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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and biological evaluation of novel *N*-substituted nipecotic acid derivatives with tricyclic cage structures in the lipophilic domain as GABA uptake inhibitors

Heinrich-Karl A. Rudy[1] · Georg Höfner[1] · Klaus T. Wanner[1]

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Abstract

A new class of GABA reuptake inhibitors with sterically demanding, highly rigid tricyclic cage structures as the lipophilic domain was synthesized and investigated in regard to their biological activity at the murine GABA transporters (mGAT1–mGAT4). The construction of these compounds, consisting of nipecotic acid, a symmetric tricyclic amine, and a plain hydrocarbon linker connecting the two subunits via their amino nitrogens, was accomplished via reductive amination of a nipecotic acid derivative with an *N*-alkyl substituent displaying a terminal aldehyde function with tricyclic secondary amines. The target compounds varied with regard to spacer length, the bridge size of one of the bridges, and the substituents of the tricyclic skeleton to study the impact of these changes on their potency. Among the tested compounds nipecotic acid ethyl ester derivates with phenyl residues attached to the cage subunit showed reasonable inhibitory potency and subtype selectivity in favor of mGAT3 and mGAT4, respectively.

Keywords GABA transporters · GABA uptake inhibitor · Nipecotic acid · Polycycles · Cage structures

Introduction

A balanced interplay between excitatory and inhibitory neurotransmission represents the fundamental basis for proper functioning of the central nervous system (CNS) in mammals. A disruption of this interplay due to, for example, an insufficient signaling of GABAergic neurons can lead to or intensify neurological disorders like Alzheimer's disease (AD) [1, 2], depression [3], epilepsy [4, 5], or Parkinson's disease (PD) [6–8]. One approach to influence the GABAergic neurotransmission and thus to treat the aforementioned diseases is to increase the release and the concentration of γ-aminobutyric acid **1** (GABA), representing the predominant inhibitory neurotransmitter in the CNS [9–11], in the synaptic cleft. As GABA is quickly removed from the synaptic cleft by reuptake into the presynaptic neurons and surrounding glia cells this may be achieved by inhibition of the GABA transporters (GATs) in charge of this process [12–14].

GATs are membrane-bound transport proteins of the solute carrier family 6. They consist of 12 transmembrane helices and translocate their substrate GABA through the cell membrane by cotransport of sodium and chloride ions [15, 16]. Latest findings suggest a stoichiometry of 3:1:1 (Na^+:Cl^-:GABA) for sodium and chloride ions and GABA in this transport process [17]. For the GATs four different subtypes are known, which are denominated differently depending on the species they were cloned from [14, 18]. When originating from mouse tissue they are termed mGAT1–mGAT4 [18–20]. For all other species including human, dog, or rat they are denominated as GAT-1 (≡ mGAT1), BGT-1 (≡ mGAT2), GAT-2 (≡ mGAT3), and GAT-3 (≡ mGAT4) whereby the individual transporter name is provided with a prefix such as h for human to indicate the individual species. This nomenclature has also been adopted by the Gene Nomenclature Committee of the Human Genome Organization (HUGO) but without any

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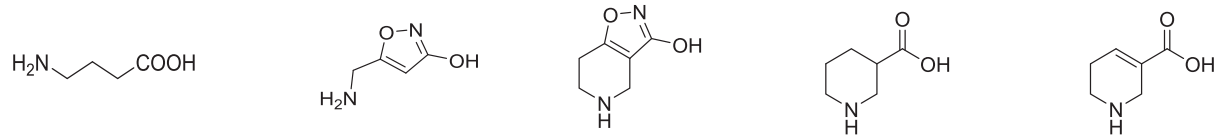
✉ Klaus T. Wanner
klaus.wanner@cup.uni-muenchen.de

[1] Department of Pharmacy – Center for Drug Research, Ludwig-Maximilians-Universität München, Butenandtstraße 5-13, Haus C, D-81377 Munich, Germany



γ-aminobutyric acid (GABA) **1** | muscimol **2** | THPO **3** | racemic nipecotic acid *rac*-**4** | guvacine **5**

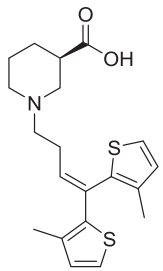
Fig. 1 Structures of GABA and some low molecular weight GAT inhibitors

prefix as which it has also found use as a species independent nomenclature system [18, 20, 21]. As the biological test system applied in this study is based on GATs originating from mice, for the sake of consistency the corresponding nomenclature mGAT1–mGAT4 will be used throughout this paper.

