention may also form internal salts, and such compounds are within the scope of the invention.

Generally, pharmaceutically acceptable salts of compounds of Formula I may for example be prepared as follows:

(i) by reacting the compound of Formula I with the desired acid;

(ii) by reacting the compound of Formula I with the desired base;

(iii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of Formula I or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid; or

(iv) by converting one salt of the compound of Formula I to another by reaction with an appropriate acid or by means of a suitable ion exchange column.

All these reactions are typically carried out in solution. The salt, may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the salt may vary from completely ionized to almost non-ionized.

The term "solvate" is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

All references to compounds of Formula I include references to salts and solvates thereof.
The compounds of the invention include compounds of Formula I as hereinbefore defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) and isotopically-labeled compounds of Formula I.

In addition, although generally, with respect to the salts of the compounds of the invention, pharmaceutically acceptable salts are preferred, it should be noted that the invention in its broadest sense also includes non-pharmaceutically acceptable salts, which may for example be used in the isolation and/or purification of the compounds of the invention. For example, salts formed with optically active acids or bases may be used to form diastereoisomeric salts that can facilitate the separation of optically active isomers of the compounds of Formula I above.

The term "patient" refers to a warm-blooded animal, more preferably a human, who/which is awaiting or receiving medical care or is or will be the object of a medical procedure.

The term "human" refers to subjects of both genders and at any stage of development (i.e. neonate, infant, juvenile, adolescent, adult). In one embodiment, the human is an adolescent or adult, preferably an adult.

The terms "treat", "treating" and "treatment", as used herein, are meant to include alleviating or abrogating a condition or disease and/or its attendant symptoms.

The terms "prevent", "preventing" and "prevention", as used herein, refer to a method of delaying or precluding the onset of a condition or disease and/or its attendant symptoms, barring a patient from acquiring a condition or disease, or reducing a patient's risk of acquiring a condition or disease.

The term "therapeutically effective amount" (or more simply an "effective amount") as used herein means the amount of active agent or active ingredient (e.g. TGR5 agonist) which is sufficient to achieve the desired therapeutic or prophylactic effect in the individual to which it is administered.

The term "administration", or a variant thereof (e.g./"administering"), means providing the active agent or active ingredient (e.g. a TGR5 agonist), alone or as part of a pharmaceutically acceptable composition, to the patient in whom/which the condition, symptom, or disease is to be treated or prevented.

By "pharmaceutically acceptable" is meant that the ingredients of a
pharmaceutical composition are compatible with each other and not deleterious to the patient thereof.

The term "agonist" as used herein means a ligand that activates an intracellular response when it binds to a receptor.

The term "pharmaceutical vehicle" as used herein means a carrier or inert medium used as solvent or diluent in which the pharmaceutically active agent is formulated and/or administered. Non-limiting examples of pharmaceutical vehicles include creams, gels, lotions, solutions, and liposomes.

The term "lipid disorder" as used herein means any plasma lipid disorder including but not limited to dyslipidemia such as mixed or diabetic dyslipidemia, hypercholesterolemia, low HDL cholesterol, high LDL cholesterol, hyperlipidemia and hypertriglyceridemia.

The present invention will be better understood with reference to the following examples. These examples are intended to representative of specific embodiments of the invention, and are not intended as limiting the scope of the invention.

CHEMISTRY EXAMPLES

All reagents, solvents and starting materials were purchased from commercial suppliers and used without further purification. $^1$H NMR spectra were recorded on a Brucker Avance 300 MHz spectrometer with methanol-d6, CDCl$_3$ or DMSO-d6 as the solvent. $^{13}$C NMR spectra are recorded at 100 MHz. All coupling constants are measured in hertz (Hz) and the chemical shifts ($\delta$) are quoted in parts per million (ppm). Liquid chromatography mass spectroscopy analyses (LC-MS) were performed using LCMS-MS triple-quadrupole system (Waters) with a C18 TSK-GEL Super ODS (2 $\mu$m particle size column, 50 * 4.6 mm). LCMS gradient starting from 98% H$_2$O / 0.1% formic acid and reaching 2% H2O / 98% MeOH within 5 min (method A) at a flow rate of 2 mL/min or starting from 100% H$_2$O / 0.1% formic acid and reaching 5% H$_2$O / 95% MeOH within 10 min (method B) at a flow rate of 1 mL/min was used.

Purity (%) was determined by Reversed Phase HPLC, using UV detection (215 nM). High resolution mass spectroscopy (HRMS) were carried out on a Waters LCT Premier XE (TOF), ESI ionization mode, with a Waters XBridge C18 (150*4.6 mm, 3.5 $\mu$m particle size). LCMS gradient starting from 98% ammonium formate buffer 5 mM (pH 9.2) and reaching 95% CH3CN / 5% ammonium formate buffer 5 mM (pH 9.2) within 15 min at a flow rate of 1 mL/min was used.

Solvents, reagents and starting materials were purchased from well-known
Solvents, reagents and starting materials were purchased from well known chemical suppliers such as for example Sigma Aldrich, Acros Organics, Fluorochem, Eurisotop, VWR International, Sopachem and Polymer labs.

As illustrated in the Examples hereafter, the compounds of the invention bearing a
polyethylenoxy side chain \((OCH_2CH_2)_m\) may be prepared from poly(ethylene glycol) starting materials which are in the form of a polydisperse mixture of polymers having different degrees of polymerization \((i.e.\) the chain lengths) \((m)\). These starting materials are thus characterized by a degree of polymerization given in the form of range and/or by a Mn.

Therefore, the exemplified compounds of the invention bearing a polyethylenoxy side chain \((OCH_2CH_2)_m\) may be obtained as mixtures of compounds having different degrees of polymerization \((m)\) given as a range.

Therefore, within the meaning of the invention, a compound of the invention having a moiety of the following formula

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{m}
\end{array}
\]

wherein the degree of polymerization \(m\) is identified as range, \(i.e.\) as \(m\) is \(x\) to \(y\) or as \(m=x-y\), \(x\) and \(y\) being integers different from one another, are comprised all compounds bearing said moiety with a polymerization degree superior or equal to \(x\) and inferior or equal to \(y\) as well as mixtures thereof.

For instance, in the compound depicted by the following formula

![Formula Image]

the indication \(m=8-13\) means that all compounds with \(m\) superior or equal to \(8\) and inferior or equal to \(13\) as well as mixtures thereof are comprised within this formula.

**GENERAL PROCEDURE A.**

Appropriate aldehyde \((1\) equiv), meldrum acid \((1\) equiv), acetoacetate \((1\) equiv) and ammonium acetate \((1.5\) equiv) were dissolved in acetic acid \((1\) N). The reaction mixture was stirred overnight under reflux. The solvent was removed. The crude was precipitated in EtOH and filtered to give the desired compound.

Table 2
**EXAMPLE 1:** 2-Methyl-6-oxo-4-o-tolyl-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester

2-Methyl-6-oxo-4-o-tolyl-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester was prepared according to general protocol A, starting from 2-methylbenzaldehyde (0.27 ml), benzoyl acetylacetate (384 mg) and obtained as a white powder (137 mg, 20%) after purification by preparative LC-MS, $^1$H NMR (CDCl$_3$) $\delta$ 7.61 (s, 1H); 7.30-6.95 (m, 9H); 5.14 (d, J=12.6 Hz, 1H); 5.08 (d, J=12.6 Hz, 1H); 4.26 (d, J=7.4Hz, 1H); 2.93 (ddd, J=16.5Hz and 8.1Hz, 1H); 2.70 (ddd, J=16.5Hz and 1.2Hz, 1H); 2.43 (s, 3H); 2.29 (s, 3H); MS [M+H]$^+$ =336; HRMS: calcd for C$_{2}$H$_{22}$NO$_{3}$, (MH$^+$) 336.1600, found 336.1588

**EXAMPLE 2:** 2-Methyl-6-oxo-4-m-tolyl-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester

2-Methyl-6-oxo-4-m-tolyl-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester was prepared according to general protocol A, starting from 3-methylbenzaldehyde (0.27 ml), benzoyl acetylacetate (384 mg) and obtained as a white powder (78 mg, 11%) after precipitation in ethanol. $^1$H NMR (CDCl$_3$) $\delta$ 7.41 (s, 1H); 7.30-6.95 (m, 9H); 5.14 (d, J=12.6 Hz, 1H); 5.08 (d, J=12.6 Hz, 1H); 4.26 (d, J=7.4Hz, 1H); 2.93 (dd, J=16.5Hz and 8.1Hz, 1H); 2.70 (ddd, J=16.5Hz and 1.2Hz, 1H); 2.43 (s, 3H); 2.29 (s, 3H); MS [M+H]$^+$ =336; HRMS: calcd for C$_{2}$H$_{22}$NO$_{3}$, (MH$^+$)
EXAMPLE 3: 2-Methyl-6-oxo-4-p-tolyl-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester

2-Methyl-6-oxo-4-p-tolyl-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester was prepared according to general protocol A, starting from 4-methylbenzaldehyde (0.27 ml), benzoyl acetylacetate (384 mg) and obtained as a white powder (137 mg, 20%) after precipitation in ethanol. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.58 (s, 1H); 7.30-7.04 (m, 9H); 5.12 (s, 2H); 4.27 (d, \(J=7.5\) Hz, 1H); 2.93 (dd, \(J=16.5\) Hz and 8.0 Hz, 1H); 2.68 (dd, \(J=16.5\) Hz and 1.2 Hz, 1H); 2.42 (s, 3H); 2.32 (s, 3H);

MS[M+H]+ =336; HRMS: calcd for C\(_{21}\)H\(_{22}\)NO\(_3\), (MH\(^+\)) 336.1600, found 336.1591

EXAMPLE 4: 4-(2-Methoxy-phenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester

4-(2-Methoxy-phenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester was prepared according to general protocol A, starting from 2-methoxybenzaldehyde (150 mg), benzoyl acetylacetate (210 mg) and obtained as a white powder (63 mg) after precipitation in ethanol (16%). \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.51 (s, 1H); 7.25-6.81 (m, 9H); 5.07 (d, \(J=12.7.0\) Hz, 1H); 5.03 (d, \(J=12.7.0\) Hz, 1H); 4.67 (d, \(J=8.2\) Hz, 1H); 3.79 (s, 3H); 2.86 (dd, \(J=16.6\) Hz and 7.9 Hz, 1H); 2.70 (d, \(J=16.7\) Hz, 1H); 2.46 (s, 3H); MS [M+H]+ = 352; HRMS: calcd for C\(_2\)H\(_{22}\)NO\(_4\), (MH\(^+\)) 352.1549, found 352.1548

EXAMPLE 5: 4-(3-Methoxy-phenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester

4-(3-Methoxy-phenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester was prepared according to general protocol A, starting from 3-methoxybenzaldehyde (0.3 ml), benzoyl acetylacetate (384 mg) and obtained as a white powder (36 mg, 5%) after precipitation in ethanol. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.52 (s, 1H); 7.30-6.70 (m, 9H); 5.14 (d, \(J=12.7\) Hz, 1H); 5.09 (d, \(J=12.7\) Hz, 1H); 4.27 (d, \(J=7.2\) Hz, 1H); 3.74 (s, 3H); 2.93 (dd, \(J=16.5\) Hz and 8.1 Hz, 1H); 2.70 (dd, \(J=16.5\) Hz and 1.1 Hz, 1H); 2.43 (s, 3H); MS[M+H]+ = 352; HRMS: calcd for C\(_2\)H\(_{22}\)NO\(_4\), (MH\(^+\)) 352.1549, found 352.1548

EXAMPLE 6: 4-(4-Methoxy-phenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester

4-(4-Methoxy-phenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester was prepared according to general protocol A, starting from 4-methoxybenzaldehyde (0.3 ml), benzoyl acetylacetate (384 mg) and obtained as a yellow powder (27mg, 5%) after purification by preparative LC-MS.; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.59 (s, 1H); 7.31-6.79 (m, 9H); 5.14 (d, \(J=12.5\) Hz, 1H); 5.09 (d, \(J=12.5\) Hz, 1H); 4.25 (d, \(J=7.3\) Hz, 1H); 3.79 (s, 3H); 2.91 (dd, \(J=16.4\) Hz and 8.0 Hz,
EXAMPLE 7: 2-Methyl-6-oxo-4-(2-trifluoromethyl-phenyl)-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester

2-Methyl-6-oxo-4-(2-trifluoromethyl-phenyl)-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester was prepared according to general protocol A, starting from 2-trifluoromethylbenzaldehyde (0.27 mL), benzoyl acetylacetate (384 mg) and obtained as a white powder (138 mg, 18%) after precipitation in ethanol. $^1$H NMR (CDCl$_3$) $\delta$ 7.66 (s, 1H); 7.64-6.96 (m, 9H); 5.04 (d, $J$=12.3 Hz, 1H); 4.98 (d, $J$=12.3 Hz, 1H); 4.70 (d, $J$=8.7 Hz, 1H); 3.00 (dd, $J$=16.8 Hz and 9Hz, 1H); 2.65 (d, $J$=17.3 Hz, 1H); 2.48 (s, 3H); MS[M+H]$^+$ = 390; HRMS: calcd for C$_{21}$H$_{19}$NO$_3$F$_3$, (MH$^+$) 390.1317, found 390.1306

EXAMPLE 8: 2-Methyl-6-oxo-4-(3-trifluoromethyl-phenyl)-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester

2-Methyl-6-oxo-4-(3-trifluoromethyl-phenyl)-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester was prepared according to general protocol A, starting from 3-trifluoromethylbenzaldehyde (0.45 mL), benzoyl acetylacetate (384 mg) and obtained as a white powder (141 mg, 18%) after precipitation in ethanol. $^1$H NMR (CDCl$_3$) $\delta$ 7.71 (s, 1H); 7.51-7.1 1 (m, 9H); 5.14 (d, $J$=12.6 Hz, 1H); 5.07 (d, $J$=12.6 Hz, 1H); 4.35 (d, $J$=7.9 Hz, 1H); 2.99 (dd, $J$=16.6 Hz and 8.3Hz, 1H); 2.69 (d, $J$=16.5Hz, 1H); 2.46 (s, 3H); MS [M+H]$^+$ = 390; HRMS: calcd for C$_{21}$H$_{19}$NO$_3$F$_3$, (MH$^+$) 390.1317, found 390.1319

EXAMPLE 9: 2-Methyl-6-oxo-4-(4-trifluoromethyl-phenyl)-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester

2-Methyl-6-oxo-4-(4-trifluoromethyl-phenyl)-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester was prepared according to general protocol A, starting from 4-trifluoromethylbenzaldehyde (0.44 mL), benzoyl acetylacetate (384 mg) and obtained as a white powder (96 mg, 13%) after precipitation in ethanol. $^1$H NMR (CDCl$_3$) $\delta$ 7.59 (s, 1H); 7.54-7.09 (m, 9H); 5.15 (d, $J$=12.5 Hz, 1H); 5.06 (d, $J$=12.5 Hz, 1H); 4.34(d, $J$=7.7 Hz, 1H); 2.99 (dd, $J$=16.6 Hz and 8.2Hz, 1H); 2.69 (d, $J$=16.7Hz, 1H); 2.45 (s, 3H); MS [M+H]$^+$=390; HRMS: calcd for C$_{21}$H$_{19}$NO$_3$F$_3$, (MH$^+$) 390.1317, found 390.131 1

EXAMPLE 10: 4-(2-Chloro-phenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester

4-(2-Chloro-phenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester was prepared according to general protocol A, starting from 2-chlorobenzaldehyde (0.19 mL), benzoyl acetylacetate (205 mg). 26 mg of white powder were obtained after precipitation in
ethanol. $^1$H NMR (CDCl$_3$) $\delta$: 7.65 (s, 1 H, NH); 7.41-7.05 (m, 9 H, ArH); 5.08 (d, $J$=12.7 Hz, 1H, CH$_2$); 5.04 (d, $J$=2.7 Hz, 1H, CH$_3$); 4.79 (d, $J$=8.25Hz, 1H, CH); 2.94 (dd, $J$=1 6.7Hz and 8.5Hz, 1H, CH$_2$); 2.73 (d, $J$=16,7Hz, 1H, CH$_2$); 2.50 (s, 3H, CH$_3$); MS [M+H]$^+$ 356; HRMS: calcld for C$_3$H$_9$NO$_3$Cl, (MH$^+$) 356.1053, found 356.1048

EXAMPLE 11: 4-(3-Chloro-phenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester

4-(3-Chloro-phenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-ca rboxylic acid benzyl ester was prepared according to general protocol A, starting from 3-chlorobenzaldehyde (0.35 mL), benzoyl acetylacetate (384 mg) and obtained as a white powder (185 mg, 26 %) after precipitation in ethanol $^1$H NMR (CDCl$_3$) $\delta$: 7,54 (s, 1H); 7,32-7,03 (m, 9H); 5,14 (d, $J$=12.4 Hz, 1H); 5,07 (d, $J$=1.2 4 Hz, 1H); 4.27 (d, $J$=7.7Hz, 1H); 2.95 (dd, $J$=16,6Hz and 8,2Hz, 1H); 2.68 (dd, $J$=1 6.6Hz and 0,9Hz, 1H); 2.45 (s, 3H); MS [M+H]$^+$=356; HRMS: calcld for C$_{20}$H$_{19}$NO$_3$Cl, (MH$^+$) 390.1053, found 390.1058

EXAMPLE 12: Benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate

Benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate was prepared according to general protocol A, starting from p-chlorobenzaldehyde (15 mmol, 2.108 g), benzoyl acetylacetate (15 mmol, 2.58 mL) and obtained as a pale yellow powder (1.54 g, 29%) after precipitation in ethanol. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 2.44 (s, 3H), 2.66 (dd, $J$=16.6Hz and 1.5 Hz, 1H), 2.95 (dd, $J$=16.6hz and 8.2 Hz, 1H), 4.27 (d, $J$=8.2 Hz, 1H), 5.08 (d, $J$=12.6 Hz, 1H), 5.15 (d, $J$=12.6 Hz, 1H), 7.10 (d, $J$=8.5 Hz, 2H), 7.13-7.18 (m, 2H), 7.25 (d, $J$=8.5 Hz, 2H), 7.29-7.33 (m, 3H), 8.40 (s, 1H). MS [M+H]$^+$=356

EXAMPLE 13: 4-(4-Fluoro-phenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester

4-(4-Fluoro-phenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-ca rboxylic acid benzyl ester was prepared according to general protocol A, starting from 4-fluorobenzaldehyde (0.22 mL), benzoyl acetylacetate (384 mg) and obtained as a white powder (122 mg) after precipitation in ethanol (18%). $^1$H NMR (CDCl$_3$) $\delta$: 7.76 (s, 1H); 7.30-6.92 (m, 9H); 5.14 (d, $J$=1 2.5 Hz, 1H); 5.08 (d, $J$=12.5 Hz, 1H); 4.27 (d, $J$=7.74Hz, 1H); 2.94 (dd, $J$=1 6.5Hz and 8.1Hz, 1H); 2.66 (dd, $J$=16.5Hz and 0.9Hz, 1H); 2.43 (3H, s, 3H), MS [M+H]$^+$=340

EXAMPLE 14: 2-Methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester

2-Methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester was prepared according to general protocol A, starting from benzaldehyde (0.22 mL), benzoyl
acetylacetate (384 mg) and obtained as a white powder (171 mg, 26%) after precipitation in ethanol. \(^{1}\)H NMR (CDCl\(_3\)) \(\delta\) 7.79 (s, 1H); 7.29-7.12 (m, 10H); 5.13 (d, \(J = 12.6\) Hz, 1H); 5.08 (d, \(J = 12.6\) Hz, 1H); 4.30 (d, \(J = 7.8\) Hz, 1H); 2.95 (dd, \(J = 16.5\) Hz and 8.1 Hz, 1H); 2.70 (d, \(J = 16.5\) Hz, 1H); 2.43 (s, 3H); MS \([\text{M+H}]^+ = 322\); HRMS: calcd for \(C_{20}H_{19}NO_3Br\), \([\text{M+H}]^+ = 400.0548\), found 400.0567.

**EXAMPLE 15:** benzyl 4-(4-chloro-2-fluoro-phenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate

benzyl 4-(4-chloro-2-fluoro-phenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate was prepared according to general protocol A, starting from 4-Chloro-2-fluorobenzaldehyde (800 mg), benzoyl acetylacetate (860 \(\muL\)) and obtained as a white powder (730 mg, 39%) after precipitation in ethanol. \(^{1}\)H NMR (CDCl\(_3\)) \(\delta\) 8.17 (s, 1H); 7.29 (m, 3H); 7.12-6.91 (m, 5H); 5.11 (d, \(J = 12.6\) Hz, 1H), 5.05 (d, \(J = 12.6\) Hz, 1H), 4.57 (d, \(J = 8.1\) Hz, 1H); 2.96 (dd, \(J = 16.5\) Hz and 8.4 Hz, 1H); 2.64 (d, \(J = 15.6\) Hz, 1H); 2.46 (s, 3H); MS \([\text{M+H}]^+ = 373\)

**EXAMPLE 16:** benzyl 4-(4-bromophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate

p-bromobenzaldehyde (15.0 mmol, 2.77 g), meldrum acid (15.0 mmol, 2.16 g), benzyl acetoacetate (15.0 mmol, 2.58 mL) and ammonium acetate (22.5 mmol, 1.73 g) were dissolved in acetic acid (15 mL). The reaction mixture was stirred at 110 °C for 18 h. The solvent was removed. The crude was precipitated in EtOH, cooled to 0 °C and filtered to give the desired benzyl 4-(4-bromophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate as a white powder (2.35 g, 39%). \(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.42 (s, 3H), 2.64 (dd, \(J = 16.6, 1.5\) Hz, 1H), 2.93 (dd, \(J = 16.6, 8.2\) Hz, 1H), 4.23 (d, \(J = 8.2\) Hz, 1H), 5.05 (d, \(J = 12.5\) Hz, 1H), 5.13 (d, \(J = 12.5\) Hz, 1H), 7.01 (d, \(J = 8.4\) Hz, 2H), 7.09-7.16 (m, 2H), 7.26-7.32 (m, 3H), 7.38 (dt, \(J = 8.4, 2.0\) Hz, 2H), 7.93 (brs, 1H). MS \([\text{M+H}]^+ = 400\). HRMS : calcd for \(C_{20}H_{19}NO_3Br\), \([\text{M+H}]^+ = 400.0548\), found 400.0567.

**Table 3:**

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EXAMPLE 17: 4-(4-Chloro-phenyl)-1,2-dimethyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester

Benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate (300 mg, 0.84 mmol) was dissolved in DMF (4 mL). NaH (33 mg) and iodomethane (52 µL) were added. After completion, water was added and reaction mixture was extracted with Et₂O. The organic layer was dried over MgSO₄ and evaporated under reduced pressure. The product was purified by flash chromatography (Cyclohexane/EtOAc 4:1) to give 4-(4-Chloro-phenyl)-1,2-dimethyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl ester as a white powder (31 mg, 10%).

MS(ESI) = [M+H]+ 370; ¹H NMR (CDCl₃) δ 7.31-7.00 (m, 9H); 5.14 (d, J = 12.5 Hz, 1H), 5.09 (d, J = 12.5 Hz, 1H), 4.21 (d, J=5,79 Hz, 1H, CH); 3,21 (s, 3H); 2,90 (dd, J=16,0 Hz and 7,4 Hz, 1H); 2,75 (dd, J=16,0 Hz and 2,4 Hz, 1H); 2,58 (s, 3H); HRMS: calcd for C21H21NO3CI, (MH+) 370.1210, found 370.1205

EXAMPLE 18: Benzyl 4-(4-chlorophenyl)-6-ethyl-1-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

Step 1. p-chlorobenzaldehyde (15 mmol, 2.108 g), meldrum acid (15 mmol, 2.16 g), ethyl propionylacetate (15 mmol, 2.13 mL) and ammonium acetate (22.5 mmol, 1.73 g) were dissolved in acetic acid (15 mL). The reaction mixture was stirred overnight under reflux. The solvent was removed. The crude was dissolved in EtOAc and washed by an aqueous solution of HCl 1N and a saturated solution of NaHCO₃. The organic layer was dried on MgSO₄, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/EtOAc (8/2) as eluent to give the desired compound as yellow oil (470 mg, 11%).

¹H NMR (300 MHz, CDCl₃) δ  1.20 (t, J = 7.2 Hz, 3H), 1.26 (t, J =7.2 Hz, 3H), 2.60-3.00 (m, 4H), 4.07-4.18 (m, 2H), 4.24 (dd, J = 8.0, 2.0 Hz, 1H), 7.12 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H). MS [M+H]+ 308.

Step 2. The dihydropyridone intermediate obtained in step 1 (180 mg, 0.58 mmol) was dissolved in anhydrous DMF (2 mL). Cesium carbonate (377 mg, 1.16 mmol) and iodomethane
(72 µL, 1.16 mmol) were added. The reaction mixture was stirred at 60 °C for 3 h. The DMF was removed under reduced pressure. The residue was diluted in water and extracted by EtOAc. The organic layers were assembled, washed by brine and dried on MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/DCM (1/1) as eluent to give the desired compound as a colorless oil (143 mg, 76 %).

1H NMR (300 MHz, CDCl₃) δ 1.16-1.28 (m, 6H), 2.75 (dd, J = 15.9, 2.8 Hz, 1H), 2.82-2.97 (m, 2H), 3.03-3.19 (m, 1H), 3.21 (s, 3H), 4.03-4.22 (m, 3H), 7.07 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H). MS [M+H]⁺ 322. HRMS : calcd for C₁₇H₂₁NO₃Cl, [M+H]⁺ 322.1210, found 322.1217.

Step 3. The dihydropyridone intermediate obtained in step 2 (83 mg, 0.26 mmol) was dissolved in MeOH (1 mL) and a solution of aqueous NaOH 1 N (1 mL, 4.0 equiv.) was added. The reaction mixture was stirred at 60 °C for 18 h. The reaction mixture was cooled to RT and extracted once with diethyl ether. The aqueous phase was then acidified until pH = 1 with an aqueous solution of hydrochloric acid. The aqueous phase was extracted by EtOAc. The organic layer was then washed with brine and dried with MgSO₄. The solvent was removed under reduced pressure to give the desired acid (56 mg, 0.19 mmol). The crude product was then used without further purification in the next step. The acid was dissolved in anhydrous DMF (2 mL) then Cs₂CO₃ (123 mg, 0.38 mmol) and benzyl bromide (45 µL, 0.38 mmol) were added. The reaction mixture was stirred for 1 h at RT. Water was then added and the aqueous phase was extracted with diethyl ether. The organic layer was then washed with brine and dried with MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of cyclohexane/dichloromethane 3/1 to give the desired benzyl 4-(4-chlorophenyl)-6-ethyl-1-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate (28 mg, 28 %). 1H NMR (300 MHz, CDCl₃) δ 1.24 (dd, J = 7.7Hz, 3H), 2.76 (t, J = 16.2, 2.8 Hz, 1H), 2.83-2.89 (m, 2H), 3.07-3.20 (m, 2H), 3.24 (s, 3H), 4.18 (dd, J = 7.3, 2.8 Hz, 1H), 5.13 (s, 2H), 7.02 (d, J = 8.4 Hz, 2H), 7.12-7.19 (m, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.28-7.34 (m, 3H). MS [M+H]⁺ 384; HRMS : calcd for C₂₂H₂₃NO₃Cl, [M+H]⁺ 384.1366, found 384.1375.

EXAMPLE 19: Benzyl 4-(4-chlorophenyl)-1-methyl-2-oxo-6-phenyl-3,4-dihydropyridine-5-carboxylate

Step 1. p-chlorobenzaldehyde (15 mmol, 2.108 g), meldrum acid (15 mmol, 2.16 g), ethyl benzoyleacetate (15 mmol, 2.6 mL) and ammonium acetate (22.5 mmol, 1.73 g) were dissolved in acetic acid (15 mL). The reaction mixture was stirred overnight under reflux. The solvent was removed. The crude was precipitated in EtOH and filtered to give the desired compound as a white powder (1.1 g, 21 %). 1H NMR (300 MHz, CDCl₃) δ 0.85 (t, J = 7.1 Hz, 3H), 2.78 (dd, J = 16.5, 2.4 Hz, 1H), 3.08 (dd, J = 16.5, 8.0 Hz, 1H), 3.89 (q, J = 6.9 Hz, 2H), 4.33 (dd, J = 8.0, 2.4 Hz, 1H), 7.17 (brs, 1H), 7.27-7.60 (m, 9H). MS [M+H]⁺ 356

Step 2. The dihydropyridone intermediate obtained in step 1 (213 mg, 0.6 mmol) was dissolved
in anhydrous DMF (2 mL). Cesium carbonate (292 mg, 0.9 mmol) and iodomethane (56 µl, 0.9 mmol) were added. The reaction mixture was stirred at 60 °C for 1 h. The DMF was removed under reduced pressure. The residue was diluted in water and extracted by EtOAc. The organic layers were assembled, washed by brine and dried on MgSCv The solvent was removed under reduced pressure to give the desired compound as a white powder (224 mg, 100 %). ¹H NMR (300 MHz, CDCl₃) δ 0.80 (t, J = 7.1 Hz, 3H), 2.78 (s, 3H), 2.91 (dd, J = 16.2, 2.8 Hz, 1H), 3.10 (dd, J = 16.2, 7.2 Hz, 1H), 3.83 (q, J = 7.1 Hz, 2H), 4.23 (dd, J = 7.2, 2.8 Hz, 1H), 7.20-7.35 (m, 6H), 7.41-7.49 (m, 3H). MS [M+H]+ =370. HRMS : calcd for C₂₂H₅₂N₂O₃Cl, [M+H]+ 370.1210, found 370.1219.

**Step 3.** The dihydropyridone intermediate obtained in step 2 (184 mg, 0.50 mmol) was dissolved in MeOH (2 mL) and a solution of aqueous NaOH 1 N (2 mL, 4.0 equiv.) was added. The reaction mixture was stirred at 60 °C for 18 h. The reaction mixture was cooled to RT and extracted once with diethyl ether. The aqueous phase was then acidified until pH = 1 with an aqueous solution of hydrochloric acid. The aqueous phase was extracted by EtOAc. The organic layer was then washed with brine and dried with MgSCv The solvent was removed under reduced pressure to give the desired acid (116 mg, 0.34 mmol). The crude product was then used without further purification in the next step. The acid was dissolved in anhydrous DMF (3 mL) then Cs₂CO₃ (221 mg, 0.68 mmol) and benzyl bromide (81 µl, 0.68 mmol) were added. The reaction mixture was stirred for 1 h at RT. Water was then added and the aqueous phase was extracted with diethyl ether. The organic layer was then washed with brine and dried with MgSCv The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of cyclohexane/dichloromethane 7/3 to give the benzyl 4-(4-chlorophenyl)-1-methyl-2-oxo-6-phenyl-3,4-dihydropyridine-5-carboxylate as a white powder (21 mg, 10 %). ¹H NMR (300 MHz, CDCl₃) δ 2.77 (s, 3H), 2.91 (dd, J = 16.3, 2.9 Hz), 3.10 (dd, J = 16.3, 7.2 Hz, 1H), 4.23 (dd, J = 7.2, 2.9 Hz, 1H), 4.81 (d, J = 12.3 Hz, 1H), 4.87 (d, J = 12.3 Hz, 1H), 6.91 (dd, J = 7.3, 2.1 Hz, 2H), 7.19-7.33 (m, 9H), 7.36-7.44 (m, 3H). MS [M+H]+ 433. HRMS : calcd for C₂₄H₂₃NO₃Cl, [M+H]+ 432.1366, found 432.1360.

**EXAMPLE 20:** Ethyl 4-(4-chlorophenyl)-1-methyl-2-oxo-6-phenyl-3,4-dihydropyridine-5-carboxylate (intermediate product)

**Step 1.** p-chlorobenzaldehyde (15 mmol, 2.108 g), meldrum acid (15 mmol, 2.16 g), ethyl benzoylacetae (15 mmol, 2.6 mL) and ammonium acetate (22.5 mmol, 1.73 g) were dissolved in acetic acid (15 mL). The reaction mixture was stirred overnight under reflux. The solvent was removed. The crude was precipitated in EtOH and filtered to give the desired compound as a white powder (1.1 g, 21 %). ¹H NMR (300 MHz, CDCl₃) δ 0.85 (t, J = 7.1 Hz, 3H), 2.78 (dd, J = 16.5, 2.4 Hz, 1H), 3.08 (dd, J = 16.5, 8.0 Hz, 1H), 3.89 (q, J = 6.9 Hz, 2H), 4.33 (dd, J = 8.0, 2.4 Hz, 1H), 7.17 (brs, 1H), 7.27-7.60 (m, 9H). MS [M+H]+ 356.

**Step 2.** The intermediate obtained in step 1 (213 mg, 0.6 mmol) was dissolved in anhydrous
DMF (2 ml). Cesium carbonate (292 mg, 0.9 mmol) and iodomethane (56 µl, 0.9 mmol) were added. The reaction mixture was stirred at 60 °C for 1 h. The DMF was removed under reduced pressure. The residue was diluted in water and extracted by EtOAc. The organic layers were assembled, washed by brine and dried on MgSO₄. The solvent was removed under reduced pressure to give the desired compound as a white powder (224 mg, 100 %). ¹H NMR (300 MHz, CDCl₃) δ 0.80 (t, J = 7.1 Hz, 3H), 2.78 (s, 3H), 2.91 (dd, J = 16.2, 2.8 Hz, 1H), 3.10 (dd, J = 16.2, 7.2 Hz, 1H), 3.83 (q, J = 7.1 Hz, 2H), 4.23 (dd, J = 7.2, 2.8 Hz, 1H), 7.20-7.35 (m, 6H), 7.41-7.49 (m, 3H). MS [M+H]+ 370. HRMS : calcd for C₂¹H₂¹NO₃Cl, [M+H]+ 370.1210, found 370.1219.

EXAM P LE 21: Ethyl 4-(4-chlorophenyl)-6-ethyl-1-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate (intermediate product)

Step 1. p-chlorobenzaldehyde (15 mmol, 2.108 g), meldrum acid (15 mmol, 2.16 g), ethyl propionylacetate (15 mmol, 2.13 mL) and ammonium acetate (22.5 mmol, 1.73 g) were dissolved in acetic acid (15 mL). The reaction mixture was stirred overnight under reflux. The solvent was removed. The crude was dissolved in EtOAc and washed by an aqueous solution of HCl 1N and a saturated solution of NaHCO₃. The organic layer was dried on MgSO₄, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/EtOAc (8/2) as eluent to give the desired compound as yellow oil (470 mg, 11 %). ¹H NMR (300 MHz, CDCl₃) δ 1.20 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 2.60-3.00 (m, 4H), 4.07-4.18 (m, 2H), 4.24 (dd, J = 8.0, 2.0 Hz, 1H), 7.12 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H). MS [M+H]+ 308.

Step 2. The intermediate obtained in step 1 (180 mg, 0.58 mmol) was dissolved in anhydrous DMF (2 mL). Cesium carbonate (377 mg, 1.16 mmol) and iodomethane (72 µl, 1.16 mmol) were added. The reaction mixture was stirred at 60 °C for 3 h. The DMF was removed under reduced pressure. The residue was diluted in water and extracted by EtOAc. The organic layers were assembled, washed by brine and dried on MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/DCM (1/1) as eluent to give a colorless oil (143 mg, 76 %). ¹H NMR (300 MHz, CDCl₃) δ 1.16-1.28 (m, 6H), 2.75 (dd, J = 15.9, 2.8 Hz, 1H), 2.82-2.97 (m, 2H), 3.03-3.19 (m, 1H), 3.21 (s, 3H), 4.03-4.22 (m, 3H), 7.07 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H). MS [M+H]+ 322. HRMS : calcd for C₁₁H₁₂NO₃Cl, [M+H]+ 322.1210, found 322.1217.

EXAM P LE 22: benzyl 4-(4-chlorophenyl)-6-(2-methoxyethyl)-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate

Step 1. p-chlorobenzaldehyde (12 mmol, 1.68 g), meldrum acid (12 mmol, 1.73 g), Methyl 5-methoxy-3-oxovalerate (12 mmol, 1.5mL) and ammonium acetate (18 mmol, 1.39 g) were dissolved in acetic acid (12 mL). The reaction mixture was stirred overnight under reflux. The
solvent was removed. The crude was dissolved in EtOAc and washed by an aqueous solution of HCl 1N and a saturated solution of NaHCO₃. The organic layer was dried on MgSO₄, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/EtOAc (8/2) as eluent to give the desired compound as yellow oil (344 mg, 10 %).

**Step 2.** The dihydropyridone intermediate obtained (300 mg, 0.93 mmol) was dissolved in MeOH (4 mL) and a solution of aqueous NaOH 1 N (3.3 mL) was added. The reaction mixture was stirred at 60 °C for 8 h. The reaction mixture was cooled to RT. The aqueous phase was acidified until pH = 1 with an aqueous solution of hydrochloric acid. The aqueous phase was extracted by EtOAc. The organic layer was then washed with brine and dried with MgSO₄. The solvent was removed under reduced pressure to give the desired acid as an oil (260 mg, 0.91 mmol, 97 %).

**Step3.** A fraction of this crude (80 mg, 0.26 mmol) was then used without further purification in the next step. The acid was dissolved in anhydrous DMF (3 mL) then DIEA (54 µL, 0.31 mmol) and benzyl bromide (31 µL, 0.26 mmol) were added. The reaction mixture was stirred for 18 h at RT. The reaction was controlled by LCMS and showed an incomplete conversion of the starting material. DIEA (54 µL, 0.31 mmol) and benzyl bromide (31 µL, 0.26 mmol) were added. The reaction mixture was stirred for 18 h at r.t. and then 3 h at 40 °C. The reaction mixture was cooled to RT. Water was then added and the aqueous phase was extracted with EtOAc. The organic layer was then washed with brine and dried with MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of cyclohexane/EtOAc 9/1 to give the desired compound (44 mg, 43 %). 

1H NMR (300 MHz, CDCl₃) δ 2.62 (d, J = 16.3 Hz, 1H), 2.86-3.02 (m, 2H), 3.95 (s, 3H), 3.48 (ddd, J = 15.5, 6.3, 3.5 Hz, 1H), 3.59-3.75 (m, 2H), 4.25 (d, J = 8.5 Hz, 1H), 5.04 (d, J = 12.0 Hz, 1H), 5.11 (d, J = 12.0 Hz, 1H), 7.04-7.16 (m, 4H), 7.23 (dt, J = 8.5, 2.2 Hz, 2H), 7.28-7.33 (m, 3H), 8.11 (s, 1H). MS [M+H]⁺ 400. HRMS : calcd for C₂₂H₂₃N₂O₄Cl, [M+H]⁺ 400.1316, found 400.1306.

### Table 4

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EXAMPLE 23: benzyl 4-(4-chlorophenyl)-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate :

The methyl 4-(4-chlorophenyl)-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (265 mg, 1.0 mmol) was dissolved in anhydrous methanol (2 mL) and water (2 mL). LiOH·H₂O (72 mg, 3.0 mmol) was added. The reaction mixture was stirred for 4 h at 60 °C. Water was added, the aqueous phase was washed with Et₂O and then extracted by EtOAc. The organic phase was washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure to give the desired 4-(4-chlorophenyl)-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylic acid as a white powder (160 mg, 64 %). The 4-(4-chlorophenyl)-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylic acid (89 mg, 0.35 mmol) was dissolved in anhydrous DMF (1 mL) then DIEA (122 µL, 0.71 mmol) and benzyl bromide (63 µL, 0.53 mmol) were added. The reaction mixture was stirred for 1 h at RT. The solvent was removed under reduced pressure to give the desired benzyl 4-(4-chlorophenyl)-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate as a white powder (90 mg, 74 %). ¹H NMR (300 MHz, CDCl₃) δ 2.72 (d, J = 16.5 Hz, 1H), 3.01 (dd, J = 16.5, 8.4 Hz, 1H), 4.20 (dd, J = 8.4, 1.3 Hz, 1H), 5.09 (d, J = 12.2 Hz, 1H), 5.20 (d, J = 12.2 Hz, 1H), 7.15 (d, J = 8.6 Hz, 2H), 7.22-7.27 (m, 4H), 7.31-7.37 (m, 3H), 7.53 (d, J = 5.7 Hz, 1H). MS [M+H]⁺ 340.

EXAMPLE 24: Benzyl 4-(4-chlorophenyl)-1-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate :

The benzyl 4-(4-chlorophenyl)-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (70 mg, 0.20 mmol) was dissolved in anhydrous DMF (1 mL). Cesium carbonate (133 mg, 0.41 mmol) and iodomethane (26 µL, 0.41 mmol) were added. The reaction mixture was stirred at 60 °C for 3 h. The DMF was removed under reduced pressure. The residue was diluted in water and extracted by EtOAc. The organic layers were assembled, washed by brine and dried on MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/EtOAc (95/5) as eluent to give the desired benzyl 4-(4-chlorophenyl)-1-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a yellow oil (48
mg, 68 %). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.72 (d, $J = 16.5$ Hz, 1H), 3.01 (dd, $J = 16.5$, 8.4 Hz, 1H), 4.20 (dd, $J = 12.2$ Hz, 1H), 5.09 (d, $J = 12.2$ Hz, 1H), 5.20 (d, $J = 12.2$ Hz, 1H), 7.15 (d, $J = 8.6$ Hz, 2H), 7.22-7.27 (m, 4H), 7.31-7.37 (m, 3H), 7.53 (d, $J = 5.7$ Hz, 1H). MS [M+H]$^+$ 340. HRMS : calcd for C$_{22}$H$_{22}$N$_2$O$_3$Cl, [M+CH$_3$CN]+ 397.1319, found 397.1350.

EXAMPLE 25: yV-benzyl-4-(4-chlorophenyl)-2-oxo-3,4-dihydro-1H-pyridine-5-carboxamide

The methyl 4-(4-chlorophenyl)-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (265 mg, 1.0 mmol) was dissolved in anhydrous methanol (2 mL) and water (2 mL). LiOH.H$_2$O (72 mg, 3.0 mmol) was added. The reaction mixture was stirred for 4 h at 60 °C. Water was added, the aqueous phase was washed with Et$_2$O and then extracted by EtOAc. The organic phase was washed with brine and dried over MgSO$_4$ . The solvent was removed under reduced pressure to give the desired 4-(4-chlorophenyl)-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylic acid as a white powder (160 mg, 64 %).

The 4-(4-chlorophenyl)-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylic acid Swas used without further purification in the next step. The acid (77 mg, 0.31 mmol) was dissolved in anh. EtOAc (3 mL). Benzylamine (51 µL, 0.46 mmol), DIEA (158 µL, 0.93 mmol) and a 50 % solution of T3P in EtOAc (365 µL, 0.62 mmol) were added. The same amount of all the reactants (except substrate) were added again 3 times more. The reaction mixture was stirred at RT. for 48 h overall. The solvent was removed under reduced pressure. The crude was purified by flash chromatography on silica using a mixture DCM/EA/acetone 2/1/1 to afford the desired 7/V-benzyl-4-(4-chlorophenyl)-2-oxo-3,4-dihydro-1H-pyridine-5-carboxamide as a white powder (12 mg, 11 %). $^1$H NMR (300 MHz, DMSO d$_6$) $\delta$ 2.40 (d, $J = 16.2$ Hz, 1H), 2.45-2.55 (s, 3H), 2.96 (dd, $J = 16.2$, 8.2 Hz, 1H), 4.14-4.38 (m, 3H), 7.10-7.32 (m, 8H), 7.36 (d, $J = 8.5$ Hz, 1H), 8.31 (t, $J = 5.7$ Hz, 1H), 9.76 (d, $J = 5.4$ Hz, 1H). MS [M+H]$^+$ 351 . HRMS : calcd for C$_{19}$H$_{18}$N$_2$O$_2$Cl, [M+H]$^+$ 341.1057, found 341.1056.

EXAMPLE 26: /V-benzyl-4-(4-chlorophenyl)-1-methyl-2-oxo-3,4-dihydropyridine-5-carboxamide

The methyl 4-(4-chlorophenyl)-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (131 mg, 0.50 mmol) was dissolved in anhydrous DMF (2 mL). Cesium carbonate (325 mg, 1.0 mmol) and iodomethane (62 µL, 1.0 mmol) were added. The reaction mixture was stirred at 30°C for 1 h. The DMF was removed under reduced pressure. The residue was diluted in water and extracted by EtOAc. The organic layers were assembled, washed by brine and dried on MgSO$_4$. The solvent was removed under reduced pressure. The crude 4-(4-chlorophenyl)-1-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate (143 mg) was used in the next step without further purification . The crude methyl 4-(4-chlorophenyl)-1-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate was dissolved in methanol (0.75 mL) and water (1.5 mL). Lithium hydroxide (36 mg, 1.5 mmol) was added. The reaction mixture was stirred at 50 °C for 3 h. The reaction mixture
was washed with diethyl ether. The aqueous phase was then acidified to pH = 1 and extracted by EtOAc. The organic phases were assembled, washed with brine and dried over MgSO$_4$. The solvent were removed under reduced pressure to afford the crude 4-(4-chlorophenyl)-1-methyl-2-0X0-3,4-dihydropyridine-5-carboxylic acid as a whiteish powder (100 mg). The crude 4-(4-chlorophenyl)-1-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (100 mg) was dissolved in anhydrous EtOAc (2 mL). Benzylamine (66 µL, 0.60 mmol), DIEA (215 µL, 1.25 mmol) and a 50 % solution of T3P in EtOAc (454 µL, 0.75 mmol) were added. The reaction mixture was stirred for 4 h at RT. The solvent was removed under reduced pressure. The reaction mixture was washed with water and extracted with EtOAc. The organic phases were assembled, washed with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure. The crude was purified by flash chromatography on silica using a mixture cyclohexane/EA (7/3 to 3/7) to afford the desired /V-benzyl-4-(4-chlorophenyl)-1-methyl-2-oxo-3,4-dihydropyridine-5-carboxamide as a white powder (68 mg, 38 % over the 3 steps). $^1$H NMR (300 MHz, DMSO d$_6$) $\delta$ 2.50-2.56 (m, 1H), 3.01 (dd, $J = 16.0, 7.7$ Hz, 1H), 3.06 (s, 3H), 4.15-4.41 (m, 3H), 7.10-7.30 (m, 7H), 7.35 (d, $J = 8.3$ Hz, 2H), 7.47, s, 1H), 7.53 (t, $J = 6.0$ Hz, 1H). MS [M+H]$^+$ 355. HRMS: calcd for C$_2$H$_2$O$_2$N$_2$Cl, [M+H]$^+$ 355.1213, found 355.1212.

EXAMPLE 27: yV-benzyl-4-(4-chlorophenyl)-yV-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxamide

**Step 1.** Nicotinic acid (472 mg, 3.0 mmol) was dissolved in ethyl acetate (30 mL). DIEA (1.29 mL, 7.5 mmol), /V-methylbenzylamine (460 µL, 3.6 mmol) and a solution of propylphosphonic anhydride 50% in ethyl acetate (2.64 mL, 4.5 mmol) were added. The reaction mixture was stirred 18 h at RT. A 5% aqueous solution of NaHCO$_3$ was added and the aqueous phase extracted with ethyl acetate. The organic phases were assembled, washed with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure. The crude was purified by flash chromatography using a mixture of Cy/EA (8/2) as eluent to give the desired /V-benzyl-6-chloro-/V-methylnicotinamide as a yellow oil (421 mg, 54 %).

**Step 2.** The /V-benzyl-6-chloro-/V-methylnicotinamide (390 mg, 1.5 mmol) was dissolved in anh. THF (1.5 mL). The solution was cooled to 0 °C. A solution 1.0 M of 4-chlorophenylmagnesium chloride in Et$_2$O (3.0 mL, 3.0 mmol) was added slowly over a period of 30 min. The reaction mixture was allowed to warm to r.t. and stirred for 18 h at RT. The reaction was stopped by addition of AcOH (1.0 mL). The reaction mixture was stirred for 10 min then a saturated solution
of ammonium chloride was added and the reaction mixture extracted with ethyl acetate. The organic phases were assembled and dried over MgSO₄, the solvents were removed under reduced pressure. The crude was purified by flash chromatography using a mixture of DCM/MeOH (9/1) as eluent to give the desired \( \text{V-benzyl-4-(4-chlorophenyl)-2-oxo-3,4-dihydro-1/-pyridine-5-carboxamide} \) as a white powder (15 mg, 28 %). \(^1\)H NMR (300 MHz, CDCls)  δ 2.71 (dd, \( J = 16.7, 6.1 \) Hz, 1H), 2.83 (s, 3H), 2.98 (dd, \( J = 16.7, 8.0 \) Hz, 1H), 4.22 (dd, \( J = 8.0, 6.1 \) Hz, 1H), 4.51 (s, 2H), 6.50 (d, \( J = 5.0 \) Hz, 2H), 6.93 (m, 2H), 7.16 (d, \( J = 8.5 \) Hz, 2H), 7.23-7.30 (m, 4H), 7.82 (brs, 1H). MS [M+H]+ 355. HRMS : calcd for \( C_{20}H_{20}N_2O_2Cl, [M+H]^{+} \) 355. 12 13, found 355.12 12.

**Preparation of Benzyl 4-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxo-3,4-dihydropyridine-5-carboxylate (EXAMPLE 29) and W-benzyl-4-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxo-3,4-dihydropyridine-5-carboxamide (EXAMPLE 30)**

**Step 1.** To a solution of diisopropylamine (1.52 mL, 10.8 mmol) in anh. THF (6 mL) at 0 °C was added slowly a 2.5 M solution of \( n-\text{BuLi} \) in hexane (4.32 mL, 10.8 mmol). The reaction mixture was turred 20 min at r.t. and then cooled at -55 °C. To this LDA solution, a solution of 3-(4-chlorophenyl)-5-methoxy-5-oxo-pentanoic acid (1.38 g, 5.4 mmol) in anh. THF (6 mL) was
added over 20 min. After 40 min at -45 °C, methyl formate (826 µL, 13.5 mmol) was added. The mixture was slowly warmed to -20 °C and then stirred at -20 °C for 1 h. The mixture was slowly quenched with cone. HCl until pH = 1 and the aqueous phase was extracted with EtOAc. The organic layer was separated, washed with brine and dried over MgSO₄. The solvents were removed under reduced pressure to give 3-(4-chlorophenyl)-1-formyl-5-methoxy-5-oxo-pentanoic acid as a thick oil.

**Step 2.** This thick oil was then dissolved into acetic acid (18 mL) and ammonium acetate was added (1.25 g, 16.2 mmol). The reaction mixture was stirred at 80 °C for 18 h. The solvent was removed under reduced pressure. Precipitation of the crude in EtOH afforded the desired methyl 4-(4-chlorophenyl)-2-oxo-3,4-dihydropyridine-5-carboxylate as a white powder (487 mg, 34 %). ¹H NMR (300 MHz, CDCl₃) δ 2.70 (d, J = 16.8 Hz, 1H), 3.00 (dd, J = 16.8, 8.5 Hz, 1H), 3.71 (s, 3H), 4.18 (d, J = 8.5 Hz, 1H), 7.16 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 5.4 Hz, 1H), 7.83 (brs, 1H). MS [M-H]⁺ 264.

**Step 3.** Methyl 4-(4-chlorophenyl)-2-oxo-3,4-dihydropyridine-5-carboxylate (240 mg, 0.9 mmol) was dissolved in anhydrous DMF (3 mL). Cesium carbonate (585 mg, 1.8 mmol) and (bromomethyl)cyclopropane (172 µL, 1.8 mmol) were added. The reaction mixture was stirred at 60 °C for 4 h. The DMF was removed under reduced pressure. The residue was diluted in water. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine and dried over MgSO₄. Removal of the solvent was removed under reduced pressure gave the desired (methyl 4-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (287 mg, 100 %).

**Step 4.** The (methyl 4-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxo-3,4-dihydropyridine-5-carboxylate (287 mg, 0.90 mmol) was dissolved in an aqueous solution of NaOH 1 N (20 mL, 20.0 mmol). The reaction mixture was stirred at 60 °C for 18 h. The reaction mixture was cooled to r.t. and extracted once with diethyl ether. The aqueous phase was then acidified until pH = 1 with an aqueous solution of hydrochloric acid. The aqueous phase was extracted by EtOAc. The organic layer was then washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure to give the desired 4-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 28) (210 mg, 78 %).

**EXAM P L E 2 9 :** Benzyl 4-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxo-3,4-dihydropyridine-5-carboxylate

**Step 5.** 4-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 28, 70 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (160 mg, 0.45 mmol) and benzyl bromide (38 µL, 0.36 mmol) were added. The reaction mixture was stirred at RT for 18 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over MgSO₄. The solvent was
removed under reduced pressure to give the desired benzyl 4-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (76 mg, 83%). 1H NMR (300 MHz, CDCl3) δ 0.28-0.36 (m, 2H), 0.54-0.63 (m, 2H), 1.04 - 1.18 (m, 1 H), 2.75 (dd, J = 16.2, 1.6 Hz, 1H), 3.00 (dd, J = 16.2, 8.2 Hz, 1H), 3.25 (dd, J = 14.1, 7.1 Hz, 1H), 3.72 (dd, J = 14.1, 7.2 Hz, 1H), 5.10 (d, J = 12.6 Hz, 1H), 5.22 (d, J = 12.6 Hz, 1H), 7.15 (d, J = 8.5 Hz, 2H), 7.22-7.28 (m, 4H), 7.30-7.42 (m, 3H), 7.61 (s, 1H). MS [M+H]+ 396. HRMS: calcd for C23H23NO5Cl, [M+H]+ 396.1366, found 396.1371.

**EXAMPLE 30:** /V-benzyl-4-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxo-3,4-dihydropyridine-5-carboxamide

**Step 5.** 4-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 28, 90 mg, 0.30 mmol) was dissolved in anhydrous EtOAc (2 mL) then benzylamine (52 µL, 0.48 mmol), DIEA (172 µL, 1.0 mmol) and a 50% solution of T3P in EtOAc (353 µL, 0.6 mmol) were added. The reaction mixture was stirred at RT for 24 h. The same amount of reactants was added again twice every 24 h. After 72 h at RT overall, water was added and the aqueous phase was extracted with EtOAc. The organic phases were combined, washed with brine and dried over MgSO4. The solvent was removed under reduced pressure. Purification of the crude by flash chromatography using a mixture of Cyclohexane/EtOAc (8/2) as eluent gave the desired /V-benzyl-4-(4-chlorophenyl)-1-(cyclopropylmethyl)-2-oxo-3,4-dihydropyridine-5-carboxamide as a yellow oil (67 mg, 55 %). 1H NMR (300 MHz, CDCl3) δ 0.27-0.38 (m, 2H), 0.53-0.62 (m, 2H), 1.04 - 1.14 (m, 1 H), 2.69 (dd, J = 16.1, 2.5 Hz, 1H), 3.02 (dd, J = 16.1, 8.1 Hz, 1H), 3.24 (dd, J = 13.9, 7.0 Hz, 1H), 3.91 (dd, J = 13.9, 7.2 Hz, 1H), 4.41 (t, J = 6.3 Hz, 1H), 5.66 (t, J = 5.5 Hz, 1H), 7.03-7.09 (m, 2H), 7.16 (d, J = 8.5 Hz, 2H), 7.23-7.32 (m, 5H), 7.54 (s, 1H). MS [M+H]+ 395. HRMS: calcd for C23H23NO5Cl, [M+H]+ 395.1526, found 395.1530.

**Preparation of Benzyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-2-oxo-3,4-dihydropyridine-5-carboxylate (Example 32)** and **yV-benzyl-4-(4-chlorophenyl)-1-(2-methoxyethyl)-2-oxo-3,4-dihydropyridine-5-carboxamide (Example 33)**
Step 1. Methyl 4-(4-chlorophenyl)-2-oxo-3,4-dihydropyridine-5-carboxylate (227 mg, 0.86 mmol) was dissolved in anhydrous DMF (3 mL). Cesium carbonate (556 mg, 1.71 mmol) and 2-bromoethyl methyl ether (161 µL, 1.71 mmol) were added. The reaction mixture was stirred at 60 °C for 18 h. The DMF was removed under reduced pressure. The residue was diluted in water. The aqueous phase was extracted by EtOAc and the combined organic layers were washed with brine and dried over MgSO₄. Removal of the solvents under reduced pressure gave the desired methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (254 mg, 91%). MS [M+H]⁺ 324.

Step 2. The methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-2-oxo-3,4-dihydropyridine-5-carboxylate (254 mg, 0.78 mmol) was dissolved in methanol (5 mL) and an aqueous solution of NaOH 1 N (20 mL, 20.0 mmol). The reaction mixture was stirred at 60 °C for 4 h. The reaction mixture was cooled to RT and extracted once with diethyl ether. The aqueous phase was then acidified until pH = 1 with an aqueous solution of hydrochloric acid. The aqueous phase was extracted by EtOAc. The organic layer was then washed with brine and dried over MgSO₄. Removal of the solvent under reduced pressure gave the desired 4-(4-chlorophenyl)-1-(2-methoxyethyl)-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 31) (214 mg, 89%). MS [M-H]⁻ 308.

EXAMPLE 32: Benzyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-2-oxo-3,4-dihydropyridine-5-carboxylate
4-(4-chlorophenyl)-1-(2-methoxyethyl)-2-oxo-3,4-dihydropyridine-5-carboxylic acid (97 mg, 0.31 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (305 mg, 0.86 mmol) and benzyl bromide (69 µL, 0.65 mmol) were added. The reaction mixture was stirred at RT for 24 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The combined organic layers were
washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure.

Purification of the crude by flash chromatography using a mixture of Cyclohexane/EtOAc (8/2) as eluent gave the desired benzyl 4-(4-chlorophenyl)-1-(2-methoxethyl)-2-oxo-3,4-dihydropyridine-5-carboxylate as a yellow oil (59 mg, 47%). ¹H NMR (300 MHz, CDCl₃) δ 2.72 (dd, J = 16.4, 1.8 Hz, 1H), 3.00 (dd, J = 16.4, 8.2 Hz, 1H), 3.37 (s, 3H), 3.46-3.57 (m, 3H), 3.96-4.07 (m, 1H), 4.13 (dd, J = 8.2, 1.8 Hz, 1H), 5.09 (d, J = 12.6 Hz, 1H), 5.22 (dd, J = 12.6 Hz, 1H), 7.16 (d, J = 8.7 Hz, 2H), 7.22-7.28 (m, 4H), 7.30-7.38 (m, 3H), 7.59 (s, 1H). MS [M+H]+ 400. HRMS : calcd for C₂₂H₂₅NO₄Cl, [M+H]+ 400.1316, found 400.1317.

EXAMPLE 33 yV-benzyl-4-(4-chlorophenyl)-1-(2-methoxethyl)-2-oxo-3,4-dihydropyridine-5-carboxamide

4-(4-chlorophenyl)-1-(2-methoxethyl)-2-oxo-3,4-dihydropyridine-5-carboxylic acid (116 mg, 0.38 mmol) was dissolved in anhydrous EtOAc (2 mL) then benzylamine (168 µL, 1.55 mmol), DIPEA (555 µL, 1.0 mmol) and a 50% solution of T3P in EtOAc (1.14 mL, 0.6 mmol) were added. The reaction mixture was stirred at RT for 18 h. Water was added and the aqueous phase was extracted with EtOAc. The organic phases were combined, washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure. Purification of the crude by flash chromatography using a mixture of Cyclohexane/EtOAc (1/1) as eluent gave the desired N-benzyl-4-(4-chlorophenyl)-1-(2-methoxethyl)-2-oxo-3,4-dihydropyridine-5-carboxamide as a yellow powder (67 mg, 55 %). ¹H NMR (300 MHz, CDCl₃) δ 2.67 (dd, J = 16.2, 2.2 Hz, 1H), 3.00 (dd, J = 16.2, 8.3 Hz, 1H), 3.36 (s, 3H), 3.43-3.55 (m, 3H), 3.92-4.02 (m, 2H), 4.40 (t, J = 5.5 Hz, 2H), 5.77 (t, J = 5.5 Hz, 1H), 7.07 (dd, J = 7.0, 1.7 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.23-7.30 (m, 5H), 7.42 (s, 1H). MS [M+H]+ 399. HRMS : calcd for C₂₂H₂₅NO₃Cl, [M+H]+ 399.1475, found 399.1479.

EXAMPLE 33a N-benzyl-4-(4-chlorophenyl)-N, 1-dimethyl-2-oxo-3,4-dihydropyridine-5-carboxamide :

N/V-benzyl-4-(4-chlorophenyl)-N-methyl-2-oxo-3,4-dihydropyridine-5-carboxamide (example 27, 120 mg,0.34 mmol) was dissolved in anhydrous DMF (1 mL). Cesium carbonate (220 mg, 0.68 mmol) and iodomethane (42 µL, 0.68 mmol) were added. The reaction mixture was stirred at 60 °C for 1 h. The DMF was removed under reduced pressure. The residue was diluted in water and extracted with EtOAc. The organic layers were combined, washed by brine and dried on MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of DCM/EtOAc (8/2) as eluent to give the desired N-benzyl-4-(4-chlorophenyl)-N/V, 1-dimethyl-2-oxo-3,4-dihydropyridine-5-carboxamide as a colorless oil (72 mg, 58 %). ¹H NMR (300 MHz, CDCl₃) δ 2.74 (dd, J = 16.4, 7.2 Hz, 1H), 2.84 (s, 3H), 2.95 (dd, J = 16.4, 7.6 Hz, 1H), 3.09 (s, 3H), 4.16 (t, J = 7.4 Hz, 1H), 4.46 (d, J = 15.4 Hz, 1H), 4.52 (d, J = 15.4 Hz, 1H), 6.47 (d, J = 1.2 Hz, 1H), 6.93 (dd, J = 6.5, 1.8 Hz, 2H), 7.13 (d, J = 8.5
Hz, 2H), 7.23-7.31 (m, 6 H). [M+H]^+ = 369 g/mol, HRMS: calcd for C_{21}H_{22}N_{2}O_{2}Cl, [M+H]^+ 369.1370, found 369.1378.

Table 5:
The benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (1 equiv.) was dissolved in anhydrous DMF (0.1-0.3 M). Cesium carbonate (1.5 equiv.) and R12-X (1-3 equiv.) were added. The reaction mixture was stirred at 60 °C until completion. The DMF was removed under reduced pressure. The residue was diluted in water and extracted by EtOAc. The organic layers were assembled, washed by brine, dried on MgSO₄ and evaporated under
EXAMPLE 34: Benzyl 4-(4-chlorophenyl)-1-ethyl-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

Benzyl 4-(4-chlorophenyl)-1-ethyl-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate was obtained according general procedure B starting from benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (0.42 mmol) and obtained as a colorless oil (100 mg, 62%) after flash chromatography purification (cyclohexane/EtOAc). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.14 (t, J=7.2 Hz, 3H), 2.60 (s, 3H), 2.74 (dd, J=2.4 and 15.6 Hz, 1H), 2.91 (dd, J=7.5 and 15.6 Hz, 1H), 3.67 (m, 1H), 3.97 (m, 1H), 4.21 (d, J=5.7Hz, 1H), 5.09 (d, J = 12.6 Hz, 1H), 5.15 (d, J = 12.6 Hz, 1H), 7.03 (d, J=8.4 Hz, 2H), 7.12-7.16 (m, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.28-7.32 (m, 3H). MS [M+H]+ 384.

EXAMPLE 35: Benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1-propyl-3,4-dihydropyridine-5-carboxylate

Benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1-propyl-3,4-dihydropyridine-5-carboxylate was obtained according general procedure B starting from benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (0.42 mmol) and obtained as a colorless oil (108 mg, 65%) after flash chromatography purification (cyclohexane/EtOAc). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.88 (t, J=7.5 Hz, 3H), 1.51 (m, 2H), 2.59 (s, 3H), 2.76 (dd, J=2.4 and 15.9 Hz, 1H), 2.91 (dd, J=7.5 and 15.9 Hz, 1H), 3.48 (m, 1H), 3.91 (m, 1H), 4.22 (d, J=5.7Hz, 2H), 5.09 (d, J = 12.6 Hz, 1H), 5.15 (d, J = 12.6 Hz, 1H), 7.04 (d, J=8.4 Hz, 2H), 7.13-7.16 (m, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.29-7.31 (m, 3H). MS [M+H]+ 398.

EXAMPLE 36: Benzyl 1-butyl-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

Benzyl 1-butyl-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate was obtained according general procedure B starting from benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (0.42 mmol) and obtained as a colorless oil (111 mg, 64%) after flash chromatography purification (cyclohexane/EtOAc). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.90 (t, J=7.2 Hz, 3H), 1.27 (m, 2H), 1.44 (m, 2H), 2.58 (s, 3H), 2.75 (dd, J=2.4 and 15.6 Hz, 1H), 2.89 (dd, J=7.2 and 15.6 Hz, 1H), 3.51 (m, 1H), 3.95 (m, 1H), 4.21 (d, J=5.7 Hz, 2H), 5.08 (d, J = 12.6 Hz, 1H), 5.14 (d, J = 12.6 Hz, 1H), 7.03 (d, J=8.4 Hz, 2H), 7.12-7.15 (m, 2H), 7.21.
EXAMPLE 37: **Benzyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate**

Benzyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate was obtained according general procedure B starting from benzyl 4-(4-chlorophenyl)-6-methyl-2-0X0-3,4-dihydropyridine-5-carboxylate (0.42 mmol) and obtained as a yellow oil (142 mg, 81%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.63 (s, 3H), 2.72 (dd, $J = 15.8$, 2.1 Hz, 1H), 2.93 (dd, $J = 15.8$, 7.4 Hz, 1H), 3.33 (s, 3H), 3.36-3.52 (m, 4H), 3.76 (ddd, $J = 14.5$, 8.6, 3.8 Hz, 1H), 4.13-4.26 (m, 2H), 5.08 (d, $J = 11.9$ Hz, 1H), 5.14 (d, $J = 11.9$ Hz, 1H), 7.07-7.15 (m, 4H), 7.22 (d, $J = 8.3$ Hz, 2H), 7.25-7.33 (m, 3H). MS [M+H]$^+$ 414. HRMS: calcd for C$_{25}$H$_{25}$NO$_4$Cl, [M+H]$^+$ 414.1472, found 414.1459.

EXAMPLE 38: **Benzyl 1-allyl-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate**

Benzyl 1-allyl-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate was obtained according general procedure B starting from benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (0.50 mmol) and obtained as a colorless oil (152 mg, 77%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.58 (s, 3H), 2.79 (dd, $J = 2.4$ and 15.6Hz, 1H), 2.94 (dd, $J = 7.2$ and 15.6 Hz, 1H), 4.33-4.23 (m, 2H), 4.52-4.45 (m, 1H), 5.19-5.05 (m, 1H), 5.08 (d, $J = 12.6$ Hz, 1H), 5.14 (d, $J = 12.6$ Hz, 1H), 5.82-5.69 (m, 1H), 7.04 (d, $J = 8.4$ Hz, 2H), 7.12-7.15 (m, 2H), 7.22 (d, $J = 8.4$ Hz, 2H), 7.28-7.30 (m, 3H). MS [M+H]$^+$ 396.

EXAMPLE 39: **Benzyl 4-(4-chlorophenyl)-6-methyl-1-(2-methylallyl)-2-oxo-3,4-dihydropyridine-5-carboxylate**

Benzyl 4-(4-chlorophenyl)-6-methyl-1-(2-methylallyl)-2-oxo-3,4-dihydropyridine-5-carboxylate was obtained according general procedure B starting from benzyl 4-(4-chlorophenyl)-6-methyl-2-0X0-3,4-dihydro-1 H-pyridine-5-carboxylate (0.42 mmol) and obtained as a colorless oil (125 mg, 72%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.66 (s, 3H), 2.53 (s, 3H), 2.86 (dd, $J = 3.0$ and 15.9Hz, 1H), 2.96 (dd, $J = 7.2$ and 15.9 Hz, 1H), 4.25 (m, 1H), 4.28 (m, 2H), 4.54 (m, 1H), 4.82 (m, 1H), 5.09 (d, $J = 12.6$ Hz, 1H), 5.15 (d, $J = 12.6$ Hz, 1H), 7.07 (d, $J = 8.4$ Hz, 2H), 7.14-7.17 (m, 2H), 7.21 (d, $J = 8.4$ Hz, 2H), 7.29-7.31 (m, 3H). MS [M+H]$^+$ 410.

EXAMPLE 40: **Benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1-prop-2-ynyl-3,4-dihydropyridine-5-carboxylate**

Benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1-prop-2-ynyl-3,4-dihydropyridine-5-carboxylate was obtained according general procedure B starting from benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (0.42 mmol) and obtained as a colorless oil (85 mg, 51
EXAMPLE 41: Benzyl 1-benzyl-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

1-benzyl-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate was obtained according general procedure B starting from benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (0.42 mmol) and obtained as a colorless oil (23 mg, 37 %) after flash chromatography purification (cyclohexane/EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.55 (s, 3H), 2.93 (dd, J=2.7 and 15.9Hz, 1H), 3.03 (dd, J=6.9 and 15.9 Hz, 1H), 4.28 (d, J = 4.8 Hz, 1H), 4.72 (d, J = 15.9 Hz, 1H), 5.07 (d, J = 12.6 Hz, 1H), 5.13 (d, J = 12.6 Hz, 1H), 5.33 (d, J = 15.9 Hz, 1H), 7.02 (d, J=8.4 Hz, 2H), 7.05-7.00 (m, 2H), 7.1 1-7.14 (m, 2H),7.21 (d, J = 8.4 Hz, 2H), 7.25-7.31 (m, 6H). MS [M+H]$^+$ 446.

EXAMPLE 42: Benzyl 4-(4-chlorophenyl)-1-isopropyl-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

Benzyl 4-(4-chlorophenyl)-1-isopropyl-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate was obtained according general procedure B starting from benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (0.42 mmol) and obtained as a colorless oil (23 mg, 14 %) after flash chromatography purification (cyclohexane/EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.34 (d, J = 6.8 Hz, 1H), 1.46 (d, J = 6.8 Hz, 1H), 2.53 (s, 3H), 2.69 (dd, J = 16.1 , 2.4 Hz, 1H), 2.87 (dd, J = 16.1, 7.1 Hz, 1H), 4.12 (s, J = 6.8 Hz, 1H), 5.1 1 (d, J = 12.5 Hz, 1H), 5.18 (d, J = 12.5 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 1H), 7.28-7.33 (m, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 17.9, 20.2, 20.6, 35.9, 39.6, 49.3, 66.2, 111.8, 127.9, 128.1, 128.3, 128.5, 132.6, 136.0, 139.2, 151.3, 166.9, 169.5. MS [M+H]$^+$ 398. HRMS : calcd for C$_{23}$H$_{25}$NO$_3$Cl, [M+H]$^+$ 398.1523, found 398.1505.

EXAMPLE 43: Benzyl 4-(4-chlorophenyl)-1-(cyclopropylmethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

Benzyl 4-(4-chlorophenyl)-1-(cyclopropylmethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate was obtained according general procedure B starting from benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (0.42 mmol) and obtained as a colorless oil (140 mg, 81 %) after flash chromatography purification (cyclohexane/ EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.24-0.58 (m, 4H), 0.88-1.04 (m, 1H), 2.63 (s, 3H), 2.74 (dd, J = 15.7, 2.1 Hz, 1H), 2.91 (dd, J = 15.7, 7.3 Hz, 1H), 3.52 (dd, J =14.7, 6.1 Hz, 1H), 3.91 (dd, J
EXAMPLE 44: Benzyl 4-(4-chlorophenyl)-1-(cyclobutylmethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

Benzyl 4-(4-chlorophenyl)-1-(cyclobutylmethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate was obtained according general procedure B starting from benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate (0.70 mmol) and obtained as a colorless oil (163 mg, 55%) after flash chromatography purification (cyclohexane/EtOAc).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.44 (m, 1H), 1.97-1.64 (m, 6 H), 2.55 (s, 3H), 2.77 (dd, $J=2.7$ and 15.9 Hz, 1H), 2.89 (dd, $J=6.9$ and 15.9 Hz, 1H), 3.44 (dd, $J = 6.0$ and 14.4 Hz, 1H), 4.25-4.18 (m, 1H+1H), 5.09 (d, $J = 12.6$ Hz, 1H), 5.15 (d, $J = 12.6$ Hz, 1H), 7.04 (d, $J=8.4$ Hz, 2H), 7.13-7.16 (m, 2H), 7.21 (d, $J=8.4$ Hz, 2H), 7.28-7.30 (m, 3H). MS [M+H]$^+$ 524.21, found 525.15.

EXAMPLE 45: Benzyl 1-[(1-ieri-butoxy carbonylazetidin-3-yl)methyl]-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

Benzyl 1-[(1-ieri-butoxy carbonylazetidin-3-yl)methyl]-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate was obtained according general procedure B starting from benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (0.62 mmol) and obtained as a colorless oil (228 mg, 70%) after flash chromatography purification (cyclohexane/EtOAc).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.44 (s, 9H), 2.55 (s, 3H), 2.61 (brs, 1H), 2.80-2.87 (m, 2H), 3.44-3.89 (m, 5H), 4.22 (dd, $J = 5.7$, 3.3 Hz, 1H), 4.27-4.46 (brs, 1H), 5.10 (d, $J = 12.5$ Hz, 1H), 5.17 (d, $J = 12.5$ Hz, 1H), 6.99 (d, $J = 8.3$ Hz, 2H), 7.12-7.19 (m, 2H), 7.22, (d, $J = 8.3$ Hz, 2H), 7.26-7.33 (m, 3H). MS [M+H]$^+$ 469. HRMS: calcd for C$_2$I$_4$NO$_3$Cl, [M+H]$^+$ 525.21, found 525.21.

EXAMPLE 46: Benzyl 1-(azetidin-3-ylmethyl)-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

Benzyl 1-(azetidin-3-ylmethyl)-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate (180 mg, 0.34 mmol) was dissolved in DCM (255 µL). TFA (255 µL) was added and the reaction mixture was stirred at RT for 2 h. An aqueous saturated solution of ammonium chloride was added and the aqueous phase was extracted by DCM. The organic phase was dried under MgSO$_4$. The solvent was removed under reduced pressure. The crude was purified by flash chromatography on silica using a mixture of DCM/MeOH (98:2 to 9:1) to give the desired benzyl 1-(azetidin-3-ylmethyl)-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a white powder (105 mg, 72%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.55 (s, 3H), 2.74 (dd, $J=15.7$, 2.6 Hz, 1H), 2.84 (dd, $J=15.7$, 6.6 Hz, 1H), 2.98 (q, $J=7.6$ Hz, 2H).
EXAMPLE 47: Benzyl 4-(4-chlorophenyl)-6-methyl-1-[(1-methylazetidin-3-yl)methyl]-2-oxo-3,4-dihydropyridine-5-carboxylate

Benzyl 4-(4-chlorophenyl)-6-methyl-1-[(1-methylazetidin-3-yl)methyl]-2-oxo-3,4-dihydropyridine-5-carboxylate (180 mg, 0.42 mmol) in DMSO (300 MHz, CDCl₃) δ 2.27 (s, 3H), 2.57 (s, 3H), 2.78 (dd, J = 16.1, 2.8 Hz, 1H), 2.81-2.94 (m, 4H), 3.17 (t, J = 7.1 Hz, 1H), 3.30 (t, J = 7.1 Hz, 1H), 3.65 (dd, J = 14.5, 6.4 Hz, 1H), 4.22 (dd, J = 7.1, 2.0 Hz, 1H), 4.27 (dd, J = 14.5, 6.4 Hz, 1H), 5.09 (d, J = 13.5 Hz, 1H), 5.15 (d, J = 13.5 Hz, 1H), 7.00 (d, J = 8.5 Hz, 2H), 7.11-7.17 (m, 2H), 7.22 (d, J = 8.5 Hz, 2H), 7.26-7.32 (m, 3H). MS [M+H]⁺ 439; HRMS: calcd for C₂₆H₃₀N₂O₃Cl, [M+H]⁺ 439.1788, found 439.1796.

EXAMPLE 48: Benzyl 4-(4-chlorophenyl)-6-methyl-1-[(1,1-dimethylazetidin-1-ium-3-yl)methyl]-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate iodide

Benzyl 4-(4-chlorophenyl)-6-methyl-1-[(1,1-dimethylazetidin-1-ium-3-yl)methyl]-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate iodide as a colorless oil (18 mg, 100%). ¹H NMR (300 MHz, DMSO d₆) δ 2.50 (s, 3H), 2.40 - 2.60 (m, 1H), 2.93-3.19 (m, 1H), 3.09 (s, 3H), 3.14 (s, 3H), 3.30 - 3.50 (m, 1H), 3.70-3.89 (m, 2H), 3.94 - 4.12 (m, 2H), 4.15 - 4.29 (m, 3H), 5.04 (d, J = 13.0 Hz, 1H), 5.12 (d, J = 13.0 Hz, 1H), 7.06 - 7.18 (m, 4H), 7.22 - 7.30 (m, 3H), 7.36 (d, J = 8.6 Hz, 2H). ¹³C NMR (75 MHz, DMSO d₆) 16.9, 27.7, 36.6, 43.3, 51.7, 53.3, 65.8, 68.7, 69.2, 110.4, 127.8, 128.3, 128.7, 129.1, 131.9, 136.7, 140.5, 150.5, 166.7, 170.0. MS [M+H]⁺ 453 HRMS: calcd for C₂₆H₃₀N₂O₃Cl, [M+H]⁺ 453.1945, found 453.1923.
EXAMPLE 49: Benzyl 4-(4-chlorophenyl)-1-isobutyl-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

Benzyl 4-(4-chlorophenyl)-1-isobutyl-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate was obtained according general procedure B starting from benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (0.56 mmol) and obtained as a colorless oil (171 mg, 74 %) after flash chromatography purification (cyclohexane/EtOAc). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.70 (d, \(J=6.6\) Hz, 3 H), 0.84 (d, \(J=6.6\) Hz, 3 H), 1.74 (m, 1 H), 2.55 (s, 3 H), 2.94-2.86 (m, 2H), 3.25 (dd, \(J = 6.3\) and 14.4 Hz, 1H), 3.91 (dd, \(J = 8.1\) and 14.1 Hz, 1H), 4.2 (m, 1H), 5.10 (d, \(J = 12.6\) Hz, 1H), 5.16 (d, \(J = 12.6\) Hz, 1H), 7.08 (d, \(J=8.4\) Hz, 2H), 7.14-7.17 (m, 2H), 7.21 (d, \(J = 8.4\) Hz, 2H), 7.28-7.30 (m, 3H). MS [M+H]+ 412.

EXAMPLE 50: Benzyl 4-(4-chlorophenyl)-1-[2-(dimethylamino)ethyl]-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

Benzyl 4-(4-chlorophenyl)-1-[2-(dimethylamino)ethyl]-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate was obtained according general procedure B starting from benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (0.42 mmol) and obtained as a colorless oil (177 mg, 98 %). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.26 (s, 6H), 2.26-2.43 (m, 2H), 2.60 (m, 3H), 2.73 (dd, \(J = 15.7\) and 2.2 Hz, 2H), 2.90 (dd, \(J = 15.7\), 7.1 Hz, 2H), 3.38-3.67 (m, 1H), 4.02-4.12 (m, 1H), 4.22 (d, \(J = 7.0\) Hz, 1H), 5.06 (d, \(J = 12.7\) Hz, 1H), 5.13 (d, \(J = 12.7\) Hz, 1H), 7.07 (d, \(J = 8.4\) Hz, 2H), 7.09-7.14 (m, 2H), 7.21 (d, \(J = 8.4\) Hz, 2H), 7.25-7.31 (m, 3H). MS [M+H]+ 427. HRMS: calcd for C\(_{24}\)H\(_{28}\)N\(_2\)O\(_3\)Cl, [M+ H]+ 427.1788, found 427.1775.

EXAMPLE 51: 2-[5-benzyloxy carbonyl-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridin-1-yl]ethyl-trimethyl- ammonium iodide

The benzyl 4-(4-chlorophenyl)-1-[2-(dimethylamino)ethyl]-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate (65 mg, 0.15 mmol) was dissolved in anh. DMF (1 mL). Iodomethane (14 \(\mu\)L, 0.23 mmol) was added. The reaction mixture was stirred at RT for 2 h. The solvent was removed under reduced pressure to afford the desired 2-[5-benzyloxy carbonyl-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridin-1-yl]ethyl-trimethyl-ammonium iodide as a yellow powder (79 mg, 93 %). \(^1\)H NMR (300 MHz, DMSO \(d_6\)) \(\delta\) 2.61 (s, 3H), 2.61-2.68 (d, \(J = 15.5, 2.3\) Hz, 1H), 3.02-3.12 (1H, \(J = 15.5, 7.0\) Hz, 1H), 3.12-3.24 (m, 1H), 3.32 (s, 3H), 3.32-3.52 (m, 1H), 3.90-4.20 (m, 2H), 4.25 (d, \(J = 6.0\) Hz, 1H), 5.07 (d, \(J = 12.9\) Hz, 1H), 5.14 (d, \(J = 12.9\) Hz, 1H), 7.09-7.16 (m, 2H), 7.18 (d, \(J = 8.3\) Hz, 2H), 7.24-7.30 (m, 3H), 7.34 (d, \(J = 8.3\) Hz, 2H). MS [M]+ 441. HRMS: calcd for C\(_{23}\)H\(_{26}\)N\(_2\)O\(_3\)Cl, [M+ H]+ 441.1945, found 441.1943.

EXAMPLE 52: Benzyl 1-[2-(i-tert-butoxycarbonylamino)ethyl]-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

Benzyl 1-[2-(i-tert-butoxycarbonylamino)ethyl]-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-
Dihydropyridine-5-carboxylate was obtained according general procedure B starting from benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (0.60 mmol) and obtained as a colorless oil (157 mg, 52 %) after flash chromatography purification (cyclohexane/EtOAc). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.44 (s, 9H), 2.59 (s, 3H), 2.80 (dd, \(J = 16.0, 2.7\) Hz, 1H), 2.91 (dd, \(J = 16.0, 7.1\) Hz, 1H), 3.15 (q, \(J = 6.2\) Hz, 1H), 3.69-3.81 (m, 1H), 3.89-4.0 (m, 1H), 4.24 (dd, \(J = 7.1, 2.7\) Hz, 1H), 4.50 (t, \(J = 5.5\) Hz, 1H), 5.10 (d, \(J = 12.6\) Hz, 1H), 5.16 (d, \(J = 12.6\) Hz, 1H), 7.05 (d, \(J = 8.4\) Hz, 2H), 7.13-7.20 (m, 2H), 7.24 (d, \(J = 8.4\) Hz, 2H), 7.26-7.33 (m, 3H). MS [M+H]\(^+\) = 499; HRMS : calcd for C\(_{22}\)H\(_{22}\)N\(_2\)O\(_3\)Cl, [M+H]\(^+\) = 499.2000, found 499.2008.

**EXAMPLE 53:** Hydrochloride salt of benzyl 1-(2-aminoethyl)-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

Benzyl 1-[2-(ie/f-butoxycarbonylamino)ethyl]-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate (38 mg, 0.076 mmol) was dissolved in a 4M solution of hydrochloric acid in dioxane (1 mL). The reaction mixture was stirred 1 h at RT. The solvents were removed under reduced pressure to give the desired hydrochloride salt of benzyl 1-(2-aminoethyl)-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (32 mg, 97 %). \(^1\)H NMR (300 MHz, DMSO \(d_6\)) \(\delta\) 2.57 (s, 3H), 2.67-2.8 (m, 1H), 2.81-2.95 (m, 1H), 3.02 (dd, \(J = 15.9, 7.5\) Hz, 1H), 3.62-3.75 (m, 1H), 3.80-4.04 (m, 2H), 4.20 (d, \(J = 6.0\) Hz, 1H), 5.04 (d, \(J = 13.5\) Hz, 1H), 5.10 (d, \(J = 13.5\) Hz, 1H), 7.07-7.13 (m, 1H), 7.16 (d, \(J = 7.9\) Hz, 2H), 7.21-7.28 (m, 4H), 7.31 (d, \(J = 7.9\) Hz, 2H), 8.21 (b, 3H). MS [M+H]\(^+\) = 399; HRMS : calcd for C\(_{22}\)H\(_{24}\)N\(_2\)O\(_3\)Cl, [M+H]\(^+\) = 399.1475, found 399.1486.

**EXAMPLE 54:** Benzyl 4-(4-chlorophenyl)-1-[3-(dimethylamino)propyl]-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

Benzyl 4-(4-chlorophenyl)-1-[3-(dimethylamino)propyl]-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate was obtained according general procedure B starting from benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (0.28 mmol) and obtained as a colorless oil (66 mg, 53 %) after flash chromatography purification (cyclohexane/EtOAc). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.37-1.62 (m, 2H), 2.06 (s, 6H), 2.08 (t, \(J = 7.2\) Hz, 2H), 2.56 (s, 3H), 2.57-2.62 (m, 1H), 2.97 (dd, \(J = 15.7, 7.2\) Hz, 1H), 3.51 (ddd, \(J = 14.6, 9.1, 3.7\) Hz, 1H), 3.82 (ddd, \(J = 14.6, 9.1, 5.4\) Hz, 1H), 4.18 (d, \(J = 6.4\) Hz, 1H), 5.05 (d, \(J = 13.2\) Hz, 1H), 5.12 (d, \(J = 13.2\) Hz, 1H), 7.12-7.16 (m, 4H), 7.26 (m, 3H), 7.32 (d, \(J = 8.1\) Hz, 2H). MS [M+H]\(^+\) = 441. HRMS : calcd for C\(_{39}\)H\(_{47}\)N\(_2\)O\(_3\)Cl, [M+H]\(^+\) = 441.1945, found 441.1950.

**EXAMPLE 55:** Benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1-(2-pyrrolidin-1-ylethyl)-3,4-dihydropyridine-5-carboxylate

The benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (71 mg,
0.20 mmol) was dissolved in anhydrous DMF (1 mL). Sodium hydride (14 mg, 0.60 mmol) was added. The reaction mixture was stirred at r.t. for 15 min. N-(2-chloroethyl)pyrrolidine hydrochloride (55 mg, 0.30 mmol) were added. The reaction mixture was stirred at 60 °C for 4 h. LCMS analysis showed the reaction was incomplete. Sodium hydride (7 mg, 0.30 mmol) and N-(2-chloroethyl)pyrrolidine hydrochloride (18 mg, 0.10 mmol) were added. The reaction mixture was stirred for an additional hour at 60 °C. The DMF was removed under reduced pressure. The residue was washed with water and extracted by EtOAc. The organic layers were assembled, washed by brine and dried on MgSO4. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of DCM/Acetone (8/2) as eluent to give the desired compound as a white powder (55 mg, 61%). 1H NMR (300 MHz, CDCl3) δ 1.72 - 1.86 (m, 4H), 2.45-2.66 (m, 6H), 2.62 (s, 3H), 2.74 (dd, J = 15.9, 2.3 Hz, 1H), 2.92 (dd, J = 15.9, 7.5 Hz, 1H), 3.69 (ddd, J = 14.5, 8.8, 5.9 Hz, 1H), 4.14 (ddd, J = 14.5, 8.8, 5.9 Hz, 1H), 4.22 (dd, J = 7.5, 2.3 Hz, 1H), 5.09 (d, J = 12.6 Hz, 1H), 5.15 (d, J = 12.6 Hz, 1H), 7.07 (dt, J = 8.6, 2.2 Hz, 2H), 7.11-7.18 (m, 2H), 7.22 (dt, J = 8.6, 2.2 Hz, 2H), 7.26-7.34 (m, 3H). MS [M+H]+ 453. HRMS : calcd for C2gH30N2O3Cl, [M+H]+ 453. 1945, found 453. 1920.

EXAMPLE 56: Benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1-[2-(1-piperidyl)ethyl]-3,4-dihydropyridine-5-carboxylic acid

The benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (71 mg, 0.20 mmol) was dissolved in anhydrous DMF (1 mL). Sodium hydride (14 mg, 0.60 mmol) was added. The reaction mixture was stirred at RT for 15 min. N-(2-chloroethyl)piperidine hydrochloride (55 mg, 0.30 mmol) were added. The reaction mixture was stirred at 60 °C for 4 h. LCMS analysis showed the reaction was incomplete. Sodium hydride (7 mg, 0.30 mmol) and N-(2-chloroethyl)piperidine hydrochloride (18 mg, 0.10 mmol) were added. The reaction mixture was stirred for an additional hour at 60 °C. The DMF was removed under reduced pressure. The residue was washed with water and extracted by EtOAc. The organic layers were assembled, washed by brine and dried on MgSO4. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of DCM/Acetone (8/2) as eluent to give the desired compound as a white powder (48 mg, 52%). 1H NMR (300 MHz, CDCl3) δ 1.40-1.50 (m, 2H), 1.53 -1.66 (m, 4H), 2.29-2.53 (m, 6H), 2.61 (s, 3H), 2.74 (dd, J = 15.8, 2.3 Hz, 1H), 2.92 (dd, J = 15.8, 7.5 Hz, 1H), 3.67 (dt, J = 14.0, 7.5 Hz, 1H), 4.07 (ddd, J = 14.0, 7.5, 5.5 Hz, 1H), 4.22 (dd, J = 7.5, 2.3 Hz, 1H), 5.10 (d, J = 12.8 Hz, 1H), 5.15 (d, J = 12.8 Hz, 1H), 7.08 (dt, J = 8.5, 2.3 Hz, 2H), 7.11-7.17 (m, 2H), 7.22 (dt, J = 8.5, 2.3 Hz, 2H), 7.26-7.33 (m, 3H). MS [M+H]+ 467. HRMS : calcd for C2gH32N2O3Cl, [M+H]+ 467.2 101, found 467.21 20.

EXAMPLE 57: Benzyl 4-(4-chlorophenyl)-1-(2-methoxy-2-oxo-ethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid
The benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (75 mg, 0.21 mmol) was dissolved in anhydrous DMF (1 ml). Sodium hydride (10 mg, 0.42 mmol) and methylbromoacetate (45 µL, 0.42 mmol) were added. The reaction mixture was stirred at RT for 5 h. The DMF was removed under reduced pressure. The residue was diluted in water and extracted by EtOAc. The organic layers were assembled, washed by brine and dried on MgSO₄. The solvent was removed under reduced pressure to give the desired compound as a yellow oil (90 mg, 100 %). ¹H NMR (300 MHz; CDCl₃) δ 2.50 (s, 3H), 2.78 (dd, J = 16.0, 2.0 Hz, 1H), 2.99 (dd, J = 16.0, 7.9 Hz, 1H), 3.76 (s, 3H), 4.25 (d, J = 7.9 Hz, 1H), 4.43 (d, J = 18.0 Hz, 1H), 4.65 (d, J = 18.0 Hz, 1H), 5.07 (d, J = 12.6 Hz, 1H), 5.14 (d, J = 12.6 Hz, 1H), 7.07-7.14 (m, 2H), 7.16 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H), 7.26-7.33 (m, 3H). MS [M+H]⁺ 428. HRMS: calcd for C₂₅H₂₅NO₂Cl, [M+H]⁺ 428.1265, found 428.1251.