Although they are structurally closely related, mGAT1–mGAT4 are expressed very differently. The predominating transporter subtype in the CNS is mGAT1, which is primarily located on the plasma membrane of presynaptic GABAergic neurons [14, 18, 22]. mGAT4 represents the second most abundant GAT in the brain, albeit with distinctly lower concentration than mGAT1, where it is responsible for the transport of GABA into glia cells which are neighboring the GABAergic neurons [21–24]. In contrast mGAT2 and mGAT3 are only weakly expressed in the brain and occur mainly in kidney and liver. As the level of mGAT2 and mGAT3 in the brain is too low for having a reasonable effect on the termination of GABAergic neurotransmission, mGAT1 and mGAT4 are the most promising targets amongst these proteins to be addressed for the treatment of above-mentioned diseases [22, 25, 26].

Muscimol (**2**) and THPO (**3**) which are structurally related to GABA (Fig. 1), the natural substrate of GATs, were identified to be weak inhibitors at GATs. Structural alterations of the isoxazolol function of THPO (**3**) led to racemic nipecotic acid (*rac*-**4**) and guvacine (**5**) as the first reasonably potent inhibitors of the GATs. However, because of their zwitterionic character at physiological pH and their high polarity these compounds are not able to pass the blood–brain barrier (BBB). In order to increase lipophilicity and BBB permeation di- and triaryl residues were added via a linker to the amino nitrogen of the parent compounds. GAT inhibitors of this general structure have been synthesized in large numbers and broad structural diversity [27–33]. This includes the most prominent GAT inhibitor Tiagabine **6**, a mGAT1 selective inhibitor, which is used in the treatment of epileptic seizures [34, 35]. The *N*-linked lipophilic aryl-alkyl side chain does not only improve the permeation of the BBB but often also mediates a substantial increase in potency and subtype selectivity of the GAT inhibitors. Modeling studies revealed the putative binding pose for mGAT1 inhibitors such as Tiagabine (**6**). According to that the amino acid subunit binds in the substrate-binding pocket (S1) whereas the lipophilic residue is accommodated in a binding site (S2) equipped with aliphatic residues and located in the vestibule oriented towards the extracellular space [36–38]. NO711 (**7**) and (*S*)-SNAP-5114 (**8**) represent two further well known GAT inhibitors (Fig. 2) of which the former, **7**, like Tiagabine (**6**) is highly selective for mGAT1 and can be considered like **6** as prototype for compounds exhibiting this subtype selectivity. A major difference of (*S*)-SNAP-5114 (**8**) as compared to these compounds is to be attributed to the lipophilic domain, which by comprising a triarylmethyl unit is distinctly larger than that of **6** and **7**. It is this large steric demand of the lipophilic triarylmethyl subunit together with the (*S*)-configuration of nipecotic acid that is thought to mediate the subtype selectivity for mGAT4 of (*S*)-SNAP-5114 (**8**) [16, 39].

Tiagabine (**6**) suffers from a series of adverse side effects and (*S*)-SNAP-5114 (**8**), though among the most potent mGAT4 inhibitors, of moderate potency [39, 40]. Thus there is still a great need for GAT inhibitors with less adverse effects and higher potency. Structural changes to the aforementioned prototypic structures led to compounds with partially rigidized lipophilic domains at the terminal position of alkyl or heteroalkyl chains originating from the amino nitrogen of the polar subunit [41, 42]. That way aryl groups present in the lipophilic domain were forced to adopt specific spatial orientations. Another option to achieve a well-defined orientation of substituents in the lipophilic domain is to use compounds with a polycyclic cage structure as central unit. The high rigidity of cage structures allows to reduce the flexibility of attached substituents and may lower the conformational entropy penalty resulting from target binding [43, 44]. In addition, the high lipophilicity of cage-derived hydrocarbon rich structures may positively affect the pharmacokinetic and pharmacodynamic properties of drugs as it can facilitate the crossing of the BBB and the binding to lipophilic domains [45, 46]. As a result of their inherent stability and steric bulk, polycyclic cage compounds also can slow down metabolic degradation [45–47]. Currently drugs with polycyclic cage structures are in use for the treatment of neurodegenerative diseases like

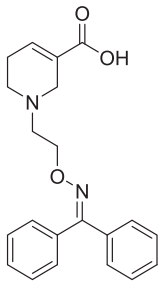


Tiagabine (**6**)

pIC_{50} = 6.88 ± 0.12 (mGAT1)

pIC_{50} = 73% (mGAT4)

Kragler et al. [55]

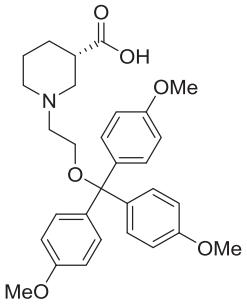


NO711 (**7**)

pIC_{50} = 6.83 ± 0.06 (mGAT1)

pIC_{50} = 3.07 ± 0.05 (mGAT4)

Kragler et al. [55]

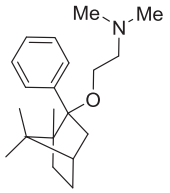


(*S*)-SNAP-5114 (**8**)

pIC_{50} = 4.07 ± 0.09 (mGAT1)

pIC_{50} = 5.71 ± 0.07 (mGAT4)

Pabel et al. [64]



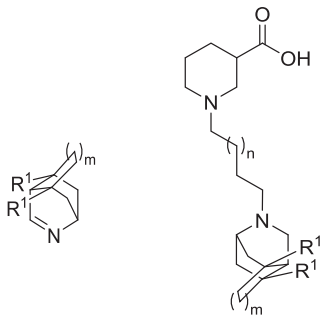
Deramciclane (*rac*-**9**)

pIC_{50} = 4.59 (mGAT1)[a]

pIC_{50} = 4.34 (mGAT4)[a]

Dhar et al. [39]

Fig. 2 Structures of important GAT inhibitors. The inhibitory potencies for mGAT1 and mGAT4 are given as pIC_{50} ± SEM (if determined), that have been obtained in [^{3}H]GABA uptake assays and reported literature. Percentage values represent the remaining [^{3}H] GABA uptake at a concentration of 100 µM test compound. [a]The values refer to the human GAT subtypes hGAT1 and hGAT3



10 *rac*-**11**

Fig. 3 General structure of the polycycles **10** to be used as starting material for the construction of the desired GAT inhibitors *rac*-**11**

AD and PD [46]. The drug Deramciclane (*rac*-**9**) is a rare example for a GAT inhibitor albeit with moderate inhibitory activity at all four GAT subtypes in which a polycyclic cage serving as lipophilic residue is present [48]. Since no systematic study aiming at the development of GAT inhibitors with a polycyclic cage subunit as lipophilic domain has been presented so far, though this appears to be quite rewarding, we intended to carry out such a study.

To this end, polycyclic cage structures based on a 2-azabicyclo[2.2.2]octane scaffold should be used, as they are easily available by an efficient and straightforward synthesis recently reported by us [49, 50]. For the present study the symmetric tricyclic imines **10** should be used (for general structure see Fig. 3). Though these polycyclic imines **10** display the same 2-azabicyclo[2.2.2]octane skeleton, the size of the bridge between the two substituted bridgehead atoms and thus the size of the tricyclic scaffold but also the orientation of the bridgehead substituents may be varied [51], thus allowing to study the impact of these two parameters on the inhibitory potency of the target compounds. As bridgehead substituents initially exclusively methyl and phenyl residues should be used as the synthesis of the respective symmetric tricyclic imines is known [51]. For the connection of these tricyclic cage units via their amino nitrogen, resulting from reduction of the imine function, with the amino nitrogen of racemic nipecotic acid (*rac*-**4**) a plain alky chain linker of varying length should be used. That way, the influence of the linker length on the biological activity should be explored as well.

Materials and methods

Anhydrous reactions were performed under an argon atmosphere in vacuum-dried glassware. All solvents were distilled prior to use and dry 1,4-dioxane and CH_2Cl_2 were prepared under a nitrogen atmosphere according to standard procedures [52]. The CH_2Cl_2 employed as solvent in reactions was stabilized with amylene, the CH_2Cl_2 used for workups was stabilized with ethanol. All purchased chemicals were used without further purification. TLC was performed with plates from Merck KGaA (silica gel 60 F_{254}). For purification via flash chromatography (FC) silica gel 60 (40–63 µm mesh size) from Merck KGaA was employed. Purification by preparative RP-MPLC was performed using an Büchi instrument (C-605 binary pump system, C-630 UV detector at 254 nm and C-660 fraction collector) and a Sepacore glass column B-685 (26 × 230 mm) equipped with YMC Gel Triart Prep C18-S (12 nm, 5–20 µm). Melting points were determined with a BÜCHI 510 melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin Elmer Paragon 1000 and a Jasco FT/IR-410. Solid substances were