EXAMPLE 58: Benzyl 1-(2-tert-butoxy-2-oxo-ethyl)-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

The benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (106 mg, 0.30 mmol) was dissolved in anhydrous DMF (2 ml). Sodium hydride (9 mg, 0.36 mmol) was added. The reaction mixture was stirred at RT for 30 min. ie/l-butylnbromoacetate (73 µL, 0.45 mmol) were added. The reaction mixture was stirred at r.t. for 4 h. LCMS analysis showed the reaction was incomplete. Sodium hydride (4 mg, 0.15 mmol) and ie/l-butylnbromoacetate (24 µL, 0.15 mmol) were added. The reaction mixture was stirred for 1 h at RT The DMF was removed under reduced pressure. The residue was diluted in water and extracted by EtOAc. The organic layers were assembled, washed by brine and dried on MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/EtOAc (9/1) as eluent to give the desired benzyl 1-(2-tert-butoxy-2-oxo-ethyl)-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a white powder (112 mg, 79 %). ¹H NMR (300 MHz; CDCl₃) δ 1.49 (s, 9H), 2.50 (s, 3H), 2.76 (dd, J = 16.1, 2.4 Hz, 1H), 2.99 (dd, J = 16.1, 7.9 Hz, 1H), 4.24 (d, J = 7.9 Hz, 1H), 4.38 (d, J = 17.8 Hz, 1H), 4.52 (d, J = 17.8 Hz, 1H), 5.06 (d, J = 12.5 Hz, 1H), 5.13 (d, J = 12.5 Hz, 1H), 7.08-7.14 (m, 2H), 7.17 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.7 Hz, 2H), 7.28-7.32 (m, 3H). MS [M+H]⁺ 470. HRMS: calcd for C₂₆H₂₅NO₂Cl+[M+NH₄]⁺ 487.2000, found 487.1992.

EXAMPLE 59: Benzyl 4-(4-chlorophenyl)-6-methyl-1-[(3-methyl-1,2,4-oxadiazol-5-yl)methyl]-2-oxo-3,4-dihydropyridine-5-carboxylate
Step 1. 2-[[5-benzyloxycarbonyl-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridin-1-yl]acetic acid

Benzyl 1-(2-ethyl-2-oxo-ethyl)-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate (100 mg, 0.21 mmol) was dissolved in DCM (160 µL). Trifluoroacetic acid (160 µL, 2.3 mmol) was added. The reaction mixture was stirred at RT for 1 h. Water was added. The acid was extracted by EtOAc. The organic layers were assembled, washed by brine and dried on MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/Acetone/EtOAc (3/1/1) as eluent to give a mixture of the desired compound and unidentified byproducts (80 mg). This mixture was diluted in diethyl ether and washed with an aqueous solution of NaHCO₃ (1 M). The aqueous solution was acidified by hydrochloric acid until pH = 1 and extracted by EtOAc. The organic layers were assembled, washed by brine and dried on MgSO₄. The solvent was removed under reduced pressure to give the desired 2-[[5-benzyloxycarbonyl-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridin-1-yl]acetic acid as a white powder (44 mg, 50 %). ¹H NMR (300 MHz, CDCl₃) δ 2.48 (s, 3H), 2.75 (d, J = 16.0 Hz, 1H), 2.97 (dd, J = 16.0, 7.5 Hz, 1H), 4.38-4.67 (m, 4H), 5.05 (d, J = 12.6 Hz, 1H), 5.12 (d, J = 12.6 Hz, 1H), 6.34 (brs, 1H), 7.05-7.15 (m, 4H), 7.18 (d, J = 8.4 Hz, 2H), 7.24-7.31 (m, 3H). MS [M+H]⁺ 414. HRMS : calcld for C₂₂H₂₁NO₅Cl, [M+H]⁺ 414.1 108, found 414.1 121.

Step 2. Benzyl 4-(4-chlorophenyl)-6-methyl-1-[[[3-methyl-1,2,4-oxadiazol-5-yl)methyl]-2-oxo-3,4-dihydropyridine-5-carboxylate

The 2-[5-benzyloxycarbonyl-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridin-1-yl]acetic acid (207 mg, 0.5 mmol) of step 1 was dissolved in anh. DMF (2 mL). DIEA (430 µL, 2.5 mmol) and HBTU (228 mg, 0.6 mmol) were added. The reaction mixture was stirred at RT for 10 min. The amidoxime (41 mg, 0.55 mmol) was then added. The reaction mixture was stirred at RT for 1 h. Water was added. The aqueous phase was extracted with EtOAc. The organic phases were assembled, washed with brine and dried over MgSO₄. The solvents were removed under reduced pressure. The crude was dissolved in anh. DMF (2 mL). The reaction mixture was stirred at 110 °C for 3 h. The solvent was removed under reduced pressure. Water was added.
The aqueous phase was extracted with EtOAc. The organic phases were assembled, washed with brine and dried over MgSO\textsubscript{4}. The solvents were removed under reduced pressure. Purification of the crude by Flash chromatography using a mixture Cyclohexane/EtOAc (8/2) gave the desired benzyl 4-(4-chlorophenyl)-6-methyl-1-[(3-methyl-1,2,4-oxadiazol-5-yl)methyl]-2-oxo-3,4-dihydropyridine-5-carboxylate as a white powder (124 mg, 55 %). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 2.38 (s, 3H), 2.56 (s, 3H), 2.81 (dd, \( J = 16.0, 2.3 \) Hz, 1H), 3.01 (dd, \( J = 16.0, 7.6 \) Hz, 1H), 4.28 (d, \( J = 7.6 \) Hz, 1H), 5.03 (d, \( J = 17.5 \) Hz, 1H), 5.07 (d, \( J = 12.4 \) Hz, 1H), 5.14 (d, \( J = 12.4 \) Hz, 1H), 5.28 (d, \( J = 17.5 \) Hz, 1H), 7.08-7.17 (m, 4H), 7.21 (d, \( J = 8.2 \) Hz, 2H), 7.24-7.32 (m, 3H). \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \) 11.6, 16.8, 36.9, 37.9, 38.1, 66.5, 111.5, 127.9, 128.2, 128.5, 128.9, 132.9, 135.7, 139.3, 148.2, 166.5, 167.5, 168.9, 174.6. MS [M+H]+ 452. HRMS: calcd for C\textsubscript{26}H\textsubscript{33}N\textsubscript{3}O\textsubscript{4}Cl, [M+H]+ 452. 1377, found 452.1355.

**EXAMPLE 60:** Benzyl 1-(2-amino-2-oxo-ethyl)-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

The benzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (106 mg, 0.30 mmol) was dissolved in anhydrous DMF (2 mL). Sodium hydride (9 mg, 0.36 mmol) was added. The reaction mixture was stirred at RT for 30 min. 2-bromoacetamide (62 mg, 0.45 mmol) were added. The reaction mixture was stirred at RT for 4 h. LCMS analysis showed the reaction was incomplete. Sodium hydride (4 mg, 0.15 mmol) and 2-bromoacetamide (21 mg, 0.15 mmol) were added. The reaction mixture was stirred for 1 h at RT. The DMF was removed under reduced pressure. The residue was diluted in water and extracted by EtOAc. The organic layers were assembled, washed by brine and dried on MgSO\textsubscript{4}. The solvent was removed under reduced pressure. The crude product was purified by Flash chromatography using a mixture Cyclohexane/EtOAc (9/1) as eluent to give the desired compound as a white powder (100 mg, 81 %). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 2.58 (s, 3H), 2.83 (dd, \( J = 16.0, 2.4 \) Hz, 1H), 3.00 (dd, \( J = 16.0, 7.3 \) Hz, 1H), 4.27 (dd, \( J = 7.3, 2.4 \) Hz, 1H), 4.31 (d, \( J = 16.2 \) Hz, 1H), 4.51 (d, \( J = 12.5 \) Hz, 1H), 5.16 (d, \( J = 12.5 \) Hz, 1H), 5.46 (brs, 1H), 5.68 (brs, 1H), 7.10-7.18 (m, 4H), 7.24 (dt, \( J = 8.6, 2.2 \) Hz, 2H), 7.28-7.34 (m, 3H). MS [M-H] - 411. HRMS: calcd for C\textsubscript{22}H\textsubscript{28}N\textsubscript{2}O\textsubscript{4}Cl, [M-H] - 413.1268, found 413.1250.

**EXAMPLE 61:** 2-[5-benzylloxycarbonyl-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridin-1-yl]acetic acid

The benzyl 1-(2-iodo-2-oxo-ethyl)-4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate (100 mg, 0.21 mmol) was dissolved in DCM (160 \( \mu \text{L} \)). Trifluoroacetic acid (160 \( \mu \text{L}, 2.3 \) mmol) was added. The reaction mixture was stirred at RT for 1 h. Water was added. The acid was extracted by EtOAc. The organic layers were assembled, washed by brine and dried on MgSO\textsubscript{4}. The solvent was removed under reduced pressure. The crude product was purified.
by flash chromatography using a mixture of Cyclohexane/Acetone/EtOAc (3/1/1) as eluent to
give a mixture of the desired compound and unidentified byproducts (80 mg). This mixture was
diluted in diethyl ether and washed with an aqueous solution of NaHCO₃ (1 M). The aqueous
solution was acidified by hydrochloric acid until pH = 1 and extracted by EtOAc. The organic
layers were assembled, washed by brine and dried on MgSO₄. The solvent was removed under
reduced pressure to give the desired 2-[5-benzylxoycarbonyl-4-(4-chlorophenyl)-6-methyl-2-
oxo-3,4-dihydropyridin-1-yl]acetic acid as a white powder (44 mg, 50 %). ^1H NMR (300 MHz,
CDCl₃)  δ 2.48 (s, 3H), 2.75 (d, J = 16.0 Hz, 1H), 2.97 (dd, J = 16.0, 7.5 Hz, 1H), 4.38-4.67 (m,
4H), 5.05 (d, J = 12.6 Hz, 1H), 5.12 (d, J = 12.6 Hz, 1H), 6.34 (brs, 1H), 7.05-7.15 (m, 4H), 7.18
(d, J = 8.4 Hz, 2H), 7.24-7.31 (m, 3H). MS [M+H]⁺ 414. HRMS : calcd for C₂₂H₂₀N₂O₃Cl, [M+H]⁺
414.1108, found 414.1121.

**EXAMPLE 62:** Benzyl 4-(4-chlorophenyl)-6-methyl-1-(2-methylsulfonyl)ethyl)-2-oxo-3,4-
dihydropyridine-5-carboxylate

Benzyl 4-(4-chlorophenyl)-6-methyl-1-(2-methylsulfonyl)ethyl)-2-oxo-3,4-dihydropyridine-5-
carboxylate was obtained according general procedure B starting from benzyl 4-(4-
chlorophenyl)-6-methyl-2-oxo-2,3,4-dihydro-1H-pyridine-5-carboxylate (0.50 mmol) and obtained
as a white powder (51 mg, 22 %) after flash chromatography purification (cyclohexane/EtOAc).
^1H NMR (300 MHz, CDCl₃)  δ 2.61 (s, 3H), 2.79 (dd, J = 16.0, 2.7 Hz, 1H), 2.87-2.97 (m, 1H),
2.94 (s, 3H), 3.17 (t, J = 7.3 Hz, 2H), 3.98-4.28 (m, 2H), 4.26 (d, J = 7.6 Hz, 1H), 5.10 (d, J =
12.4 Hz, 1H), 5.16 (d, J = 7.4 Hz, 2H), 7.03 (d, J = 8.3 Hz, 2H), 7.12-7.18 (m, 2H), 7.24 (d, J =
8.3 Hz, 2H), 7.27-7.33 (m, 3H). ^13C NMR (75 MHz, CDCl₃)  δ 16.8, 36.3, 36.5, 38.2, 41.1, 52.8,
66.5, 111.8, 127.9, 128.1, 128.2, 128.5, 129.0, 133.0, 135.7, 138.9, 148.3, 166.5, 169.4. MS

**EXAMPLE 63:** Benzyl 4-(4-chlorophenyl)-1-(cyanomethyl)-6-methyl-2-oxo-3,4-
dihydropyridine-5-carboxylate

Benzyl 4-(4-chlorophenyl)-1-(cyanomethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate
was obtained according general procedure B starting from benzyl 4-(4-chlorophenyl)-6-methyl-
2-0X0-3,4-dihydro-1H-pyridine-5-carboxylate (0.50 mmol) and obtained as a colorless oil (162
mg, 88 %) after flash chromatography purification (dichloromethane). ^1H NMR (300 MHz,
CDCl₃)  δ 2.68 (s, 3H), 2.82 (dd, J = 16.1, 2.5 Hz, 1H), 2.96 (dd, J = 16.1, 7.3 Hz, 1H), 4.27 (dd,
J = 7.3, 2.5 Hz, 1H), 4.53 (d, J = 17.7 Hz, 1H), 4.81 (d, J = 17.7 Hz, 1H), 5.10 (d, J = 12.4 Hz,
1H), 5.15 (d, J = 12.4 Hz, 1H), 7.01 (d, J = 8.5 Hz, 2H), 7.12-7.18 (m, 2H), 7.24 (d, J = 8.5 Hz,
2H), 7.28-7.35 (m, 3H). ^13C NMR (75 MHz, CDCl₃)  δ 16.7, 29.5, 36.7, 38.1, 66.6, 112.8, 114.7,
127.9, 128.0, 128.3, 128.5, 129.1, 133.2, 135.5, 138.4, 146.8, 166.1, 168.3. MS [M+H]+ 395;
EXAMPLE 64: (2-methoxyphenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

2-methoxybenzyl alcohol (268 µL, 2.0 mmol) and triethylamine (335 µL, 2.4 mmol) were dissolved in anh. DCM (7 mL). Thionyl chloride (218 µL, 3.0 mmol) was added slowly. The reaction mixture was stirred at RT for 1 h. The reaction mixture was washed with an aqueous solution of HCl 1 N. The organic phase was dried over MgSO₄. The solvent was removed under reduced pressure to give the desired 2-methoxybenzyl chloride (300 mg, 96 %) as a yellowish oil. 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 85 mg, 0.26 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (169 mg, 0.52 mmol) and 2-methoxybenzyl chloride (81 mg, 0.52 mmol) were added.
The reaction mixture was stirred at RT for 18 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over MgSO\textsubscript{4}. The solvent was removed under reduced pressure. Purification of the crude by flash chromatography using a mixture of Cyclohexane/EtOAc (8:2) as eluent gave the desired (2-methoxyphenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a yellowish oil (36 mg, 31%). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 2.60 (s, 3H), 2.71 (dd, \( J = 15.9, 2.4 \) Hz, 1H), 2.91 (dd, \( J = 15.9, 7.6 \) Hz, 1H), 3.31 (s, 3H), 3.36 (ddd, \( J = 9.8, 8.3, 3.7 \) Hz, 1H), 3.46 (dt, \( J = 9.8, 4.2 \) Hz, 1H), 3.74 (s, 3H), 3.69-3.78 (m, 1H), 4.13-4.21 (m, 2H), 5.10 (d, \( J = 12.9 \) Hz, 1H), 5.19 (d, \( J = 12.9 \) Hz, 1H), 6.80-6.85 (m, 2H), 6.98 (dd, \( J = 7.8, 1.6 \) Hz, 1H), 7.09 (d, \( J = 8.4 \) Hz, 2H), 7.19 (d, \( J = 8.4 \) Hz, 2H), 7.26 (t, \( J = 7.8 \) Hz, 1H). \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \) 17.0, 36.8, 38.6, 41.8, 55.1, 58.8, 61.8, 71.0, 110.1, 110.3, 120.2, 124.2, 128.4, 128.6, 129.1, 129.2, 132.4, 139.8, 150.6, 157.2, 167.1, 169.0. MS [M+H]\textsuperscript{+} 444. HRMS : calcd for C\textsubscript{26}H\textsubscript{27}NO\textsubscript{5}Cl, [M+H]\textsuperscript{+} 444.1578, found 444.1585.

**EXAMPLE 65a** o-methoxybenzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (intermediate)

\[ \text{example 65a} \]

The (2-methoxyphenyl)methyl 3-oxobutanoate (1334 mg, 6.0 mmol) was dissolved in acetic acid (6 ml). p-chlorobenzaldehyde (843 mg, 6.0 mmol), meldrum acid (865 mg, 6.0 mmol) and ammonium acetate (676 mg, 9.0 mmol) were added and the reaction mixture was stirred at 110°C for 18 h. The reaction mixture was cooled to RT. The solvent was removed under reduced pressure. The crude was precipitated in EtOH, cooled to 0°C and filtered to give the desired o-methoxybenzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate as a white powder (1.041 g, 45%). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 2.42 (s, 3H), 2.64 (d, \( J = 16.5 \) Hz, 1H), 2.94 (dd, \( J = 16.5, 8.1 \) Hz, 1H), 3.75 (s, 3H), 4.26 (d, \( J = 8.1 \) Hz, 1H), 5.10 (d, \( J = 12.7 \) Hz, 1H), 5.21 (d, \( J = 12.7 \) Hz, 1H), 6.80-6.90 (m, 2H), 7.03 (d, \( J = 7.5 \) Hz, 1H), 7.08 (d, \( J = 8.5 \) Hz, 2H), 7.22 (d, \( J = 8.5 \) Hz, 2H), 7.28 (dd, \( J = 8.1, 2.1 \) Hz, 1H), 8.47 (s, 1H). \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \)106.8, 110.2, 120.3, 124.2, 128.2, 128.8, 129.4, 129.4, 132.6, 140.7, 146.7, 157.4, 166.5, 170.9.

**EXAMPLE 65** (2-methoxyphenyl)methyl 4-(4-chlorophenyl)-1-(2-hydroxyethyl)-6-methyl-
2-oxo-3,4-dihydropyridine-5-carboxylate

o-methoxybenzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (example 65a, 96 mg, 0.25 mmol) was dissolved in anhydrous DMF (1 mL). Cesium carbonate (162 mg, 0.50 mmol) and 2-bromoethanol (35 μL, 0.50 mmol) were added. The reaction mixture was stirred at 60 °C for 24 h. The reaction was incomplete. Cesium carbonate (324 mg, 1.00 mmol) and 2-bromoethanol (70 μL, 1.00 mmol) were added 4 times more every 24 h. The DMF was removed under reduced pressure. The residue was diluted in water. The aqueous phase was extracted by EtOAc and the combined organic layers were washed with brine and dried over MgSCo. The solvent was removed under reduced pressure. Purification of the crude by flash chromatography using a mixture of Cyclohexane/EtOAc (4/6) as eluent gave the desired (2-methoxyphenyl)methyl 4-(4-chlorophenyl)-1-(2-hydroxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (9 mg, 8%). 1H NMR (300 MHz, CDCl3) δ 1.88 (brs, 1H), 2.58 (s, 3H), 2.78 (dd, J = 16.0, 2.4 Hz, 1H), 2.95 (dd, J = 16.0, 7.5 Hz, 1H), 3.74 (s, 3H), 3.74-3.85 (m, 3H), 4.02-4.13 (m, 1H), 4.24 (d, J = 7.0 Hz, 1H), 5.12 (d, J = 12.8 Hz, 1H), 5.23 (d, J = 12.8 Hz, 1H), 6.84-6.90 (m, 2H), 6.99-7.07 (m, 1H), 7.10 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.3 Hz, 2H), 7.25-7.32 (m, 1H). MS [M+H]+ 430. HRMS: calcd for C26H25N05Cl, [M+H]+ 466.1421, found 466.1433.

EXAMPLE 66: 2-benzyl 4-(4-chlorophenyl)-1-(2-furymethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

o-methoxybenzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (example 65a, 96 mg, 0.25 mmol) was dissolved in anhydrous DMF (1 mL). Cesium carbonate (162 mg, 0.50 mmol) and 2-chloromethylfuran (145 mg, 0.50 mmol) were added. The reaction mixture was stirred at 60 °C for 18 h. The DMF was removed under reduced pressure. The residue was diluted in water. The aqueous phase was extracted by EtOAc and the combined organic layers were washed with brine and dried over MgSCo. The solvent was removed under reduced pressure. Purification of the crude by flash chromatography using a mixture of Cyclohexane/EtOAc (9/1) as eluent gave the desired 2-benzyl 4-(4-chlorophenyl)-1-(2-furymethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a yellow oil (43 mg, 50%). 1H NMR (300 MHz, CDCl3) δ 2.70 (s, 3H), 2.74 (dd, J = 16.1, 2.1 Hz, 1H), 2.94 (dd, J = 16.1, 7.3 Hz, 1H), 3.73 (s, 3H), 4.18 (d, J = 7.3 Hz, 1H), 4.66 (d, J = 15.8 Hz, 1H), 5.11 (d, J = 12.8 Hz, 1H), 5.20 (d, J = 12.8 Hz, 1H), 5.28 (d, J = 15.8 Hz, 1H), 6.20 (d, J = 3.2 Hz, 1H), 6.34 (dd, J = 3.2, 1.8 Hz, 1H), 6.80-6.88 (m, 2H), 7.00 (dd, J = 7.4, 1.3 Hz, 1H), 7.09 (d, J = 8.5 Hz, 2H), 7.24-7.32 (m, 1H), 7.33-7.36 (m, 1H). 13C NMR (75 MHz, CDCl3) δ 16.9, 36.8, 37.9, 38.4, 55.2, 61.9, 108.9, 110.2, 110.5, 111.5, 120.2, 124.1, 128.3, 128.6, 129.3, 129.4, 132.4, 139.5, 142.0, 149.2, 150.3, 157.3, 166.9, 168.7. MS [M+H]+ 466. HRMS: calcd for C26H25NO5Cl, [M+H]+ 466.1421, found 466.1433.
EXAMPLE 67: (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate (racemic)

The 4-methoxybenzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (example 65a, 96 mg, 0.25 mmol) was dissolved in anhydrous DMF (1 mL). Cesium carbonate (162 mg, 0.50 mmol) and tetrahydrofurfuryl bromide (57 µL, 0.50 mmol) were added. The reaction mixture was stirred at 60 °C for 18 h. Cesium carbonate (162 mg, 0.50 mmol) and tetrahydrofurfuryl bromide (57 µL, 0.50 mmol) were added 3 times more every 12 h. Overall, the reaction mixture was stirred at 60 °C for 66 h. The DMF was removed under reduced pressure. The residue was diluted in water. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure. Purification of the crude by flash chromatography using a mixture of Cyclohexane/EtOAc (9:1) as eluent gave the desired (2-methoxyphenyl)methyl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate as a colorless oil (25 mg, 21 %).

1H NMR (300 MHz, CDCl₃) δ 1.41-1.53 (m, 1H), 1.78-1.99 (m, 3H), 2.63 (s, 3H), 2.92 (dd, J = 15.7, 2.4 Hz, 1H), 2.92 (dd, J = 15.7, 7.3 Hz, 1H), 3.41 (dd, J = 14.4, 8.6 Hz, 1H), 3.73 (s, 3H), 3.63-3.95 (m, 3H), 4.21 (d, J = 7.3 Hz, 1H), 4.26 (dd, J = 14.4, 3.7 Hz, 1H), 5.10 (d, J = 13.2 Hz, 1H), 5.20 (d, J = 13.2 Hz, 1H), 6.79-6.87 (m, 2H), 6.97 (dd, J = 7.7, 1.7 Hz, 1H), 7.15-7.30 (m, 5H).

13C NMR (75 MHz, CDCl₃) δ 17.1, 25.5, 29.2, 37.0, 39.0, 45.6, 55.2, 61.8, 68.1, 77.9, 110.2, 110.5, 120.2, 124.4, 128.6, 128.7, 129.0, 129.2, 132.5, 139.6, 150.9, 157.2, 167.1, 169.0. MS [M+H]+ 470. HRMS: calcd for C₂₅H₂₃NO₅Cl, [M+H]+ 470.1734, found 470.1714.

EXAMPLE 68: (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[[(2S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate (racemic)

The 4-methoxybenzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (example 65a, 96 mg, 0.25 mmol) was dissolved in anhydrous DMF (1 mL). Cesium carbonate (162 mg, 0.50 mmol) and tetrahydrofurfuryl bromide (57 µL, 0.50 mmol) were added. The reaction mixture was stirred at 60 °C for 18 h. Cesium carbonate (162 mg, 0.50 mmol) and tetrahydrofurfuryl bromide (57 µL, 0.50 mmol) were added 3 times more every 12 h. Overall, the reaction mixture was stirred at 60 °C for 66 h. The DMF was removed under reduced pressure. The residue was diluted in water. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure. Purification of the crude by flash chromatography using a mixture of Cyclohexane/EtOAc (9:1) as eluent gave the desired (2-methoxyphenyl)methyl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[[(2S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate as a colorless oil (21 mg, 18 %).

1H NMR (300 MHz, CDCl₃) δ 1.25-1.37 (m, 1H), 1.74-1.94 (m, 3H), 2.62 (s, 3H), 2.79 (dd, J = 15.9, 2.4 Hz, 1H), 2.94 (dd, J = 15.9, 7.4 Hz, 1H), 3.75 (s, 3H), 3.65-3.84 (m, 3H), 3.89-4.06 (m, 2H), 4.23 (dd, J = 7.4, 2.4 Hz, 1H), 5.11 (d, J = 12.6 Hz, 1H), 5.23 (d, J = 12.6 Hz, 1H),
EXAMPLE 69: (2-methoxyphenyl)methyl 4-(4-chlorophenyl)-1-(2-ethoxy-2-oxo-ethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

O-methoxybenzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (example 65a, 75mg, 0.19 mmol) was dissolved in anhydrous DMF (0.3M). Cesium carbonate (114 mg, 0.35 mmol) and Methylbromacetate (33 µL, 0.35 mmol) were added. The reaction mixture was stirred at RT for 2 hours. The DMF was removed under reduced pressure. The residue was diluted in water. The aqueous phase was extracted by EtOAc and the combined organic layers were washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure. EtOH was added and was removed under reduced pressure (transesterification). Purification of the crude by flash chromatography using a DCN as eluent gave the desired compound as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 1.29 (t, J = 7.1 Hz, 3H), 2.49 (s, 3H), 2.77 (dd, J = 15.9, 2.1 Hz, 1H), 3.00 (dd, J = 15.9, 7.9 Hz, 1H), 3.74 (s, 3H), 4.22 (q, J = 7.1 Hz, 2H), 4.22-4.28 (m, 1H), 4.43 (d, J = 17.9 Hz, 1H), 4.61 (d, J = 17.9 Hz, 1H), 5.10 (d, J = 12.8 Hz, 1H), 5.21 (d, J = 12.8 Hz, 1H), 6.81-6.89 (m, 2H), 7.02 (dd, J = 7.2, 1.4 Hz, 1H), 7.16 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 7.28 (td, J = 8.1, 2.1 Hz, 1H). MS [M-H]⁻ 472; HRMS: calcd for C₃₁H₄₈O₄N₄, [M+H]⁺ 472.1549, found 472.1545.

EXAMPLE 70: o-methoxybenzyl 4-(4-chlorophenyl)-1-(cyclopropylmethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

The o-methoxybenzyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (example 65a, 96 mg, 0.25 mmol) was dissolved in anhydrous DMF (1 ml). Cesium carbonate (162 mg, 0.50 mmol) and (bromomethyl)cyclopropane (48 µL, 0.50 mmol) were added. The reaction mixture was stirred at 60 °C for 18 h. The DMF was removed under reduced pressure. The residue was diluted in water. The aqueous phase was extracted by EtOAc and the combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure. Purification of the crude by flash chromatography using a mixture of Cyclohexane/EtOAc (9/1) as eluent gave the desired o-methoxybenzyl 4-(4-chlorophenyl)-1-(cyclopropylmethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a yellow oil (77 mg, 71%). ¹H NMR (300 MHz, CDCl₃) δ 0.22-0.36 (m, 2H), 0.36-0.46 (m, 1H), 0.46-0.56 (m, 1H), 0.86-1.04 (m, 1H), 2.61 (s, 3H), 2.73 (dd, J = 15.8, 2.4 Hz, 1H), 2.91 (dd, J = 15.8, 7.3 Hz, 1H), 3.50 (dd, J = 14.6, 5.8 Hz, 1H), 3.74 (s, 3H), 3.90 (dd, J = 14.6, 7.9 Hz, 1H), 4.22 (d, J = 7.3 Hz, 1H), 5.12 (d, J = 12.8 Hz, 1H), 5.23 (d, J = 12.8 Hz, 1H), 6.82-6.89 (m, 2H), 7.04 (dd, J = 7.4, 1.1 Hz, 1H), 7.12 (d, J = 7.6 Hz, 2H), 7.20 (d, J = 7.6 Hz, 2H), 7.28 (td, J = 7.7,
EXAMPLE 71: (2-methoxyphenyl)methyl 4-(4-chlorophenyl)-1-(3-methoxypropyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

The (2-methoxyphenyl)methyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (115 mg, 0.30 mmol) was dissolved in anhydrous DMF (1 ml). Cesium carbonate (195 mg, 0.60 mmol) and 1-bromo-3-methoxypropane (68 μL, 0.60 mmol) were added. The reaction mixture was stirred at 60 °C for 18 h. The DMF was removed under reduced pressure. The residue was diluted in water and extracted by EtOAc. The organic layers were assembled, washed by brine and dried on MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/EtOAc (9/1) as eluent to give the desired (2-methoxyphenyl)methyl 4-(4-chlorophenyl)-1-(3-methoxypropyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (96 mg, 70%). ¹H NMR (300 MHz, CDCl₃) δ 1.62-1.84 (m, 2H), 2.57 (s, 3H), 2.76 (dd, J = 15.9, 2.4 Hz, 1H), 2.89 (dd, J = 15.9, 7.5 Hz, 1H), 3.18-3.35 (m, 2H), 3.28 (s, 3H), 3.64 (ddd, J = 14.6, 8.9, 6.0 Hz, 1H), 3.74 (s, 3H), 3.99 (ddd, J = 14.6, 8.7, 6.5 Hz, 1H), 4.22 (td, J = 7.5, 2.4 Hz, 1H), 5.12 (d, J = 12.7 Hz, 1H), 5.23 (d, J = 12.7 Hz, 1H), 6.82-6.89 (m, 2H), 7.02-7.08 (m, 3H), 7.20 (d, J = 8.5 Hz, 2H), 7.28 (td, J = 7.8, 1.7 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 29.3, 36.3, 38.2, 39.5, 55.2, 58.6, 61.9, 69.8, 110.2, 111.0, 120.2, 124.1, 128.2, 128.6, 129.3, 129.4, 132.5, 139.6, 149.5, 157.3, 167.0, 169.0. MS [M+H]^+ 458; HRMS: calcd for C_{26}H_{29}NO_{5}Cl, [M+H]^+ 458.1734, found 458.1744.

EXAMPLE 72: (2-methoxyphenyl)methyl 4-(4-chlorophenyl)-1-(1,3-dioxolan-2-ylmethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

The (2-methoxyphenyl)methyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (115 mg, 0.30 mmol) was dissolved in anhydrous DMF (1 ml). Cesium carbonate (195 mg, 0.60 mmol) and 2-Bromomethyl-1,3-dioxolane (62 μL, 0.60 mmol) were added. The reaction mixture was stirred at 60 °C for 18 h. The DMF was removed under reduced pressure. The residue was diluted in water and extracted by EtOAc. The organic layers were assembled, washed by brine and dried on MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/EtOAc (8/2) as eluent to give the desired (2-methoxyphenyl)methyl 4-(4-chlorophenyl)-1-(1,3-dioxolan-2-ylmethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (73 mg, 52%). ¹H NMR (300 MHz, CDCl₃) δ 2.61 (s, 3H), 2.76 (dd, J = 15.9, 2.2 Hz, 1H), 2.93 (dd, J = 15.9, 7.4 Hz, 1H), 3.64 (dd, J = 14.6, 5.4 Hz, 1H), 3.83 (s, 3H), 3.78-3.94 (m, 4H), 4.23 (dd, J = 7.4, 2.2 Hz, 1H), 6.82-6.89 (m, 2H), 7.02-7.08 (m, 3H), 7.20 (d, J = 8.5 Hz, 2H), 7.28 (td, J = 7.8, 1.7 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 29.3, 36.3, 38.2, 39.5, 55.2, 58.6, 61.9, 69.8, 110.2, 111.0, 120.2, 124.1, 128.2, 128.6, 129.3, 129.4, 132.5, 139.6, 149.5, 157.3, 167.0, 169.0. MS [M+H]^+ 458; HRMS: calcd for C_{26}H_{29}NO_{5}Cl, [M+H]^+ 458.1734, found 458.1744.
EXAMPLE 73: (2-methoxyphenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxy-2-oxo-ethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

(2-methoxy phenyl) methyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (116 mg, 0.30 mmol) was dissolved in anh. DMF (1 mL). 2-bromomethylacetate (41 µL, 0.45 mmol) and Cs$_2$CO$_3$ were added. The reaction mixture was stirred at RT for 18 h. 2-bromomethylacetate (28 µL, 0.30 mmol) was added again and the reaction mixture was stirred at 50°C during 6h. The solvent was removed under reduced pressure. Water was added and the aqueous phase was extracted by Et$_2$O, washed with brine and dried over Na$_2$SO$_4$. Removal of the solvent afforded the desired (2-methoxyphenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxy-2-oxo-ethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (120 mg, 87%).

$^1$H NMR (300 MHz, CDCl$_3$) δ 2.48 (s, 3H), 2.78 (dd, J = 16.0, 2.3 Hz, 1H), 3.00 (dd, J = 16.0, 7.8 Hz, 1H), 3.74-3.74 (s, 3H), 3.76 (s, 3H), 4.25 (d, J = 7.8 Hz, 1H), 4.45 (d, J = 17.8 Hz, 1H), 4.62 (d, J = 17.8 Hz, 1H), 5.10 (d, J = 12.5 Hz, 1H), 5.20 (d, J = 12.5 Hz, 1H), 6.86 (m, 2H), 7.02 (dd, J = 7.5, 1.5 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 7.25-7.30 (m, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 16.7, 36.8, 38.0, 43.4, 52.5, 55.2, 62.0, 110.2, 110.9, 120.3, 124.1, 128.7, 129.5, 129.5, 132.6, 139.8, 148.2, 166.8, 169.1, 169.2. MS [M+H]$^+$ 458, HRMS : calcd for C$_{24}$H$_{25}$N$_0$6CI, [M+H]$^+$ 458.1370, found 458.1378.

Table 7:

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Table 7:
EXAMPLE 74: 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (intermediate product)

4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (4.55 g, 13.5 mmol) was dissolved in methanol (47 mL). An aqueous solution of NaOH 1 M (47 mL) was added. The reaction mixture was stirred at 50 °C for 18 h. The reaction mixture was washed with diethyl ether. The aqueous phase was acidified to pH = 1 with a concentrated solution of hydrochloric acid and then extracted with EtOAc. The organic phases were assembled, washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure. Precipitation of the crude in diethyl ether gave the desired 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid as a white powder (2.82 g, 65%). $^1$H NMR (300 MHz, CDCl₃) δ 2.62 (s, 3H), 2.75 (dd, $J = 15.7, 2.1$ Hz, 1H), 2.91 (dd, $J = 15.7, 7.1$ Hz, 1H), 3.09 (s, 3H), 3.30-3.38 (m, 1H), 3.46 (dt, $J = 9.9, 4.0$ Hz, 1H), 3.76 (ddd, $J = 14.7, 8.9, 3.8$ Hz, 1H), 4.13-4.23 (m, 2H), 7.13 (d, $J = 8.5$ Hz, 2H), 7.23 (d, $J = 8.5$ Hz, 2H). $^{13}$C NMR (300 MHz, CDCl₃) δ 17.4, 36.5, 38.7, 42.0, 58.8, 71.0, 109.1, 128.3, 128.8, 132.7, 139.3, 153.6, 169.1, 172.7. MS [M-H] - 322.

EXAMPLE 75: N-benzyl-4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxamide

4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 323 mg, 1.0 mmol), benzylamine (262 µL, 2.4 mmol), DIEA (860 µL, 5.0 mmol) and a 50% solution of T3P in ethyl acetate (883 µL, 3.0 mmol) were dissolved in anhydrous EtOAc (3 mL). After stirring the reaction mixture at RT for 24 h, the reaction was uncomplete. Benzylamine (131 µL, 1.2 mmol), DIEA (430 µL, 2.5 mmol) and a 50% solution of T3P in ethyl acetate (441 µL, 1.5 mmol) were added. The reaction mixture was stirred at r.t. for 6 h. 1 M hydrochloric acid aqueous solution (20 mL) was added and the aqueous phase was extracted by EtOAc. The organic phases were combined, washed with brine and dried over MgSO₄. The
solvent was removed under reduced pressure. Purification of the crude by flash chromatography on silica using a mixture of DCM/MeOH 9/1 gave the desired (2-methoxyphenyl methyl 1-(2-methoxyethyl)-6-methyl-2-oxo-4-propyl-3,4-dihydropyridine-5-carboxylate as a white powder (267 mg, 65 %). $^1$H NMR (300 MHz, CDCl$_3$) δ 2.34 (s,3H), 2.67 (dd, $J = 15.8$, 2.6 Hz, 1H), 3.01 (dd, $J = 15.8$, 7.6 Hz, 1H), 3.35 (s, 3H), 3.43-3.52 (m, 2H), 3.66 (ddd, $J = 14.5$, 7.9, 4.7 Hz, 1H), 3.87 (dd, $J = 7.6$, 2.6 Hz, 1H), 4.14 (dt, $J = 14.5$, 4.7 Hz, 1H), 4.33 (dd, $J = 14.9$, 5.4 Hz, 1H), 4.49 (dd, $J = 14.9$, 5.4 Hz, 1H), 5.55 (t, $J = 5.4$ Hz, 1H), 7.05-7.13 (m, 2H), 7.17 (d, $J = 8.4$ Hz, 1H), 7.25 (d, $J = 8.4$ Hz, 1H), 7.27-7.35 (m, 3H). MS [M+H]$^+$ 413. HRMS : calcd for C$_2$H$_2$N$_2$O$_3$Cl, [M+H]$^+$ 413.1632, found 413.1641.

**EX A M P L E 76:** 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-N-phenyl-3,4-dihydropyridine-5-carboxamide

4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 97 mg, 0.30 mmol), aniline (31 μL, 0.33 mmol), EDCI (69 mg, 0.36 mmol) and DMAP (36 mg, 0.30 mmol) were dissolved in anh. DCM (2 mL). The reaction mixture was stirred for 18 h at RT. An aqueous solution of hydrochloric acid 1 M was added. The aqueous phase was extracted with DCM. The organic phases were assembled and dried over MgSO$_4$. The solvent was removed under reduced pressure. Purification of the crude by flash chromatography on silica using a mixture of Cyclohexane/EtOAc 7/3 gave the desired 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-N-phenyl-3,4-dihydropyridine-5-carboxamide as a white powder (62 mg, 52 %). $^1$H NMR (300 MHz, CDCl$_3$) δ 2.42 (s, 3H), 2.69 (dd, $J = 15.8$, 2.3 Hz, 1H), 3.03 (dd, $J = 15.8$, 7.6 Hz, 1H), 3.38 (s, 3H), 3.45-3.55 (m, 2H), 3.70 (ddd, $J = 14.5$, 8.2, 4.5 Hz, 1H), 3.93 (dd, $J = 7.6$, 2.3 Hz, 1H), 4.19 (dt, $J = 14.6$, 3.5 Hz, 1H), 6.99-7.15 (m, 2H), 7.20-7.38 (m, 7H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 16.8, 38.6, 39.2, 41.7, 58.9, 71.2, 114.2, 119.8, 124.4, 128.6, 128.9, 129.5, 133.6, 137.5, 138.7, 143.1, 167.1, 168.2. MS [M+H]$^+$ 399. HRMS : calcd for C$_2$H$_2$N$_2$O$_3$Cl, [M+H]$^+$ 399.1475, found 399.1498.

**EX A M P L E 77:** 4-(4-chlorophenyl)-5-(3,4-dihydro-2H-quinoline-1-carbonyl)-1-(2-methoxyethyl)-6-methyl-3,4-dihydropyridin-2-one

4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 97 mg, 0.30 mmol), tetrahydroquinoline (44 μL, 0.33 mmol), EDCI (69 mg, 0.36 mmol) and DMAP (36 mg, 0.30 mmol) were dissolved in anh. DCM (2 mL). The reaction mixture was stirred for 72 h at RT. The reaction was uncomplete; tetrahydroquinoline (44 μL, 0.33 mmol) and EDCI (69 mg, 0.36 mmol) were added. The reaction mixture was stirred for 24 h at RT. An aqueous solution of hydrochloric acid 1 M was added. The aqueous phase was extracted with DCM. The organic phases were assembled and dried over MgSO$_4$. The solvent was removed under reduced pressure. Purification of the crude by flash chromatography on silica using a mixture of Cyclohexane/EtOAc 6/4 gave the desired 4-(4-chlorophenyl)-5-(3,4-

Table 8:

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EXAMPLE 78: 4-(4-chlorophenyl)-1,6-dimethyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid
acid (intermediate product)

Step 1. The dihydropyridone intermediate obtained following general procedure A (1.05 g, 3.75 mmol) was dissolved in anhydrous DMF (12.5 mL). Cesium carbonate (1.83 g, 5.63 mmol) and iodomethane (350 µL, 5.63 mmol) were added. The reaction mixture was stirred at 60 °C for 1 h. The DMF was removed under reduced pressure. The residue was washed by brine and dried on MgSO₄. Removal of the solvents under reduced pressure gave the desired compound as a yellow oil (1.10 g, quantitative). MS [M+H]⁺ 294.

Step 2. The intermediate obtained in step 1 (1.10 mg, 3.75 mmol) was dissolved in MeOH (15 mL) and an aqueous solution of NaOH 1 N (13 mL, 13.1 mmol) was added. The reaction mixture was cooled to r.t. and extracted once with diethyl ether. The aqueous phase was then acidified until pH = 1 with an aqueous solution of hydrochloric acid. The aqueous phase was extracted by EtOAc. The organic layer was then washed with brine and dried with MgSO₄. The solvent was removed under reduced pressure to give the 4-(4-chlorophenyl)-1,6-dimethyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (680 mg, 62%).

EXAMPLE 79: p-tolylmethyl 4-(4-chlorophenyl)-1,6-dimethyl-2-oxo-3,4-dihydropyridine-5-carboxylate

4-(4-chlorophenyl)-1,6-dimethyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 78, 0.36 mmol) was dissolved in anhydrous DMF (1.2 mL) then Cs₂CO₃ (349 mg, 1.07 mmol) and alpha bromo-p-xylene (66 mg, 0.36 mmol) were added. The reaction mixture was stirred for 1 h at RT. Water was then added and the aqueous phase was extracted with EtOAc. The organic layer was then washed with brine and dried with MgSO₄. The solvent was removed under reduced pressure to give the desired compound as a white solid (87 mg, 63%). ¹H NMR (300 MHz,
EXAMPLE 80: [4-(trifluoromethyl)phenyl]methyl 4-(4-chlorophenyl)-1,6-dimethyl-2-oxo-3,4-dihydropyridine-5-carboxylate

4-(4-chlorophenyl)-1,6-dimethyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 78, 0.36 mmol) was dissolved in anhydrous DMF (1.2 mL) then Cs$_2$CO$_3$ (349 mg, 1.07 mmol) and 4-(trifluoromethyl)benzyl bromide (85 mg, 0.36 mmol) were added. The reaction mixture was stirred for 1 h at RT. Water was then added and the aqueous phase was extracted with EtOAc. The organic layer was then washed with brine and dried with MgSO$_4$. The solvent was removed under reduced pressure to give a white solid (117 mg, 75 %). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.59 (s, 3H), 2.76 (dd, $J = 2.4$ and 15.9 Hz, 1H), 2.92 (dd, $J = 7.5$ and 15.9 Hz, 1H), 3.23 (s, 3H), 4.21 (d, J=6.3Hz, 1H), 5.11 (d, J=13.0 Hz, 1H), 5.19 (d, J =13.1 Hz, 1H), 7.02 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 6.2 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 6.0 Hz, 2H), MS [M+H]$^+$ 438.

EXAMPLE 81: (2-chloro-4-fluoro-phenyl)methyl 4-(4-chlorophenyl)-1,6-dimethyl-2-oxo-3,4-dihydropyridine-5-carboxylate

4-(4-chlorophenyl)-1,6-dimethyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 78, 0.36 mmol) was dissolved in anhydrous DMF (1.2 mL) then Cs$_2$CO$_3$ (349 mg, 1.07 mmol) and 2-Chloro-4-fluorobenzyl bromide (85 mg, 0.36 mmol) were added. The reaction mixture was stirred at RT. Water was then added and the aqueous phase was extracted with EtOAc. The organic layer was then washed with brine and dried with MgSO$_4$. The solvent was removed under reduced pressure to give the desired compound as a colorless oil (38 mg, 26 %). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.59 (s, 3H), 2.76 (dd, $J = 2.4$ and 15.9 Hz, 1H), 2.92 (dd, $J = 7.5$ and 15.9 Hz, 1H), 3.22 (s, 3H), 4.19 (d, J=5.7Hz, 1H), 5.12 (d, J=13.2 Hz, 1H), 5.21 (d, J =12.9 Hz, 1H), 6.86 (dt, $J = 2.4$ and 8.1 Hz, 1H), 7.00 (d, J = 8.4 Hz, 2H), 7.12-7.04 (m, 2H)7.20 (d, J = 8.4 Hz, 2H), MS [M+H]$^+$ 422.

EXAMPLE 82: (2,6-difluorobenzyl)methyl 4-(4-chlorophenyl)-1,6-dimethyl-2-oxo-3,4-dihydropyridine-5-carboxylate

4-(4-chlorophenyl)-1,6-dimethyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 78, 75 mg, 0.27 mmol) was dissolved in anhydrous DMF (1 mL) then Cs$_2$CO$_3$ (131 mg, 0.68 mmol) and 2,6-difluorobenzyl bromide (83 mg, 0.40 mmol) were added. The reaction mixture was stirred for 1 h at RT. Water was then added and the aqueous phase was extracted with EtOAc. The organic layer was then washed with brine and dried with MgSO$_4$. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a
mixture of cyclohexane/EtOAc 9/1 to give the desired compound as a colorless oil (73 mg, 66 %). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.53 (s, 3H), 2.72 (dd, J = 16.0, 2.4 Hz, 1H), 2.87 (dd, J = 16.0, 7.5 Hz, 1H), 3.19 (s, 3H), 4.12 (dd, J = 7.5, 2.4 Hz, 1H), 5.18 (d, J = 12.6 Hz, 1H), 5.23 (d, J = 12.6 Hz, 1H), 6.82-6.92 (m, 2H), 6.96 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.23-7.36 (m, 3H). MS [M+H]+ 406. HRMS : calcd for C\(_{23}\)H\(_{24}\)N\(_2\)FCl, [M+H]+ 447.1287, found 447.1310.

**EXAMPLE 83:** (3,4-dimethoxyphenyl)methyl 4-(4-chlorophenyl)-1,6-dimethyl-2-oxo-3,4-dihydropyridine-5-carboxylate

The appropriate acid intermediate (75 mg, 0.27 mmol) was dissolved in anhydrous DMF (1 mL) then Cs\(_2\)CO\(_3\) (104 mg, 0.32 mmol) and 3,4-dimethoxybenzyl chloride (60 mg, 0.32 mmol) were added. The reaction mixture was stirred for 1 h at RT. The solvents were removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted 3 times with EtOAc. The organic layer was then washed with brine and dried with MgSO\(_4\). The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of cyclohexane/EtOAc 95/5 to give the desired compound as a colorless oil (115 mg, 100 %). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.58 (d, J = 0.7 Hz, 3H), 2.76 (dd, J = 16.1, 2.5 Hz, 1H), 2.91 (dd, J = 16.1, 7.5 Hz, 1H), 3.21 (s, 3H), 3.77 (s, 3H), 3.89 (s, 3H), 4.21 (d, J = 7.5 Hz, 1H), 5.02 (d, J = 12.3 Hz, 1H), 5.09 (d, J = 12.3 Hz, 1H), 6.68 (d, J = 1.8 Hz, 1H), 6.73-6.82 (m, 2H), 7.02 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H). MS [M+H]+ 430. HRMS : calcd for C\(_{23}\)H\(_{25}\)NO\(_5\)Cl\(_2\), [M+H]+ 430.1421 , found 430.1421 .

**EXAMPLE 84:** (2-fluorophenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and 2-fluorobenzyl bromide (30 µL, 0.25 mmol) were added. The reaction mixture was stirred for 1 h at RT. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO\(_4\). The solvent was removed under reduced pressure to give the desired (2-fluorophenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (94 mg, 95 %). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.53 (s, 3H), 2.64 (dd, J = 15.7, 2.2 Hz, 1H), 2.84 (dd, J = 15.7, 7.6 Hz, 1H), 3.24 (s, 3H), 3.31 (ddd, J = 9.9, 8.6, 4.0 Hz, 1H), 3.39 (dt, J = 9.9, 4.0 Hz, 1H), 3.68 (ddd, J = 14.2, 8.6, 4.0 Hz, 1H), 4.04-4.13 (m, 2H), 5.06 (d, J = 14.0 Hz, 1H), 5.11 (d, J = 14.0 Hz, 1H), 6.91-6.98 (m, 3H), 7.01 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.6 Hz, 2H), 7.16-7.24 (m, 1H). MS [M+H]+ 432. HRMS : calcd for C\(_{23}\)H\(_{24}\)N\(_2\)FCl, [M+H]+ 432.1378, found 432.1378.
EXAMPLE 85: (3-fluorophenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and 3-fluorobenzyl bromide (33 µl, 0.25 mmol) were added. The reaction mixture was stirred at RT. for 1 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO4. The solvent was removed under reduced pressure to give the desired (3-fluorophenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a white powder (95 mg, 95%). 1H NMR (300 MHz, CDCl3) δ 2.63 (s, 3H), 2.72 (dd, J = 15.7, 2.3 Hz, 1H), 2.93 (dd, J = 15.7, 7.5 Hz, 1H), 3.32 (s, 3H), 3.38 (ddd, J = 9.9, 8.6, 3.5 Hz, 1H), 3.47 (dt, J = 9.9, 3.9 Hz, 1H), 3.76 (ddd, J = 14.6, 8.6, 3.9 Hz, 1H), 4.14-4.21 (m, 2H), 5.04 (d, J = 13.1 Hz, 1H), 5.12 (d, J = 13.1 Hz, 1H), 6.76 (dt, J = 9.6, 1.7 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 6.95 (td, J = 8.7, 2.4 Hz, 1H), 7.10 (d, J = 8.4 Hz, 2H), 7.19-7.24 (m, 3H). MS [M+H]+: 432. HRMS: calcd for C23H24N4O4ClF, [M+H]+: 432.1378, found 432.1384.

EXAMPLE 86: (4-fluorophenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

(4-fluorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 45 mg, 0.14 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (68 mg, 0.21 mmol) and 4-fluorobenzyl bromide (19 µl, 0.15 mmol) were added. The reaction mixture was stirred for 18 h at RT. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO4. The solvent was removed under reduced pressure to give the desired (4-fluorophenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (48 mg, 80%). 1H NMR (300 MHz, CDCl3) δ 2.53 (s, 3H), 2.63 (dd, J = 15.7, 2.3 Hz, 1H), 2.84 (dd, J = 15.7, 7.3 Hz, 1H), 3.24 (s, 3H), 3.30 (ddd, J = 9.9, 8.6, 4.0 Hz, 1H), 3.39 (dt, J = 9.9, 4.0 Hz, 1H), 3.68 (ddd, J = 14.8, 8.6, 3.6 Hz, 1H), 4.06-4.13 (m, 2H), 4.94 (d, J = 12.6 Hz, 1H), 5.00 (d, J = 12.6 Hz, 1H), 6.88 (t, J = 8.6 Hz, 2H), 6.97-7.03 (m, 4H), 7.14 (d, J = 8.4 Hz, 2H). MS [M+H]+: 432.

EXAMPLE 87: (2-chlorophenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and 2-chlorobenzyl bromide (33 µl, 0.25 mmol) were added.
The reaction mixture was stirred at RT. for 1 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure to give the desired (2-chlorophenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a white powder (99 mg, 96 %). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.55 (s, 3H), 2.65 (dd, $J = 15.8$, 2.2 Hz, 1H), 2.86 (dd, $J = 15.8$, 7.7 Hz, 1H), 3.25 (s, 3H), 3.31 (ddd, $J = 9.9$, 8.6, 3.6 Hz, 1H), 3.40 (dt, $J = 9.9$, 4.0 Hz, 1H), 3.69 (ddd, $J = 14.5$, 8.6, 4.0 Hz, 1H), 4.04-4.16 (m, 2H), 5.09 (d, $J = 13.4$ Hz, 1H), 5.16 (d, $J = 13.4$ Hz, 1H), 6.93 (dd, $J = 7.5$, 1.4 Hz, 1H), 7.01-7.07 (m, 3H), 7.11-7.17 (m, 3H), 7.26 (dd, $J = 8.0$, 1.3 Hz, 1H). MS [M+H]$^+$ 448. HRMS : calcd for C$_{23}$H$_{24}$N0$_4$Cl2, [M+H]$^+$ 448. 1082, found 448. 1083.

EXAMPLE 88: (3-chlorophenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and 3-chlorobenzyl bromide (33 $\mu$L, 0.25 mmol) were added. The reaction mixture was stirred for 1 h at RT. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure to give the desired (3-chlorophenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (100 mg, 97 %). $^1$H NMR (300 MHz, CDCl$_3$), $\delta$ 2.56 (s, 3H), 2.65 (dd, $J = 15.7$, 2.1 Hz, 1H), 2.86 (dd, $J = 15.7$, 7.3 Hz, 1H), 3.26 (s, 3H), 3.32 (ddd, $J = 9.6$, 8.5, 3.7 Hz, 1H), 3.41 (dt, $J = 9.6$, 3.7 Hz, 1H), 3.70 (ddd, $J = 14.5$, 8.5, 3.7 Hz, 1H), 4.07-4.14 (m, 2H), 4.93 (d, $J = 12.9$ Hz, 1H), 5.04 (d, $J = 12.9$ Hz, 1H), 6.89 (d, $J = 7.3$ Hz, 1H), 6.96 (s, 1H), 7.03 (d, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 7.3$ Hz, 1H), 7.15-7.18 (m, 3H). MS [M+H]$^+$ 448. HRMS : calcd for C$_{24}$H$_{24}$N0$_3$Cl2, [M+H]$^+$ 448. 1082, found 448. 1085.

EXAMPLE 89: (4-chlorophenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and 4-chlorobenzyl bromide (51 mg, 0.25 mmol) were added. The reaction mixture was stirred at RT. for 1 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure to give the desired (4-chlorophenyl)methyl 4-(4-chlorophenyl)-
1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a white powder (68 mg, 66%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.54 (s, 3H), 2.64 (dd, $J = 15.8, 2.4$ Hz, 1H), 2.84 (dd, $J = 15.8, 7.5$ Hz, 1H), 3.25 (s, 3H), 3.30 (ddd, $J = 9.9, 8.7, 3.6$ Hz, 1H), 3.39 (dt, $J = 9.9, 4.2$ Hz, 1H), 3.68 (ddd, $J = 14.7, 8.7, 4.2$ Hz, 1H), 4.06-4.13 (m, 2H), 4.93 (d, $J = 12.9$ Hz, 1H), 5.01 (d, $J = 12.9$ Hz, 1H), 6.94 (d, $J = 8.4$ Hz, 2H), 7.01 (d, $J = 8.4$ Hz, 2H), 7.10-7.21 (m, 4H). MS [M+H]$^+$ 448. HRMS : calcd for C$_{23}$H$_{24}$NO$_4$Cl$_2$, [M+H]$^+$ 448.1082, found 448.1085.

**EXAMPLE 90:** [2-(trifluoromethyl)phenyl]methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and 2-trifluoromethylbenzyl bromide (38 $\mu$L, 0.25 mmol) were added. The reaction mixture was stirred for 2 h at RT. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted 3 times with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure to give the desired [2-(trifluoromethyl)phenyl]methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (100 mg, 90%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.63 (s, 3H), 2.72 (dd, $J = 15.7, 2.1$ Hz, 1H), 2.94 (dd, $J = 15.7, 7.4$ Hz, 1H), 3.33 (s, 3H), 3.35-3.42 (m, 1H), 3.48 (dt, $J = 10.0, 3.7$ Hz, 1H), 3.77 (ddd, $J = 14.5, 8.5, 3.7$ Hz, 1H), 4.14-4.22 (m, 2H), 5.24 (d, $J = 13.5$ Hz, 1H), 5.34 (d, $J = 13.5$ Hz, 1H), 7.03-7.06 (m, 1H), 7.10 (d, $J = 8.3$ Hz, 2H), 7.21 (d, $J = 8.3$ Hz, 2H), 7.32-7.42 (m, 2H), 7.61-7.64 (m, 1H). MS [M+H]$^+$ 482. HRMS : calcd for C$_{44}$H$_{34}$NO$_4$F$_3$Cl, [M+H]$^+$ 482.1346, found 482.1352.

**EXAMPLE 91:** [3-(trifluoromethyl)phenyl]methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

The 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and 3-trifluoromethylbenzyl bromide (38 $\mu$L, 0.25 mmol) were added. The reaction mixture was stirred for 1 h at RT. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted 3 times with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure to give the desired [3-(trifluoromethyl)phenyl]methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (108 mg, 98%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.64 (s, 3H), 2.72 (dd, $J = 15.7, 2.2$ Hz, 1H), 2.93 (dd, $J = 15.7, 7.5$ Hz, 1H), 3.33 (s, 3H), 3.35-3.42 (m, 1H), 3.48 (dt, $J = 9.8, 4.0$ Hz, 1H), 3.77 (ddd, $J = 14.7, 8.9, 4.0$ Hz, 1H), 4.09-4.22 (m, 2H), 5.09 (d, $J = 13.1$ Hz, 1H), 5.17 (d, $J = 13.1$ Hz, 1H), 7.10 (d, $J = 8.4$ Hz, 2H), 7.22 (d, $J = 8.4$ Hz, 2H).
EXAMPLE 92: [4-(trifluoromethyl)phenyl]methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

The 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and 4-trifluoromethylbenzyl bromide (60 mg, 0.25 mmol) were added. The reaction mixture was stirred for 1 h at RT. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted 3 times with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure to give the desired [4-(trifluoromethyl)phenyl]methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a white powder (103 mg, 93 %).¹H NMR (300 MHz, CDCl₃) δ 2.63 (s, 3H), 2.73 (dd, J = 15.7, 2.3 Hz, 1H), 2.93 (dd, J = 15.7, 7.6 Hz, 1H), 3.33 (s, 3H), 3.34-3.50 (m, 2H), 3.72-3.81 (m, 1H), 4.13-4.21 (m, 2H), 5.09 (d, J = 13.0 Hz, 1H), 5.19 (d, J = 13.0 Hz, 1H), 7.10 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.3 Hz), 7.23 (d, J = 8.5 Hz), 7.51 (d, J = 8.3 Hz, 2H).MS [M+H]⁺ 482. HRMS: calcd for C₂₄H₂₄N₂O₄F₃Cl, [M+H]⁺ 482.1346, found 482.1356.

EXAMPLE 93: (2-cyanophenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

The 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and 2-cyanobenzyl bromide (49 mg, 0.25 mmol) were added. The reaction mixture was stirred for 1 h at RT. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure to give the desired (2-cyanophenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (100 mg, 99 %).¹H NMR (300 MHz, CDCl₃) δ 2.56 (s, 3H), 2.65 (dd, J = 15.8, 2.3 Hz, 1H), 2.87 (dd, J = 15.8, 7.6 Hz, 1H), 3.25 (s, 3H), 3.29-3.35 (m, 1H), 3.40 (dt, J = 9.8, 3.9 Hz, 1H), 3.70 (dd, J = 14.6, 8.5, 3.6 Hz, 1H), 4.10 (dt, J = 14.6, 3.9 Hz, 1H), 4.17 (d, J = 7.6 Hz, 1H), 5.15 (d, J = 13.3 Hz, 1H), 5.26 (d, J = 13.3 Hz, 1H), 7.00-7.05 (m, 3H), 7.12 (d, J = 8.5 Hz, 2H), 7.30 (td, J = 7.5, 1.6 Hz, 1H), 7.38 (td, J = 7.5, 1.6 Hz, 1H), 7.55 (dd, J = 7.5, 1.7 Hz, 1H).MS [M+H]⁺ 439. HRMS: calcd for C₂₄H₂₄N₂O₄Cl, [M+H]⁺ 439.1425, found 439.1425.

EXAMPLE 94: (3-cyanophenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate
4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and 3-cyanobenzyl bromide (49 mg, 0.25 mmol) were added. The reaction mixture was stirred for 18 h at RT. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure to give the desired (3-cyanophenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (100 mg, 99 %). ¹H NMR (300 MHz, CDCl₃) δ 2.57 (s, 3H), 2.66 (dd, J = 15.7, 2.2 Hz, 1H), 2.87 (dd, J = 15.7, 7.6 Hz, 1H), 3.26 (s, 3H), 3.28-3.36 (m, 1H), 3.41 (dt, J = 9.8, 3.9 Hz, 1H), 3.71 (dd, J = 14.5, 8.8, 3.9 Hz, 1H), 4.07-4.15 (m, 2H), 4.97 (d, J = 13.4 Hz, 1H), 5.08 (d, J = 13.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 2H), 7.16-7.20 (m, 3H), 7.26-7.31 (m, 2H), 7.48 (d, J = 7.4 Hz, 1H). MS [M+H]+ 439. HRMS: calcd for C₂₆H₂₄N₂O₄Cl, [M+H]+ 439.1425, found 439.1422.

EXAMPLE 95: (4-cyanophenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and 4-cyanobenzyl bromide (49 mg, 0.25 mmol) were added. The reaction mixture was stirred for 3 h at RT. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/EtOAc (9/1 to 8/2) as eluent to give the desired (4-cyanophenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a white powder (62 mg, 62 %). ¹H NMR (300 MHz, CDCl₃) δ 2.64 (s, 3H), 2.74 (dd, J = 15.6, 2.1 Hz, 1H), 2.95 (dd, J = 15.6, 7.6 Hz, 1H), 3.34 (s, 3H), 3.36-3.43 (m, 1H), 3.78 (dd, J = 14.5, 8.6, 3.9 Hz, 1H), 4.15-4.23 (m, 2H), 5.06 (d, J = 13.7 Hz, 1H), 5.21 (d, J = 13.7 Hz, 1H), 7.08-7.14 (m, 4H), 7.25 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H). MS [M+H]+ 439. HRMS: calcd for C₂₆H₂₄N₂O₄Cl, [M+H]+ 439.1425, found 439.1425.

EXAMPLE 96: (3-methoxycarbonylphenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and 3-(Bromomethyl)benzoic acid methyl ester (57 mg, 0.25 mmol) were added. The reaction mixture was stirred for 3 h at RT. The solvent was removed
under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO4. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/EtOAc (9/1 to 8/2) as eluent to give the desired (3-methoxy carbonylphenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a yellowish oil (108 mg, 99 %).

1H NMR (300 MHz, CDCl3) δ 2.62 (s, 3H), 2.71 (dd, J = 15.7, 2.2 Hz, 1H), 2.92 (dd, J = 15.7, 7.4 Hz, 1H), 3.32 (s, 3H), 3.38 (sdd, J = 9.9, 8.6, 3.7 Hz, 1H), 3.46 (dt, J = 9.9, 4.2 Hz, 1H), 3.76 (dd, J = 14.5, 8.6, 3.8 Hz, 1H), 3.92 (s, 3H), 4.13-4.21 (m, 2H), 5.10 (d, J = 12.9 Hz, 1H), 5.15 (d, J = 12.9 Hz, 1H), 7.09 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 7.24-7.27 (m, 1H), 7.34 (t, J = 7.7 Hz, 1H). MS [M+H]+ 472. HRMS: calcd for C25H27NO6Cl, [M+H]+ 472.1527, found 472.1539.

EXAMPLE 97: (4-methoxy carbonylphenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and 4-(Bromomethyl)benzoic acid methyl ester (57 mg, 0.25 mmol) were added. The reaction mixture was stirred for 3 h at RT. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO4. The solvent was removed under reduced pressure to give the desired (4-methoxy carbonylphenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a white powder (101 mg, 93 %).

1H NMR (300 MHz, CDCl3) δ 2.64 (s, 3H), 2.73 (dd, J = 15.8, 2.1 Hz, 1H), 2.94 (dd, J = 15.8, 7.4 Hz, 1H), 3.34 (s, 3H), 3.35-3.43 (m, 1H), 3.48 (dt, J = 9.9, 4.8 Hz, 1H), 3.77 (dddd, J = 14.5, 8.4, 3.8 Hz, 1H), 3.93 (s, 3H), 4.12-4.23 (m, 2H), 5.11 (d, J = 13.4 Hz, 1H), 5.19 (d, J = 13.4 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.1 Hz, 2H). MS [M+H]+ 472. HRMS: calcd for C25H27NO6Cl, [M+H]+ 472.1527, found 472.1539.

EXAMPLE 98: o-tolyl methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

The 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and o-methylbenzyl bromide (34 µL, 0.25 mmol) were added. The reaction mixture was stirred for 1 h at RT. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted 3 times with EtOAc. The organic layers were assembled, washed with brine and dried over
MgSO₄. The solvent was removed under reduced pressure to give the desired o-tolylmethyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a white powder (91 mg, 93 %). ¹H NMR (300 MHz, CDCl₃) δ 2.05 (s, 3H), 2.55 (s, 3H), 2.63 (dd, J = 15.7, 2.1 Hz, 1H), 2.83 (dd, J = 15.7, 7.4 Hz, 1H), 3.25 (s, 3H), 3.30 (ddd, J = 12.3, 8.5, 3.7 Hz, 1H), 3.39 (dt, J = 9.9, 4.1 Hz, 1H), 3.68 (dd, J = 14.6, 8.5, 4.1 Hz, 1H), 4.06-4.14 (m, 2H), 5.00 (d, J = 13.4 Hz, 1H), 5.04 (d, J = 13.4 Hz, 1H), 6.95-7.08 (m, 5H), 7.09-7.17 (m, 3H). MS [M+H]+ 428. HRMS : calcd for C₂₉H₂₇NO₄Cl, [M+H]+ 428.1629, found 428.1636.

EXAMPLE 99: m-tolylmethyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

The 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and m-methylbenzyl bromide (34 µL, 0.25 mmol) were added. The reaction mixture was stirred for 1 h at RT. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted 3 times with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure to give the desired m-tolylmethyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (91 mg, 93 %). ¹H NMR (300 MHz, CDCl₃) δ 2.27 (s, 3H), 2.62 (s, 3H), 2.71 (dd, J = 15.6, 2.2 Hz, 1H), 2.93 (dd, J = 15.6, 7.4 Hz, 1H), 3.33 (s, 3H), 3.35-3.51 (m, 2H), 3.71-3.81 (m, 1H), 4.14-4.23 (m, 2H), 5.03 (d, J = 12.8 Hz, 1H), 5.12 (d, J = 12.8 Hz, 1H), 6.85 (s, 1H), 6.91 (d, J = 7.7 Hz, 1H), 7.05-7.19 (m, 4H), 7.22 (d, J = 8.6 Hz, 2H). MS [M+H]+ 428. HRMS : calcd for C₂₉H₂₇NO₄Cl, [M+H]+ 428.1629, found 428.1627.

EXAMPLE 100: p-tolylmethyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

The 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and p-methylbenzyl bromide (34 µL, 0.25 mmol) were added. The reaction mixture was stirred for 1 h at RT. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted 3 times with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure to give the desired p-tolylmethyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (94 mg, 96 %). ¹H NMR (300 MHz, CDCl₃) δ 2.26 (s, 3H), 2.53 (s, 3H), 2.63 (dd, J = 15.8, 2.2 Hz, 1H), 2.83 (dd, J = 15.8, 7.6 Hz, 1H), 3.24 (s, 3H), 3.30 (ddd, J = 9.8, 8.5, 3.9 Hz, 1H), 3.39 (dt, J = 9.8, 3.9 Hz, 1H), 3.67 (ddd, J = 14.4, 8.3, 4.0 Hz, 1H), 4.04-4.13 (m, 2H), 4.98 (s, 2H), 6.94 (d, J = 8.4 Hz, 2H), 6.99-7.05 (m, 4H), 7.14 (d, J = 8.4 Hz, 2H). MS [M+H]+ 428.

EXAMPLE 101: (2,4,6-trimethyl phenyl)methyl 4-(4-chlorophenyl)-1 -(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

Step 1. 2,4,6-trimethylbenzyl alcohol (150 mg, 1.0 mmol) was dissolved in anhydrous DCM (4 mL). Thionyl chloride (87 µL, 1.2 mmol) was added slowly at 0 °C. The reaction mixture was stirred at RT. for 1 h. Removal of the solvent under reduced pressure gave the desired 2,4,6-trimethylbenzyl chloride (168 mg, 100 %) as a white powder. $^1$H NMR (300 MHz, CDCl$_3$) δ 2.29 (s, 3H), 2.42 (s, 6H), 4.68 (s, 2H), 6.89 (s, 2H). MS [M+H] + 133.

Step 2. 4-(4-chlorophenyl)-1 -(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 97 mg, 0.3 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (97 mg, 0.3 mmol) and 2,4,6-trimethylbenzyl chloride (50 mg, 0.3 mmol) were added. The reaction mixture was stirred at RT. for 1 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over MgSO$_4$. Removal of the solvent under reduced pressure gave the desired (2,4,6-trimethylphenyl)methyl 4-(4-chlorophenyl)-1 -(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a yellowish oil (111 mg, 81 %). $^1$H NMR (300 MHz, CDCl$_3$) δ 2.16 (s, 6H), 2.28 (s,3H), 2.61 (s, 3H), 2.67 (dd, J = 15.7, 2.3 Hz, 1H), 2.88 (dd, J = 15.7, 7.7 Hz, 1H), 3.32 (s, 3H), 3.35-3.51 (m, 2H), 3.75 (ddd, J = 14.7, 8.3, 4.0 Hz, 1H), 3.10 (ddd, J = 7.7, 2.3 Hz, 1H), 4.16 (dt, J = 14.7, 4.2 Hz, 1H), 5.01 (d, J = 12.1 Hz, 1H), 5.25 (d, J = 12.1 Hz, 1H), 6.83 (s, 2H), 7.02 (d, J = 8.6 Hz, 1H), 7.17 (d, J = 8.6 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 17.1, 19.3, 21.0, 36.8, 38.6, 41.9, 58.8, 60.9, 71.0, 110.1, 128.3, 128.6, 128.9, 129.0, 132.5, 138.1, 138.3, 139.7, 150.8, 167.2, 168.9. MS [M+H] + 456. HRMS : calcd for C$_26$H$_{33}$NClO$_4$, [M+H] + 456.1942, found 456.1938.

EXAMPLE 103: (3-methoxyphenyl)methyl 4-(4-chlorophenyl)-1 -(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

3-methoxybenzyl alcohol (248 µL, 2.0 mmol) and triethylamine (335 µL, 2.4 mmol) were dissolved in anhydrous DCM (7 mL). Thionyl chloride (218 µL, 3.0 mmol) was added slowly. The reaction mixture was stirred at RT. for 1 h. The reaction mixture was washed with an aqueous solution of HCl 1N. The organic phase was dried over MgSO$_4$. The solvent was removed under reduced pressure to give the desired 2-methoxybenzyl chloride (313 mg, 100 %) as a yellowish oil. 4-(4-chlorophenyl)-1 -(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 85 mg, 0.26 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (169 mg, 0.52 mmol) and 3-methoxybenzyl chloride (81 mg, 0.52 mmol) were added. The reaction mixture was stirred at r.t. for 18 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted...
with EtOAc. The combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure. Purification of the crude by flash chromatography using a mixture of Cyclohexane/EtOAc (8:2) as eluent gave the desired (3-methoxyphenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a yellowish oil (11 mg, 9 %). ¹H NMR (300 MHz, CDCl₃) δ 2.62 (s,3H), 2.71 (dd, J = 15.8, 2.2 Hz, 1H), 2.92 (dd, J = 15.8, 7.5 Hz, 1H), 3.31 (s, 3H), 3.37 (ddd, J = 10.0, 8.5, 3.6 Hz, 1H), 3.46 (dt, J = 10.0, 4.1 Hz, 1H), 3.70-3.79 (m, 4H), 4.13-4.23 (m, 2H), 5.04 (d, J = 12.7 Hz, 1H), 5.11 (d, J = 12.7 Hz, 1H), 6.64 (s, 1H), 6.70 (d, J = 7.5, 1H), 6.81 (dd, J = 8.2, 2.5 Hz, 1H), 7.10 (d, J = 8.4 Hz, 2H), 7.16-7.23 (m,3H). MS [M+H]+ 444. HRMS : calcd for C₂₄H₂₇N⁰₅Cl, [M+H]+ 444.1578, found 444.1579.

EXAMPLE 104: (4-methoxyphenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate
p-methoxybenzyl alcohol (54 mg, 0.39 mmol) was dissolved in anh. THF (1 mL). 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 85 mg, 0.26 mmol) and triphenylphosphine (102 mg, 0.39 mmol) were added. A solution of DEAD (61 µL, 68 mg) in anh. THF (0.4 mL) was added slowly. The reaction mixture was stirred for 18 h at RT. The reaction was uncompleted. Triphenylphosphine (102 mg, 0.39 mmol), p-methoxybenzyl alcohol (54 mg, 0.39 mmol) and a solution of DEAD (61 µL, 68 mg) in anh. THF (0.4 mL) were added at 0 °C and the reaction mixture was stirred at 60 °C for 24 h. A saturated aqueous solution of NaHCO₃ was added. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over MgSO₄. Purification of the crude by flash chromatography on silica using a mixture Cy/EtOAc (8:2) gave the desired (4-methoxyphenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (74 mg, 64 %). ¹H NMR (300 MHz, CDCl₃) δ 2.59 (s,3H), 2.70 (dd, J = 15.8, 2.3 Hz, 1H), 2.89 (dd, J = 15.8, 7.5 Hz, 1H), 3.31 (s, 3H), 3.37 (ddd, J = 9.9, 8.6, 3.9 Hz, 1H), 3.45 (dt, J = 9.9, 3.9 Hz, 1H), 3.74 (ddd, J = 14.3, 8.6, 3.9 Hz, 1H), 3.80 (s, 3H), 4.10-4.20 (m, 2H), 5.02 (s, 2H), 6.80 (d, J = 8.7 Hz, 2H), 7.05-7.09 (m, 4H), 7.20 (d, J = 8.7 Hz, 2H). MS [M+H]+ 444. HRMS : calcd for C₂₄H₂₇N⁰₅Cl, [M+H]+ 444.1578, found 444.1576.

EXAMPLE 105: (2-trifluoromethoxyphenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate
4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 97 mg, 0.3 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (146 mg, 0.45 mmol) and 2-trifluoromethoxybenzyl bromide (63 µL, 0.33 mmol) were added. The reaction mixture was stirred at RT. for 18 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted
with EtOAc. The combined organic layers were washed with brine and dried over MgSO₄. The solvents were removed under reduced pressure. Purification of the crude by flash chromatography on silica using a mixture of Cyclohexane/EtOAc 9/1 gave the desired (2-trifluoromethoxy phenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (121 mg, 81%). ¹H NMR (300 MHz, CDCl₃) δ 2.63 (s, 3H), 2.72 (dd, J = 15.7, 2.2 Hz, 1H), 2.94 (dd, J = 15.7, 7.5 Hz, 1H), 3.33 (s, 3H), 3.34-3.52 (m, 2H), 4.18 (ddd, J = 14.7, 8.6, 4.0 Hz, 1H), 4.13-4.23 (m, 2H), 5.16 (d, J = 13.4 Hz, 1H), 5.22 (d, J = 13.4 Hz, 1H), 7.04 (dd, J = 7.7, 1.6 Hz, 1H), 7.10 (d, J = 8.6 Hz, 2H), 7.15 (t, J = 7.6, 1.2 Hz, 1H), 7.22 (d, J = 8.6 Hz, 2H), 7.19-7.25 (m, 1H), 7.33 (d, J = 7.9, 1.8Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 7.6, 128.3, 129.4, 129.8, 132.6, 139.7, 151.7, 166.7, 168.9. MS [M+H]+ 498. HRMS: calcd for C₉H₁₇N₂O₂Cl, [M+H]+ 498.1261, found 498.1294.

EXAMPLE 106: 2-naphthylmethyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

The 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (14 mg, 0.35 mmol) and 4-(bromomethyl)pyridine hydrobromide (63 mg, 0.25 mmol) were added. The reaction mixture was stirred for 1 h at RT. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted 3 times with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure to give the desired product as a white powder (92 mg, 87%). ¹H NMR (300 MHz, CDCl₃) δ 2.63 (s, 3H), 2.71 (dd, J = 15.7, 2.0 Hz, 1H), 2.93 (dd, J = 15.7, 7.5 Hz, 1H), 3.32 (s, 3H), 3.34-3.42 (m, 1H), 3.47 (dt, J = 9.9, 4.2 Hz, 1H), 3.76 (ddd, J = 14.7, 8.7, 4.2 Hz, 1H), 4.17 (dt, J = 14.7, 3.9 Hz, 1H), 4.23 (d, J = 7.5 Hz, 1H), 5.20 (d, J = 12.9 Hz, 1H), 5.31 (d, J = 12.9 Hz, 1H), 7.12 (d, J = 8.6 Hz, 2H), 7.19 (dd, J = 8.4, 1.6 Hz, 1H), 7.22 (d, J = 8.4 Hz, 2H), 7.46-7.50 (m, 3H), 7.67-7.70 (m, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.79-7.82 (m, 1H). MS [M+H]+ 464. HRMS: calcd for C₂₆H₂₁N₂O₄Cl, [M+H]+ 464.1629, found 464.1629.

EXAMPLE 107: 4-pyridylmethyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

The 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (14 mg, 0.35 mmol) and 4-(bromomethyl)pyridine hydrobromide (63 mg, 0.25 mmol) were added. The reaction mixture was stirred for 1 h at RT. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted 3 times with EtOAc. The organic layers were assembled, washed with brine and dried.
The solvent was removed under reduced pressure to give the desired 4-pyridyl methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a white powder (95 mg, 99%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.58 (s, 3H), 2.67 (dd, $J = 15.7, 2.2$ Hz, 1H), 2.88 (dd, $J = 15.7, 7.5$ Hz, 1H), 3.26 (s, 3H), 3.29-3.36 (m, 1H), 3.41 (dt, $J = 9.9, 4.0$ Hz, 1H), 3.71 (ddd, $J = 14.5, 8.7, 3.7$ Hz, 1H), 4.08-4.17 (m, 2H), 4.96 (d, $J = 14.1$ Hz, 1H), 5.11 (dd, $J = 14.1$ Hz, 1H), 6.87 (d, $J = 5.2$ Hz, 2H), 7.06 (d, $J = 8.3$ Hz, 2H), 7.18 (d, $J = 8.3$ Hz, 2H), 8.41 (d, $J = 5.2$ Hz, 2H). MS [M+H]$^+$ 415. HRMS : calcd for C$_{22}$H$_{24}$N$_2$O$_4$Cl, [M+H]$^+$ 415.1425, found 415.1424.

EXAMPLE 108: (4-phenylphenyl)methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and 4-phenylbenzyl chloride (65 mg, 0.33 mmol) were added. The reaction mixture was stirred for 18 h at RT. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The organic layers were washed, with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/EtOAc (9/1 to 8/2) as eluent to give the desired product.

EXAM PLE 109: Benzhydryl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 97 mg, 0.3 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (146 mg, 0.45 mmol) and chlorodiphenylnmethane (58 $\mu$L, 0.33 mmol) were added. The reaction mixture was stirred at RT for 18 h. The reaction wasn’t complete. Chlorodiphenylnmethane (58 $\mu$L, 0.33 mmol) was added again. The reaction mixture was stirred at 50 °C for 24 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over MgSO$_4$. The solvents were removed under reduced pressure. Purification
of the crude by flash chromatography on silica using a mixture of Cy/EtOAc 9/1 gave the desired benzhydryl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a white powder (107 mg, 73%). $^1$H NMR (300 MHz, CDCl$_3$) δ 2.63 (s, 3H), 2.75 (dd, $J = 15.7$, 2.0 Hz, 1H), 2.96 (dd, $J = 15.7$, 7.7 Hz, 1H), 3.33 (s, 3H), 3.36-3.52 (m, 2H), 3.77 (ddd, $J = 14.6$, 8.6, 4.0 Hz, 1H), 4.18 (dt, $J = 14.6$, 4.0 Hz, 1H), 4.29 (d, $J = 7.7$ Hz, 1H), 6.81-6.87 (m, 3H), 7.08-7.19 (m, 5H), 7.24-7.37 (m, 7H). MS [M+H]$^+$ 490. HRMS : calcd for C$_2$H$_2$NO$_4$Cl, [M+H]$^+$ 490.1785, found 490.1806.

**EXAMPLE 110**: 2-phenylethyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and (2-Bromoethyl)benzene (43 µL, 0.33 mmol) were added. The reaction mixture was stirred for 18 h at RT. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/EtOAc (9/1 to 8/2) as eluent to give the desired 2-phenylethyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (64 mg, 65%). $^1$H NMR (300 MHz, CDCl$_3$) δ 2.56 (s, 3H), 2.69 (dd, $J = 15.5$, 2.1 Hz, 1H), 2.83-2.92 (m, 3H), 3.32 (s, 3H), 3.34-3.38 (m, 1H), 3.45 (dt, $J = 9.9$, 4.0 Hz, 1H), 3.72 (ddd, $J = 14.6$, 8.7, 4.0 Hz, 1H), 4.07 (d, $J = 7.3$ Hz, 1H), 4.17 (dt, $J = 14.6$, 4.0 Hz, 1H), 4.29 (t, $J = 6.6$ Hz, 1H), 4.31 (d, $J = 6.6$ Hz, 1H), 7.02-7.07 (m, 4H), 7.20-7.23 (m, 5H). MS [M+H]$^+$ 428. HRMS : calcd for C$_{24}$H$_{20}$NO$_4$Cl, [M+H]$^+$ 428.1629, found 428.1624.

**EXAMPLE 111**: 3-phenylpropyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and (3-Bromopropyl)benzene (38 µL, 0.25 mmol) were added. The reaction mixture was stirred for 3 h at RT. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/EtOAc (9/1 to 8/2) as eluent to give the desired 3-phenyl propyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (58 mg, 57%). $^1$H NMR (300 MHz, CDCl$_3$) δ 1.72-1.82 (m, 2H), 2.41 (t, $J = 7.7$ Hz, 2H), 2.55 (s, 3H), 2.65 (dd, $J = 15.7$, 2.1 Hz, 1H), 2.85 (dd, $J = 15.7$, 7.4 Hz, 1H, 2.85 (dd, $J = 15.7$, 7.4 Hz, 2.85 (dd, $J = 15.7$, 7.4 Hz,
EXAM PLE 112: Phenacyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and 2-bromoacetophenone (65 mg, 0.33 mmol) were added. The reaction mixture was stirred for 18 h at RT. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/EtOAc (9/1 to 8/2) as eluent to give the desired product.

EXAM PLE 113: [cyclohexylmethyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 75 mg, 0.23 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (114 mg, 0.35 mmol) and cyclohexylmethylbromide (49 µL, 0.35 mmol) were added. The reaction mixture was stirred at 50 °C for 24 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc. The organic layers were assembled, washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure to give the desired product.

HRMS: calcd for C₂₃H₂₈NO₄Cl, [M+H]⁺ 442. 1785, found 442. 1779.
EXAMPLE 114: Methyl 4-[3-(dimethylamino)propoxy]benzoate (intermediate product)

Methyl 4-hydroxybenzoate (3.04 g, 20.0 mmol), potassium carbonate (4.14 g, 30.0 mmol) and 3-dimethylaminopropyl chloride hydrochloride were dissolved in anh. DMF (30 mL). The reaction mixture was stirred at 60 °C for 18 h. The reaction was incomplete; potassium carbonate (4.14 g, 30.0 mmol) and 3-dimethylaminopropyl chloride hydrochloride (4.74 g, 30.0 mmol) were added again. The reaction mixture was stirred for a further 24 h at 60 °C. Removal of the solvent under reduced pressure afforded the desired methyl 4-[3-(dimethylamino)propoxy]benzoate (1.6 g, 34 %) that was used in the next step without purification.

EXAMPLE 115: [4-[3-(dimethylamino)propoxy]phenyl]methanol (intermediate product)

Methyl 4-[3-(dimethylamino)propoxy]benzoate (474 mg, 2.0 mmol) was dissolved in anh. THF (7 mL). The reaction mixture was cooled to 0 °C. A 1 M solution of lithium aluminium hydride in diethyl ether (2.4 mL, 2.4 mmol) was added slowly. The reaction mixture was then stirred for 5 h at RT. Water was added and the aqueous phase was extracted with diethyl ether. The organic phases were assembled, washed with brine and dried over MgSO₄. Removal of the solvent under reduced pressure gave the desired [4-[3-(dimethylamino)propoxy]phenyl]methanol as a white oil (208 mg, 50 %). ¹H NMR (300 MHz, CDCl₃) δ 2.00 (q, J = 6.8 Hz, 2H), 2.31 (s, 6H), 2.52 (t, J = 7.2 Hz, 2H), 4.02 (t, J = 6.2 Hz, 2H), 4.02 (t, J = 6.2 Hz, 2H), 4.62 (s, 2H), 6.89 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H).

EXAMPLE 116: [4-[3-(dimethylamino)propoxy]phenyl]methyl 4-(4-chlorophenyl)-1-(2-
methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 330 mg, 1.02 mmol), [4-[3-(dimethylamino)propoxy]phenyl]methanol (194 mg, 0.93 mmol), EDCI (213 mg, 1.12 mmol) and DMAP (113 mg, 0.93 mmol) were dissolved in anh. DCM (4 ml). The reaction mixture was stirred for 18 h at RT. An aqueous solution of NaHCO₃ 5% was added. The aqueous phase was extracted with DCM. The organic phases were assembled and dried over MgSO₄. The solvent was removed under reduced pressure. Purification of the crude by flash chromatography on silica using a mixture of DCM/MeOH 97/3 gave the desired [4-[3-(dimethylamino)propoxy]phenyl]methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (87 mg, 18 %).

1H NMR (300 MHz, CDCl₃) δ 1.94 (q, J = 6.8 Hz, 2H), 2.24 (s, 6H), 2.43 (t, J = 7.3 Hz, 2H), 2.58 (s, 3H), 2.69 (dd, J = 15.9, 2.2 Hz, 1H), 2.89 (dd, J = 15.9, 7.5 Hz, 1H), 3.30 (s, 3H), 3.31-3.48 (m, 2H), 3.72 (dd, J = 14.3, 8.2, 3.8 Hz, 1H), 3.99 (t, J = 6.2 Hz, 2H), 4.10-4.20 (m, 2H), 5.01 (s, 2H), 6.79 (d, J = 8.7 Hz, 2H), 7.04 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H).

13C NMR (75 MHz, CDCl₃) δ 17.0, 27.4, 36.7, 38.6, 41.7, 45.4, 56.2, 58.7, 65.8, 66.1, 70.9, 110.0, 114.2, 127.9, 128.3, 128.6, 129.4, 132.4, 134.7, 150.8, 158.8, 166.9, 168.8. MS [M+H]+ 515. HRMS : calcd for C28H36N2O5Cl, [M+H]+ 515.2313, found 515.2307.

EXAMPLE 117: 3-[4-[4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carbonyl]oxymethyl]phenoxypyropyl-trimethyl-ammonium iodide

[4-[3-(dimethylamino)propoxy]phenyl]methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate (example 116) 27 mg, 0.05 mmol) was dissolved in anh. DMF (150 µl). Iodomethane (8 µl, 0.12 mmol) was added. The reaction mixture was stirred at RT for 24 h. The solvent was removed under reduced pressure to afford the desired 3-[4-[4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carbonyl]oxymethyl]phenoxypyropyl-trimethyl-ammonium iodide as a colorless oil (34 mg, 100 %).

1H NMR (300 MHz, CDCl₃) δ 2.24-2.36 (m, 2H), 2.60 (s, 3H), 2.63 (dd, J = 15.4, 2.0 Hz, 1H), 2.98 (dd, J = 15.4, 7.5 Hz, 1H), 3.22 (s, 9H), 3.30-3.33 (m, 5H), 3.33-3.40 (m, 1H), 3.46 (dt, J = 9.7, 4.1 Hz, 1H), 3.57-3.67 (m, 2H), 3.81 (ddd, J = 14.8, 8.4, 3.8 Hz, 1H), 4.11 (t, J = 5.9 Hz, 2H), 4.12-4.18 (m, 1H), 4.20 (d, J = 7.8 Hz, 1H), 4.98 (d, J = 12.1 Hz, 1H), 5.07 (d, J = 12.1 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H). MS [M+H]+ 529. HRMS : calcd for C28H36N2O5Cl, [M+H]+ 529.2469, found 529.2458.

EXAMPLE 118: 1-(chloromethyl)-4-(2-methoxyethoxy)benzene (intermediate product)

Step 1: [4-(2-methoxyethoxy)phenyl]methanol
4-hydroxybenzoic methyl ester (5.0 mmol, 760 mg) was dissolved in DMF (6 mL), potassium carbonate (7.5 mmol, 1.036 g) was added then bromoethylmethyl ether (7.5 mmol, 704 μL). The reaction mixture was stirred at 60 °C for 18 h. The solvents were removed under reduced pressure. Water was added to the residue. The aqueous phase was extracted with EtOAc. The organic phase were assembled, washed with brine and dried over Na₂SO₄. The solvents were removed under reduced pressure to afford the desired methyl 4-(2-methoxyethoxy)benzoate as a colorless oil (m = 960 mg, 91 %).

**Step 2**: 4-(2-methoxyethoxy)phenyl)methanol

Methyl 4-(2-methoxyethoxy)benzoate was dissolved in anhydrous DMF (15 mL). The reaction mixture was cooled to 0 °C and a solution of LiAlH₄ in THF (1 M, 4.6 mL) was added slowly. The reaction mixture was stirred at 0 °C for 3 h. The reaction was quenched by slow addition of an aqueous solution of HCl 1N. The organic phase was extracted with Et₂O, washed with brine and dried over Na₂SO₄. The solvents were removed under reduced pressure to afford the desired [4-(2-methoxyethoxy)phenyl)methanol as a colorless oil (m = 554 mg, 67 %) ¹H NMR (300 MHz, CDCl₃) δ 3.46 (s, 3H), 3.74-3.78 (m, 2H), 4.11-4.16 (m, 2H), 4.63 (s, 2H), 6.93 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 8.6 Hz, 2H).

**Step 3**: 1-(chloromethyl)-4-(2-methoxyethoxy)benzene

Thionyl chloride (109 μL, 1.5 mmol) was added to benzotriazole (179 mg, 1.5 mmol). The resulting yellow solution was dissolved in dry DCM (2 mL). After 5 min, this solution was added slowly to a solution of [4-(2-methoxyethoxy)phenyl)methanol (218 mg, 1.2 mmol) in DCM (8 mL). The benzotriazole salt started to precipitate. After 20 min of reaction, the salt was filtered. The organic phase was washed with water (10 mL) and NaOH solution (0.05 M, 10 mL). The organic phase was dried on Na₂SO₄ and the solvents were removed under reduced pressure to give the desired 1-(chloromethyl)-4-(2-methoxyethoxy)benzene as a yellow oil (190 mg, 79 %).