measured as KBr pellets and oils as film on NaCl. HRMS were obtained with a Finnigan MAT 95 (EI) and a Finnigan LTQ FT (ESI). ^{1}H and ^{13}C NMR spectra were acquired with a Avance III HD Bruker BioSpin (400 or 500 MHz), referenced to the solvent residual peak as internal standard [53] and analyzed with MestReNova (Version 12.0.0–20080; Mestrelab Research S.L.; released 26.09.2017) . Nonequivalent protons attached to the same carbon center were differentiated by superscript a and b (e.g., NCH_2^a, NCH_2^b). The purity of the biologically tested compounds was determined by quantitative ^{1}H NMR (qH NMR) according to a method described by Pauli et al. with internal calibration [54]. The qH NMR measurements were carried out under conditions allowing complete relaxation to assure the exact determination of peak area ratios. Used internal standards were benzyl benzoate (LOT# BCBN 6347V; purity 99.43%) and 1,3,5-trimethoxy benzene (LOT# BCBW 3670; purity 99.96%) in $CDCl_3$, CD_2Cl_2, CD_3OD or $CD_3OD + 1M$ NaOD in D_2O (6:1). All tested esters had a purity >95%. The tested carboxylic acids contained varying amounts of water which was not considered an impurity as the acids were dissolved in aqueous media later on to perform the assays. The amount of water was identified by qH NMR and calculated from the change of the peak area ratio of the exchangeable protons (water peak) to the solvent residual protons compared to the same peak area ratio determined for pure solvent. In due consideration of the amount of water contained, the purity of all carboxylic acids was >95% with exception of the biologically inactive acids *rac*-**18b** and *rac*-**11m**, for which no purity was determined.

General procedures

Synthesis of ethyl nipecotate precursors *rac*-15a–15f (general procedure/GP1)

Potassium carbonate and sodium iodide were added to a solution of racemic ethyl nipecotate *rac*-**16** (1.0 equiv) in the solvent stated. The organic halide was added to this mixture that was stirred for the time period and at the temperature indicated in the respective experiment. The mixture was concentrated under vacuum, dissolved in ethyl acetate, and washed with water. Drying of the organic phase (Na_2SO_4) and removal of the solvent under vacuum afforded the crude product which was purified by FC.

Deprotection and reductive amination of the dimethoxy protected aldehydes *rac*-15e–15f with tricyclic imines 10a–10d (general procedure/GP2)

Part A: The tricyclic imine was dissolved in CH_2Cl_2 (15 mL/mmol) and sodium triacetoxyborohydride (2.5 equiv) and acetic acid (2.1 equiv) were added. The solution was stirred at 20 °C for 45 min.

Part B: In the meantime, the dimethoxy acetal (2.0 equiv) was dissolved in CH_2Cl_2 (16 mL/mmol), and $FeCl_3 \cdot 6\ H_2O$ was added. The acetal/salt suspension was rotated on a rotary evaporator at 45 °C (no vacuum) for 20 min. In doing so, the total volume was maintained by regular solvent addition. The suspension was quenched with concentrated aqueous $NaHCO_3$, extracted with CH_2Cl_2 (stabilized with amylene) for three times, dried (Na_2SO_4), and concentrated under vacuum. The remaining crude aldehyde was dissolved in CH_2Cl_2 (6.25 mL/$mmol_{Acetal}$), added to the imine/triacetoxyborohydride solution and stirred for the time period and at the temperature stated in the experiment. The reaction was quenched with potassium carbonate solution (1 mol/L), extracted with CH_2Cl_2 for three times, dried (Na_2SO_4), and concentrated under vacuum to afford the crude product which was finally purified by FC (SiO_2, EtOAc/MeOH/NEt_3 88:10:2) and, if denoted, by RP-MPLC (DCM/MeOH 1:1).

Deprotection and reductive amination of the dimethoxy protected aldehydes *rac*-15e–15f with tricyclic imines 10e–10f (general procedure/GP3)

Part A: The tricyclic imine was dissolved in MeOH (13.3 mL/mmol) and sodium cyanoborohydride (5 equiv) and hydrochloric acid (1 mol/L in Et_2O, 10 equiv) were added. The solution was stirred at 20 °C for 3 h. The reaction was quenched with water, adjusted to pH = 11 with K_2CO_3 and the crude amine was extracted with CH_2Cl_2 for three times. After drying (Na_2SO_4) and removal of the solvent under vacuum the crude amine was dissolved in CH_2Cl_2 (15 mL/mmol) again and sodium triacetoxyborohydride (2.5 equiv) and acetic acid (2.1 equiv) were added.

Part B: Identical with *Part B* from **GP2**.