¹H NMR (300 MHz, CDCl₃) δ 3.46 (s, 3H), 3.74-3.79 (m, 2H), 4.11-4.16 (m, 2H), 4.57 (s, 2H), 6.92 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 8.7 Hz, 2H).

**EXAMPLE 119**: [4-(2-methoxy oxy) phenyl]methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

1-(chloromethyl)-4-(2-methoxyethoxy)benzene (180 mg, 0.9 mmol) and 4-(4-chlorophenyl)-1-(2-methoxyethyl)-2-oxo-3,4-dihydropyridine-5-carboxylic acid (example 74, 194 mg, 0.6 mmol) were dissolved in anhy. DMF (2 mL). Cesium carbonate (293 mg, 0.9 mmol) was added and the reaction mixture stirred at RT. for 4 h. The solvents were removed. Water was added and the aqueous phase was extracted with EtOAc. The organic layers were assembled, washed with brine and dried over Na₂SO₄. The solvents were removed under reduced pressure. Purification of the crude by flash chromatography using a mixture Cy/EA (95/5) as eluent gave the desired [4-(2-methoxyethoxy)phenyl]methyl 4-(4-chlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a white powder (123 mg, 42 %). ¹H NMR (300 MHz, CDCl₃) s
2.59 (s, 3H), 2.70 (dd, J = 15.7, 2.2 Hz, 1H), 2.91 (dd, J = 15.7, 7.6 Hz, 1H), 3.31 (s, 3H), 3.30-3.54 (m, 2H), 3.46 (s, 3H), 3.68-3.80 (m, 3H), 4.08-4.22 (m, 4H), 5.02 (s, 2H), 6.83 (d, J = 8.5 Hz, 2H), 7.02-7.12 (m, 4H), 7.21 (d, J = 8.5 Hz, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 17.1, 36.8, 38.7, 41.8, 58.8, 59.2, 65.9, 67.2, 71.0, 71.0, 110.0, 114.4, 128.3, 128.4, 128.7, 129.4, 132.5, 139.8, 150.9, 158.6, 167.0, 168.9. MS [M+H]$^+$ 488; HRMS : calcd for C$_{26}$H$_{31}$NO$_4$ [M+H]$^+$ 488.1705, found 488.1708.

Table 9:

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EXAM P L E 120: (2-methoxyphenyl)methyl 6-methyl-2-oxo-4-propyl-3,4-dihydro-1H-pyridine-5-carboxylate (intermediate product)

The (2-methoxyphenyl)methyl 3-oxobutanoate (444 mg, 2.0 mmol) was dissolved in acetic acid (2 mL), n-butanal (180 μL, 2.0 mmol), meldrum acid (288 mg, 2.0 mmol) and ammonium acetate (231 mg, 3.0 mmol) were added and the reaction mixture was stirred at 110°C for 18 h. The reaction mixture was cooled to RT. The solvent was removed under reduced pressure. Purification of the crude by flash chromatography on silica using as eluent a mixture of cyclohexane/EtOAc (85/15) gave the desired (2-methoxyphenyl)methyl 6-methyl-2-oxo-4-propyl-3,4-dihydro-1H-pyridine-5-carboxylate as a yellow oil (42 mg, 6%). $^1$H NMR (300 MHz, CDCl$_3$) δ 0.84 (t, J = 6.7 Hz, 3H), 1.13-1.54 (m, 4H), 2.31 (s, 3H), 2.46 (dd, J = 16.6, 1.8 Hz, 1H), 2.57 (dd, J = 16.6, 6.8 Hz, 1H), 2.94-3.05 (m, 1H), 3.84 (s, 3H), 5.21 (d, J = 12.7 Hz, 1H), 5.27 (d, J = 12.7 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.95 (td, J = 7.1, 0.9 Hz, 1H), 7.26-7.36 (m, 2H), 8.43 (brs, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 13.9, 19.0, 19.7, 31.9, 34.9, 55.3, 61.6, 109.1, 110.3, 120.3, 124.6, 129.4, 129.6, 145.0, 157.6, 167.1, 172.3. MS [M+H]$^+$ 318. HRMS : calcd for C$_{18}$H$_{24}$N$_2$O$_4$, [M+H]$^+$ 318.1705, found 318.1708.
EXAMPLE 121: (2-methoxyphenyl)methyl 1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

(2-methoxyphenyl)methyl 6-methyl-2-oxo-4-propyl-3,4-dihydro-1 H-pyridine-5-carboxylate (42 mg, 0.13 mmol) was dissolved in anhydrous DMF (1 mL). Cesium carbonate (85 mg, 0.26 mmol) and 2-bromoethyl methyl ether (25 µL, 0.26 mmol) were added. The reaction mixture was stirred at 60 °C for 4 days. The same amount of cesium carbonate (85 mg, 0.26 mmol) and 2-bromoethyl methyl ether (25 µL, 0.26 mmol) were added everyday. After 4 days at 60 °C, the DMF was removed under reduced pressure. The residue was diluted in water. The aqueous phase was extracted by EtOAc and the combined organic layers were washed with brine and dried over MgSCV. The solvent was removed under reduced pressure. Purification of the crude by flash chromatography using a mixture of Cyclohexane/EtOAc (8/2) as eluent gave the desired product (2-methoxyphenyl)methyl 1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (32mg, 67 %). 1H NMR (300 MHz, CDCl3) δ 0.82 (t, J = 7.0 Hz, 3H), 1.10-1.50 (m, 4H), 2.43 (s, 3H), 2.49 (dd, J = 15.7, 2.4 Hz, 1H), 2.57 (dd, J = 15.7, 5.9 Hz, 1H), 2.87-2.98 (m, 1H), 3.30 (s, 3H), 3.40-3.55 (m, 2H), 3.69 (ddd, J = 14.4, 6.5, 5.1 Hz, 1H), 3.84 (s, 3H), 4.13 (dt, J = 14.4, 5.6 Hz, 1H), 5.19 (d, J = 12.8 Hz, 1H), 5.26 (d, J = 12.8 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.95 (d, J = 7.5, 0.9 Hz, 1H), 7.27-7.37 (m, 2H). 13C NMR (75 MHz, CDCl3) δ 14.0, 16.9, 19.7, 31.3, 34.1, 35.8, 41.5, 55.2, 58.8, 61.7, 70.7, 71.0, 110.3, 113.6, 120.3, 124.4, 129.4, 129.6, 147.7, 157.5, 167.7, 170.4. MS [M+H]+ 376. HRMS : calcd for C23H29NO4Br, [M+H]+ 458. Found 458.0970.

EXAMPLE 122: Benzyl 4-(4-bromophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate (intermediate product)

Benzyl 4-(4-bromophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (2.04 g, 5.1 mmol) was dissolved in anhydrous DMF (20 mL). Cesium carbonate (3.31 mg, 10.2 mmol) and (bromoethyl)methyl ether (960 µL, 10.2 mmol) were added. The reaction mixture was stirred at 60 °C for 24 h. The DMF was removed under reduced pressure. The residue was diluted in water and extracted by EtOAc. The organic layers were assembled, washed with brine and dried over MgSCV. Removal of the solvent under reduced pressure gave the desired benzyl 4-(4-bromophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (2.08 g, 89 %). 1H NMR (300 MHz, CDCl3) δ 2.61 (s, 3H), 2.71 (dd, J = 15.8, 2.3 Hz, 1H), 2.91 (dd, J = 15.8, 7.7 Hz, 1H), 3.32 (s, 3H), 3.34-3.51 (m, 2H), 3.75 (ddd, J = 14.8, 8.5, 2.0 Hz, 1H), 4.12-4.21 (m, 2H), 5.06 (d, J = 12.7 Hz, 1H), 5.12 (d, J = 12.7 Hz, 1H), 7.04 (d, J = 8.4 Hz, 2H), 7.07-7.14 (m, 2H), 7.25-7.30 (m, 3H), 7.36 (d, J = 8.4 Hz, 2H). MS [M+H]+ 458. HRMS : calcd for C23H25NO4Br, [M+H]+ 458.0967, found 458.0970.

EXAMPLE 123: Benzyl 1-(2-methoxyethyl)-6-methyl-2-oxo-4-(4-phenylphenyl)-3,4-dihydropyridine-5-carboxylate
Benzyl 4-(4-bromophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate (120 mg, 0.26 mmol), phenylboronic acid (63 mg, 0.52 mmol), sodium carbonate (41 mg, 0.39 mmol) and PdCl₂-dppf (21 mg, 0.026 mmol) were dissolved in a mixture DME/water 1/1 (1 mL). The reaction mixture was warmed at 115 °C under microwaves for 30 min. The reaction mixture was cooled to r.t. then filtered on celite and washed with Et₂O. The organic phase was washed with a saturated aqueous solution of NaHCO₃. The aqueous phase was extracted with EtOAc. The organic phases were combined, washed with brine and dried over MgSO₄. The solvents were removed under reduced pressure. Purification of the crude by flash chromatography using a mixture of Cyclohexane/EtOAc (85:15) as eluent gave the desired benzyl 1-(2-methoxyethyl)-6-methyl-2-oxo-4-(4-phenylphenyl)-3,4-dihydropyridine-5-carboxylate as a white powder (56 mg, 46%). ¹H NMR (300 MHz, CDCl₃) δ 2.63 (s, 3H), 2.80 (dd, J = 15.6, 2.2 Hz, 1H), 2.95 (dd, J = 15.6, 7.4 Hz, 1H), 3.32 (s, 3H), 3.35-3.52 (m, 2H), 3.76 (dd, J = 14.7, 8.5, 4.0 Hz, 1H), 4.18 (dd, J = 14.6, 6.1 Hz, 1H), 4.29 (dd, J = 7.4, 2.2 Hz, 1H), 5.09 (d, J = 12.7 Hz, 1H), 5.15 (d, J = 12.7 Hz, 1H), 7.08-7.14 (m, 2H), 7.22-7.26 (m, 5H), 7.29-7.36 (m, 1H), 7.38-7.50 (m, 4H), 7.52-7.58 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 17.2, 37.0, 38.8, 41.9, 58.9, 65.9, 71.1, 110.2, 127.0, 127.1, 127.4, 127.5, 127.8, 128.3, 128.7, 136.1, 139.8, 140.2, 140.9, 150.9, 167.1, 169.2. MS [M+H]+ 456 HRMS : calcd for C₅₉H₄₀NO₄, [M+H]+ 456.21 75, found 456.21 77.

**EXAMPLE 124:** (2-methoxyphenyl)methyl 4-(4-cyanophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (intermediate product)

The (2-methoxyphenyl)methyl 3-oxobutanoate (667 mg, 3.0 mmol) was dissolved in acetic acid (3 mL). 4-cyanobenzaldehyde (393 mg, 3.0 mmol), meldrum acid (432 mg, 3.0 mmol) and ammonium acetate (338 mg, 4.5 mmol) were added and the reaction mixture was stirred at 110°C for 18 h. The reaction mixture was cooled to RT. The solvent was removed under reduced pressure. The crude was precipitated in EtOH, cooled to 0 °C and filtered to give the desired (2-methoxyphenyl)methyl 4-(4-cyanophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate as a white powder (476 mg, 42 %). ¹H NMR (300 MHz, CDCl₃) δ 2.43 (s, 3H), 2.64 (dd, J = 16.7 Hz, 1H), 2.97 (dd, J = 16.7 Hz, 1H), 3.74 (s, 3H), 4.31 (d, J = 8.4 Hz, 1H), 5.09 (d, J = 12.4 Hz, 1H), 5.21 (d, J = 12.4 Hz, 1H), 6.81-6.89 (m, 2H), 7.04 (d, J = 7.5 Hz, 1H), 7.26 (d, J = 8.5 Hz, 2H), 7.30 (dd, J = 8.0, 1.5 Hz, 1H), 7.53 (d, J = 8.5 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 18.9, 37.3, 38.0, 55.1, 61.7, 105.9, 110.2, 110.7, 118.6, 120.2, 123.9, 127.6, 129.5, 129.6, 132.5, 147.2, 147.7, 157.4. MS [M-H]⁻ 375.

**EXAMPLE 125:** (2-methoxyphenyl)methyl 4-(4-cyanophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

o-methoxybenzyl 4-(4-cyanophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (113 mg, 0.30 mmol) was dissolved in anhydrous DMF (1 mL). Cesium carbonate (195 mg, 0.60 mmol) and 2-bromoethyl methyl ether (56 µL, 0.60 mmol) were added. The reaction mixture
was stirred at 60 °C for 18 h. The reaction was incomplete and Cesium carbonate (39 mg, 0.12 mmol) and 2-bromoethyl methyl ether (11 µL, 0.12 mmol) were added. The reaction mixture was stirred at 60 °C for 18 h. The DMF was removed under reduced pressure. The residue was diluted in water and extracted by EtOAc. The organic layers were assembled, washed by brine and dried on MgSCl·4. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/EtOAc (100/0 to 95/5) as eluent to give the desired (2-methoxyphenyl)methyl 4-(4-cyanophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (102 mg, 78%). 1H NMR (300 MHz, CDCl3) δ 2.62 (s, 3H), 2.72 (dd, J = 15.9, 2.2 Hz, 1H), 2.96 (dd, J = 15.9, 7.7 Hz, 1H), 3.31 (s, 3H), 3.33-3.50 (m, 2H), 3.73 (s, 3H), 3.75 (ddd, J = 14.6, 8.5, 3.8 Hz, 1H), 4.18 (dt, J = 14.6, 3.8 Hz, 1H), 4.26 (d, J = 7.7 Hz, 1H), 5.10 (d, J = 13.1 Hz, 1H), 5.18 (d, J = 13.1 Hz, 1H), 6.79-6.87 (m, 2H), 6.99 (dd, J = 7.8, 1.9 Hz, 1H), 7.23-7.32 (m, 3H), 7.52 (d, J = 8.3 Hz, 2H).

13C NMR (75 MHz, CDCl3) δ 17.0, 37.5, 38.2, 41.8, 55.1, 58.8, 61.9, 70.9, 109.4, 110.2, 110.6, 118.7, 120.2, 124.0, 127.9, 129.2, 129.4, 132.3, 147.0, 151.2, 157.3, 166.8, 168.5. MS [M+H]+ 435; HRMS : calcd for C25H27N2O5Cl, [M+H]+ 435.1920, found 435.1918.

**EXAMPLE 126**: 4-(3,4-dichlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (intermediate product)

[Chemical Structure Image]

3,4-dichlorobenzaldehyde (3.0 mmol, 525 g), meldrum acid (3.0 mmol, 432 g), o-methoxybenzyl acetoacetate (3.0 mmol, 666 mg) and ammonium acetate (4.5 mmol, 338 mg) were dissolved in acetic acid (3 mL). The reaction mixture was stirred at 110 °C for 18 h. The solvent was removed. The crude didn’t precipitate in EtO H. The crude has been purified by flash chromatography (Cy/EA (85/15) and precipitated in EtOH to give the desired (2-methoxyphenyl)methyl 4-(3,4-dichlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate as a white powder (384 mg, 30%). 1H NMR (300 MHz, CDCl3) δ 2.43 (s, 3H), 2.63 (dd, J = 16.7, 1.3 Hz, 1H), 2.94 (dd, J = 16.7, 8.1 Hz, 1H), 3.76 (s, 3H), 4.23 (d, J = 7.7 Hz, 1H), 5.12 (d, J = 12.6 Hz, 1H), 5.22 (d, J = 12.6 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.88 (td, J = 7.4, 1.0 Hz, 1H), 6.99 (dd, J = 8.5, 2.3 Hz, 1H), 7.08 (dd, J = 7.4, 1.7 Hz, 1H), 7.22 (d, J = 2.0 Hz, 1H), 7.26-7.33 (m, 2H), 8.34 (bs, 1H). 13C NMR (75 MHz, CDCl3) δ 19.1, 37.3, 37.7, 55.2, 61.8, 106.3, 110.3, 120.3, 124.0, 126.2, 128.9, 129.6, 130.6, 130.9, 132.6, 142.5, 147.0, 157.4, 166.3, 170.3. MS [M-H]- 418.

**EXAMPLE 127**: (2-methoxyphenyl)methyl 4-(3,4-dichlorophenyl)-1-(2-methoxyethyl)-6-
methyl-2-oxo-3,4-dihydropyridine-5-carboxylate
Ho-m eth oxybenzyl 4-(3,4-dichlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate
(126 mg, 0.30 mmol) was dissolved in anhydrous DMF (1 mL). Cesium carbonate (195 mg, 0.60 mmol) and 2-bromoethyl methyl ether (56 μL, 0.60 mmol) were added. The reaction mixture was stirred at 60 °C for 18 h. The DMF was removed under reduced pressure. The residue was diluted in water and extracted by EtOAc. The organic layers were assembled, washed by brine and dried on MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/EtOAc (100/0 to 85/15) as eluent to give the desired (2-methoxyphenyl)methyl 4-(3,4-dichlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (102 mg, 71 %). H NMR (300 MHz, CDCl₃) δ 2.63 (s, 3H), 2.71 (dd, J = 15.7, 2.0 Hz, 1H), 2.93 (dd, J = 15.7, 7.5 Hz, 1H), 3.33 (s, 3H), 3.37-3.51 (m, 2H), 3.74 (s, 3H), 3.70-3.81 (m, 1H), 4.15-4.26 (m, 2H), 5.11 (d, J = 12.8 Hz, 1H), 5.20 (d, J = 12.8 Hz, 1H), 6.81-6.90 (m, 2H), 6.98-7.06 (m, 2H), 7.21-7.32 (m, 3H). C NMR (75 MHz, CDCl₃) δ 17.1, 36.8, 38.4, 41.9, 55.2, 59.0, 61.9, 71.0, 109.6, 110.2, 120.2, 124.1, 126.5, 129.1, 129.3, 129.4, 130.4, 130.7, 132.4, 141.8, 151.1, 157.3, 166.9, 168.7. MS [M+H]+ 478; HRMS: calcd for C₂₄H₂₆NO₅Cl₂, [M+H]+ 478.1188, found 478.1190.

EXAMPLE 128: (2-methoxyphenyl)methyl 4-(2,4-dichlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (intermediate product)

2,4-dichlorobenzaldehyde (3.0 mmol, 525 mg), meldrum acid (3.0 mmol, 432 mg), the o-methoxybenzyl acetoacetate (3.0 mmol, 666 mg) and ammonium acetate (4.5 mmol, 338 g) were dissolved in acetic acid (3 mL). The reaction mixture was stirred at 110 °C for 18 h. The solvent was removed. The crude was precipitated in EtOH, cooled to 0 °C and filtered to give the desired (2-methoxyphenyl)methyl 4-(2,4-dichlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate as a white powder (600 mg, 48 %). H NMR (300 MHz, CDCl₃) δ 2.48 (s, 3H), 2.67 (dd, J = 16.9, 1.5 Hz, 1H), 2.92 (dd, J = 16.9, 8.7 Hz, 1H), 3.73 (s, 3H), 4.70 (d, J = 8.7 Hz, 1H), 5.06 (d, J = 12.9 Hz, 1H), 5.70 (d, J = 12.9 Hz, 1H), 6.78-6.87 (m, 2H), 6.94-7.01 (m, 2H), 7.13 (dd, J = 8.5, 2.3 Hz, 1H), 7.25 (td, J = 8.0, 1.6 Hz, 1H), 7.37 (d, J = 2.0 Hz, 1H), 8.73 (brs, 1H). C NMR (75 MHz, CDCl₃) δ 18.8, 34.7, 36.1, 55.1, 61.6, 105.6, 110.1, 120.1, 124.1, 127.3, 128.2, 128.8, 129.2, 129.8, 133.3, 134.0, 137.2, 148.0, 157.1, 166.0, 170.7. MS [M-H]- 418.
EXAM PLE 129: (2-methoxyphenyl)methyl 4-(2,4-dichlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

O-methoxybenzyl 4-(2,4-dichlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (126 mg, 0.30 mmol) was dissolved in anhydrous DMF (1 ml). Cesium carbonate (195 mg, 0.60 mmol) and 2-bromoethyl methyl ether (56 μl, 0.60 mmol) were added. The reaction mixture was stirred at 60 °C for 18 h. The DMF was removed under reduced pressure. The residue was diluted in water and extracted with EtOAc. The organic layers were assembled, washed by brine and dried on MgSO4. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/EtOAc (100/0 to 85/15) as eluent to give the desired (2-methoxyphenyl)methyl 4-(2,4-dichlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a colorless oil (111 mg, 77%). 1H NMR (300 MHz, CDCl3) δ 2.67 (s, 3H), 2.78 (dd, J = 15.9, 2.1 Hz, 1H), 2.89 (dd, J = 15.9, 7.6 Hz, 1H), 3.38 (s, 3H), 3.43-3.53 (m, 2H), 3.73 (s, 3H), 3.74-3.85 (m, 1H), 4.20 (td, J = 14.6, 3.6 Hz, 1H), 4.62 (d, J = 7.6 Hz, 1H), 5.09 (d, J = 12.9 Hz, 1H), 5.15 (d, J = 12.9 Hz, 1H), 6.78-6.86 (m, 2H), 6.96 (d, J = 7.4 Hz, 1H), 7.05-7.15 (m, 2H), 7.21-7.31 (m, 1H), 7.36 (d, J = 1.8 Hz, 1H). 13C NMR (75 MHz, CDCl3) δ 17.0, 26.9, 34.4, 36.5, 41.9, 55.1, 58.9, 61.7, 71.2, 109.1, 110.0, 120.1, 124.2, 127.1, 128.7, 128.9, 129.1, 129.6, 133.2, 134.3, 136.6, 152.1, 157.1, 166.7, 168.7. MS [M+H]+ 478. HRMS: calcd for C24H26NO5Cl2 [M+H]+ 478.1188, found 478.1173.

EXAM PLE 130: o-methoxybenzyl 4-(2,4-dichlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (intermediate product)

2-methoxybenzoyl acetoacetate (3.0 mmol, 666 mg) was dissolved in acetic acid (3 ml). Meldrum acid (3.0 mmol, 432 mg), 2,5-dichlorobenzaldehyde (3.0 mmol, 432 mg) and ammonium acetate (4.5 mmol, 338 mg) were added and the reaction mixture was stirred for 18 h at 110°C. The reaction mixture was cooled at RT. The solvent was removed under reduced pressure. The residue was dissolved in the minimum of ethanol. The mixture was sonicated with ultrasound and the product precipitated. The mixture was cooled and the precipitate was filtered, then washed with cold ethanol to give the desired o-methoxybenzyl 4-(2,4-dichlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate as a white powder (686 mg, 54%). 1H NMR (300 MHz, CDCl3) δ 2.50 (s, 3H), 2.70 (d, J = 16.8 Hz, 1H), 2.94 (dd, J = 16.8, 8.7 Hz, 1H), 3.74 (s, 3H), 4.72 (d, J = 8.7 Hz, 1H), 5.09 (d, J = 12.9 Hz, 1H), 5.17 (d, J = 12.9 Hz, 1H), 6.77-6.87 (m, 2H), 6.95-7.02 (m, 2H), 7.14 (dd, J = 8.5, 2.3 Hz, 1H), 7.21-7.32
EXAMPLE 131: (2-methoxyphenyl)methyl 4-(2,5-dichlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate

5 o-methoxybenzyl 4-(2,4-dichlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (126 mg, 0.30 mmol) was dissolved in anhydrous DMF (1 mL). Cesium carbonate (195 mg, 0.60 mmol) and 2-bromoethyl methyl ether (56 μL, 0.60 mmol) were added. The reaction mixture was stirred at 60 °C for 18 h. The DMF was removed under reduced pressure. The residue was diluted in water and extracted by EtOAc. The organic layers were assembled, washed by brine and dried on MgSO4. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/EtOAc (9/1) as eluent to give the desired (2-methoxyphenyl)methyl 4-(2,5-dichlorophenyl)-1-(2-methoxyethyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate as a white powder (91 mg, 63%). 1H NMR (300 MHz, CDCl3) δ 2.71 (s, 3H), 2.79 (dd, J = 15.9, 2.1 Hz, 1H), 2.90 (dd, J = 15.9, 7.8 Hz, 1H), 3.42 (s, 3H), 3.44-3.56 (m, 2H), 3.73 (s, 3H), 3.78 (ddd, J = 14.2, 7.8, 3.2 Hz, 1H), 4.24 (dt, J = 14.6, 4.0 Hz, 1H), 4.64 (d, J = 7.8 Hz, 1H), 5.09 (d, J = 13.2 Hz, 1H), 5.17 (d, J = 13.2 Hz, 1H), 6.78-6.85 (m, 2H), 6.96 (dd, J = 7.4, 1.2 Hz, 1H), 7.07-7.16 (m, 2H), 7.20-7.30 (m, 2H). 13C NMR (75 MHz, CDCl3) δ 17.0, 34.9, 36.3, 41.9, 55.1, 59.4, 61.7, 71.2, 108.5, 110.0, 120.1, 124.2, 127.8, 128.4, 128.6, 129.0, 131.0, 131.8, 132.9, 139.9, 152.3, 157.0, 166.6, 168.7. MS [M+H]+ 478. HRMS: calcd for C24H26N05Cl2, [M+H]+ 478.1188, found 478.1187.

EXAMPLE 132: (2-methoxyphenyl)methyl 6-methyl-2-oxo-4-(4-pyridyl)-3,4-dihydro-1 H-pyridine-5-carboxylate (intermediate product)

4-pyridylcarboxaldehyde (3.0 mmol, 280 μL), meldrum acid (3.0 mmol, 432 mg), o-methoxybenzyl acetoacetate (3.0 mmol, 666 mg) and ammonium acetate (3.0 mmol, 338 mg) were dissolved in acetic acid (3 mL). The reaction mixture was stirred at 110 °C for 18 h. The solvent was removed. The crude product was purified by flash chromatography using a mixture of DCM/MeOH (99/1 to 99/2) as eluent and then precipitated in EtOH and filtered to afford the desired (2-methoxyphenyl)methyl 6-methyl-2-oxo-4-(4-pyridyl)-3,4-dihydro-1 H-pyridine-5-carboxylate as a white powder (164 mg, 16%). 1H NMR (300 MHz, CDCl3) δ 2.43 (s, 3H), 2.67 (d, J = 16.7 Hz, 1H), 2.95 (dd, J = 16.7, 8.0 Hz, 1H), 3.73 (s, 3H), 4.25 (d, J = 8.0 Hz, 1H), 5.11 (d, J = 12.3 Hz, 1H), 5.21 (d, J = 12.3 Hz, 1H), 6.80-6.90 (m, 2H), 7.02-7.12 (m, 3H), 7.28
EXAMPLE 133: (2-methoxyphenyl)methyl 1-(2-methoxyethyl)-6-methyl-2-oxo-4-(4-pyridyl)-3,4-dihydropyridine-5-carboxylate

(2-methoxyphenyl)methyl 6-methyl-2-oxo-4-(4-pyridyl)-3,4-dihydropyridine-5-carboxylate (105 mg, 0.30 mmol) was dissolved in anhydrous DMF (1 mL). Cesium carbonate (195 mg, 0.6 mmol) and 2-bromoethyl methyl ether (56 µL, 0.6 mmol) were added. The reaction mixture was stirred at 60 °C for 18 h. Water (25 mL) was added. The product was extracted by EtOAc. The organic layers were assembled, washed with brine and dried on MgSO_4. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of Cyclohexane/EtOAc (8/2 - 6/4 to 1/1) as eluent to give the desired (2-methoxyphenyl)methyl 1-(2-methoxyethyl)-6-methyl-2-oxo-4-(4-pyridyl)-3,4-dihydropyridine-5-carboxylate as a colorless oil (104 mg, 84%). ¹H NMR (300 MHz, CDCl₃) δ 2.62 (s, 3H), 2.74 (dd, J = 16.0, 2.2 Hz, 1H), 2.94 (dd, J = 16.0 and 7.5 Hz, 1H), 3.28 (s, 3H), 3.28-3.38 (m, 1H), 3.44 (dt, J = 9.8, 4.0 Hz, 1H), 3.70 (s, 3H), 3.74 (ddd, J = 14.6, 8.2, 3.6 Hz, 1H), 4.13-4.23 (m, 2H), 5.10 (d, J = 12.7 Hz, 1H), 5.20 (d, J = 12.7 Hz, 1H), 6.79-6.87 (m, 2H), 7.04 (dd, J = 7.3, 1.8 Hz, 1H), 7.08-7.13 (m, 2H), 7.26 (td, J = 7.8, 1.7 Hz, 1H), 8.43-8.47 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 17.0, 36.7, 37.7, 41.8, 55.1, 58.7, 62.0, 70.9, 109.1, 110.2, 120.2, 122.3, 124.0, 129.3, 129.5, 149.8, 150.5, 151.4, 157.3, 166.8, 168.6. MS [M+H]+ 412. HRMS: calcd for C₂₃H₂₇N₂O₅, [M+H]+ 411.1920, found 411.1930.

Table 10:

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EXAMPLE 134: Methyl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and Methyl (4R)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2(S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate (intermediate product)

The methyl 4-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (3.40 g, 12.15 mmol) was dissolved in anh. DMF (10 ml). Cesium carbonate (7.92 g, 24.31 mmol) and sodium iodide (91 mg, 0.61 mmol) were added followed by tetrahydrofurfuryl bromide (2.77 ml, 24.31 mmol). The reaction mixture was stirred at 50 °C for 18 h. The solvents were removed under reduced pressure. Water was added and the aqueous phase extracted by EtOAc. The organic phases were assembled, washed with brine and dried over MgSO₄. The crude was dissolved again in anh. DMF (10 ml). Cesium carbonate (7.92 g, 24.31 mmol) and sodium iodide (91 mg, 0.61 mmol) were added followed by tetrahydrofurfuryl bromide (2.77 ml, 24.31 mmol). The reaction mixture was stirred at 50 °C for 18 h. The solvents were removed under reduced pressure. Water was added and the aqueous phase extracted by EtOAc. The organic phases were assembled, washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure. The crude was purified by flash chromatography on silica using a mixture Cy/EA (95/5 to 88/12) as eluent to give methyl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and its enantiomer as a colorless oil (1.58 g, 36 %)

¹H NMR (300 MHz, CDCl₃) δ 1.40-1.50 (m, 1H), 1.80-2.00 (m, 3H), 2.62 (s, 3H), 2.71 (dd, J = 15.5, 2.2 Hz, 1H), 2.91 (dd, J = 15.5, 7.0 Hz, 1H), 3.41 (dd, J = 14.3, 8.8 Hz, 1H), 3.65 (s, 3H), 3.65-3.82 (m, 2H), 3.86-3.96 (m, 2H), 3.86-3.96 (m, 1H), 4.18 (dd, J =7.0, 2.2 Hz, 1H), 4.27 (dd, J = 14.3, 3.2 Hz, 1H), 7.21 (s, 4H). MS [M+H]⁺ 364.
EXAMPLE 135: (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylic acid and (4R)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[[2S]-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylic acid (intermediate product)

An aqueous solution of NaOH 1N (15 mL) was added to a solution of methyl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and its enantiomer (example 134, 1.58 g, 4.35 mmol) in MeOH (15 mL). The reaction mixture was stirred overnight at 40 °C. The solvent was removed under reduced pressure, the aqueous phase was washed with Et2O, then acidified to pH = 1 with HCl cone. The aqueous phase was extracted with DCM. The organic phases were assembled and dried over Na2SO4. The solvents were removed under reduced pressure to afford the desired (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylic acid as a white powder (m = 1.3 g, 88 %). 1H NMR (300 MHz, DMSO d6) δ 1.34-1.48 (m, 1H), 1.74-1.88 (m, 3H), 2.49 (dd, J = 15.5, 1.9 Hz, 1H), 2.53 (s, 3H), 2.95 (dd, J = 15.5, 6.9 Hz, 1H), 3.42 (dd, J = 14.2, 8.6 Hz, 1H), 3.60-3.72 (m, 2H), 3.78-3.88 (m, 1H), 4.05 (dd, J = 14.8, 3.5 Hz, 1H), 4.11 (d, J = 6.9 Hz, 1H), 7.25 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H), 12.24 (brs, 1H). 13C NMR (75 MHz, DMSO d6) δ 17.1, 25.4, 29.0, 37.0, 39.3, 45.3, 67.9, 78.1, 110.6, 128.7, 129.4, 131.6, 140.9, 150.5, 168.8, 169.0. MS [M+H]+ 348. HRMS : calcd for C18H19NO4Cl, [M-H]- 348.1003, found 348.1025.

EXAMPLE 136: 4-(2-methoxyethoxy)phenyl)methyl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and 4-(2-methoxyethoxy)phenyl)methyl (4R)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[[2S]-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate

1-(chloromethyl)-4-(2-methoxyethoxy)benzene (example 118, 125 mg, 0.60 mmol) and racemic mixture of (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylic acid and its enantiomer (example 135, 192 mg, 0.55 mmol) were dissolved in anhydrous DMF (2 mL). Cesium carbonate (269 mg, 0.825 mmol) was added and the reaction mixture was stirred at r.t. for 18 h. The solvents were removed under reduced pressure. Water was added and the aqueous phase was extracted with diethyl ether, washed with brine and dried over Na2SO4. The solvents were removed under reduced pressure.
Purification of the crude by flash chromatography using a mixture of Cy/EtOAc (9/1) as eluent gave the expected [4-(2-methoxyethoxy)phenyl]methyl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate as a colorless oil (m = 105 mg, 37 %). 1H NMR (300 MHz, CDCl₃) δ 1.23-1.30 (m, 1H), 1.78-1.98 (m, 3H), 2.61 (s, 3H), 2.70 (dd, J = 15.5, 2.0 Hz, 1H), 2.90 (dd, J = 15.5, 7.3 Hz, 1H), 3.41 (dd, J = 14.5, 8.9 Hz, 1H), 3.46 (s, 3H), 3.64-3.94 (m, 5H), 4.11 (dd, J = 4.8, 3.4 Hz, 2H), 4.17 (dd, J = 7.3, 2.0 Hz, 1H), 4.25 (dd, J = 14.5, 3.4 Hz, 1H), 5.02 (s, 2H), 6.82 (d, J = 8.6 Hz, 2H), 7.04 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 9.0 Hz, 2H), 7.20 (d, J = 9.0 Hz, 2H). 13C NMR (75 MHz, CDCl₃) δ 17.0, 25.4, 29.1, 36.9, 38.9, 45.5, 59.1, 65.7, 67.1, 68.0, 70.9, 77.7, 110.1, 114.3, 128.3, 128.5, 128.6, 129.2, 132.3, 139.5, 151.0, 158.4, 166.9, 168.8. MS [M+H]+ 514, HRMS : calcd for CzsHssNOeCl, [M+H]+ 514.1966, found 514.04.04.

**EXAMPLE 137:** Indan-1-yl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate (racemic)

1-chloroindane (55 mg, 0.36 mmol) and (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylic acid and its enantiomer (example 135, 115 mg, 0.33 mmol) were dissolved in anh. DMF (2 ml). Cesium carbonate (107 mg, 0.33 mmol) and sodium iodide (25 mg, 0.17 mmol) were added. The reaction mixture was stirred at r.t. for 24h, at 60 °C for 2h and at 80 °C for 1h. The reaction mixture was cooled down to r.t. Water was added and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure. Purification of the crude by flash chromatography using a mixture of Cyclohexane/EtOAc (93/7) as eluent gave the desired indan-1-yl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate as a single diastereomer and a yellow oil (30 mg, 17 %). 1H NMR (300 MHz, CDCl₃) δ 1.38-1.52 (m, 1H), 1.71-1.82 (m, 1H), 1.82-1.98 (m, 3H), 2.26-2.40 (m, 1H), 2.63 (s, 3H), 2.65 (dd, J = 15.9, 2.2 Hz, 1H), 2.72-2.96 (m, 3H), 3.42 (dd, J = 14.3, 8.5 Hz, 1H), 3.69-3.96 (m, 3H), 4.08 (d, J = 7.6 Hz, 1H), 4.25 (dd, J = 14.3, 3.4 Hz, 1H), 6.19 (dd, J = 6.9, 3.7 Hz, 1H), 7.14 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.21-7.34 (m, 3H), 7.43 (d, J = 7.3 Hz, 1H). MS [M+H]+ 466; HRMS : calcd for C₂₈H₂₉NO₄Cl, [M+H]+ 466.1785, found 466.1798.

**EXAMPLE 138:** 1-(2-methoxyphenyl)ethyl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate (diastereoisomers mixture)

1-(1-chloroethyl)-2-methoxy-benzene (68 mg, 0.36 mmol) and racemic mixture of (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylic acid and its enantiomer (example 135, 126 mg, 0.36 mmol) were dissolved in anh. DMF (2 ml). Cesium carbonate (117 mg, 0.36 mmol) was added and the reaction mixture was
stirred at RT for 24h, at 60 °C for 24h and at 90 °C for 6h. The reaction mixture was cooled down to r.t. Water was added and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure. Purification of the crude by flash chromatography using a mixture of Cyclohexane/EtOAc (93/7) as eluent gave the desired 1-(2-methoxynaphthyl)ethylnaphthyl-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2R]-3,4-dihydro-2-yl][methyl]-3,4-dihydropyridine-5-carboxylate as a yellow oil and a mixture of diastereomers 1/1 (m = 30 mg, 17%). ¹H NMR (300 MHz, CDCl₃) δ 1.25-1.32 (d, J = 6.5 Hz, 1.5H), 1.38-1.52 (m, 2.5H), 1.80-2.00 (m, 3H), 2.61 (s, 3H), 2.68-2.78 (m, 1H), 2.86-3.02 (m, 1H), 3.36-3.46 (m, 1H), 3.66-3.93 (m, 3H), 3.74 (s, 1.5H), 3.82 (s, 3H), 4.18-4.32 (m, 2H), 6.17-6.28 (m, 1H), 6.50 (dd, J = 7.7 , 1.7 Hz, 0.5H), 6.63 (t, J = 7.6 Hz, 0.5H), 6.76 (d, J = 8.5 Hz, 0.5H), 6.86 (d, J = 8.0 Hz, 0.5H), 6.91 (t, J = 7.0 Hz, 0.5H), 7.10-7.17 (m, 1H), 7.22-7.25 (m, 4.5H). MS [M+H]+ 484; HRMS : calcd for C₂₆H₂₉NO₅Cl, [M+H]+ 484.1904, found 484.1896.

EXAMPLE 139: [4-(polyethyleneglycoxymethylether)phenyl]methanol (intermediate product)

Poly(ethylene glycol) methyl ether (Sigma-Aldrich, ref 202487, average Mn 550, 1 mmol) was dissolved in THF (3 ml). The solution was cooled at 0°C. NaH (36 mg, 1.5 mmol) was added and the reaction mixture was stirred at 0°C to 20 °C for 2 h. Then p-toluenesulfonyl chloride...
(381 mg, 2 mmol) was added at 0°C and the reaction mixture was stirred at r.t. until completion. The solvent was removed under reduced pressure. Purification of the crude by flash chromatography using a mixture of DCM/MeOH 97/3 as eluent gave the desired poly(ethylene glycol) methyl ether tosylate (515 mg, 73%). Poly(ethylene glycol) methyl ether tosylate (0.73 mmol, 502 mg) was dissolved in MeCN (3 mL), the phenol (1.10 mmol, 136 mg) and K₂CO₃ (1.10 mmol, 151 mg) were added. The reaction mixture was stirred overnight under reflux. The reaction mixture became pink and, after being cooled down, it has been filtered. The filtrate has been concentrated under vacuum and purified by Flash Chromatography (DCM/MeOH 100:0 to 8/2) to give the expected [4-(polyethyleneglycoxy methylether)phenyl]methanol as a yellow oil (390 mg, 78%). ¹H NMR (300 MHz, CDCl₃) δ 3.38 (s, 3H), 3.52-3.77 (m, 47H), 3.84-3.90 (m, 2H), 4.10-4.17 (m, 2H), 4.62 (s, 2H), 6.91 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H). MS [M+NH₄]⁺ 684

**EXAMPLE 140:** 1-chloromethyl-4-((polyethyleneglycoxy methylether)benzene (intermediate product)

Thionyl chloride (0.71 mmol, 52 µL) was added to benzotriazole (0.71 mmol, 85 mg). The resulting yellow solution was dissolved in dry DCM (1 mL). After 5 min, this solution was added slowly to a solution of [4-(polyethyleneglycoxy methylether)phenyl]methanol in DCM (6 mL). After 1 h of reaction, the reaction mixture was quenched by addition of MgSO₄.7H₂O and then filtered. The solvents were removed under reduced pressure to afford 1-chloromethyl-4-((polyethyleneglycoxy methylether)benzene as a yellow oil (m = 400 mg, quantitative). ¹H NMR (300 MHz, CDCl₃) δ 3.38 (s, 3H), 3.52-3.77 (m, 47H), 3.84-3.90 (m, 2H), 4.10-4.17 (m, 2H), 4.57 (s, 2H), 6.89 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H).

**EXAMPLE 141:** [4-(polyethyleneglycoxy methylether)phenyl]methyl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2R]-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate (mixture m=8:13)
1-chloromethyl-4-(polyethyleneglycoxymethylether)benzene (example 140, 125mg, 0.60 mmol) a n d (4 S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylic acid (example 135, 192 mg, 0.55 mmol) were dissolved in anh. DMF (2 mL). Cesium carbonate (269 mg, 0.82 mmol) was added and the reaction mixture stirred at RT for 24h. An aqueous hydrochloric acid solution 1N and brine were added. The aqueous phase was extracted with ethyl acetate. The crude was purified by flash chromatography using a mixture DCM/MeOH (100/0 to 9/1) to give the desired product but not clean. A second purification by HPLC (acidic conditions) afforded the desired [4-(polyethyleneglycoxy methylether)phenyl]methyl(4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate as a colorless oil (m = 87 mg, 17 %). 1H NMR (300 MHz, CDCl₃) δ 1.38-1.52 (m, 1H), 1.80-2.04 (m, 3H), 2.61 (s, 3H), 2.68 (dd, J = 15.6, 2.2 Hz, 1H), 2.89 (dd, J = 15.6, 7.2 Hz, 1H), 3.38 (s, 3H), 3.40 (dd, J = 14.6, 8.8 Hz, 1H), 3.52-3.59 (m, 2H), 3.60-3.95 (m, 44H), 4.08-4.13 (m, 2H), 4.16 (dd, J = 7.2, 2.2 Hz, 1H), 4.25 (dd, J = 14.3, 3.1 Hz, 1H), 5.02 (s, 2H), 6.81 (d, J = 8.5 Hz, 2H), 7.04 (d, J = 8.5 Hz, 2H), 7.16 (d, J = 8.9 Hz, 2H), 7.20 (d, J = 8.9 Hz, 2H). 13C NMR (75 MHz, CDCl₃) δ 17.1, 25.5, 29.2, 37.0, 39.0, 45.6, 59.0, 65.8, 67.4, 68.1, 69.7, 70.5, 70.8, 71.9, 77.8, 110.2, 114.4, 128.3, 128.6, 129.4, 132.5, 139.5, 151.1, 158.6, 167.0, 169.0. MS [M+NH₄]⁺ 884, 928, 972, 1016, 1060, HRMS : calcd for C₅₀H₆₀N₂O₇Cl, [M+NH₄]⁺ 1015.5146, found 1015.5122.

EXAM PLE 144: Ammonium 2-[[4S]-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carbonyl]oxymethyl]phenoxy]ethanesulfonate
**EXAMPLE 142: [4-(2-chloroethoxy)phenyl]methanol (intermediate product)**

1-bromo-2-chloroethane (30 mmol, 2.5 mL), 4-hydroxybenzyl alcohol (6 mmol, 745 mg) and potassium carbonate (30 mmol, 4.15 g) were added in acetonitrile (20 mL). The reaction mixture was stirred under reflux for 60 h. The solvent was removed under reduced pressure. The crude was dissolved in EtOAc and washed with water. The aqueous phase was extracted by EtOAc and washed with brine, dried under Na₂SO₄. The solvent was removed under reduced pressure to and the crude was purified by flash chromatography (Cy/EA 85/15) to afford the desired compound as a white powder (m = 888 mg, 79%). \(^1\)H NMR (300 MHz, CDCl₃) δ 1.67 (brs, 1H), 3.82 (t, J = 5.9 Hz, 2H), 4.24 (t, J = 5.9 Hz, 2H), 4.63 (brs, 2H), 6.92 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 8.7 Hz, 2H).