Hydrolysis of the *N*-substituted nipecotic acid ethyl esters (general procedure/GP4)

The ester (1 equiv) was dissolved in MeOH (23 mL/mmol) and successively H_2O (5.7 mL/mmol) and $Ba(OH)_2 \cdot 8\ H_2O$ (4 equiv) were added. The mixture was stirred at 20 °C for 16 h. Then CO_2 was bubbled through the solution until all barium carbonate had precipitated and pH = 8 was reached. The suspension was diluted with MeOH (28.7 mL/mmol) and for all experiments with ≥0.1 mmol nipecotic acid ethyl ester the suspension was centrifuged (20 min, 3000 *g*) and the clear supernatant filtered via a syringe filter (PTFE, 0.2 µm pore size). For experiments carried out with ≤0.1 mmol nipecotic acid ethyl ester the centrifugation step was omitted. The solvent was removed under vacuum and

the crude *N*-substituted nipecotic acid was purified by RP-MPLC (MeOH).

rac-1-[3-(1,7-Dimethyl-4-azatricyclo[3.3.1.0^{2,7}]nonan-4-yl) propyl]piperidine-3-carboxylic acid *rac*-11a

According to **GP4**: Ester *rac*-**19a** (10 mg, 29 µmol, 1.0 equiv) and $Ba(OH)_2 \cdot 8\ H_2O$ (36 mg, 0.12 mmol, 4 equiv). The product was obtained as colorless oil (8 mg, 87%). IR (film) $\tilde{\nu} = 3398$, 2937, 2858, 2800, 1587, 1450, 1398, 1375, 1217, 1151, 1126, 1099 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): $\delta = 3.52$ (s, 1 H, CHN), 3.25 (dd, $J = 13.3/2.3$ Hz, 1 H, $CHNC\mathit{H}_2{}^aCH$), 3.21–3.11 (m, 3 H, $CHNC\mathit{H}_2CH_2$, $CHNC\mathit{H}_2{}^bCH$), 3.11–3.01 (m, 1 H, $OCCHC\mathit{H}_2{}^aN$), 2.91–2.83 (m, 1 H, $CHCH_2CH_2C\mathit{H}_2{}^a$), 2.70–2.59 (m, 2 H, $CHN(CH_2)_2C\mathit{H}_2$), 2.45–2.33 (m, 2 H, $OCCHC\mathit{H}_2{}^bN$, OCCH), 2.33–2.21 (m, 1 H, $CHCH_2CH_2C\mathit{H}_2{}^b$), 1.97–1.74 (m, 8 H, $CHNCH_2C\mathit{H}_2$, $NCH(C\mathit{H}_2)_2$, $CHC\mathit{H}_2{}^aCH_2$, $CHCH_2C\mathit{H}_2{}^a$), 1.71–1.64 (m, 2 H, $CCH_2{}^aC$, $CHNCH_2C\mathit{H}$), 1.64–1.52 (m, 2 H, $CHC\mathit{H}_2{}^bCH_2$, $CHCH_2C\mathit{H}_2{}^b$), 1.50 (d, $J = 9.1$ Hz, 1 H, $CCH_2{}^bC$), 1.10 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3) ppm; ^{13}C NMR (125 MHz, CD_3OD) $\delta = 181.6$ (CO), 58.3 (CHN $(CH_2)_2\mathit{C}H_2$), 58.0 ($OCCH\mathit{C}H_2N$), 57.4 ($CHN\mathit{C}H_2CH_2$), 56.0 (NCH), 55.4 ($CHCH_2CH_2\mathit{C}H_2$), 50.7 ($C\mathit{C}H_2C$), 47.9 ($CHN\mathit{C}H_2CH$), 45.8 ($OC\mathit{C}H$), 43.7 ($CHNCH_2\mathit{C}H$), 37.5 ($NCH\mathit{C}H_2$), 37.2 ($NCH\mathit{C}H_2$), 36.5 ($\mathit{C}CH_3$), 36.3 ($\mathit{C}CH_3$), 28.6 ($CH\mathit{C}H_2CH_2$), 25.7 ($CHCH_2\mathit{C}H_2$), 24.9 (CH_3), 24.9 (CH_3), 22.0 ($CHNCH_2\mathit{C}H_2$) ppm; HRESIMS *m*/*z* (pos): 321.2534 $C_{19}H_{33}N_2O_2$ (calcd. 321.2537).

rac-1-[3-(1,7-Diphenyl-4-azatricyclo[3.3.1.0^{2,7}]nonan-4-yl) propyl]piperidine-3-carboxylic acid *rac*-11b