**EXAMPLE 143: 1-(2-chloroethoxy)-4-(chloromethyl)benzene (intermediate product)**

Thionyl chloride (45 µL, 0.63 mmol) was added to benzotriazole (75 mg, 0.63 mmol). The resulting yellow solution was dissolved in dry DCM (0.5 mL). After 5 min, this solution was added slowly to a solution of the alcohol 142 (93 mg, 0.50 mmol) in DCM (4 mL). After 20 min of reaction, the salt was filtered. The organic phase was washed with water (4 mL) and an aqueous solution of NaOH (0.05 M, 4 mL). The organic phase was dried on Na₂SO₄ and the solvent was removed under reduced pressure to give the desired chlorinated compound as a colorless oil (70 mg, 68%). \(^1\)H NMR (300 MHz, CDCl₃) δ 3.82 (t, J = 6.1 Hz, 2H), 4.25 (t, J = 6.1 Hz, 2H).
EXAMPLE 143a: [4-(2-chloroethoxy)phenyl]methyl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-\([(2R)-\text{tetrahydrofuran-2-yl}][\text{methyl}]-3,4\text{-dihydropyridine-5-carboxylate (racemic mixture) (intermediate product)}

\[
\begin{align*}
&\text{The (4S)-4-}(4\text{-chlorophenyl})-6\text{-methyl-2-oxo-1-}\text{[}(2R)\text{-tetrahydrofuran-2-yl}[\text{methyl]}-3,4\text{-dihydropyridine-5-carboxylate (example 135, 105 mg, 0.30 mmol)} \text{and cesium carbonate (108 mg, 0.33 mmol)} \text{were dissolved in anhydrous DMF (2 mL). 1-(2-chloroethoxy)-4-(chloromethyl)benzene 143 (67 mg, 0.33 mmol) was added. The reaction mixture was stirred at RT for 18 h. The solvents were removed under reduced pressure. The residue was dissolved in EtOAc and washed with water. The aqueous phase was extracted by EtOAc. The organic layers were washed with brine and dried with Na\textsubscript{2}SO\textsubscript{4}. The orange residue was purified by flash chromatography (Cy/DCM 1/1 to DCM) to afford the desired [4-(2-chloroethoxy)phenyl]methyl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-\text{[}(2R)-\text{tetrahydrofuran-2-yl)[methyl]}-3,4\text{-dihydropyridine-5-carboxylate as a colorless oil (m = 145 mg, 93 \%).}^{1}H \text{NMR (300 MHz, CDCl}\textsubscript{3}) \delta \text{1.40-1.50 (m, 1H), 1.80-2.00 (m, 3H), 2.62 (s, 3H), 2.69 (dd, } J = 15.8, 2.2 \text{ Hz, 1H), 2.89 (dd, } J = 15.8, 7.4 \text{ Hz, 1H), 3.41 (dd, } J = 14.3, 8.8 \text{ Hz, 1H), 3.68-3.96 (m, 3H), 3.82 (t, } J = 6.0 \text{ Hz, 2H), 4.17 (dd, } J = 7.4 \text{ Hz, 1H), 4.22 (t, } J = 6.0 \text{ Hz, 2H), 4.22-4.29 (m, 1H), 5.03 (s, 2H), 6.81 (d, } J = 8.6 \text{ Hz, 2H), 7.05 (d, } J = 8.6 \text{ Hz, 2H), 7.17 (d, } J = 8.8 \text{ Hz, 2H), 7.21 (d, } J = 8.8 \text{ Hz, 2H). MS [M+H]+ 518.}
\end{align*}
\]

EXAMPLE 143b: 4-(2-iodoethoxy)phenyl]methyl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-\text{[}(2R)-\text{tetrahydrofuran-2-yl][methyl]}-3,4\text{-dihydropyridine-5-carboxylate (intermediate product)

\[
\begin{align*}
&\text{[4-(2-chloroethoxy)phenyl]methyl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-}\text{[}(2R)-\text{tetrahydrofuran-2-yl][methyl]}-3,4\text{-dihydropyridine-5-carboxylate 143a (145 mg, 0.288 mmol) was dissolved in butanone (1 mL). Sodium iodide (168 mg, 1.12 mmol) was added and the reaction}
\end{align*}
\]
mixture was stirred at 80 °C for 32 h. The solution was cooled to RT, filtered and washed by acetone. The solvents were removed under reduced pressure. Purification of the crude by flash chromatography using a mixture of Cyl/DCM (1/1 to 0/1) gave the desired [4-(2-iodoethoxy)phenyl]methyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2R]-tetrahydropyran-2-yl][methyl]-3,4-dihydropyridine-5-carboxylate as a colorless oil (m = 137 mg, 80 %) 1H NMR (300 MHz, CDCl3) δ 1.39-1.51 (m, 1H), 1.81-2.00 (m, 3H), 2.62 (s, 3H), 2.69 (dd, J = 15.6, 2.4 Hz, 1H), 2.90 (dd, J = 15.6, 7.4 Hz, 1H), 3.36-3.46 (m, 3H), 3.68-3.96 (m, 3H), 4.17 (d, J = 7.4 Hz, 1H), 4.20-4.30 (m, 3H), 5.03 (s, 2H), 6.81 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 7.16 (d, J = 8.7 Hz, 2H). MS [M+H]⁺ 610

EXAMPLE 144: Ammonium 2-[4-[[4(S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2R]-tetrahydropyran-2-yl][methyl]-3,4-dihydropyridine-5-carbonyl]oxymethyl]phenoxyl]ethanesulfonate

T he 4-(2-iodoethoxy)phenyl[methyl] (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2R]-tetrahydropyran-2-yl][methyl]-3,4-dihydropyridine-5-carboxylate 143b (145 mg, 0.24 mmol) was dissolved in a mixture /PrOH/water 1/1 (1 mL). Sodium sulfite (60 mg, 0.48 mmol) was added and the reaction mixture was stirred under reflux for 48 h. The solvents were removed under reduced pressure. Purification of the crude by HPLC (basic conditions) gave the ammonium 2-[4-[[4(S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2R]-tetrahydropyran-2-yl][methyl]-3,4-dihydropyridine-5-carbonyl]oxymethyl]phenoxyl]ethanesulfonate as a white powder (m = 60 mg, 45 %). 1H NMR (300 MHz, CDCl3) δ 1.34-1.48 (m, 1H), 1.74-1.96 (m, 3H), 2.56 (s, 3H), 2.60 (d, J = 15.9 Hz, 1H), 2.70-2.88 (m, 3H), 3.26 (t, J = 6.1 Hz, 2H), 3.35 (dd, J = 14.3-9.0 Hz, 1H), 3.62-3.90 (m, 3H), 4.09 (d, J = 6.1 Hz, 1H), 4.14-4.28 (m, 3H), 4.82 (d, J = 12.5 Hz, 1H), 4.94 (d, J = 12.5 Hz, 1H), 6.73 (d, J = 8.5 Hz, 2H), 6.89 (brs, 4H), 6.96 (d, J = 8.5 Hz, 2H), 7.13 (s, 3H). 13C NMR (75 MHz, CDCl3) δ 17.1, 25.5, 29.1, 36.9, 38.9, 45.6, 50.6, 63.5, 65.6, 68.1, 77.2, 77.8, 110.0, 114.6, 128.7, 129.1, 129.5, 132.4, 139.5, 151.1, 157.8, 167.0, 169.0. MS [M-H]⁻ = 562; HRMS : calcd for C27H23NO6SCl, [M+H]⁺ 562.1302, found 562.1322.

EXAMPLE 145: 2-pyridylmethyl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2R]-tetrahydropyran-2-yl][methyl]-3,4-dihydropyridine-5-carboxylate and 2-pyridylmethyl (4R)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2S]-tetrahydropyran-2-yl][methyl]-3,4-dihydropyridine-5-carboxylate

R acemic mixture of (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2R]-tetrahydropyran-2-yl][methyl]-3,4-dihydropyridine-5-carboxylic acid and its enantiomer (example 135, 105 mg, 0.30 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (215 mg, 0.66 mmol) and 2-(Chloromethyl)pyridine hydrochloride (132 mg, 0.36 mmol) were added. The reaction mixture was stirred at RT for 18 h. Cesium carbonate (60 mg, 0.18 mmol) and 2-(Chloromethyl)pyridine hydrochloride (30 mg, 0.18 mmol) were added again. The reaction
mixture was stirred at 60 °C for 12 h. The solvent was removed under reduced pressure. Water was added. The aqueous phase was extracted with Et$_2$O. The combined organic layers were washed with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure.

Purification of the crude by flash chromatography on silica using a mixture of DCM/MeOH (7/3) gave the desired (2-pyridylmethyl)(4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate as a colorless oil (83 mg, 63%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$  1.42-1.51 (m, 1H), 1.83-2.00 (m, 3H), 2.65 (s, 3H), 2.71 (dd, $J = 15.8, 2.2$ Hz, 1H), 2.94 (dd, $J = 15.5, 7.4$ Hz, 1H), 3.42 (dd, $J = 14.4, 8.8$ Hz, 1H), 3.70-3.77 (m, 1H), 3.79-3.84 (m, 1H), 3.87-3.94 (m, 1H), 4.23-4.29 (m, 2H), 5.13 (d, $J = 14.0$ Hz, 1H), 5.29 (d, $J = 14.0$ Hz, 1H), 6.80 (d, $J = 8.1$ Hz, 1H), 7.15 (dd, $J = 7.4, 5.0$ Hz, 2H), 7.22 (s, 4H), 7.51 (t, $J = 7.7, 2.2$ Hz, 1H), 8.51 (d, $J = 5.0$ Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$  17.3, 25.6, 29.2, 37.1, 39.2, 46.1, 66.3, 68.1, 77.9, 109.6, 121.2, 122.7, 128.7, 128.8, 132.6, 136.8, 139.5, 149.0, 152.1, 156.0, 166.7, 168.9. MS [M+H]$^+$: 441, HRMS: calcd for C$_{26}$H$_{26}$N$_2$O$_4$Cl, [M+H]$^+$ 441.1581, found 441.1580.

**EXAMPLE 146:** 3-pyridylmethyl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and 3-pyridylmethyl (4R)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[(2S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate

**Racemic mixture of (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylic acid and its enantiomer (example 135, 105 mg, 0.30 mmol) was dissolved in anhydrous DMF (1 mL) then cesium carbonate (215 mg, 0.66 mmol) and 3-(Chloromethyl)pyridine hydrochloride (132 mg, 0.36 mmol) were added. The reaction mixture was stirred at RT for 18 h. The solvent was removed under reduced pressure. Water was added. The aqueous phase was extracted with Et$_2$O. The combined organic layers were washed with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure.

Purification of the crude by flash chromatography on silica using a mixture of DCM/MeOH (8/2) gave the desired (3-pyridylmethyl)(4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate (racemic) as a colorless oil (101 mg, 76%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$  1.42-1.51 (m, 1H), 1.83-2.00 (m, 3H), 2.65 (s, 3H), 2.71 (dd, $J = 15.5, 2.2$ Hz, 1H), 2.94 (dd, $J = 15.5, 7.4$ Hz, 1H), 3.42 (dd, $J = 14.4, 8.8$ Hz, 1H), 3.70-3.77 (m, 1H), 3.79-3.84 (m, 1H), 3.87-3.94 (m, 1H), 4.23-4.29 (m, 2H), 5.13 (d, $J = 14.0$ Hz, 1H), 5.29 (d, $J = 14.0$ Hz, 1H), 6.80 (d, $J = 8.1$ Hz, 1H), 7.15 (dd, $J = 7.4, 5.0$ Hz, 2H), 7.22 (s, 4H), 7.51 (t, $J = 7.7, 2.2$ Hz, 1H), 8.51 (d, $J = 5.0$ Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$  17.2, 25.5, 29.2, 37.1, 39.1, 45.8, 63.4, 68.1, 77.8, 109.49, 123.4, 128.6, 128.7, 131.8, 132.6, 135.5, 139.4, 149.0, 149.3, 152.2, 166.7, 168.9. MS [M+H]$^+$: 441, HRMS: calcd for C$_{26}$H$_{26}$N$_2$O$_4$Cl, [M+H]$^+$ 441.1581, found 441.1580.
EXAMPLE 147: [4-(2-methoxyethoxy)phenyl]methyl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[[(2S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and [4-(2-methoxyethoxy)phenyl]methyl (4R)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate

1-(chloromethyl)-4-(2-methoxyethoxy)benzene (example 118, 125mg, 0.60 mmol) and (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[[(2S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylic acid (192 mg, 0.55 mmol) were dissolved in anh. DMF (2 mL). Cesium carbonate (269 mg, 0.825 mmol) was added and the reaction mixture was stirred at RT for 18 h. The solvents were removed under reduced pressure. Water was added and the aqueous phase was extracted with diethyl ether, washed with brine and dried over Na$_2$SO$_4$. The solvents were removed under reduced pressure. Purification of the crude by flash chromatography using a mixture of Cy/DCM 1/1 to DCM gave the expected [4-(2-methoxyethoxy)phenyl]methyl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[[(2S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate as a colorless oil (59 mg, 21%). $^1$H NMR (300 MHz, CDCl$_3$) δ 1.24-1.36 (m, 1H), 1.74-1.94 (m, 3H), 2.61 (s, 3H), 2.78 (dd, $J = 15.9, 2.7$ Hz, 1H), 2.91 (dd, $J = 15.9, 7.3$ Hz, 1H), 3.46 (s, 3H), 3.66-3.84 (m, 5H), 3.88-4.06 (m, 2H), 4.09-4.14 (m, 2H), 4.18 (dd, $J = 7.3, 2.1$ Hz, 1H), 5.01 (d, $J = 12.2$ Hz, 1H), 5.07 (d, $J = 12.2$ Hz, 1H), 6.85 (d, $J = 8.6$ Hz, 2H), 7.06 (d, $J = 8.4$ Hz, 2H), 7.08 (d, $J = 8.6$ Hz, 2H), 7.19 (d, $J = 8.4$ Hz, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 17.4, 25.3, 28.9, 36.4, 38.3, 45.2, 59.2, 65.9, 67.2, 67.7, 71.0, 110.4, 114.4, 128.3, 128.4, 128.6, 129.6, 132.5, 139.8, 150.6, 158.6, 167.0, 169.4. MS [M+H]$^+$ 514, HRMS: calcd for C$_{29}$H$_{33}$NO$_5$Cl, [M+H]$^+$ 514.1996, found 514.2003.
**EXAMPLE 148:** (2-methoxyphenyl)methyl (4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate

**Step 1.** 6-chloropyridine-3-carbaldehyde (3 mmol), meldrum acid (3 mmol), (2-methoxyphenyl)methyl-3-oxobutanoate (3 mmol) and ammonium acetate (4.5 equiv) were dissolved in acetic acid (1 N). The reaction mixture was stirred overnight under reflux. The solvent was removed. The crude product was purified by flash chromatography and engaged in step 2.

**Step 2.** The intermediate obtained in step 1 (1.3 g, 3.36 mmol) was dissolved in anh. DMF (12 mL). Tetrahydrofurfuryl bromide (573 µL, 5.04 mmol), Cs₂CO₃ (1.64 g, 5.04 mmol), sodium iodide (25 mg, 0.17 mmol) were added. The reaction mixture was stirred at 50 °C for 18 h. The DMF was removed under reduced pressure. The residue was diluted in water. The aqueous phase was extracted by EtOAc and the combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure. The crude was dissolved...
again in anh. DMF (1 mL). Tetrahydrofurfuryl bromide (573 µL, 5.04 mmol) and Cs₂CO₃ (1.64 g, 5.04 mmol) were added. The reaction mixture was stirred at 50 °C for 18 h. The DMF was removed under reduced pressure. The residue was diluted in water. The aqueous phase was extracted by EtOAc and the combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure. Purification of the crude by flash chromatography using a mixture of Cyclohexane/EtOAc (8/2) as eluent gave the desired (2-methoxyphenyl)methyl (4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and its enantiomer as a colorless oil (204 mg, 13 %). ¹H NMR (300 MHz, CDCl₃) δ 1.39-1.51 (m, 1H), 1.81-2.07 (m, 3H), 2.60 (s, 3H), 2.64 (dd, J = 16.0, 2.0 Hz, 1H), 2.92 (dd, J = 15.7, 7.5 Hz, 1H), 3.39 (dd, J = 14.2, 9.3 Hz, 1H), 3.70 (s, 3H), 3.72-3.77 (m, 1H), 3.83-3.90 (m, 2H), 4.23 (dd, J = 14.0, 2.8 Hz, 2H), 5.08 (d, J = 12.5 Hz, 1H), 5.14 (d, J = 12.5 Hz, 1H), 6.80-6.87 (m, 2H), 7.02 (dd, J = 7.5, 1.7 Hz, 1H), 7.13 (d, J = 8.3 Hz, 1H), 7.22-7.28 (td, J = 7.8, 1.7 Hz, 1H), 7.57 (dd, J = 8.3, 2.5 Hz, 1H), 8.21 (d, J = 2.5 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 17.08, 25.61, 29.18, 34.88, 38.62, 45.96, 55.21, 62.04, 68.16, 77.63, 109.31, 110.30, 120.25, 123.97, 124.02, 129.46, 129.58, 135.94, 137.88, 149.16, 149.79, 151.66, 157.42, 166.71, 168.4. MS [M+H]+ 471 g/mol. HRMS : calcd for C₂5H₂₈N₂O₅Cl₂, [M+H]+ 471.1687, found 471.1695.

**Example 149a**: 4-(3,4-dichlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (intermediate product)

\[
\text{Cl} - \text{Cl} - \text{Cl} - \text{O} - \text{O} - \text{N} - \text{O}
\]

3,4-dichlorobenzaldehyde (3.0 mmol, 525 g), meldrum acid (3.0 mmol, 432 g), o-methoxybenzyl acetoacetate (3.0 mmol, 666 mg) and ammonium acetate (4.5 mmol, 338 mg) were dissolved in acetic acid (3 mL). The reaction mixture was stirred at 110 °C for 18 h. The solvent was removed. The crude didn’t precipitate in EtOH. The crude was purified by flash chromatography (Cy/EA (85/15) to and precipitated in EtOH. Then, a filtration yielded the desired (2-methoxyphenyl)methyl 4-(3,4-dichlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate as a white powder (384 mg, 30 %). ¹H NMR (300 MHz, CDCl₃) δ 2.43 (s, 3H), 2.63 (dd, J = 16.7, 1.3 Hz, 1H), 2.94 (dd, J = 16.7, 8.1 Hz, 1H), 3.76 (s, 3H), 4.23 (d, J = 7.7 Hz, 1H), 5.12 (d, J = 12.6 Hz, 1H), 5.22 (d, J = 12.6 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.88 (td, J = 7.4, 1.0 Hz, 1H), 6.99 (dd, J = 8.5, 2.3 Hz, 1H), 7.08 (dd, J = 7.4, 1.7 Hz, 1H), 7.22 (d, J = 2.0 Hz, 1H), 7.26-7.33 (m, 2H), 8.34 (brs, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 19.1, 37.3, 37.7, 55.2, 61.8, 106.3, 110.3, 120.3, 124.0, 126.2, 128.9, 129.6, 130.6, 130.9, 132.6, 142.5, 147.0,
EXAMPLE 149: (2-methoxyphenyl)methyl (4S)-4-(3,4-dichlorophenyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and (2-methoxyphenyl)methyl (4R)-4-(3,4-dichlorophenyl)-6-methyl-2-oxo-1-[[2(S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate

4-(3,4-dichlorophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylic acid (example 149a, 150 mg, 0.36 mmol) was dissolved in anhydrous DMF (1 mL). Tetrahydrofurfuryl bromide (81 µL, 0.72 mmol) and Cs₂CO₃ (232 mg, 0.72 mmol) were added. The reaction mixture was stirred at 50 °C for 18 h. The DMF was removed under reduced pressure. The residue was diluted in water. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure. The crude product was dissolved again in anhydrous DMF (1 mL). Tetrahydrofurfuryl bromide (81 µL, 0.72 mmol) and Cs₂CO₃ (232 mg, 0.72 mmol) were added. The reaction mixture was stirred at 50 °C for 18 h. The DMF was removed under reduced pressure. The residue was diluted in water. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure. Purification of the crude by flash chromatography using a mixture of Cyclohexane/EtOAc (8:2) as the eluent gave the desired (2-methoxyphenyl)methyl (4S)-4-(3,4-dichlorophenyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate as a colorless oil (52 mg, 29 %) and its diastereomer as a colorless oil (33 mg, 18 %). ¹H NMR (300 MHz, CDCl₃) δ 1.46-1.52 (m, 1H), 1.87-2.00 (m, 3H), 2.64 (s, 3H), 2.69 (dd, J = 15.6, 2.1 Hz, 1H), 2.91 (dd, J = 15.6, 7.5 Hz, 1H), 3.41 (dd, J = 14.3, 9.0 Hz, 1H), 3.73 (s, 3H), 3.76-3.95 (m, 3H), 4.17 (d, J = 6.7 Hz, 1H), 4.29 (dd, J = 14.3, 3.1 Hz, 1H), 5.10 (d, J = 13.0 Hz, 1H), 5.20 (d, J = 13.0 Hz, 1H), 6.84 (t, J = 8.0 Hz, 2H), 7.00 (dd, J = 7.3, 1.5 Hz, 1H), 7.08 (dd, J = 8.4, 2.1 Hz, 1H), 7.27 (td, J = 5.8, 1.8 Hz, 2H), 7.38 (d, J = 2.1 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 17.1, 25.6, 26.9, 29.3, 37.1, 38.9, 45.9, 55.2, 61.9, 68.2, 77.8, 109.8, 110.2, 120.2, 124.3, 127.0, 129.1, 129.2, 129.3, 130.4, 130.7, 132.5, 141.6, 151.5, 157.3, 166.9, 168.7. MS [M+H]+ calcd for C₂₆H₂₈NO₅C₅I₂, [M+H]+ 504.1345, found 504.1351.

EXAMPLE 150 (2-Methoxyphenyl)methyl (4S)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-4-[6-(trifluoromethyl)-3-pyridyl]-3,4-dihydropyridine-5-carboxylate and (2-methoxyphenyl)methyl (4R)-6-methyl-2-oxo-1-[[2(S)-tetrahydrofuran-2-yl]methyl]-4-[6-(trifluoromethyl)-3-pyridyl]-3,4-dihydropyridine-5-carboxylate.
Example 150a. Methyl 6-methyl-2-oxo-4-[6-(trifluoromethyl)-3-pyridyl]-3,4-dihydro-1H-pyridine-5-carboxylate.

The methyl 3-oxobutanoate (0.37 mL, 3.43 mmol) was dissolved in acetic acid (9 mL). 6-(trifluoromethyl)pyridine-3-carbaldehyde (600 mg, 3.43 mmol) and Meldrum's acid (494 mg, 3.43 mmol) and ammonium acetate (396 mg, 5.14 mmol) were added and the reaction mixture was stirred for 18 h at 110°C. The reaction mixture was cooled at r.t. Solvent was removed under reduced pressure and the residue was dissolved in the minimum of ethanol. The mixture was sonicated with ultrasound and the product precipitated. The reaction mixture was cooled and the precipitate was filtered and washed with cold ethanol to give the desired product as a white powder (394 mg, 37%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.39 (s, 3H), 2.64 (d, $J = 16.2$ Hz, 1H), 2.99 (dd, $J = 16.7$, $8.2$ Hz, 1H), 3.63 (s, 3H), 4.33 (d, $J = 7.7$ Hz, 1H), 7.59 (d, $J = 8.1$ Hz, 1H), 7.65 (dd, $J = 8.1$, $1.9$ Hz, 1H), 8.57 (d, $J = 1.4$ Hz, 1H), 9.20 (s, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 19.0, 35.7, 37.4, 51.7, 105.4, 119.7, 120.7, 123.4, 135.7, 141.1, 148.1, 149.0, 166.8, 170.7. MS [M+H]$^+$ 315 g/mol.

Example 150b. Methyl (4S)-6-methyl-2-oxo-1-[(2R)-tetrahydrofuran-2-yl]methyl]-4-[6-(trifluoromethyl)-3-pyridyl]-3,4-dihydropyridine-5-carboxylate and methyl (4R)-6-methyl-2-oxo-1-[(2S)-tetrahydrofuran-2-yl]methyl]-4-[6-(trifluoromethyl)-3-pyridyl]-3,4-dihydropyridine-5-carboxylate.

The methyl 6-methyl-2-oxo-4-[6-(trifluoromethyl)-3-pyridyl]-3,4-dihydro-1H-pyridine-5-carboxylate (150a, 328 mg, 1.04 mmol) and the 2-(bromomethyl)tetrahydrofuran (345 mg, 2.09 mmol) were dissolved in anhydrous DMF (3 mL), Cs$_2$CO$_3$ (681 mg, 2.09 mmol) and NaI (8 mg, 0.05 mmol) were added and the reaction mixture was stirred at 50°C overnight. The solvent was removed under reduced pressure. Water was added and the mixture was extracted by ethyl acetate, the organic layers were washed with brine, and dried over Na$_2$SO$_4$ and filtered. The solvent was removed and the crude product was purified by column chromatography on silica gel (CH$_2$Cl$_2$/Cy 70/30 to 100/0 and CH$_2$Cl$_2$/MeOH 100/0 to 96/4) to give the expected product as oil (100 mg, 24%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.34-1.52 (m, 1H), 1.78-2.01 (m, 3H), 2.60 (s, 3H), 2.69 (dd, $J = 15.8$, 2.0 Hz, 1H), 2.89-3.04 (m, 1H), 3.38 (dd, $J = 14.2$, 9.4 Hz, 1H), 3.61 (s, 3H), 3.66-3.93 (m, 1H), 4.15-4.35 (m, 2H), 7.50 (d, $J = 8.1$ Hz, 1H), 7.79-7.87 (m, 1H), 8.59 (d, $J = 1.9$ Hz, 1H). $^{13}$C
NMR (75 MHz, CDCl$_3$) $\delta$ 17.2, 25.7, 29.2, 35.3, 38.6, 46.0, 51.8, 68.2, 77.7, 108.8, 119.9, 120.4, 123.5, 136.1, 140.1, 149.8, 152.2, 167.3, 168.3. MS [M+H]$^+$ 399 g/mol.

**Example 150c.** (4S)-6-methyl-2-oxo-1-[[[2R]-tetrahydrofuran-2-yl][methyl]-4-[6-(trifluoromethyl)-3-pyridyl]-3,4-dihydropyridine-5-carboxylic acid and (4R)-6-methyl-2-oxo-1-[[[2S]-tetrahydrofuran-2-yl][methyl]-4-[6-(trifluoromethyl)-3-pyridyl]-3,4-dihydropyridine-5-carboxylic acid.

150b (95 mg, 0.24 mmol) was dissolved in MeOH (2 mL). NaOH 1N (1 mL) was added. The reaction mixture was stirred overnight at 40 °C. The MeOH was evaporated under reduced pressure, the aqueous phase was extracted by Et$_2$O, then acidified to pH=1 with HCl (1N). The aqueous phase was extracted by EtOAc. The organic phases were assembled, dried under Na$_2$SO$_4$ and filtered. The solvents were removed under reduced pressure to afford a product as oil. (m = 86 mg, 92%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.37-1.50 (m, 1H), 1.80-1.99 (m, 3H), 2.61 (s, 3H), 2.73 (dd, $J$ = 15.8, 1.8 Hz, 1H), 2.98 (dd, $J$ = 15.8, 7.5 Hz, 1H), 3.40 (dd, $J$ = 14.2, 9.4 Hz, 1H), 3.65-3.90 (m, 3H), 4.22 (dd, $J$ = 14.3, 2.7 Hz, 1H), 4.31 (d, $J$ = 6.8 Hz, 1H), 7.51 (d, $J$ = 8.2 Hz, 1H), 7.83 (dd, $J$ = 8.1, 2.0 Hz, 1H), 8.62 (d, $J$ = 2.0 Hz, 1H), 10.40 (s, 1H).$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 17.5, 25.7, 29.2, 35.2, 38.4, 46.2, 68.3, 77.6, 108.2, 120.4, 123.5, 136.2, 140.1, 149.7, 154.5, 168.6, 172.0, 175.6. MS [M+H]$^+$ 385 g/mol.

**EXAMPLE 150 (2-Methoxyphenyl)methyl (4S)-6-methyl-2-oxo-1-[[[2R]-tetrahydrofuran-2-yl][methyl]-4-[6-(trifluoromethyl)-3-pyridyl]-3,4-dihydropyridine-5-carboxylate and (2-methoxyphenyl)methyl (4R)-6-methyl-2-oxo-1-[[[2S]-tetrahydrofuran-2-yl][methyl]-4-[6-(trifluoromethyl)-3-pyridyl]-3,4-dihydropyridine-5-carboxylate.**

The 1-(chloromethyl)-2-methoxy-benzene (39 mg, 0.25 mmol) and the acid 150c (86 mg, 0.22 mmol) were dissolved in dry DMF (2 mL). Cesium carbonate (109 mg, 0.34 mmol) was added and the reaction mixture was stirred at RT overnight. The solvent was removed. Water was added and the aqueous phase was extracted by Et$_2$O, washed with brine and dried under Na$_2$SO$_4$. After filtration the solvent was removed and the crude product was purified by column chromatography on silica gel (Cy/EA 100 to 80/20) then by HPLC (acid conditions) to give the expected product as white solid (65 mg, 58%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.50-1.67 (m, 1H), 1.79-2.12 (m, 3H), 2.58-2.80 (m, 4H), 2.99 (dd, $J$ = 15.4, 7.2 Hz, 1H), 3.42 (dd, $J$ = 14.1, 9.3 Hz, 1H), 3.59-3.80 (m, 4H), 3.81-3.99 (m, 2H), 4.17-4.38 (m, 2H), 5.12 (q, $J$ = 12.3 Hz, 2H), 6.82 (dd, $J$ = 11.2, 7.9 Hz, 2H), 7.01 (d, $J$ = 7.1 Hz, 1H), 7.25 (d, $J$ = 7.5 Hz, 1H), 7.49 (d, $J$ = 8.0 Hz, 1H), 7.81 (d, $J$ = 7.4 Hz, 1H), 8.55 (s, 1H).$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 17.2, 25.7, 29.3, 35.5, 38.5, 46.2, 55.3, 62.3, 68.3, 77.7, 109.1, 110.4, 120.3, 120.4, 123.6, 124.0, 129.7, 129.8, 136.1, 140.5, 146.7, 149.9, 152.1, 157.6, 166.8, 168.4. MS [M+H]$^+$ 505 g/mol.
EXAMPLE 151: (2-Methoxyphenyl)methyl (4R)-4-(2-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and (2-methoxypyphenyl)methyl (4S)-4-(2-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[2(S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.

Example 151a. Methyl 4-(2-chloro-3-pyridyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate.

The methyl 3-oxobutanoate (0.68 mL, 6.30 mmol) was dissolved in acetic acid (7 mL). 2-chloropyridine-3-carbaldehyde (892 mg, 6.30 mmol), Meldrum’s acid (908 mg, 6.30 mmol) and ammonium acetate (729 mg, 9.45 mmol) were added and the reaction mixture was stirred for 18 h at 110°C. The reaction mixture was cooled at RT. Solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (CH₂Cl₂) to give the desired product as a white powder (850 mg, 48%).

¹H NMR (300 MHz, CDCl₃) δ 2.44 (s, 3H), 2.74 (dd, J = 16.8, 1.1 Hz, 1H), 2.92 (dd, J = 16.9, 8.3 Hz, 1H), 3.58 (s, 3H), 4.60 (d, J = 7.8 Hz, 1H), 7.13 (dd, J = 7.6, 4.7 Hz, 1H), 7.33 (dd, J = 7.6, 1.8 Hz, 1H), 8.25 (dd, J = 4.7, 1.9 Hz, 1H), 9.05 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 18.9, 35.0, 35.9, 51.7, 104.8, 123.0, 135.0, 136.3, 148.2, 148.7, 150.8, 166.7, 170.8. MS [M-H]⁻ 279 g/mol.

Example 151b. Methyl (4R)-4-(2-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and methyl (4S)-4-(2-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[2(S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.

The Methyl 4-(2-chloro-3-pyridyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (151a, 700 mg, 2.55 mmol) and the 2-(bromomethyl)tetrahydrofuran (0.57 mL, 5.0 mmol) were dissolved in dry DMF (6 mL), Cs₂CO₃ (1.63 g, 5.0 mmol) and NaI (19 mg, 0.13 mmol) were added and the reaction mixture was stirred at 50°C overnight. The solvent was removed under reduced pressure. Water was added and the aqueous phase was extracted by ethyl acetate, the organic layers were washed with brine and dried over Na₂SO₄. The solvent was removed. The residue was extracted again in 6 mL of DMF, 1.63 g of Cs₂CO₃, 19 mg of NaI and the alkyl bromide (0.57 mL) were added and the mixture was stirred at 50°C for 18 h. Reaction finished. The solvent was removed under reduced pressure. Water was added and the aqueous phase was extracted by ethyl acetate, the organic layers were washed with brine, and dried over Na₂SO₄. The solvent was removed. The purification by column chromatography on silica (CH₂Cl₂/C₂H₅OH 95:5).
Example 151c. (4R)-4-(2-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylic acid and (4S)-4-(2-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[2(S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylic acid.

151b (130 mg, 0.36 mmol) was dissolved in MeOH (3 mL). NaOH 1N (2 mL) was added. The reaction mixture was stirred overnight at 40 °C. The MeOH was evaporated under reduced pressure and the aqueous phase was extracted by Et₂O, then acidified to pH = 1 with HCl (1N). The aqueous phase was extracted by EtOAc and the organic layers were assembled and dried under Na₂SO₄. The solvent was removed under reduced pressure to afford a product as white solid (m = 110 mg, 88%).

1H NMR (300 MHz, CDCl₃) δ 1.40-1.55 (m, 1H), 1.78-2.07 (m, 3H), 2.63 (s, 3H), 2.88 (d, J = 4.5 Hz, 2H), 3.38 (dd, J = 14.1, 9.7 Hz, 1H), 3.70-3.85 (m, 2H), 3.90 (dd, J = 14.5, 6.9 Hz, 1H), 4.23 (d, J = 14.2 Hz, 1H), 4.55 (t, J = 4.2 Hz, 1H), 7.07 (dd, J = 7.5, 4.8 Hz, 1H), 7.74 (d, J = 7.5 Hz, 1H), 8.23 (d, J = 3.4 Hz, 1H), 9.84 (s, 1H). 13C NMR (75 MHz, CDCl₃) δ 17.6, 25.8, 29.2, 34.7, 36.2, 46.1, 68.3, 77.9, 108.1, 122.9, 134.2, 137.8, 148.0, 150.9, 155.0, 168.9, 172.1. MS [M+H]+ 351 g/mol.

EXAM PLE 151. (2-Methoxyphenyl)methyl (4R)-4-(2-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and (2-methoxyphenyl)methyl (4S)-4-(2-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[2(S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.

The 1-(chloromethyl)-2-methoxy-benzene (44 mg, 0.28 mmol) and the acid 151c (90 mg, 0.26 mmol) were dissolved in dry DMF (2 mL). Cesium carbonate (125 mg, 0.38 mmol) was added and the reaction mixture was stirred at RT overnight.

The solvent was removed. Water was added and the aqueous phase was extracted by Et₂O, organic layer was washed with brine and dried under Na₂SO₄. The solvent was removed. The purification by column chromatography on silica gel (Cy/EtOAc 100/0 to 80/20) give the expected product as white powder (m = 90 mg, 75%).

1H NMR (300 MHz, CDCl₃) δ 1.39-1.56 (m, 1H), 1.77-2.06 (m, 3H), 2.65 (s, 3H), 2.86 (d, J = 5.8, 4.6 Hz, 2H), 3.39 (dd, J = 14.2, 9.5 Hz, 1H), 3.69 (s, 3H), 3.70-3.87 (m, 2H), 3.87-3.97 (m, 1H), 4.23 (dd, J = 14.3, 2.6 Hz, 1H), 4.59 (dd, J = 6.7, 2.6 Hz, 1H), 5.09 (s, 2H), 6.81 (ddd, J = 8.2, 7.4, 3.5 Hz, 2H), 6.96-7.10 (m, 2H), 7.17-7.26 (m, 1H), 7.72-7.82 (m, 1H), 8.20 (dd, J = 4.7,
1.9 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 17.1, 25.8, 29.2, 34.9, 36.3, 46.0, 55.3, 62.0, 68.3, 77.9, 108.9, 110.2, 120.3, 122.8, 124.2, 129.0, 129.4, 134.5, 137.8, 148.0, 151.0, 152.6, 157.3, 166.7, 168.7. MS [M+H]$^+$ 471 g/mol.

EXAMPLE 152 (2-Methoxyphenyl)methyl (4S)-4-(2,1,3-benzothiadiazol-5-yl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and (2-methoxyphenyl)ethyl (4R)-4-(2,1,3-benzothiadiazol-5-yl)-6-methyl-2-oxo-1-[[2(S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.

Example 152a. Methyl 4-(2,1,3-benzothiadiazol-5-yl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate.

The methyl 3-oxobutanoate (0.4 mL, 3.65 mmol) was dissolved in acetic acid (9 mL). 2,1,3-benzothiadiazole-5-carbaldehyde (600 mg, 3.65 mmol), Meldrum's acid (527 mg, 3.65 mmol) and ammonium acetate (422 mg, 5.48 mmol) were added and the reaction mixture was stirred for 18 h at 110°C. The reaction mixture was cooled at RT. Solvent was removed under reduced pressure and the residue was dissolved in the minimum of ethanol. The mixture was sonicated with ultrasound and the product precipitated. The mixture was cooled and the precipitate was filtered and washed with cold ethanol to give the desired product as a beige powder (490 mg, 44%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.44 (s, 3H), 2.77 (d, J = 16.6 Hz, 1H), 3.02 (dd, J = 16.6, 8.2 Hz, 1H), 3.64 (s, 3H), 4.41 (d, J = 7.8 Hz, 1H), 7.46 (dd, J = 9.1, 1.7 Hz, 1H), 7.70 (s, 1H), 7.93 (d, J = 9.1 Hz, 1H), 8.75 (s, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 19.3, 37.7, 38.1, 51.7, 105.8, 118.1, 122.1, 130.2, 143.5, 147.8, 154.3, 155.2, 167.1, 170.7. MS [M+H]$^+$ 304 g/mol.

Example 152b. Methyl (4S)-4-(2,1,3-benzothiadiazol-5-yl)-6-methyl-2-oxo-1-[[2(S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and methyl (4R)-4-(2,1,3-benzothiadiazol-5-yl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.

The methyl 4-(2,1,3-benzothiadiazol-5-yl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate (152a, 400 mg, 1.32 mmol) and the 2-(bromomethyl)tetrahydrofuran (435 mg, 2.64 mmol) were dissolved in anhydrous DMF (3 mL), Cs$_2$CO$_3$ (861 mg, 2.64 mmol) and Nal (10 mg, 0.07 mmol)
were added and the reaction mixture was stirred at 50°C overnight. The solvent was removed under reduced pressure. Water was added and the mixture was extracted by ethyl acetate, the organic layers washed with brine, and dried over Na₂SO₄ and filtered. The solvent was removed and the crude product was purified by column chromatography on silica gel (CH₂Cl₂/MeOH 100/0 to 96/4) to give the expected product as oil (m = 120 mg, 24 %).

¹H NMR (300 MHz, CDCl₃) δ 1.25-1.28 (m, 1H), 1.57-1.88 (m, 3H), 2.68 (s, 3H), 2.89 (dd, J = 16.0, 2.3 Hz, 1H), 3.03 (dd, J = 15.9, 7.4 Hz, 1H), 3.59-3.73 (m, 4H), 3.74-3.92 (m, 2H), 3.92-4.07 (m, 2H), 4.36 (d, J = 7.1 Hz, 1H), 7.47 (dd, J = 9.1, 1.8 Hz, 1H), 7.60-7.72 (m, 1H), 7.91 (dd, J = 9.1, 0.7 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 17.6, 25.3, 29.2, 37.3, 38.3, 45.2, 51.8, 67.9, 77.5, 109.4, 118.6, 121.8, 130.4, 142.8, 151.7, 154.2, 155.2, 167.7, 169.2. MS [M+H]⁺ 388 g/mol.

Example 152c. (4S)-4-(2,1,3-benzothiadiazol-5-yl)-6-methyl-2-oxo-1-[[[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylic acid and (4R)-4-(2,1,3-benzothiadiazol-5-yl)-6-methyl-2-oxo-1-[[[(2S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylic acid.

Example 152b (88 mg, 0.23 mmol) was dissolved in MeOH (2 ml), NaOH 1N (1 mL) was added. The reaction mixture was stirred overnight at 40 °C. The MeOH was evaporated under reduced pressure, the aqueous phase was extracted by Et₂O, then acidified to pH=1 with HCl (1N). The aqueous phase was extracted by EtOAc. The organic layers were assembled, dried under Na₂SO₄ and filtered. The solvents were removed under reduced pressure to afford a product as oil (m = 70 mg, 82%).

¹H NMR (300 MHz, CDCl₃) δ 1.30-1.47 (m, 1H), 1.70-1.93 (m, 3H), 2.66 (s, 3H), 2.80 (dd, J = 15.7, 2.0 Hz, 1H), 2.97 (dd, J = 15.7, 7.3 Hz, 1H), 3.42 (dd, J = 14.2, 8.9 Hz, 1H), 3.67-3.70 (m, 1H), 3.77-4.01 (m, 2H), 4.20-4.40 (m, 2H), 7.46 (dd, J = 9.1, 1.8 Hz, 1H), 7.86 (dd, J = 8.9, 0.8 Hz, 2H), 10.42 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 17.6, 25.4, 29.2, 37.6, 38.5, 45.8, 68.1, 78.0, 109.0, 118.9, 121.7, 130.5, 142.2, 154.3, 155.3, 168.9, 172.4. MS [M+H]⁺ 374 g/mol.

EXAM PLE 152: (2-Methoxyphenyl)methyl (4S)-4-(2,1,3-benzothiadiazol-5-yl)-6-methyl-2-oxo-1-[[[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and (2-methylphenyl)methyl (4R)-4-(2,1,3-benzothiadiazol-5-yl)-6-methyl-2-oxo-1-[[[(2S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.

The 1-(chloromethyl)-2-methoxy-benzene (32 mg, 0.21 mmol) and the acid 152c (70 mg, 0.19 mmol) were dissolved in dry DMF (2 mL). Cesium carbonate (92 mg, 0.28 mmol) was added and the reaction mixture was stirred at RT overnight. The solvent was removed. Water was added and the aqueous phase was extracted by Et₂O,
washed with brine and dried under Na$_2$SO$_4$. After filtration the solvent was removed and the crude product was purified by column chromatography on silica gel (Cy/EA 100 to 80/20) to give the expected product as oil (80 mg, 86 %).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.35-1.51 (m, 1H), 1.75-1.97 (m, 3H), 2.69 (s, 3H), 2.79 (dd, $J =$ 15.7, 2.1 Hz, 1H), 3.01 (dd, $J =$ 15.7, 7.5 Hz, 1H), 3.45 (dd, $J =$ 14.2, 8.8 Hz, 1H), 3.64 (s, 3H), 3.71-3.83 (m, 1H), 3.82-3.40 (m, 2H), 4.29 (dd, $J =$ 14.2, 3.2 Hz, 1H), 4.38 (d, $J =$ 6.5 Hz, 1H), 5.13 (d, $J =$ 3.8 Hz, 2H), 6.65-6.75 (m, 2H), 6.99 (dd, $J =$ 7.4, 1.5 Hz, 1H), 7.18 (ddd, $J =$ 8.2, 7.5, 1.8 Hz, 1H), 7.47 (dd, $J =$ 9.1, 1.8 Hz, 1H), 7.89 (dddd, $J =$ 9.8, 5.4, 0.8 Hz, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 17.3, 25.4, 29.3, 37.9, 38.6, 45.7, 55.2, 62.0, 68.1, 78.0, 110.0, 110.2, 119.1, 120.2, 121.5, 124.3, 129.2, 129.3, 130.6, 142.8, 151.8, 154.3, 155.4, 157.3, 167.0, 168.8. MS [M+H]$^+$ 494 g/mol.

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EXAMPLE 153a. Methyl 4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate.

The methyl 3-oxobutanoate (1.52 ml, 14.13 mmol) was dissolved in acetic acid (14 ml). 6-chloropyridine-3-carbaldehyde (2 g, 14.13 mmol), Meldrum’s acid (2 g, 14.13 mmol) and ammonium acetate (1.63 g, 21.19 mmol) were added and the reaction mixture was stirred for 18 h at 110°C. The reaction mixture was cooled at RT. Solvent was removed under reduced pressure and the residue was dissolved in the minimum of ethanol. The mixture was sonicated with ultrasound and the product precipitated. The mixture was cooled and the precipitate was filtered and washed with cold ethanol to give the desired product as a beige powder (1.76 g, 44%).

$^1$H NMR (300 MHz, Acetone) δ 2.45 (s, 3H), 2.55 (dd, $J = 16.4, 1.9$ Hz, 1H), 3.02 (dd, $J = 16.4, 7.8$ Hz, 1H), 3.61 (s, 3H), 4.31 (d, $J = 7.5$ Hz, 1H), 7.36 (d, $J = 8.3$ Hz, 1H), 7.67 (dd, $J = 8.3, 2.6$ Hz, 1H), 8.27 (d, $J = 2.6$ Hz, 1H), 9.00 (s, 1H). $^{13}$C NMR (75 MHz, Acetone) δ 18.8, 36.1, 38.4, 51.5, 105.2, 125.0, 138.7, 149.5, 149.7, 149.8, 150.2, 167.5, 169.5. MS [M+H]$^+$ 281 g/mol.

EXA M P L E 1 5 3 b. Methyl (4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[2R]-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and methyl (4R)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[2S]-tetrahydrofuran-2-yl]methyl]-3,4-
dihydropyridine-5-carboxylate.

The methyl 4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate (600 mg, 2.14 mmol) and the 2-(bromomethyl)tetrahydrofuran (0.49 mL, 4.27 mmol) were dissolved in dry DMF (5 mL), Cs₂CO₃ (1.395 g, 4.28 mmol) and NaI (16.34 mg, 0.11 mmol) were added and the reaction mixture was stirred at 50°C overnight. The solvent was removed under reduced pressure. Water was added and the aqueous phase was extracted by ethyl acetate, the organic layers were washed with brine and dried over Na₂SO₄. The solvent was removed. The residue was dissolved again in 5 mL of DMF, 1.395 g of Cs₂CO₃, 16 mg of NaI and the alkyl bromide (0.5 mL) were added and the mixture was stirred at 50°C for 18 h. Reaction finished.

The solvent was removed under reduced pressure. Water was added and the aqueous phase was extracted by ethyl acetate, the organic layers were washed with brine, and dried over Na₂SO₄. The solvent was removed. The purification by columns chromatography on silica gel (Cy/EOAc 100/0 to 70/30 and CH₂Cl₂/Cy 70/30 to 100/0) gave the desired product as white product (m = 200 mg, 26%).

**EXAM PLE 153c.** (4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[2R]-tetrahydrofuran-2-yl][methyl]-3,4-dihydropyridine-5-carboxylic acid and (4R)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[2S]-tetrahydrofuran-2-yl][methyl]-3,4-dihydropyridine-5-carboxylic acid.

The previous ester (200 mg, 0.55 mmol) was dissolved in MeOH (3 mL), NaOH 1N (2 mL) was added. The reaction mixture was stirred overnight at 40 °C.