According to **GP4**: Ester *rac*-**19b** (14 mg, 30 µmol, 1.0 equiv) and $Ba(OH)_2 \cdot 8\ H_2O$ (37 mg, 0.12 mmol, 4 equiv). The product was obtained as colorless viscous oil (12 mg, 91%). IR (film) $\tilde{\nu} = 3456$, 3057, 3024, 2927, 2854, 2804, 1574, 1495, 1446, 1402, 1333, 1155, 1030, 758, 698 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): $\delta = 7.37–7.29$ (m, 4 H, $CCHC\mathit{H}$), 7.29–7.24 (m, 4 H, $CC\mathit{H}CH$), 7.18 (t, $J = 7.1$ Hz, 2 H, $CCHCHC\mathit{H}$), 3.29 (d, $J = 2.3$ Hz, 2 H, $CHNC\mathit{H}_2CH$), 3.24 (br s, 1 H, CHN), 3.17 (d, $J = 10.4$ Hz, 1 H, $NC\mathit{H}_2{}^aCHCO$), 2.98 (d, $J = 11.5$ Hz, 1 H, $CHCH_2CH_2C\mathit{H}_2{}^a$), 2.85–2.70 (m, 2 H, $CHNC\mathit{H}_2CH_2$), 2.70–2.54 (m, 3 H, $CHNCH_2C\mathit{H}$, $CHN(CH_2)_2C\mathit{H}_2$), 2.45 (tt, $J = 10.3/3.5$ Hz, 1 H, CHCO), 2.42–2.28 (m, 4 H, $CC\mathit{H}_2{}^aC$, $NCH(C\mathit{H}_2{}^a)_2$, $NC\mathit{H}_2{}^bCHCO$), 2.28–2.11 (m, 4 H, $CC\mathit{H}_2{}^bC$, $NCH(C\mathit{H}_2{}^b)_2$, $CHCH_2CH_2C\mathit{H}_2{}^b$), 2.01–1.90 (m, 1 H, $CHC\mathit{H}_2{}^aCH_2$), 1.85 (p, $J = 7.4$ Hz, 2 H, $CHNCH_2C\mathit{H}_2$), 1.76 (dp, $J = 13.7/3.7$ Hz, 1 H, $CHCH_2C\mathit{H}_2{}^a$), 1.67–1.54 (m, 1 H, $CHCH_2C\mathit{H}_2{}^b$), 1.54–1.41 (m, 1 H, $CHC\mathit{H}_2{}^bCH_2$) ppm; ^{13}C NMR (125 MHz, CD_3OD) $\delta = 181.8$ (CO), 149.5 ($\mathit{C}CHCH$), 129.6 ($CCH\mathit{C}H$), 127.1 ($CCHCH\mathit{C}H$), 125.9 ($C\mathit{C}HCH$), 58.0 ($CHN(CH_2)_2\mathit{C}H_2$), 57.9 ($OCCH\mathit{C}H_2N$), 56.3 ($CHN\mathit{C}H_2CH_2$), 54.9 ($CHCH_2CH_2\mathit{C}H_2$), 54.6 (NCH), 50.3 ($CHN\mathit{C}H_2CH$), 50.0 ($C\mathit{C}H_2C$), 45.5 ($OC\mathit{C}H$), 43.9 ($CHNCH_2\mathit{C}H$), 43.1 ($\mathit{C}CH_2\mathit{C}$), 40.4 ($NCH\mathit{C}H_2$), 40.3 ($NCH\mathit{C}H_2$), 28.8 ($CH\mathit{C}H_2CH_2$), 25.3 ($CHCH_2\mathit{C}H_2$), 24.8 ($CHNCH_2\mathit{C}H_2$) ppm; HRESIMS *m*/*z* (pos): 445.2852 $C_{29}H_{37}N_2O_2$ (calcd. 445.2850).

rac-1-[3-(3,6-Dimethyl-9-azatricyclo[4.3.1.0^{3,7}]decan-9-yl) propyl]piperidine-3-carboxylic acid *rac*-11c