The MeOH was evaporated under reduced pressure and the aqueous phase was extracted by Et₂O, then acidified to pH = 1 with HCl (1N). The aqueous phase was extracted by EtOAc and the organic layers were assembled and dried under Na₂SO₄. The solvent was removed under reduced pressure to afford a product as white solid (m = 175 mg, 91%).

**EXAM PLE 153d.** [4-(2-Chloroethoxy)phenyl]methanol.

The 1-bromo-2-chloroethane (2.5 mL, 30 mmol), the 4-hydroxybenzyl alcohol (1.24 g, 10 mmol)
and the potassium carbonate (1.38 g, 10 mmol) were added in acetonitrile (33 mL) and the reaction mixture was stirred at 50 °C for 24 h. 4 equivalent of reactant and base were added and the reaction stirred under reflux over the week end. Reaction finished. The solvent was removed under reduced pressure. The crude was dissolved in EtOAc and washed by water. 

The aqueous phase was extracted by EtOAc and the organic layers were washed with brine, dried under Na₂SO₄. The solvent was removed under reduced pressure to afford the title compound. This crude was purified by flash chromatography (Cy/EA 100/0 to 70/30) to afford the desired compound as a white powder (m = 1.2 g, 64 %).

**EXAMPLE 153e. 1-(2-Chloroethoxy)-4-(chloromethyl)benzene.**

Thionyl chloride (0.10 mL, 1.34 mmol) was added to benzotriazole (192 mg, 1.61 mmol). The resulting mixture was dissolved in dry CH₂Cl₂ (1 mL). After 5 min, this solution was added slowly to a solution of the alcohol (200 mg, 1.07 mmol) in CH₂Cl₂ (8 mL). The benzotriazole salt started to precipitate. After 20 min of reaction, the salt was filtered. The organic phase was washed by water (8 mL) and NaOH solution (0.05 M, 8 mL) then, dried under Na₂SO₄, the solvent was removed under reduced pressure to give the desired chlorinated compound as colorless oil (m = 120 mg, 55 %).

1H NMR (300 MHz, CDCl₃) δ 3.81 (t, J = 5.9 Hz, 2H), 4.23 (t, J = 5.9 Hz, 2H), 4.57 (s, 2H), 6.90 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H). 3C NMR (75 MHz, CDCl₃) δ 41.9, 46.2, 68.2, 115.1, 130.3, 130.6, 158.4.

**EXAMPLE 153f. [4-(2-Chloroethoxy)phenyl]methyl (4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[(4S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.**

The (4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[(4S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylic acid and its enantiomer (162 mg, 0.46 mmol) and cesium carbonate (165 mg, 0.51 mmol) were dissolved in dry DMF (2 mL). The 1-(2-Chloroethoxy)-4-(chloromethyl)benzene (104 mg, 0.51 mmol) was added and the reaction mixture was stirred at r.t. for 18 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and washed with water. The aqueous phase was extracted by EtOAc and the organic layers were assembled, washed with brine and dried with Na₂SO₄. The purification by flash chromatography (Cy/CH₂Cl₂ 1/1 to CH₂Cl₂) afford the desired product as a colorless oil (m = 170 mg, 71 %).

1H NMR (300 MHz, CDCl₃) δ 1.42-1.56 (m, 1H), 1.81-2.06 (m, 3H), 2.56-2.71 (m, 4H), 2.93 (dd, J = 15.7, 7.4 Hz, 1H), 3.40 (dd, J = 14.2, 9.3 Hz, 1H), 3.69-3.95 (m, 5H), 4.13-4.32 (m, 4H), 5.02 (d, J = 4.4 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.6 Hz, 1H), 7.32 (d, J = 8.7 Hz, 2H).
EXAMPLE 153. [4-(4-iodoethoxy)phenyl]methyl (4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[2R]-tetrahydrofuran-2-yl][methyl]-3,4-dihydropyridine-5-carbonyl]oxymethyl]phenoxyethanesulfonate and [4-(2-iodoethoxy)phenyl]methyl (4R)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[2S]-tetrahydrofuran-2-yl][methyl]-3,4-dihydropyridine-5-carbonylate.

The previous compound (164 mg, 0.32 mmol) was dissolved in butanone (1.5 mL). NaI (189 mg, 1.26 mmol) was added and the reaction mixture stirred at 80 °C for 32 h. The solution was cooled to RT and then filtered. The solvent was removed under reduced pressure to afford yellowish oil. This residue was purified by flash chromatography (Cy/CH₂Cl₂ 1/1 to CH₂Cl₂) to give the desired product as white powder (m = 130 mg, 67%).

1H NMR (300 MHz, CDCl₃) δ 1.36-1.41 (m, 1H), 1.80-2.03 (m, 3H), 2.55-2.69 (m, 4H), 2.92 (dd, J = 15.7, 7.5 Hz, 1H), 3.35-3.48 (m, 3H), 3.67-3.78 (m, 1H), 3.78-3.91 (m, 2H), 4.12-4.29 (m, 4H), 5.00 (d, J = 4.2 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 7.06 (d, J = 8.7 Hz, 2H), 7.14 (d, J = 8.3 Hz, 1H), 7.56 (dd, J = 8.3, 2.6 Hz, 1H), 8.22 (d, J = 2.3 Hz, 1H). 13C NMR (75 MHz, CDCl₃) δ 1.2, 17.2, 25.7, 29.2, 35.0, 38.7, 46.1, 66.0, 68.2, 68.7, 77.7, 109.1, 114.8, 124.1, 128.8, 129.8, 135.9, 137.9, 149.2, 150.0, 152.1, 157.9, 166.7, 168.4. MS [M+H]+ 611 g/mol.


The reaction mixture was dissolved in a mixture of iPrOH/water 1/1 (1 mL). Sodium sulfite (54 mg, 0.426 mmol) was added and the reaction mixture was stirred under reflux for 48 h. The solvents were removed under reduced pressure. Purification on the crude by HPLC (basic conditions) gave the ammonium,2-[4-[[4S]-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[2R]-tetrahydrofuran-2-yl][methyl]-3,4-dihydropyridine-5-carbonyl]oxymethyl]phenoxyl]ethanesulfonate as a white powder (m = 30 mg, 24%).

1H NMR (300 MHz, CDCl₃) δ 1.35-1.55 (m, 1H), 1.77-2.04 (m, 3H), 2.50-2.65 (m, 4H), 2.83 (dd, J = 15.6, 7.5 Hz, 2H), 3.25-3.45 (m, 3H), 3.70 (dd, J = 14.5, 7.5 Hz, 1H), 3.77-3.91 (m, 2H), 4.04-4.36 (m, 4H), 4.83 (dd, J = 26.9, 12.1 Hz, 2H), 6.73 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 7.09 (d, J = 8.2 Hz, 4H), 7.56 (dd, J = 8.3, 2.4 Hz, 1H), 8.12 (d, J = 2.3 Hz, 1H). 13C NMR (75 MHz, CDCl₃) δ 17.2, 25.8, 29.3, 35.0, 38.6, 46.1, 58.1, 63.8, 66.0, 68.3, 77.7, 109.1, 114.9,
**EXAMPLE 154**

**Example 154a. Poly (ethylene glycol) methyl ether tosylate.**

The Poly(ethylene glycol) methyl ether (Sigma-Aldrich, ref 202487, average Mn=550, (1.06 mmol) was dissolved in dry THF (3 mL). The solution was cooled at 0°C. NaH (56 mg, 60% in oil, 1.59 mmol) was added and the reaction mixture was stirred at 0°C to 20 °C for 2 h. the 4-methylbenzenesulfonyl chloride (403 mg, 2.12 mmol) was added at 0°C and the reaction mixture was stirred at RT. for 24 hours.

The solvent was evaporated and the residue was purified by flash chromatography (CH$_2$Cl$_2$ to CH$_2$Cl$_2$/MeOH 94/6) to give 497 mg of colorless oil corresponding to the expected product (m = 497 mg, 75%).

$^1$H NMR (300 MHz, CDCl$_3$) δ 2.36 (s, 3H), 3.28 (s, 3H), 3.39-3.69 (m, 42H), 4.01-4.10 (m, 2H), 7.26 (d, J = 7.9 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 21.5, 58.9, 68.5, 69.2, 70.3, 70.4, 70.6, 71.8, 127.8, 129.7, 132.9, 144.6. MS [M+NH$_4$]$^+$ 688 g/mol.

**Example 154b. 1-(Methanol)-4-[poly (ethylene glycol) methyl ether] benzene**

The poly (ethylene glycol) methyl ether tosylate (0.48 mmol, 300 mg) was dissolved in dry MeCN (3 mL), the 4-(hydroxymethyl) phenol (0.72 mmol, 89 mg) and K$_2$CO$_3$ (0.72 mmol, 99 mg) were added. The reaction mixture was stirred overnight under reflux. After being cooled down, the mixture was filtered. The filtrate was concentrated under vacuum and purified by flash chromatography (CH$_2$Cl$_2$/MeOH 97/3) to give the product as oil (m = 122 mg, 44%).
Example 154c. 1-(Chloromethyl)-4-[poly (ethylene glycol) methyl ether] benzene.

Thionyl chloride (0.26 mmol, 0.02 mL) was added to benzotriazole (0.26 mmol, 31 mg). The resulting mixture was dissolved in dry CH₂Cl₂ (1 mL). After 5 min, this solution was added slowly to a solution of the benzyl alcohol in CH₂Cl₂ (5 mL). The benzotriazole salt started to precipitate. After 1 h of reaction, the reaction mixture was quenched by addition of MgSO₄·7H₂O and then filtered. The solvent was removed under reduced pressure to afford yellow oil (m = 125 mg, 99%). ¹H NMR (300 MHz, CDCl₃) δ 3.30 (s, 3H), 3.42-3.68 (m, 36H), 3.73-3.81 (m, 2H), 4.00-4.09 (m, 2H), 4.48 (s, 2H), 6.81 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H).

EXAMPLE 154 [4-[(Poly (ethylene glycol) methyl ether)]phenyl]methyl (4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1 -[[2R]-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and [4-[(poly (ethylene glycol) methyl ether)]phenyl]methyl (4R)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1 -[[2S]-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate (mixture m=7:1).

The chlorinated compound 1-(Chloromethyl)-4-[poly (ethylene glycol) methyl ether] benzene (117 mg, 0.20 mmol) and the acid (69 mg, 0.20 mmol) were dissolved in dry DMF (2 mL). Cesium carbonate (64 mg, 0.20 mmol) and NaI (1.5 mg, 0.01 mmol) were added and the reaction mixture stirred at RT for 18h. Reaction stopped by addition of water. Solvent was removed under reduced pressure. The residue was extracted by EtOAc and the organics layers were washed by a solution of saturated NaCl, dried over Na₂SO₄ and the solvent was removed to give a crude product. Purification by flash chromatography (CH₂Cl₂/MEOH 100/0 to 80/20) then, by HPLC (basic conditions) give the expected product as white powder (m = 63 mg, 35%).

¹H NMR (300 MHz, CDCl₃) δ 1.38-1.54 (m, 1H), 1.80-2.04 (m, 3H), 2.36 (s, 1H), 2.53-2.70 (m, 4H), 2.91 (dd, J = 15.8, 7.5 Hz, 1H), 3.31-3.44 (m, 4H), 3.47-3.56 (m, 2H), 3.56-3.76 (m, 33H), 3.78-3.93 (m, 5H), 4.04-4.13 (m, 2H), 4.13-4.29 (m, 2H), 4.99 (q, J = 12.2 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 8.6 Hz, 2H), 7.13 (d, J = 8.3 Hz, 1H), 7.54 (dd, J = 8.3, 2.6 Hz, 1H), 8.22 (d, J = 2.5 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 17.2, 25.7, 29.2, 35.0, 38.7, 46.1, 59.1, 66.2, 67.5, 68.2, 69.7, 70.6, 70.6, 70.7, 70.7, 70.9, 72.0, 77.7, 109.2, 114.6, 124.1, 128.2, 129.7, 135.9, 138.0, 149.2, 150.0, 152.0, 158.8, 166.7, 168.4. MS [M+NH₄]+ 928 g/mol.

EXAMPLE 155
Example 155a. 1-(Methanol)-4-[poly (ethylene glycol) methyl ether] benzene (mixture m=18-23).

The poly(ethylene glycol) methyl ether tosylate (Sigma-Aldrich, ref 7291 16, average Mn = 900, 1.12 mmol) was dissolved in acetonitrile (4 mL), the 4-(hydroxymethyl)phenol (209 mg, 1.68 mmol) and K₂CO₃ (233 mg, 1.68 mmol) were added. The mixture was stirred overnight under reflux. The reaction became pink and after being cooled down, it has been filtered. The filtrate has been concentrated under vacuum and purified by flash chromatography (CH₂Cl₂/MeOH : 100/0 to 97/3) to give the expected product as oil (900 mg, 95%). ¹H NMR (300 MHz, CDCl₃) δ 3.31 (s, 3H), 3.44-3.70 (m, 100H), 3.75-3.85 (m, 3H), 4.01-4.11 (m, 2H), 4.52 (s, 2H), 6.83 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 8.6 Hz, 2H).

Example 155b. 1-(Chloromethyl)-4-[poly (ethylene glycol) methyl ether] benzene (mixture m=18-23).

In dry CH₂Cl₂ (1 mL), thionyl chloride (0.01 mL, 0.19 mmol) and benzotriazole (22 mg, 0.19 mmol) were added. The resulting mixture was stirred 5 min, this solution was added slowly to a solution of the 1-(Methanol)-4-[poly (ethylene glycol) methyl ether] benzene in CH₂Cl₂ (9 mL). The benzotriazole salt started to precipitate. After 1 h of reaction, the reaction mixture was quenched by addition of MgSO₄·7H₂O and then filtered. The solvent was removed under reduced pressure to afford yellow oil (quantitative).

**EXAMPLE 155:** [4-((Poly (ethylene glycol) methyl ether)]phenyl)methyl (4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1 -[[[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and [4-((poly (ethylene glycol) methyl ether)]phenyl)methyl (4R)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1 -[[[2S]-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate (mixture m=18-23).

The chlorinated compound 155b (127 mg, 0.15 mmol) and the acid (67 mg, 0.19 mmol) were dissolved in dry DMF (2 mL). Cesium carbonate (63 mg, 0.19 mmol) and Nal (1.1 mg, 0.01
mmol) were added and the reaction mixture was stirred at room temperature for 18h. Reaction stopped by addition of water. Solvent was removed under reduced pressure and the residue was extracted by EtOAc. The organics layers were washed by a solution of saturated NaCl, dried over Na₂SO₄, filtered and the solvent was removed to give the crude product. Purification by HPLC (acid conditions) gives the expected mixture of products (n=18-23) as oil (28 mg, 14 %). 

1H NMR (300 MHz, CDCl₃) δ 1.38-1.52 (m, 1H), 1.80-2.04 (m, 3H), 2.51-2.71 (m, 4H), 2.92 (dd, J = 15.7, 7.4 Hz, 1H), 3.31-3.45 (m, 5H), 3.50-3.78 (m, 9H), 3.78-3.93 (m, 5H), 4.04-4.14 (m, 2H), 4.13-4.29 (m, 2H), 4.99 (q, J = 12.1 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.3 Hz, 1H), 7.55 (dd, J = 8.3, 2.6 Hz, 1H), 8.23 (d, J = 2.6 Hz, 1H). 

13C NMR (75 MHz, CDCl₃) δ 17.3, 25.7, 29.3, 35.0, 38.7, 46.1, 59.1, 66.2, 67.5, 68.3, 69.8, 70.6, 70.7, 70.9, 72.0, 77.4, 77.7, 109.2, 114.6, 124.2, 128.2, 129.7, 135.9, 138.0, 149.2, 150.0, 152.0, 158.8, 166.7, 168.5. MS [M+NH₄⁺] + 1412 g/mol.

Example 156

Example 156a. 1-(Methanol)-4-[poly (ethylene glycol) methyl ether] benzene.

The poly (ethylene glycol) methyl ether tosylate (sigma-Aldrich, ref 729124, average Mn=2000) (1 g, 0.48 mmol) was dissolved in MeCN (4 mL). The 4-(hydroxymethyl) phenol (89 mg, 0.72 mmol) and K₂CO₃ (100 mg, 0.72 mmol) were added. The reaction mixture was stirred overnight under reflux. After being cooled down, the mixture was filtered. The filtrate was concentrated under vacuum and purified by flash chromatography (CH₂Cl₂/MeOH 97/3) to give the expected product (m = 778 mg, 80 %).

1H NMR (300 MHz, CDCl₃) δ 3.33-3.42 (m, 6H), 3.48-3.79 (m, 164H), 3.80-3.92 (m, 4H), 4.07-4.15 (m, 2H), 4.59 (s, 2H), 6.88 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H). 

13C NMR (75 MHz, CDCl₃) δ 59.1, 67.6, 69.8, 70.6, 70.7, 70.9, 72.0, 114.8, 128.7.

Example 156b. 1-(Chloromethyl)-4-[poly (ethylene glycol) methyl ether] benzene.

Thionyl chloride (0.03 mL, 0.46 mmol) was added to benzotriazole (55 mg, 0.46 mmol). The resulting yellow solution was dissolved in dry CH₂Cl₂ (2 mL). After 5 min, this solution was added slowly to a solution of the 1-(Methanol)-4-[poly (ethylene glycol) methyl ether] benzene
(750 mg, 0.37 mmol) in CH₂Cl₂ (10 mL). The benzotriazole salt started to precipitate. After 1 h of reaction, the mixture was quenched by addition of MgSO₄·7H₂O and then filtered. The solvents were removed under reduced pressure to afford the desired compound as yellow oil (m = 756 mg, 100%).

**EXAMPLE 156**: [4-((Poly (ethylene glycol) methyl ether)]phenyl)methyl (4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[2R]-tetrahydrofuran-2-yl)methyl]-3,4-dihydropyridine-5-carboxylate and [4-((poly (ethylene glycol) methyl ether)]phenyl)methyl (4R)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[2S]-tetrahydrofuran-2-yl)methyl]-3,4-dihydropyridine-5-carboxylate.

1-(Methanol)-4-[poly (ethylene glycol) methyl ether] benzene (156b, 680 mg, 0.33 mmol) and the acid 153c (158 mg, 0.43 mmol) were dissolved in dry DMF (4 mL). Cesium carbonate (140 mg, 0.43 mmol) and NaI (2.5 mg, 0.02 mmol) were added and the reaction mixture stirred at RT for 18 h. Reaction stopped by addition of water. Solvent was removed under reduced pressure. The residue was extracted by EtOAc and the organics layers were washed by a solution of saturated NaCl, dried over Na₂SO₄ and the solvent was removed to give a crude product. Purification by HPLC (acid conditions) give the expected product as white powder (m = 60 mg, 8%).

**EXAMPLE 157**

$^1$H NMR (300 MHz, CDCl₃) δ 3.17-3.28 (m, 6H), 3.33-3.66 (m, 163H), 3.66-3.76 (m, 4H), 3.92-4.02 (m, 2H), 4.40 (s, 2H), 6.73 (d, $J = 8.6$ Hz, 2H), 7.13 (d, $J = 8.6$ Hz, 2H).

$^1$H NMR (300 MHz, CDCl₃) δ 1.35-1.52 (m, 1H), 1.78-2.00 (m, 3H), 2.53-2.72 (m, 5H), 2.90 (dd, $J = 15.7$, 7.5 Hz, 1H), 3.28-3.44 (m, 5H), 3.44-3.92 (m, 159H), 4.01-4.11 (m, 2H), 4.12-4.29 (m, 2H), 4.87-5.06 (m, 2H), 6.79 (d, $J = 8.7$ Hz, 2H), 7.03 (d, $J = 8.7$ Hz, 2H), 7.12 (d, $J = 8.2$ Hz, 1H), 7.53 (dd, $J = 8.3$, 2.6 Hz, 1H), 8.21 (d, $J = 2.5$ Hz, 1H). $^{13}$C NMR (75 MHz, CDCl₃) δ 17.2, 25.6, 29.2, 34.9, 38.7, 46.0, 59.1, 66.1, 67.5, 68.2, 69.7, 70.5, 70.6, 70.8, 72.0, 77.6, 109.1, 114.7, 124.1, 128.2, 129.6, 135.9, 137.9, 149.1, 149.9, 152.0, 158.8, 166.7, 168.4. MS [M/2+NH₄]⁺ 1134 g/mol.
Example 157a. 1-(Methanol)-2-[poly (ethylene glycol) methyl ether] benzene.

The poly(ethylene glycol) methyl ether tosylate 154a (564 mg, 0.9 mmol) was dissolved in MeCN (3 mL), the 2-(hydroxymethyl)phenol (168 mg, 1.35 mmol) and K₂CO₃ (187 mg, 1.35 mmol) were added. The reaction mixture was stirred overnight under reflux. After being cooled down, it has been filtered. The filtrate has been concentrated under vacuum and purified by flash chromatography (CH₂Cl₂/MeOH: 100/0 to 97/3) to give the expected product as oil (460 mg, 77%). ¹H NMR (300 MHz, CDCl₃) δ 3.29 (s, 3H), 3.40-3.65 (m, 45H), 3.76 (dd, J = 5.4, 3.8 Hz, 2H), 4.10 (dd, J = 5.4, 3.8 Hz, 2H), 4.58 (s, 2H), 6.79 (d, J = 8.1 Hz, 1H), 6.85 (td, J = 7.5, 0.9 Hz, 1H), 7.10-7.25 (m, 2H). MS [M+NH₄]⁺ 684 g/mol.

Example 157b. 1-(Chloromethyl)-2-[poly (ethylene glycol) methyl ether] benzene.

In dry CH₂Cl₂ (3 mL), thionyl chloride (0.02 mL, 0.34 mmol) and benzotriazole (40 mg, 0.34 mmol) were added. The resulting mixture was stirred 5 min, this solution was added slowly to a solution of the alcohol Example 157a. (MMPEG = 550 g/mol) in CH₂Cl₂ (15 mL). The benzotriazole salt started to precipitate. After 1 h of reaction, the reaction mixture was quenched by addition of MgSO₄/7H₂O and then filtered. The solvent was removed under reduced pressure to afford a yellow oil (quantitative).

EXAMPLE 157: [2-[(Poly (ethylene glycol) methyl ether)]phenyl]methyl (4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and [2-[(poly (ethylene glycol) methyl ether)]phenyl]methyl (4R)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[(2S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate (mixture m=10-14).

Example 157b (152 mg, 0.25 mmol) and the acid 153c (98 mg, 0.28 mmol) were dissolved in dry DMF (3 mL). Cesium carbonate (108 mg, 0.33 mmol) and NaI (2 mg, 0.01 mmol) were added and the mixture stirred at room temperature for 18 h. Reaction stopped by addition of water. DMF was removed under reduced pressure. The residue was extracted by
EtOAc and the organics layers were washed by a solution of saturated NaCl, dried over Na₂SO₄, filtered and the solvent was removed. Purification by preparative HPLC gives the expected compound (mixture of products (m=10-14) as oil (45 mg, 17 %). ¹H NMR (300 MHz, CDCl₃) δ 1.36-1.55 (m, 1H), 1.80-2.04 (m, 3H), 2.54-2.72 (m, 4H), 2.93 (dd, J = 15.7, 7.5 Hz, 1H), 3.32-3.46 (m, 4H), 3.48-3.57 (m, 2H), 3.57-3.70 (m, 46H), 3.70-3.80 (m, 3H), 3.80-3.92 (m, 2H), 3.97-4.13 (m, 2H), 4.18-4.31 (m, 2H), 5.13 (s, 2H), 6.80-6.90 (m, 2H), 6.99 (dd, J = 7.5, 1.7 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H), 7.18-7.25 (m, 1H), 7.56 (dd, J = 8.3, 2.6 Hz, 1H), 8.21 (d, J = 2.6 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 17.2, 25.7, 29.3, 35.0, 38.7, 46.1, 59.1, 61.9, 67.8, 68.3, 69.7, 70.6, 70.7, 70.9, 72.0, 77.4, 77.7, 109.4, 111.6, 120.7, 124.1, 124.5, 129.2, 129.5, 136.0, 138.0, 149.2, 149.9, 151.8, 156.6, 166.7, 168.5. MS [M+H]⁺ 1043 g/mol.

EXAMPLE 158

Example 158a. [2-(2-Chloroethoxy)phenyl]methanol
The 1-bromo-2-chloro-ethane (0.33 mL, 4.03 mmol), 2-(hydroxymethyl)phenol (500 mg, 4.03 mmol) and potassium carbonate (557 mg, 4.03 mmol) were assembled in acetonitrile and the reaction mixture was stirred overnight at reflux. 4 eq. of bromide compound (1.34 mL) and K₂CO₃ (2.23 g) were added and the reaction mixture was stirred at reflux overnight again. End of the reaction. The solvent was removed under reduced pressure and water was added, aqueous phase was extracted with EtOAc, then the organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure. The crude was purified by flash chromatography on Silica gel using as eluant a mixture of Cy/EtOAc (100/0 to 70/30) to give the expected product as a yellow oil (m = 500 mg, 66 %). ¹H NMR (300 MHz, CDCl₃) δ 2.76 (s, 1H), 3.78-3.92 (m, 2H), 4.21-4.30 (m, 2H), 4.71 (s, 2H), 6.85 (d, J = 8.2 Hz, 1H), 6.99 (td, J = 7.5, 1.0 Hz, 1H), 7.23-7.35 (m, 2H).
Example 158b. 1-(2-Chloroethoxy)-2-(chloromethyl)benzene.

In dry CH₂Cl₂ (5 mL), thionyl chloride (0.15 mL, 2.01 mmol) and benzotriazole (287 mg, 2.41 mmol) were added. The resulting mixture was stirred 5 min, this solution was added slowly to a solution of the alcohol 158a in CH₂Cl₂ (10 mL). The benzotriazole salt started to precipitate. After 20 min of reaction, the salt was filtered. The organic phase was washed with water (10 mL) and NaOH solution (0.05 M, 10 mL). The organic phase was dried on Na₂SO₄ and the solvent was removed under reduced pressure to give the desired chlorinated compound as colorless oil (300 mg, 91 %). ¹H NMR (300 MHz, CDCl₃) δ 3.86 (t, J = 5.8 Hz, 2H), 4.30 (t, J = 5.8 Hz, 2H), 4.70 (s, 2H), 6.88 (d, J = 8.2 Hz, 1H), 7.00 (td, J = 7.5, 1.0 Hz, 1H), 7.27-7.35 (m, 1H), 7.39 (dd, J = 7.5, 1.6 Hz, 1H).

Example 158c. [2-(2-Chloroethoxy)phenyl]methyl (4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxy late and [2-(2-chloroethoxy)phenyl]methyl (4R)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[(2S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.

The acid 153c (93 mg, 0.27 mmol) and cesium carbonate (95 mg, 0.29 mmol) were dissolved in dry DMF (2 mL). Compound example 158b (60 mg, 0.29 mmol) was added. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and washed with water. The aqueous phase was extracted by EtOAc. The organic layers were assembled, washed with brine and dried with Na₂SO₄. The residue was purified by flash chromatography (Cy/CH₂Cl₂: 50/50 to 0/100) to afford the desired product as a colorless oil (m = 112 mg, 81 %). MS [M+H]⁺ 519 g/mol.


Example 158c (200 mg, 0.39 mmol) was dissolved in butanone (3 mL). NaI (231 mg, 1.54 mmol) was added and the reaction mixture stirred at 80 °C overnight. The solution was cooled to room temperature, filtered and washed with acetone. The solvents were removed under reduced pressure to afford yellowish oil. This residue was purified by flash chromatography (Cy/CH₂Cl₂: 50/50 to 0/100) to give the desired product as oil (m = 204 mg, 87%). ¹H NMR (300 MHz, CDCl₃) δ 1.34-1.50 (m, 1H), 1.77-2.02 (m, 3H), 2.54-2.67 (m, 4H), 2.91 (dd, J = 15.8, 7.5 Hz, 1H), 3.25-3.45 (m, 3H), 3.64-3.78 (m, 1H), 3.78-3.92 (m, 2H), 4.08-4.27 (m, 4H), 5.15 (q, J = 12.6 Hz, 2H), 6.74 (d, J = 7.7 Hz, 1H), 6.85 (td, J = 7.5, 0.9 Hz, 1H), 7.02 (dd, J = 7.5, 1.7 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 7.17-7.25 (m, 1H), 7.55 (dd, J = 8.3, 2.6 Hz, 1H), 8.19 (d, J = 2.5 Hz, 1H). MS [M+H]⁺ 519 g/mol.

The compound 158d (200 mg, 0.33 mmol) was dissolved in a mixture of iPrOH/water 1/1 (2 mL). Sodium sulfite (83 mg, 0.65 mmol) was added and the reaction mixture was heated at 80 °C in sealed tube for 18 h. The solvents were removed under reduced pressure. Water was added and the aqueous phase was washed with brine and dried over Na₂SO₄. The solvent was removed. Purification of the crude by HPLC (basic conditions) gave the expected product as a white powder (m = 112 mg, 59 %). ¹H NMR (300 MHz, CDCl₃) δ: 1.39-1.45 (m, 1H), 1.74-2.05 (m, 3H), 2.49-2.67 (m, 4H), 2.87 (dd, J = 15.6, 7.3 Hz, 1H), 3.27 (t, J = 6.8 Hz, 2H), 3.31-3.43 (m, 1H), 3.70 (dd, J = 14.4, 7.5 Hz, 1H), 3.76-3.90 (m, 2H), 4.16 (d, J = 10.7 Hz, 2H), 4.25 (t, J = 6.8 Hz, 2H), 5.06 (s, 2H), 6.77 (dd, J = 16.3, 8.1 Hz, 2H), 6.88-6.96 (m, 1H), 7.07-7.40 (m, 6H), 7.56 (dd, J = 8.3, 2.5 Hz, 1H), 8.28 (d, J = 2.5 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ: 17.2, 25.7, 29.3, 34.9, 38.6, 46.1, 50.8, 61.9, 63.9, 68.3, 77.7, 109.1, 111.9, 120.9, 124.4, 124.5, 129.2, 129.6, 136.6, 138.6, 149.0, 149.3, 152.3, 156.1, 167.0, 168.6. MS [M+H]^+ 565 g/mol.

EXAMPLE 159

Example 159a. Methyl-(4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[2S]-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and methyl (4R)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[2R]-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.

The methyl 4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-3,4-dihydropyridine-5-carboxylate 153a (600 mg, 2.14 mmol) and the 2-(bromomethyl)tetrahydrofuran (0.5 mL, 4.27 mmol) were dissolved in dry DMF (5 mL), Cs₂CO₃ (1.4 g, 4.28 mmol) and NaI (16 mg, 0.11 mmol) were added and the reaction mixture was stirred at 50°C overnight. The solvent was removed under reduced pressure. Water was added and the aqueous phase was extracted by ethyl acetate, the organic layers were washed with brine and dried over Na₂SO₄. The solvent was removed. The residue was dissolved again in 5 mL of DMF, 1.4 g of Cs₂CO₃, 16 mg of NaI and the alkyl bromide (0.5 mL) were added and the mixture was stirred at 50°C for 18 h. Reaction finished. The solvent was removed under reduced pressure. Water was added and the aqueous phase
Example 159b. (4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[(2S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylic acid and (4R)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylic acid.

The ester 159a (300 mg, 0.82 mmol) was dissolved in MeOH (5 mL), NaOH 1N (3 mL) was added. The reaction mixture was stirred overnight at 40 °C. The MeOH was evaporated under reduced pressure and the aqueous phase was extracted by Et₂O, then acidified to pH = 1 with HCl (1N). The aqueous phase was extracted by EtOAc and the organic layers were assembled and dried under Na₂SO₄. The solvent was removed under reduced pressure to afford a product as oil (m = 200 mg, 69 %). ¹H NMR (300 MHz, CDCl₃) δ 1.20-1.34 (m, 1H), 1.72-1.92 (m, 3H), 2.60 (s, 3H), 2.76 (dd, J = 16.1, 2.0 Hz, 1H), 2.93 (dd, J = 16.1, 7.4 Hz, 1H), 3.58-3.84 (m, 3H), 3.89-4.02 (m, 2H), 4.19 (d, J = 6.6 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 7.51 (dd, J = 8.3, 2.6 Hz, 1H), 8.21 (d, J = 2.5 Hz, 1H), 10.53 (s, 1H). MS [M+H]+ 351 g/mol.

Example 159. (2-Methoxyphenyl)methyl-(4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[(2S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and (2-methoxyphenyl)methyl-(4R)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.

The 1-(chloromethyl)-2-methoxy-benzene (98 mg, 0.63 mmol) and the acid 159b (200 mg, 0.57 mmol) were dissolved in dry DMF (2 mL). Cesium carbonate (279 mg, 0.86 mmol) was added and the reaction mixture was stirred at r.t. overnight. The solvent was removed and the aqueous phase was extracted by Et₂O, washed with brine and dried under MgSO₄. After filtration the solvent was removed and the crude product was purified by column chromatography on silica gel (Cy/AcO Et 100 to 80/20) to give the expected product as white solid (110 mg, 41 %). ¹H NMR (300 MHz, CDCl₃) δ 1.15-1.40 (m, 1H), 1.73-1.96 (m, 3H), 2.61 (s, 3H), 2.73 (dd, J = 16.0, 2.3 Hz, 1H), 2.95 (dd, J = 16.0, 7.6 Hz, 1H), 3.62-3.89 (m, 6H), 3.92-4.07 (m, 2H), 4.20 (d, J = 6.1 Hz, 1H), 5.14 (q, J = 12.4 Hz, 2H), 6.80-6.92 (m, 2H), 7.08-7.20 (m, 2H), 7.23-7.32 (m, 1H), 7.47 (ddd, J = 8.3, 2.6, 0.5 Hz, 1H), 8.16 (d, J = 2.6 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 17.4, 25.4, 29.2, 34.5, 38.1, 45.3, 55.3, 62.3, 67.9, 77.3, 109.9, 110.5.
Example 160. [4-([Poly (ethylene glycol) methyl ether])phenyl]methyl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2R]-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and [4-([poly (ethylene glycol) methyl ether])phenyl]methyl (4R)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2S]-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate. (m=1 1-18)

The 1-(Chloromethyl)-4-[poly (ethylene glycol) methyl ether] benzene. (MMpeg = 900 g/mol) 155b (225 mg, 0.26 mmol) and the acid 135 (119 mg, 0.34 mmol) were dissolved in dry DMF (4 ml). Cesium carbonate (111 mg, 0.34 mmol) and NaI (2.0 mg, 0.01 mmol) were added and the reaction mixture was stirred at room temperature for 18h. Reaction stopped by addition of water. Solvent was removed under reduced pressure. The residue was extracted by EtOAc and the organics layers were washed by a solution of saturated NaCl, dried over MgSO₄, filtered and the solvent was removed to give the crude product. Purification by HPLC (acid conditions) gives the expected product as oil (m = 139 mg, 44 %). ¹H NMR (300 MHz, CDCl₃) δ 1.30-1.49 (m, 1H), 1.71-1.95 (m, 3H), 2.52-2.67 (m, 5H), 2.84 (dd, J = 15.6, 7.4 Hz, 1H), 3.31-3.41 (m, 4H), 3.48-3.53 (m, 2H), 3.55-3.71 (m, 6H), 4.02-4.09 (m, 2H), 4.12 (d, J = 5.8 Hz, 1H), 4.19 (dd, J = 14.3, 3.2 Hz, 1H), 4.96 (s, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 7.07-7.20 (m, 4H). ¹³C NMR (75 MHz, CDCl₃) δ 17.1, 25.5, 29.2, 37.0, 39.0, 45.6, 59.0, 65.8, 67.4, 68.1, 69.7, 70.5, 70.5, 70.6, 70.8, 71.9, 77.8, 110.2, 114.4, 123.3, 128.3, 128.6, 128.7, 129.4, 132.4, 139.5, 151.1, 158.6, 167.0, 168.9. MS [M+NH₄]⁺ 1059 g/mol. [n=11 (11%), n=12 (21%), n=13 (24%), n=14 (23%), n=15 (22%), n=16 (15%), n=17 (9%), n=18 (7%)].
Example 161. [4-((Poly (ethylene glycol) methyl ether)]phenyl)methyl (4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and [4-((poly (ethylene glycol) methyl ether)]phenyl)methyl (4R)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[(2S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate. (m=38-48).

The 1-(Chloromethyl)-4-[poly (ethylene glycol) methyl ether] benzene (MMpeg = 2000 g/mol) 156b (580 mg, 0.28 mmol) and the acid 135 (128 mg, 0.37 mmol) were dissolved in dry DMF (4 ml). Cesium carbonate (120 mg, 0.37 mmol) and Nal (2 mg, 0.05 mmol) were added and the reaction mixture stirred at r.t. for 18h. Reaction stopped by addition of water. Solvent was removed under reduced pressure. The residue was extracted by EtOAc and the organics layers were washed by a solution of saturated NaCl, dried over MgSO4 and the solvent was removed to give a crude product. Purification by HPLC (acid conditions) gives the expected product as oil (m = 115 mg, 18 %). 1H NMR (300 MHz, CDCl3) δ 1.40-1.50 (m, 1H), 1.85-1.95 (m, 3H), 2.59 (s, 3H), 2.67 (dd, J = 15.6, 2.3 Hz, 1H), 2.88 (dd, J = 15.7, 7.3 Hz, 1H), 3.30-3.47 (m, 5H), 3.49-3.95 (m, 190H), 4.05-4.18 (m, 3H), 4.23 (dd, J = 14.2, 3.3 Hz, 1H), 5.00 (s, 2H), 6.79 (d, J = 8.7 Hz, 2H), 7.02 (d, J = 8.7 Hz, 2H), 7.1 1-7.22 (m, 4H). 13C NMR (75 MHz, CDCl3) δ 17.0, 25.4, 29.1, 36.9, 38.9, 45.5, 51.8, 63.4, 65.7, 67.3, 68.0, 68.9, 69.5, 70.4, 71.2, 71.8, 72.7, 73.6, 77.4, 81.9, 88.9, 110.1, 114.3, 128.2, 128.5, 128.6, 129.2, 132.3, 139.4, 151.0, 158.4, 166.9, 168.8. MS [M+2H]2+ 806 g/mol. Mixture of compounds containing PEG chains ranging from n = 38 to n = 48 (centered in: n = 43).

EXAMPLE 162
Example 162a. [(2S)-Tetrahydrofuran-2-yl)methanol.

(2S)-Tetrahydrofuran-2-carboxylic acid (2 g, 17.22 mmol) was dissolved in 20 mL of THF under argon and the flask was cooled in an ice bath. BH₃·SMes₂ (2M solution in THF, 10 mL, 20.0 mmol) was added to the reaction solution over 10 minutes. The ice bath was removed and the solution was stirred for 1 h at room temperature. The solution was again cooled in an ice bath and methanol was slowly added until no gas evolution was observed then the solution was concentrated under vacuum to give the desired product as oil (m = 1.7 g, 99%). ¹H NMR (300 MHz, CDCl₃) δ 1.44-1.63 (m, 1H), 1.69-1.88 (m, 3H), 3.23-3.44 (m, 1H), 3.51 (dd, J = 11.6, 3.5 Hz, 1H), 3.59-3.82 (m, 3H), 3.83-3.96 (m, 1H).

Example 162b. (2S)-2-(Iodomethyl)tetrahydrofuran.

The mixture of triethylamine (1.65 mL, 11.75 mmol), TsCl (1.64 g, 8.62 mmol) and 48 mg of DMAP were combined in CH₂Cl₂ (25 mL). This solution was cooled in an ice bath and to it was added a solution of tetrahydrofurfuryl alcohol 162a (800 mg, 7.83 mmol) in 10 mL of CH₂Cl₂ over 20 min. The reaction stirred for 3 h and was then concentrated in vacuum, the residue was taken up in ethyl acetate and then washed 2 times with a saturated solution of NaHCO₃ and once with a saturated solution of NaCl. The organic layers were dried over MgSO₄, filtered and concentrated in vacuum. Lil (3.1 g, 23.41 mmol) was dried under vacuum for 30 min. then added to a solution of [(2S)-tetrahydrofuran-2-yl]methyl 4-methylbenzenesulfonate (2 g, 7.8 mmol) in 40 mL of acetone, the mixture was refluxed for 24 h and cooled to room temperature.
The mixture was filtered and concentrated in vacuum to give brown oil. This oil was taken up in Et₂O and washed with water. The organic layer was dried over MgSO₄, filtered and concentrated in vacuum to give the product as brown oil (m = 1.24 g, 75%). ¹H NMR (300 MHz, CDCl₃) δ 1.52-1.70 (m, 1H), 1.78-1.99 (m, 2H), 2.00-2.13 (m, 1H), 3.05-3.28 (m, 2H), 3.70-3.80 (m, 1H), 3.85-3.95 (m, 2H).

Example 162c1. Methyl (4R)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[(2S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and Methyl (4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[(2S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.

The methyl 4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-carboxylate 153a (200 mg, 0.71 mmol) and the (2S)-2-(iodomethyl)tetrahydrofuran 162b (302 mg, 1.42 mmol) were dissolved in dry DMF (3 mL), (464 mg, 1.42 mmol) of Cs₂CO₃ and (5 mg, 0.04 mmol) of NaI were added and the reaction mixture was stirred at 50°C overnight. Little formation of product was observed by TLC and LCMS. The solvent was removed under reduced pressure.

Water was added and the aqueous phase was extracted by ethyl acetate, the organic layers were washed with brine, and dried over MgSO₄, filtered and concentrated in vacuum. The crude was dissolved again in 3 mL of DMF, 464 mg of Cs₂CO₃, 5 mg of NaI and the alkyl iodide (300 mg) were added and the mixture was stirred at 50°C for 18 h. Reaction finished. The solvent was removed under reduced pressure. Water was added and the aqueous phase was extracted by ethyl acetate, the organic layers were washed with brine, and dried over MgSO₄. The solvent was removed and the residue was purified by flash chromatography (CH₂Cl₂/CyHex: 100/0) and (MeOH/CH₂Cl₂: 0.5%) to give the desired products as oil (E1: m = 58 mg, 22%) (E2: m = 41 mg, 16%). MS [M+H]+ 365 g/mol.

Example 162c2. Methyl (4S)-4-(6-Chloro-3-pyridyl)-6-methyl-2-oxo-1-[(2S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylic acid.

The ester 162c1 (58 mg) was dissolved in MeOH (2 mL), a solution of NaOH 1 N (2 mL) was added. The reaction mixture was stirred overnight at 40°C. LCMS showed completion of the reaction. The MeOH was evaporated under reduced pressure, the aqueous phase was
extracted by Et$_2$O, then acidified to pH = 1 with a solution of HCl (1N). The aqueous phase was extracted by EtOAC. The organics layers were assembled and dried over MgSO$_4$, the solvent was removed under reduced pressure to afford a product as oil (m = 55 mg, 98%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.36-1.51 (m, 1H), 1.80-2.00 (m, 3H), 2.56-2.74 (m, 4H), 2.93 (dd, $J$ = 15.8, 7.3 Hz, 1H), 3.38 (dd, $J$ = 14.2, 9.3 Hz, 1H), 3.65-3.90 (m, 3H), 4.15-4.30 (m, 2H), 7.17 (d, $J$ = 8.3 Hz, 1H), 7.61 (dd, $J$ = 8.3, 2.6 Hz, 1H), 8.28 (d, $J$ = 2.4 Hz, 1H), 9.64 (s, 1H). MS [M+H]$^+$ 351 g/mol.

**Example 162.** (2-Methoxyphenyl)-methyl-(4R)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[(2S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.

The 1-(chloromethyl)-2-methoxy-benzene (27 mg, 0.17 mmol) and the acid 162d1 (55 mg, 0.16 mmol) were dissolved in dry DMF (2 mL). Cesium carbonate (77 mg, 0.24 mmol) was added and the reaction mixture was stirred at room temperature overnight. The solvent was removed. Water was added and the aqueous phase was extracted by Et$_2$O, washed with brine and dried over MgSO$_4$. After filtration the solvent was removed and the crude product was purified by Column chromatography on silica gel (CH$_2$Cl$_2$/MeOH : 100/0 to 99/1) to give the expected product as oil (m = 60 mg, 81 %). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.35-1.55 (m, 1H), 1.77-2.05 (m, 3H), 2.54-2.73 (m, 4H), 2.93 (dd, $J$ = 15.7, 7.5 Hz, 1H), 3.39 (dd, $J$ = 14.2, 9.2 Hz, 1H), 3.64-3.78 (m, 4H), 3.81-3.94 (m, 2H), 4.14-4.31 (m, 2H), 4.99-5.21 (m, 2H), 6.74-6.90 (m, 2H), 7.03 (dd, $J$ = 7.4, 1.6 Hz, 1H), 7.14 (d, $J$ = 8.3 Hz, 1H), 7.20-7.32 (m, 1H), 7.57 (dd, $J$ = 8.3, 2.6 Hz, 1H), 8.22 (d, $J$ = 2.5 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 17.2, 25.7, 29.3, 35.0, 38.7, 46.1, 55.3, 62.2, 68.3, 77.7, 109.4, 110.4, 120.3, 124.1, 129.6, 129.7, 136.0, 138.0, 149.2, 149.9, 151.8, 157.5, 166.8, 168.5. MS [M+H]$^+$ 471 g/mol.

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**EXAMPLE 163**

Example 162d2. (4S)-4-(6-Chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[(2S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate acid.

The ester 162c2 (40 mg) was dissolved in MeOH (2 mL), a solution of NaOH 1N (2 mL) was added. The reaction mixture was stirred overnight at 40 °C. LCMS showed completion of the reaction. The MeOH was evaporated under reduced pressure, the aqueous phase was...
extracted by Et<sub>2</sub>O, then acidified to pH = 1 with a solution of HCl (1N). The aqueous phase was extracted by EtOAC. The organics phases were assembled and dried over MgSO<sub>4</sub>, the solvents were removed under reduced pressure to afford a product as oil (quantitative). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.20-1.34 (m, 1H), 1.76-1.95 (m, 3H), 2.64 (s, 3H), 2.79 (dd, J = 16.1, 2.0 Hz, 1H), 2.96 (dd, J = 16.0, 7.4 Hz, 1H), 3.64-3.84 (m, 3H), 3.93-4.06 (m, 2H), 4.22 (d, J = 6.2 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 7.46-7.57 (m, 1H), 8.23 (d, J = 2.6 Hz, 1H), 9.55 (s, 1H). MS [M+H]<sup>+</sup> 351 g/mol.

**Example 163.** (2-Methoxyphenyl)methyl-(4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1 - [(2S)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.

The 1-(chloromethyl)-2-methoxy-benzene (19 mg, 0.12 mmol) and the acid 162d2 (38 mg, 0.11 mmol) were dissolved in dry DMF (2 mL). Cesium carbonate (53 mg, 0.16 mmol) was added and the reaction mixture was stirred at r.t. overnight. The solvent was removed. Water was added and the aqueous layer was extracted by Et<sub>2</sub>O, washed with brine and dried over MgSO<sub>4</sub>. After filtration the solvent was removed and the crude product was purified by Column chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH : 100/0 to 99/1) to give the expected product as oil (m = 28 mg, 55 %). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.19-1.41 (m, 1H), 1.78-1.98 (m, 3H), 2.62 (s, 3H), 2.73 (dd, J = 16.0, 2.3 Hz, 1H), 2.95 (dd, J = 16.0, 7.6 Hz, 1H), 3.62-3.88 (m, 6H), 3.93-4.05 (m, 2H), 4.21 (d, J = 6.2 Hz, 1H), 5.14 (q, J = 12.4 Hz, 2H), 6.77-6.94 (m, 2H), 7.04-7.19 (m, 2H), 7.28 (dt, J = 7.8, 1.4 Hz, 1H), 7.47 (dd, J = 8.3, 2.6 Hz, 1H), 8.17 (d, J = 2.6 Hz, 1H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 17.5, 25.4, 29.2, 34.5, 38.1, 45.3, 55.4, 62.3, 67.9, 77.3, 109.9, 110.5, 120.4, 124.0, 124.1, 129.9, 130.0, 136.1, 137.8, 149.0, 149.9, 151.0, 157.7, 166.8, 169.1. MS [M+H]<sup>+</sup> 351 g/mol.

**Example 164**
Example 164a. [(2R)-Tetrahydrofuran-2-yl]methanol.

(2R)-tetrahydrofuran-2-carboxylic acid (2 g, 17.22 mmol) was dissolved in 20 mL of THF under argon and the flask was cooled in an ice bath. BH₃·SMe₂ (2M solution in THF, 10 mL, 20.0 mmol) was added to the reaction solution over 10 minutes. The ice bath was removed and the solution was stirred for 1 h at room temperature. The solution was again cooled in an ice bath and methanol slowly added until no gas evolution was observed. The solution was concentrated in vacuum to give the desired product as oil (m = 1 g, 60 %). ¹H NMR (300 MHz, CDCl₃) δ 1.55-1.70 (m, 1H), 1.72-1.98 (m, 3H), 3.35-4.00 (m, 6H).

Example 164b. [(2R)-Tetrahydrofuran-2-yl]methyl 4-methylbenzenesulfonate.

The mixture of triethylamine (6.4 mL, 45.53 mmol), TsCl (6.4 g, 33.39 mmol) and 185 mg of DMAP were combined in CH₂Cl₂ (70 mL). this solution was cooled in an ice bath and to it was added a solution of tetrahydrofurfuryl alcohol 164a (3.1 g, 30.35 mmol) in 30 mL of CH₂Cl₂ over 20 min. the reaction stirred overnight and was then concentrated in vacuum, the residue was taken up in ethyl acetate and then washed 2 times with a saturated solution of NaHCO₃ and once with a brine. The organic layers were dried over MgSO₄, filtered and concentrated in vacuum. The crude product was purified by Column chromatography on silica gel (CH₂Cl₂/CyHex: 50/50) to give the expected product as oil (m = 5.6 g, 72 %). ¹H NMR (300 MHz, CDCl₃) δ 1.48-1.68 (m, 1H), 1.71-2.05 (m, 3H), 2.40 (s, 3H), 3.58-3.82 (m, 2H), 3.86-4.15 (m, 3H), 7.31 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.2 Hz, 2H). MS [M+H]⁺ 257 g/mol.
Example 164c1. Methyl-(4R)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-
[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate and and

Example 164c2. Methyl-(4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-
[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.

The methyl 4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-3,4-dihydro-1 H-pyridine-5-carboxylate 153a (400 mg, 1.42 mmol) and the (2R)-tetrahydrofuran-2-yl)methyl-4-methylbenzenesulfonate 164b (470 mg, 2.85 mmol) were dissolved in dry DMF (6 mL), (929 mg, 2.85 mmol) of Cs₂CO₃ and (11 mg, 0.05 mmol) of NaI were added and the reaction mixture was stirred at 50°C for 24 h. The solvent was removed under reduced pressure. Water was added and the aqueous phase was extracted by ethyl acetate, the organic layers were washed with brine, and dried over MgSO₄. The solvent was removed and the crude product was purified by column chromatography on silica gel (CH₂Cl₂/MeOH=100/0 to 95/5) to give the expected products as oil (e1 : m = 126 mg, 24%) (e2: m = 109 mg, 21 %). MS [M+H]+ 365 g/mol.

164c1 : ¹H NMR (300 MHz, CDCl₃) δ 1.14-1.32 (m, 1H), 1.71-1.92 (m, 3H), 2.58 (s, 3H), 2.72 (dd, J = 16.0, 2.2 Hz, 1H), 2.92 (dd, J = 16.0, 7.4 Hz, 1H), 3.53-3.83 (m, 6H), 3.97 (dt, J = 6.4, 4.4 Hz, 2H), 4.16 (d, J = 5.9 Hz, 1H), 7.16 (d, J = 8.2 Hz, 1H), 7.49 (dd, J = 8.3, 2.6 Hz, 1H), 8.16 (d, J = 2.6 Hz, 1H).

164c2 : ¹H NMR (300 MHz, CDCl₃) δ 1.35-1.45 (m, 1H), 1.76-2.01 (m, 3H), 2.57 (s, 3H), 2.63 (dd, J = 15.7, 2.0 Hz, 1H), 2.91 (dd, J = 15.7, 7.3 Hz, 1H), 3.35 (dd, J = 14.2, 9.3 Hz, 1H), 3.61 (s, 3H), 3.66-3.91 (m, 3H), 4.10-4.29 (m, 2H), 7.09-7.20 (m, 1H), 7.59 (dd, J = 8.3, 2.6, 0.5 Hz, 1H), 8.24 (d, J = 2.6 Hz, 1H).

Example 164d2. (4S)-4-(6-Chloro-3-pyridyl)-6-methyl-2-oxo-1-
[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylic acid.

The ester 164c2 (126 mg) was dissolved in MeOH (2 mL), a solution of NaOH 1N (2 mL) was added. The reaction mixture was stirred overnight at 40°C. LCMS showed completion of the reaction. The MeOH was evaporated under reduced pressure, the aqueous phase was extracted by Et₂O, then acidified to pH = 1 with HCl (1N). The aqueous phase was extracted by EtOAC. The organic phases were assem bled and dried over MgSO₄. The solvents were removed under reduced pressure to afford a product as oil (m = 66 mg, 55 %). ¹H NMR (300 MHz, CDCl₃) δ 1.35-1.52 (m, 1H), 1.79-2.00 (m, 3H), 2.60 (s, 3H), 2.68 (dd, J = 15.8, 1.9 Hz, 1H), 2.94 (dd, J = 15.8, 7.4 Hz, 1H), 3.39 (dd, J = 14.2, 9.4 Hz, 1H), 3.65-3.89 (m, 3H), 4.17-4.28 (m, 2H), 7.13-7.20 (m, 1H), 7.58-7.64 (m, 1H), 8.28 (d, J = 2.6 Hz, 1H), 9.49 (s, 1H). MS [M+H]+ 351 g/mol.

Example 164. (2-Methoxyphenyl)methyl-(4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-
[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.
The 1-(chloromethyl)-2-methoxy-benzene (33 mg, 0.21 mmol) and the acid 164d2 (66 mg, 0.19 mmol) were dissolved in dry DMF (3 mL). Cesium carbonate (92 mg, 0.28 mmol) was added and the reaction mixture was stirred at r.t. overnight. The solvent was removed. Water was added and the aqueous phase was extracted by Et2O, washed with brine and dried over MgSCv. After filtration the solvent was removed and the crude product was purified by Column chromatography on silica gel (CH2Cl2/MeOH : 100/0 to 99 /1) to give the expected product as oil (m = 48 mg, 54 %). 1H NMR (300 MHz, CDCl3) δ 1.40-1.55 (m, 1H), 1.82-2.06 (m, 3H), 2.56-2.71 (m, 4H), 2.94 (dd, J = 15.8, 7.5 Hz, 1H), 3.40 (dd, J = 14.2, 9.2 Hz, 1H), 3.67-3.79 (m, 4H), 3.80-3.94 (m, 2H), 4.16-4.29 (m, 2H), 5.03-5.20 (m, 2H), 6.79-6.90 (m, 2H), 7.04 (dd, J = 7.4, 1.7 Hz, 1H), 7.14 (d, J = 8.3 Hz, 1H), 7.22-7.31 (m, 1H), 7.58 (ddd, J = 8.3, 2.6, 0.4 Hz, 1H), 8.22 (d, J = 2.6 Hz, 1H). 13C NMR (75 MHz, CDCl3) δ 17.2, 25.7, 29.3, 35.0, 38.7, 46.1, 55.3, 62.2, 68.3, 77.7, 109.4, 110.4, 120.4, 124.1, 129.6, 129.7, 136.0, 138.0, 149.3, 149.9, 151.8, 157.6, 166.8, 168.5. MS [M+H]+ 471 g/mol.

**Example 165**

![Structure](image)

**Example 164d 1.** (4R)-4-(6-Chloro-3-pyridyl)-6-methyl-2-oxo-1-\[\[(2R)-tetrahydrofuran-2-yl\]methyl\]-3,4-dihydropyridine-5-carboxylic acid.

The ester 164c1 (109 mg) was dissolved in MeOH (2 mL), a solution of NaOH 1N (2 mL) was added. The reaction mixture was stirred overnight at 40°C. LCMS showed completion of the reaction. The MeOH was evaporated under reduced pressure, the aqueous phase was extracted by Et2O, then acidified to pH = 1 with HCl (1N). The aqueous phase was extracted by EtOAC. The organic phases were assembled and dried over MgSO4. The solvents were removed under reduced pressure to afford a product as oil (m = 98 mg, 94 %). 1H NMR (300 MHz, CDCl3) δ 1.21-1.31 (m, 1H), 1.73-1.93 (m, 3H), 2.61 (s, 3H), 2.77 (dd, J = 16.1, 2.0 Hz, 1H), 2.94 (dd, J = 16.0, 7.4 Hz, 1H), 3.61-3.81 (m, 3H), 3.93-4.03 (m, 2H), 4.20 (d, J = 6.2 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 7.52 (dd, J = 8.3, 2.6 Hz, 1H), 8.22 (d, J = 2.5 Hz, 1H), 10.47 (s, 1H). MS [M+H]+ 351 g/mol.

**Example 165.** (2-Methoxyphenyl)methyl-(4R)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[\{(2R)-tetrahydrofuran-2-yl\}methyl]-3,4-dihydropyridine-5-carboxylate.
The 1-(chloromethyl)-2-methoxy-benzene (48 mg, 0.31 mmol) and the acid 164d1 (98 mg, 0.28 mmol) were dissolved in dry DMF (4 mL). Cesium carbonate (137 mg, 0.42 mmol) was added and the reaction mixture was stirred at r.t. overnight. The solvent was removed. Water was added and the aqueous phase was extracted by Et<sub>2</sub>O, washed with brine and dried over MgSCv. After filtration the solvent was removed and the crude product was purified by Column chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH : 100/0 to 99/1) to give the expected product as oil (m = 100 mg, 76%).<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.20-1.40 (m, 1H), 1.75-1.97 (m, 3H), 2.61 (s, 3H), 2.72 (dd, J = 16.0, 2.2 Hz, 1H), 2.94 (dd, J = 16.0, 7.6 Hz, 1H), 3.62-3.86 (m, 6H), 3.93-4.06 (m, 2H), 4.20 (d, J = 6.1 Hz, 1H), 5.13 (q, J = 12.4 Hz, 2H), 6.79-6.90 (m, 2H), 7.09 (dd, J = 7.4, 1.7 Hz, 1H), 7.13 (d, J = 8.3 Hz, 1H), 7.27 (td, J = 8.1, 1.8 Hz, 1H), 7.47 (dd, J = 8.3, 2.6 Hz, 1H), 8.16 (d, J = 2.6 Hz, 1H).<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 17.4, 25.3, 29.1, 34.4, 38.0, 45.3, 55.3, 62.2, 67.9, 77.2, 109.8, 110.4, 120.3, 124.0, 124.0, 129.8, 129.9, 136.1, 137.8, 148.9, 149.9, 151.0, 157.6, 166.8, 169.0. MS [M+H]<sup>+</sup> 471 g/mol.

**EXAMPLE 166**

![Chemical structure](image)

Example 166a. [4-(3-Chloropropoxy)phenyl]methanol.

A mixture of 1-bromo-3-chloro-propane (2.4 mL, 24 mmol), 4-hydroxybenzyl alcohol (1.0 g, 8 mmol) and potassium carbonate (1.11 g, 8 mmol) was added in acetonitrile (27 mL) and the reaction was stirred overnight at 50°C. Little formation of product was observed by TLC and LCMS. RM stirred at reflux for 8 h. Little progress (20% conv. to 30% conv.). 3 equivalents of reactant and base were added. Reaction stirred under reflux overnight. Reaction finished. The solvent was removed under reduced pressure. The crude was dissolved in Et<sub>2</sub>Ac and washed by water. The aqueous phase was extracted by Et<sub>2</sub>Ac and the organic phase was washed with
brine, dried under MgSO₄. The solvents were removed under reduced pressure to afford the title compound. This crude was purified by flash chromatography (Cy/EA 100/0 to 75/25) to afford the desired compound as an oil (m = 1.34 g, 84 %). ¹H NMR (300 MHz, CDCl₃) δ 2.03 (s, 1H), 2.14-2.42 (m, 2H), 3.75 (t, J = 6.3 Hz, 2H), 4.12 (t, J = 5.8 Hz, 2H), 4.59 (s, 2H), 6.90 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H).

Example 166b. 1-(Chloromethyl)-4-(3-chloropropoxy)benzene.
Thionyl chloride (90 mL, 1.25 mmol) was added to benzotriazole (178 mg, 1.50 mmol). The resulting mixture was dissolved in CH₂Cl₂ (3 mL). After 5 min, this solution was added slowly to the solution of the [4-(3-Chloropropoxy)phenyl]methanol 166a (200 mg, 1.0 mmol) in CH₂Cl₂ (7 mL). The benzotriazole salt started to precipitate. After 20 min of reaction, the salt was filtered. The organic phase was washed by water and NaOH solution. The organic phase was dried under MgSO₄ and the solvent was removed under reduced pressure to give the desired chlorinated compound as yellow oil (m = 184 mg, 84 %). ¹H NMR (300 MHz, CDCl₃) δ 2.17-2.33 (m, 2H), 3.75 (t, J = 6.3 Hz, 2H), 4.12 (t, J = 5.9 Hz, 2H), 4.58 (s, 2H), 6.90 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H).

Example 166c. [4-(3-Chloropropoxy)phenyl]methyl-(4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[2R]-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.
The acid 164d2 (80 mg, 0.23 mmol) and cesium carbonate (111 mg, 0.34 mmol) were dissolved in dry DMF (2 mL). The chlorinated compound 166b (75 mg, 0.34 mmol) was added. The reaction mixture was stirred at r.t. for 24 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and washed with water. The aqueous phase was extracted by EtOAc. The organic layers were assembled, washed with brine and dried over MgSO₄. The residue was purified by flash chromatography (Cy/CH₂Cl₂: 50/50 to 0/100) to afford the desired product as a colorless oil (m = 97 mg, 80 %). ¹H NMR (300 MHz, CDCl₃) δ 1.37-1.54 (m, 1H), 1.80-2.08 (m, 3H), 2.17-2.31 (m, 2H), 2.54-2.73 (m, 4H), 2.92 (dd, J = 15.7, 7.5 Hz, 1H), 3.39 (dd, J = 14.2, 9.3 Hz, 1H), 3.67-3.78 (m, 3H), 3.79-3.94 (m, 2H), 4.09 (t, J = 5.8 Hz, 2H), 4.14-4.28 (m, 2H), 5.00 (q, J = 12.2 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.3 Hz, 1H), 7.56 (dd, J = 8.3, 2.6 Hz, 1H), 8.23 (d, J = 2.6 Hz, 1H). MS [M+H]+ 533 g/mol.

Example 166d. [4-(3-Iodopropoxy)phenyl]methyl(4S)-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-[[[2R]-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.
The chlorinated compound 166c (96 mg, 0.18 mmol) was dissolved in butanone (4 mL). NaI (108 mg, 0.72 mmol) was added and the reaction mixture stirred at 80°C overnight. The solution was cooled to r.t., filtered and the filtrate washed by acetone. The solvents were removed under reduced pressure to afford yellowish oil. This residue was purified by flash chromatography...
(CH$_2$Cl)$_2$) to give the desired product as oil (m = 103 mg, 92 %). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$

- 1.40-1.52 (m, 1H), 1.82-2.03 (m, 3H), 2.19-2.30 (m, 2H), 2.54-2.70 (m, 4H), 2.91 (dd, $J = 15.8$, 7.5 Hz, 1H), 3.27-3.47 (m, 3H), 3.65-3.78 (m, 1H), 3.78-3.93 (m, 2H), 4.01 (t, $J = 5.8$ Hz, 2H),

- 4.11-4.29 (m, 2H), 5.00 (q, $J = 12.2$ Hz, 2H), 6.80 (d, $J = 8.7$ Hz, 2H), 7.06 (d, $J = 8.5$ Hz, 2H),

- 7.14 (d, $J = 8.3$ Hz, 1H), 7.56 (dd, $J = 8.3$, 2.6 Hz, 1H), 8.23 (d, $J = 2.5$ Hz, 1H). MS [M+H]$^+$ 625 g/mol.

**Example 166. Ammonium, 3-[4-[[4S]-4-(6-chloro-3-pyridyl)-2-oxo-1 -[[[(2R)-
tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carbonyl]oxymerhyl]phenoxy]propane-1 -sulfonate.**

The iodide compound 166d (100 mg, 0.16 mmol) was dissolved in a mixture of iPrOH/water (1/1, 2 mL). Sodium sulfite (40 mg, 0.32 mmol) was added and the reaction mixture was heated at 80°C in a sealed tube for 18 h. The solvents were removed under reduced pressure. Purification of the crude product by HPLC (acid conditions) gave the ammonium:3-[4-[[4S]-4-(6-chloro-3-pyridyl)-2-oxo-1 -[[[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carbonyl]oxymerhyl]phenoxy]propane-1 -sulfonate as a white powder (m = 52 mg, 54 %). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$

- 1.35-1.50 (m, 1H), 1.80-2.00 (m, 3H), 2.17 (s, 2H), 2.50-2.65 (m, 4H),

- 2.85 (dd, $J = 15.8$, 7.1 Hz, 1H), 3.04 (s, 2H), 3.36 (dd, $J = 14.0$, 9.2 Hz, 1H), 3.70 (dd, $J = 14.2$, 7.1 Hz, 1H), 3.80-3.95 (m, 4H), 4.10-4.25 (m, 2H), 4.87 (dd, $J = 29.3$, 12.1 Hz, 2H), 6.69 (d, $J = 6.7$ Hz, 2H), 6.85-7.40 (m, 3H+NH$_4^+$), 7.57 (d, $J = 7.9$ Hz, 1H), 8.17 (s, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$


**Example 167**
Example 167a. Methyl-(4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.

The dihydropyridone intermediate obtained following general procedure A (1.5 g, 5.36 mmol) and the [(2R)-tetrahydrofuran-2-yl]methyl 4-methylbenzenesulfonate 164b (2.75 g, 10.72 mmol) were dissolved in dry DMF (25 mL), Cs$_2$CO$_3$ (3.5 g, 10.72 mmol) and NaI (40 mg, 0.27 mmol) were added and the reaction mixture was stirred at 50°C for 24 h. The solvent was removed under reduced pressure. Water was added and the aqueous phase was extracted by ethyl acetate, the organic layers were washed with brine, and dried over MgSO$_4$. The solvent was removed and the crude was purified by flash chromatography (CH$_2$Cl$_2$/CyHex 30/70 to 100/0) to give the expected product as oil (m = 500 mg, 26 %). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.34-1.48 (m, 1 H), 1.74-1.98 (m, 3 H), 2.57 (d, $J$ = 0.5 Hz, 3H), 2.66 (dd, $J$ = 15.6, 2.2 Hz, 1H), 2.86 (dd, $J$ = 15.6, 7.2 Hz, 1H), 3.28-3.43 (m, 1 H), 3.60 (s, 3 H), 3.65-3.79 (m, 2H), 3.80-3.90 (m, 1H), 4.14 (dd, $J$ = 7.1, 1.5 Hz, 1H), 4.22 (dd, $J$ = 14.3, 3.3 Hz, 1H), 7.17 (s, 4 H). MS [M+H]$^+$ 364 g/mol.

Example 167b. (4 S)-4-(4-Chlorophenyl)-6-methyl-2-oxo-1-[(2R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylic acid.

The ester 167a (480 mg, 1.32 mmol) was dissolved in MeOH (8 mL), a solution of NaOH 1N (8 mL) was added. The reaction mixture was stirred for 3 h at 40°C. LCMS showed completion of the reaction. The MeOH was evaporated under reduced pressure, the aqueous phase was extracted by Et$_2$O, then acidified to pH = 1 with a solution of HCl (1N). The aqueous phase was extracted by EtOAC and the organic phases were assembled and dried under MgSO$_4$. The solvents were removed under reduced pressure to afford a product as white solid (m =
Example 167. (2-Methoxyphenyl)methyl-(4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2R]-
tetrahydrofuran-2-yl][methyl]-3,4-dihydropyridine-5-carboxylate.

The 1-(chloromethyl)-2-methoxy-benzene (50 mg, 0.31 mmol) and the acid 167b (100 mg, 0.29 mmol) were dissolved in dry DMF (5 ml). Cesium carbonate (140 mg, 0.43 mmol) was added and the reaction mixture was stirred at r.t. overnight. The solvent was removed. Water was added and the aqueous phase was extracted by AcOEt, washed with brine and dried over MgSO4. After filtration the solvent was removed and the crude product was purified by Column chromatography on silica gel (CH2Cl2/MeOH : 100/0 to 99/1) to give the expected product as oil (m = 125 mg, 93%). 1H NMR (300 MHz, CDCl3) δ 1.36-1.52 (m, 1H), 1.77-1.98 (m, 3H), 2.61 (d, J = 0.5 Hz, 3H), 2.68 (dd, J = 15.6, 2.2 Hz, 1H), 2.90 (dd, J = 15.6, 7.4 Hz, 1H), 3.40 (dd, J = 14.2, 8.6 Hz, 1H), 3.66-3.96 (m, 6H), 4.15-4.30 (m, 2H), 5.14 (dd, J = 28.9, 13.0 Hz, 2H), 6.82 (ddd, J = 8.5, 5.6, 1.1 Hz, 2H), 6.93-6.98 (m, 1H), 7.18 (s, 4H), 7.21-7.28 (m, 1H). 13C NMR (75 MHz, CDCl3) δ 17.0, 25.6, 29.3, 37.0, 39.1, 45.6, 55.2, 61.8, 68.1, 77.9, 110.2, 110.4, 120.2, 124.4, 128.6, 128.7, 128.9, 129.2, 132.5, 139.7, 150.9, 157.3, 167.2, 169.0. MS [M+H]+ 470 g/mol.

Example 168a. [4-(3-Chloropropoxy)phenyl]methyl-(4S)-4-(4-chlorophenyl)-6-methyl-2-
ovo-1-[[2R]-tetrahydrofuran-2-yl][methyl]-3,4-dihydropyridine-5-carboxylate.

The acid 167b (100 mg, 0.29 mmol) and cesium carbonate (140 mg, 0.43 mmol) were dissolved
in dry DMF (3 mL), chlorinated compound 166b (94 mg, 0.43 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and washed with water. The aqueous phase was extracted by EtOAc. The organic layers were assembled, washed with brine and dried over MgSO₄. The residue was purified by flash chromatography (Cy/CH₂Cl₂: 50/50 to 0/100) to afford the desired product as a colorless oil (m = 80 mg, 53 %). ¹H NMR (300 MHz, CDCl₃) δ 1.34-1.54 (m, 1H), 1.79-2.01 (m, 3H), 2.18-2.32 (m, 2H), 2.61 (s, 3H), 2.67 (dd, J = 15.6, 2.2 Hz, 1H), 2.88 (dd, J = 15.6, 7.4 Hz, 1H), 3.40 (dd, J = 14.3, 8.7 Hz, 1H), 3.63-3.84 (m, 4H), 3.84-3.96 (m, 1H), 4.09 (t, J = 5.8 Hz, 2H), 4.16 (d, J = 5.7 Hz, 1H), 4.24 (dd, J = 14.3, 3.3 Hz, 1H), 5.01 (s, 2H), 6.79 (d, J = 8.7 Hz, 2H), 7.04 (d, J = 8.7 Hz, 2H), 7.12-7.24 (m, 4H). MS [M+H]⁺ 532 g/mol.

Example 168b. [4-(3-iodopropyloxy)phenyl][methyl-(4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-][(2R)-tetrahydrofuran-2-yl][methyl]-3,4-dihydropyridine-5-carboxylate.

The chlorinated compound 168a (80 mg, 0.15 mmol) was dissolved in butanone (4 mL), NaI (90 mg, 0.6 mmol) was added and the reaction mixture stirred at 80 °C overnight. The solution was cooled to room temperature, filtered and the filtrate washed by acetone. The solvents were removed under reduced pressure to afford yellowish oil. This residue was purified by flash chromatography (CH₂Cl₂) to give the desired product as oil (m = 76 mg, 81 %). ¹H NMR (300 MHz, CDCl₃) δ 1.33-1.53 (m, 1H), 1.78-1.99 (m, 3H), 2.25 (qd, J = 6.3, 4.7 Hz, 2H), 2.60 (d, J = 0.6 Hz, 3H), 2.67 (dd, J = 15.6, 2.2 Hz, 1H), 2.88 (dd, J = 15.6, 7.4 Hz, 1H), 3.30-3.45 (m, 3H), 3.63-3.93 (m, 3H), 4.01 (t, J = 5.8 Hz, 2H), 4.16 (d, J = 5.7 Hz, 1H), 4.23 (dd, J = 14.3, 3.3 Hz, 1H), 5.01 (s, 2H), 6.79 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 8.8 Hz, 2H), 7.14-7.20 (m, 4H). MS [M+H]⁺ 624 g/mol.

Example 168. A m m o n i u m , 3-[4-[[4S]-4-(4-chlorophenyl)-6-methyl-2-oxo-1-][(2R)-tetrahydrofuran-2-yl][methyl]-3,4-dihydropyridine-5-carbonyl][oxymethyl][phenoxy]propane-1 -sulfonate.

The iodide compound 168b (75 mg, 0.12 mmol) was dissolved in a mixture of iPrOH/water (1/1, 2 mL). Sodium sulfite (30 mg, 0.24 mmol) was added and the reaction mixture was heated at 80°C in sealed tube for 18 h. The solvents were removed under reduced pressure. Purification of the crude by HPLC (acid conditions) gave the ammonium;3-[4-[[4S]-4-(6-chloro-3-pyridyl)-6-methyl-2-oxo-1-][(2R)-tetrahydrofuran-2-yl][methyl]-3,4-dihydropyridine-5-carbonyl][oxymethyl][phenoxy]propane-1 -sulfonate as a white powder (m = 45 mg, 63 %). ¹H NMR (300 MHz, CDCl₃) δ 1.28-1.50 (m, 1H), 1.72-1.96 (m, 3H), 2.14 (s, 2H), 2.50-2.65 (m, 4H), 2.80 (dd, J = 15.6, 7.2 Hz, 1H), 3.02 (s, 2H), 3.35 (dd, J = 14.2, 8.7 Hz, 1H), 3.62-3.90 (m, 5H), 4.09 (d, J = 8.3 Hz, 1H), 4.19 (dd, J = 14.2, 2.7 Hz, 1H), 4.89 (dd, J = 25.4, 12.5 Hz, 2H), 6.66 (d, J = 8.3 Hz, 2H), 6.75-7.23 (m, 10H). ¹³C NMR (75 MHz, CDCl₃) δ 17.2, 25.0, 25.6, 29.3, 37.1, 39.1, 45.8, 48.4, 65.8, 66.4, 68.2, 77.9, 110.1, 114.5, 128.7, 128.8, 129.5, 132.5,
Example 169c. [4-(4-Chlorobutoxy)phenyl]methanol.

The mixture of 1-bromo-4-chloro-butane (1.67 mL, 14.5 mmol), 4-(hydroxymethyl)phenol (600 mg, 4.83 mmol) and potassium carbonate (668 mg, 4.83 mmol) were added in acetonitrile (16 mL) and the reaction was stirred overnight at 50 °C. Little formation of product observed by TLC (CH₂Cl₂/MeO-I: 98/2) and LCMS. 3 equivalents of reactant and base were added and the reaction stirred under reflux overnight. Reaction finished. The solvent was removed under reduced pressure. The crude was dissolved in EtOAc and washed by water. The aqueous phase was extracted by EtOAc and the organic phase washed with brine, dried over MgSO₄. The solvents were removed under reduced pressure and the crude product was purified by flash chromatography (Cy/EA 100/0 to 75/25) to afford the desired compound as an oil (m = 1 g, 96%). ¹H NMR (300 MHz, CDCl₃) δ 1.88 (s, 1H), 1.90-2.10 (m, 4H), 3.63 (t, J = 6.3 Hz, 2H), 4.00 (t, J = 5.8 Hz, 2H), 4.60 (s, 2H), 6.88 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H).

Example 169d. 1-(4-Chlorobutoxy)-4-(chloromethyl)benzene.

The thionyl chloride (0.13 mL, 1.75 mmol) was added to benzotriazole (250 mg, 2.1 mmol). The resulting mixture was dissolved in CH₂Cl₂ (5 mL). After 5 min, this solution was added slowly to the solution of the alcohol 167a (300 mg, 1.4 mmol) in CH₂Cl₂ (10 mL). The benzotriazole salt started to precipitate. After 20 min of reaction, the salt was filtered. The organic phase was washed by water and NaOH solution (0.05 M). The organic phase was dried over MgSO₄ and the solvent was removed under reduced pressure to give the desired chlorinated compound as yellow oil (m = 306 mg, 94 %). ¹H NMR (300 MHz, CDCl₃) δ 1.87-2.08 (m, 4H), 3.62 (t, J = 6.2 Hz, 2H), 4.00 (t, J = 5.7 Hz, 2H), 4.57 (s, 2H), 6.88 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H).
Example 169a. [4-(4-Chlorobutoxy)phenyl)methyl-(4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.

The acid 167b (60 mg, 0.17 mmol) and cesium carbonate (84 mg, 0.26 mmol) were dissolved in dry DMF (2 mL). The chlorinated compound 169d (60 mg, 0.26 mmol) was added. The reaction mixture was stirred at r.t. for 24 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and washed with water. The aqueous phase was extracted by EtOAc. The organic layers were assembled, washed with brine and dried over MgSO₄. The residue was purified by flash chromatography (CH₂Cl₂) to afford the desired product as a colorless oil (m = 54 mg, 58 %). ¹H NMR (300 MHz, CDCl₃) δ 1.33-1.55 (m, 1H), 1.75-2.07 (m, 7H), 2.60 (s, 3H), 2.67 (dd, J = 15.6, 2.2 Hz, 1H), 2.88 (dd, J = 15.6, 7.4 Hz, 1H), 3.40 (dd, J = 14.3, 8.7 Hz, 1H), 3.62 (t, J = 6.2 Hz, 2H), 3.67-3.94 (m, 3H), 3.98 (t, J = 5.7 Hz, 2H), 4.16 (d, J = 5.8 Hz, 1H), 4.24 (dd, J = 14.3, 3.3 Hz, 1H), 5.01 (s, 2H), 6.77 (d, J = 8.7 Hz, 2H), 7.03 (d, J = 8.7 Hz, 2H), 7.09-7.23 (m, 4H). MS [M+H]+ 546 g/mol.

Example 169b. [4-(4-Iodobutoxy)phenyl)methyl-(4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carboxylate.

The chlorinated compound 169a (54 mg, 0.11 mmol) was dissolved in butanone (3 mL). Nal (59 mg, 0.4 mmol) was added and the reaction mixture stirred at 80°C overnight. The solution was cooled to r.t., filtered and the precipitate was washed by acetone. The solvents were removed under reduced pressure to afford yellowish oil. This residue was purified by flash chromatography (CH₂Cl₂) to give the desired product as oil (m = 49 mg, 78 %). ¹H NMR (300 MHz, CDCl₃) δ 1.40-1.55 (m, 1H), 1.76-2.11 (m, 7H), 2.60 (s, 3H), 2.67 (dd, J = 15.6, 2.2 Hz, 1H), 2.88 (dd, J = 15.6, 7.4 Hz, 1H), 3.26 (t, J = 6.8 Hz, 2H), 3.40 (dd, J = 14.3, 8.7 Hz, 1H), 3.70-3.92 (m, 3H), 3.96 (t, J = 6.0 Hz, 2H), 4.16 (d, J = 5.8 Hz, 1H), 4.24 (dd, J = 14.3, 3.3 Hz, 1H), 5.01 (s, 2H), 6.77 (d, J = 8.6 Hz, 2H), 7.03 (d, J = 8.6 Hz, 2H), 7.09-7.23 (m, 4H). MS [M+H]+ 638 g/mol.

Example 169. A m m o n i a u m ; 4-{[4-(4S)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-[[2(R)-tetrahydrofuran-2-yl]methyl]-3,4-dihydropyridine-5-carbonyl]oxy}methyl|phenoxy|butane-1-sulfonate.

The iodide compound 169b (49 mg, 0.077 mmol) was dissolved in a mixture of iPrOH/water 1/1 (1 mL). Sodium sulfite (19 mg, 0.154 mmol) was added and the reaction mixture was heated at 80°C in sealed tube for 18 h. The solvents were removed under reduced pressure. Purification of the crude by HPLC (basic conditions) gave the expected product as a yellow powder (m = 40 mg, 85 %). ¹H NMR (300 MHz, CDCl₃) δ 1.30-1.52 (m, 1H), 1.65-1.99 (m, 7H), 2.48-2.69 (m, 4H), 2.73-3.02 (m, 3H), 3.36 (dd, J = 14.2, 8.7 Hz, 1H), 3.61-3.91 (m, 5H), 4.04-4.27 (m, 2H), 4.92 (dd, J = 23.7, 12.4 Hz, 2H), 6.48-7.64 (m, 12H). ¹³C NMR (75 MHz, CDCl₃) δ 17.2,
5 **BIOLOGY EXAMPLES**

**TGR5/CRE Luciferase assay**

In the following Tables TGR5 activation by compounds of the invention and subsequent increase in intracellular cAMP were evaluated using a luciferase reporter gene assay. Human embryonic kidney (HEK) 293 cells were transiently co-transfected with pCMV tag4b-TGR5h (to follow hTGR5 activation) or pCMV AC6-TGR5m (to follow mTGR5 activation) expression plasmids and the pCRE TA-Luciferase reporter plasmid using the JET PEI reagent (Polyplus transfection). Transfected cells were seeded in 96-well plates and incubated overnight with the test compounds at increasing concentrations tested in duplicate. Lithocolic acid (LCA) at 10 µM was used as a positive reference compound. The cAMP-dependent luciferase expression was followed using the BrightGlo reagent according to the manufacturer (Promega) instructions. Luminescence was read with a Mithras plate reader (Berthold) or a Victor3™ V1420 (Perkin Elmer). Data were expressed as percentage of the 10 µM LCA value and EC\textsubscript{50} values were calculated using XL fit 5 software or Graph Pad Prism 5. Concentration-response curves were fitted by a nonlinear regression analysis to a 4 parameter logistic equation.

The results of the TGR5/CRE Luciferase assay are presented in Table 14 hereafter.

<p>| Table 14 |
|---|---|---|---|---|---|
| Example | hTGR5 | mTGR5 |
| | ECSO (µM) | % trans | EC\textsubscript{50} (µM) | % trans |
| 3 | 7.4 | 65 | 10.4 | 45 |
| 4 | 10 | 17 | 8.5 | 18 |
| 5 | 10.6 | 31 | 11.1 | 34 |
| 6 | 12.8 | 19 | NC | 11 |
| 7 | 5.0 | 22 | NC | 14 |
| 9 | 1.5 | 48 | 1.4 | 37 |
| 11 | 4.5 | 17 | NC | 10 |
| 12 | 1.9 | 68 | 4.5 | 52 |
| 13 | 2.6 | 40 | 4.2 | 37 |
| 14 | 7.6 | 30 | 10.3 | 18 |
| 15 | 3.9 | 49 | - | - |</p>
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NC: not calculated
1. A compounds of general Formula I:

![Chemical Structure](image)

or pharmaceutically acceptable salts or solvates thereof,

wherein

R\(^1\) is C1-C6-alkyl, aryl or heteroaryl, wherein said aryl moiety is independently substituted by one or more groups selected from the group consisting of halo, cyano, C1-C2-alkyl, C1-C2-alkoxy, C1-C2-haloalkyl, and 5- or 6-membered aryl, and said heteroaryl moiety is optionally independently substituted by one or more groups selected from the group consisting of halo, cyano, C1-C2-alkyl, C1-C2-alkoxy, C1-C2-haloalkyl, and 5- or 6-membered aryl;

L\(^1\) is a single bond or (CH\(_2\))\(_n\), wherein n is 1, 2 or 3;

R\(^2\) is H, C1-C4 alkyl, alkenyl, alkiny, alkox, hydroxy, hydroxycarbonyl, alkoxy carbonyl, carbamoyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy carbonylamino, cyano, alkylsulfonyl, aralkyl, cycloalkyl, heterocyclyl, heteroaryl, wherein said heterocyclyl moiety is optionally substituted by one or more substituents independently selected from the group consisting of alkyl and alkoxy carbonyl, and said heteroaryl moiety is optionally substituted by one or more C1-C2-alkyl;

L\(^2\) is a single bond or (CH\(_2\))\(_n\), wherein n is 1 or 2;

R\(^3\) is aryl, heteroaryl, cycloalkyl or aryl carbonyl wherein each of said moieties is optionally substituted by one or more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, aryl, cyano, alkoxy, haloalkoxy, alkoxy carbonyl, aminoalkoxy,
alkylaminoalkoxy, dialkylaminoalkoxy, H<sub>0</sub><sub>3</sub>S-alkoxy,

\[
\text{O} \quad \text{O} \quad \text{m}
\]

wherein m is 1 to 500,

\[\text{[N(R}^8\text{)}_3\text{-alkoxy}]^+Q^-\]

wherein \(R^8\) is linear C1-C4-alkyl and \(Q^-\) is a counter anion, and

a cyclic moiety selected from the group consisting of

\[
\text{R}^A \quad \text{R}^B \quad \text{R}^C
\]

wherein \(R^A\) is H, OH, C0-C4-alkyl-COOH or C1-C6-alkyl, \(R^B\) is C1-C6-alkyl optionally substituted with -COOH, \(R^C\) is C1-C6-alkyl, and \(Q^-\) is a counter anion;

or wherein said cycloalkyl moiety is fused to a an aryl, preferably phenyl, moiety;

\(R^4\) is H, C1-C2-alkyl or 5- or 6-membered aryl;

\(R^5\) is H, C1-C4-alkyl, 5- or 6-membered aryl, alkoxyalkyl; and

\(X\) is O or NR', wherein \(R'\) is H, C1-C2-alkyl or \(R'\) taken together with \(L^2\) and \(R^3\) form a 5- or 6-membered heterocyclyl moiety which is optionally fused to an aryl moiety.
2. The compound according to claim 1 having Formula II and pharmaceutically acceptable salts and solvates thereof.

3. The compound according to claim 2 having Formula IIa and pharmaceutically acceptable salts, and solvates thereof, wherein

\[ \text{R}^6 \text{ is halo, alkyl, haloalkyl, aryl, cyano, alkoxy, haloalkoxy, alkoxy carbonyl, aminoalkoxy, alkylaminoalkoxy, dialkylaminoalkoxy, } \]

\[ \text{H}_0^3\text{S-alkoxy}, \]

\[ \text{[N(R}_8^8)^3\text{-alkoxy}]\cdot\text{Q'}, \]

wherein \( R^8 \) is linear C1-C4-alkyl and \( Q' \) is a counter anion, or a cyclic moiety selected from the group consisting of
4. The compound according to claim 1 having Formula III

wherein $R^A$ is H, OH, C0-C4-alkyl-COOH or C1-C6-alkyl, $R^B$ is C1-C6-alkyl optionally substituted with -COOH, $R^C$ is C1-C6-alkyl, and $Q^-$ is a counter anion.
and pharmaceutically acceptable salts, and solvates thereof, wherein

R^7 and R^8 are independently selected from the group consisting of H, halo, haloalkyi, and cyano, with the proviso that at least one of R^7 and R^8 is not H.

5. The compound according to claim 1 having Formula IV

![Formula IV](image)

and pharmaceutically acceptable salts, and solvates thereof, wherein

R^9 and R^{10} are independently selected from the group consisting of H, halo, haloalkyi, and cyano, with the proviso that at least one of R^9 and R^{10} is not H.

6. The compound according to claim 1 having Formula V

![Formula V](image)
and pharmaceutically acceptable salts, and solvates thereof.

7. The compound according to any one of claims 1 to 6 and pharmaceutically acceptable salts, and solvates thereof, wherein R⁵ is methyl.

8. The compound according to any one of claims 1 to 7 and pharmaceutically acceptable salts, and solvates thereof, wherein L¹ and R² are taken together to form a moiety selected from the group consisting of cycloalkylmethyl, heterocyclylmethyl, heteroarylmethyl, 2-alkoxyeth-1-yl, 3-alkoxyprop-1-yl, alkoxy carbonylmethyl, said heteroarylmethyl moiety being optionally substituted by one or more C1-C2 alkyl.

9. The compound according to any one of claims 1 to 7 and pharmaceutically acceptable salts, and solvates thereof, wherein R² is tetrahydro furanyl.

10. The compound according to claim 9 and pharmaceutically acceptable salts, and solvates thereof, wherein L¹ is CH₂.

11. The compound according to claim 1 selected from the group consisting of:
and pharmaceutically acceptable salts, and solvates thereof.

12. A pharmaceutical composition comprising a compound according to any of Claims 1 to 11 or a pharmaceutically acceptable salt or solvate thereof and at least one pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant.

13. A compound according to any of Claims 1 to 11 for use as a medicament.

14. A compound according to any of Claims 1 to 11 or a pharmaceutically acceptable salt or solvate thereof for use in treating and/or preventing a TGR5 related disease.
15. The compound or a pharmaceutically acceptable salt or solvate thereof for use according to Claim 14, wherein the disease is selected from metabolic and/or gastrointestinal diseases.

16. The compound or a pharmaceutically acceptable salt or solvate thereof for use according to Claim 15 wherein the disease is a metabolic disease selected from the group consisting of type II diabetes, obesity, dyslipidemia such as mixed or diabetic dyslipidemia, hypercholesterolemia, low HDL cholesterol, high LDL cholesterol, hyperlipidemia, hypertriglyceridemia, hypoglycemia, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypertension, hyperlipoproteinemia, metabolic syndrome, syndrome X, thrombotic disorders, cardiovascular disease, atherosclerosis and its sequelae including angina, claudication, heart attack, stroke and others, kidney diseases, ketoacidosis, nephropathy, diabetic neuropathy, diabetic retinopathy, nonalcoholic fatty liver diseases such as steatosis or nonalcoholic steatohepatitis (NASH).

17. The compound or a pharmaceutically acceptable salt or solvate thereof for use according to Claim 15, wherein the disease is a gastrointestinal disease selected from the group consisting of Inflammatory Bowel Diseases (IBD), Irritable Bowel Syndrome (IBS), intestinal injury disorders, diseases involving intestinal barrier dysfunction, and gastrointestinal disorders characterized by hypermotilenemia or gastrointestinal hypermotility.

18. Use of a compound according to any of Claims 1 to 11 or a pharmaceutically acceptable salt or solvate thereof as a modulator of TGR5 receptor activity.

19. Use according to Claim 18, wherein the compound is an agonist of TGR5 receptor activity.
### Document Title: INTERNATIONAL SEARCH REPORT

#### A. CLASSIFICATION OF SUBJECT MATTER

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#### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

- C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

- EPO-Internal
- WPI Data

#### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.

See patent family annex.

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**Date of the actual completion of the international search**

- 

**Date of mailing of the international search report**

- 

**Name and mailing address of the ISA/IB**

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**Authorized officer**

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Goss, Ilaria

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Form PCT/ISA/210 (second sheet) (April 2005)
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<td>NANTERMET P G ET AL: &quot;Selective α1-adrenoceptor antagonists based on 4-aryl-3,4-di-hydropyridine-2-one&quot;, BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 10, no. 15, 7 August 2000 (2000-08-07), pages 1625-1628, XP004213209, ISSN: 0960-894X, DOI: 10.1016/S0960-894X(99)00696-4, table 1; compounds 12-27</td>
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