According to **GP4**: Ester *rac*-**19c** (20 mg, 55 µmol, 1.0 equiv) and $Ba(OH)_2 \cdot 8\ H_2O$ (70 mg, 0.22 mmol, 4 equiv). The product was obtained as yellow oil (13 mg, 70%). IR (film) $\tilde{\nu} = 3398$, 2943, 2864, 2806, 1574, 1471, 1452, 1396, 1184, 1155, 1095, 951 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): $\delta = 3.23–3.05$ (m, 4 H, NCH, $CHNC\mathit{H}_2CH$, $OCCHC\mathit{H}_2{}^aN$) 2.98 (t, $J = 7.2$ Hz, 2 H, $CHNC\mathit{H}_2CH_2$), 2.90 (d, $J = 11.3$ Hz, 1 H, $CHCH_2CH_2C\mathit{H}_2{}^a$), 2.66–2.50 (m, 2 H, $CHN(CH_2)_2C\mathit{H}_2$), 2.41 (t, $J = 10.4/3.7$ Hz, 1 H, OCCH), 2.27 (t, $J = 9.7$ Hz, 1 H, $OCCHC\mathit{H}_2{}^bN$), 2.23–2.13 (m, 1 H, $CHCH_2CH_2C\mathit{H}_2{}^b$), 2.00–1.88 (m, 3 H, $NCH(C\mathit{H}_2{}^a)_2$, $CHC\mathit{H}_2{}^aCH_2$), 1.86 (p, $J = 7.2$ Hz, 2 H, $CHNCH_2C\mathit{H}_2$), 1.80–1.73 (m, 1 H, $CHCH_2C\mathit{H}_2{}^a$), 1.72–1.44 (m, 8 H, NCH $(C\mathit{H}_2{}^b)_2$, $CHC\mathit{H}_2{}^bCH_2$, $CHCH_2C\mathit{H}_2{}^b$, $CC\mathit{H}_2C\mathit{H}_2C$), 1.18 (d, $J = 1.8$ Hz, 6 H, CH_3), 1.14 (s, 1 H, $CHNCH_2C\mathit{H}$) ppm; ^{13}C NMR (125 MHz, CD_3OD) $\delta = 181.9$ (CO), 57.9 (CHN $(CH_2)_2\mathit{C}H_2$), 57.9 ($OCCH\mathit{C}H_2N$), 55.9 ($CHN\mathit{C}H_2CH_2$), 55.2 ($CHCH_2CH_2\mathit{C}H_2$), 53.9 (NCH), 48.8 ($CHNCH_2\mathit{C}H$), 46.3 ($CHN\mathit{C}H_2CH$), 45.9 ($OC\mathit{C}H$), 41.1 ($C\mathit{C}H_2\mathit{C}H_2C$), 40.5 ($NCHC^bH_2$), 40.4 ($NCHC^aH_2$), 39.8 ($\mathit{C}CH_3$), 28.9 ($CH\mathit{C}H_2CH_2$), 26.2 ($CH_3$), 25.7 ($CHCH_2\mathit{C}H_2$), 22.8 ($CHNCH_2\mathit{C}H_2$) ppm; HRESIMS *m*/*z* (pos): 335.2694 $C_{20}H_{35}N_2O_2$ (calcd. 335.2693).

rac-1-[3-(3,6-Diphenyl-9-azatricyclo[4.3.1.0^{3,7}]decan-9-yl) propyl]piperidine-3-carboxylic acid *rac*-11d

According to **GP4**: Ester *rac*-**19d** (19 mg, 39 µmol, 1.0 equiv) and $Ba(OH)_2 \cdot 8\ H_2O$ (49 mg, 0.16 mmol, 4 equiv). The product was obtained as colorless oil (15 mg, 84%). IR (film) $\tilde{\nu} = 3452$, 3055, 2945, 2868, 2810, 1579, 1495, 1444, 1396, 1153, 1105, 1030, 760, 700 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): $\delta = 7.50–7.44$ (m, 4 H, $CC\mathit{H}CH$), 7.42–7.36 (m, 4 H, $CCHC\mathit{H}$), 7.25–7.20 (m, 2 H, $CCHCHC\mathit{H}$), 3.24 (s, 1 H, NCH), 3.14–3.02 (m, 3 H, $CHNC\mathit{H}_2CH$, $OCCHC\mathit{H}_2{}^aN$), 2.95 (s, 1 H, $CHNCH_2C\mathit{H}$), 2.93–2.86 (m, 1 H, $CHCH_2CH_2C\mathit{H}_2{}^a$), 2.80–2.65 (m, 4 H, $CHNC\mathit{H}_2CH_2$, $CHN(CH_2)_2C\mathit{H}_2$), 2.59 (dd, $J = 14.4/2.4$ Hz, 2 H, $NCH(C\mathit{H}_2{}^a)_2$), 2.47 (br s, 1 H, $OCCHC\mathit{H}_2{}^bN$), 2.29 (br s, 1 H, $CHCH_2CH_2C\mathit{H}_2{}^b$), 2.24–2.09 (m, 3 H, $NCH(C\mathit{H}_2{}^b)_2$, OCCH), 2.05–1.86 (m, 4 H, $CC\mathit{H}_2C\mathit{H}_2C$), 1.72

(p, $J = 6.5$ Hz, 2 H, CHNCH$_2$CH_2), 1.70–1.65 (m, 1 H, CHCH_2^aCH$_2$), 1.57–1.47 (m, 1 H, CHCH$_2$CH_2^a), 1.47–1.36 (m, 1 H, CHCH_2^bCH$_2$), 1.13–0.98 (m, 1 H, CHCH$_2$CH_2^b) ppm; ^{13}C NMR (125 MHz, CD_3OD) $\delta = 180.4$ (CO), 149.3 (*C*CHCH), 129.9 (CCH*C*^{a}H), 129.8 (CCH*C*^{b}H), 127.2 (CCHCH*C*H), 126.8 (C*C*^{a}HCH), 126.8 (C*C*^{b}HCH), 58.5 (CHN(CH$_2$)$_2$*C*H$_2$), 57.5 (OCCH*C*H$_2$N), 56.5 (CHN*C*H$_2$CH$_2$), 54.5 (CHCH$_2$CH$_2$*C*H$_2$), 53.6 (NCH), 47.5 (CHN*C*H$_2$CH), 47.3 (*C*^{a}CH$_2$), 47.3 (*C*^{b}CH$_2$), 44.4 (C*C*H$_2$*C*H$_2$C), 44.3 (OC*C*H), 42.3 (CHNCH$_2$*C*H), 42.0 (NCH*C*^{b}H$_2$), 41.7 (NCH*C*^{a}H$_2$), 27.7 (CH$_2$*C*H$_2$CH), 24.1 (CHCH$_2$*C*H$_2$), 21.9 (CHNCH$_2$*C*H$_2$) ppm; HRESIMS *m/z* (pos): 459.3002 $C_{30}H_{39}N_2O_2$ (calcd. 459.3006).

rac-1-[3-(3,7-Dimethyl-10-azatricyclo[5.3.1.0^{3,8}]undecan-10-yl)propyl]piperidine-3-carboxylic acid *rac*-11e

According to **GP4**: Ester *rac*-**19e** (20 mg, 53 µmol, 1.0 equiv) and $Ba(OH)_2 \cdot 8\ H_2O$ (67 mg, 0.21 mmol, 4 equiv). The product was obtained as yellow oil (15 mg, 81%). IR (film) $\tilde{\nu} = 3419$, 2922, 1709, 1574, 1452, 1400, 1223, 1157, 1095, 953 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): $\delta =$ 3.31–3.29 (m, 2 H, CHNCH_2CH), 3.27 (s, 1 H, CHN), 3.11 (d, $J = 10.9$ Hz, 1 H, OCCHCH_2^aN), 3.04 (t, $J = 7.3$ Hz, 2 H, CHNCH_2CH$_2$), 2.90 (d, $J = 11.4$ Hz, 1 H, CHCH$_2$CH$_2$CH_2^a), 2.63–2.50 (m, 2 H, CHN(CH$_2$)$_2$CH_2), 2.41 (tt, $J = 10.6/3.7$ Hz, 1 H, OCCH), 2.24 (t, $J = 10.4$ Hz, 1 H, OCCHCH_2^bN), 2.17 (t, $J = 10.4$ Hz, 1 H, CHCH$_2$CH$_2$CH_2^b), 2.00–1.91 (m, 1 H, CHCH_2^aCH$_2$), 1.88 (p, $J = 7.3$ Hz, 2 H, CHNCH$_2$CH_2), 1.81–1.69 (m, 3 H, NCH(CH_2^a)$_2$, CHCH$_2$CH_2^a), 1.67–1.43 (m, 6 H, NCH(CH_2^b)$_2$, CCH$_2$CH_2, CHCH_2^bCH$_2$, CHCH$_2$CH_2^b), 1.43–1.35 (m, 2 H, CCH_2^aCH$_2$CH_2^aC), 1.21 (ddd, $J = 13.4/13.4/4.6$ Hz, 2 H, CCH_2^bCH$_2$CH_2^bC), 1.13 (s, 6 H, CH$_3$), 0.97 (s, 1 H, CHNCH$_2$C*H*) ppm; ^{13}C NMR (125 MHz, CD_3OD) $\delta = 182.0$ (CO), 57.8 (OCCH*C*H$_2$N), 57.7 (CHN(CH$_2$)$_2$*C*H$_2$), 55.7 (CHN*C*H$_2$CH$_2$), 55.3 (CHCH$_2$CH$_2$*C*H$_2$), 54.9 (NCH), 48.1 (CHN*C*H$_2$CH), 45.8 (OC*C*H), 45.4 (CHNCH$_2$*C*H), 41.0 (C*C*H$_2$CH$_2$*C*H$_2$C), 34.8 (NCH(*C*H$_2$)$_2$), 31.2 (*C*CH$_3$), 30.4 (CH$_3$), 29.0 (CH*C*H$_2$CH$_2$), 25.7 (CHCH$_2$*C*H$_2$), 23.1 (CHNCH$_2$*C*H$_2$), 19.7 (CCH$_2$*C*H$_2$) ppm; HRESIMS *m/z* (pos): 349.2851 $C_{21}H_{37}N_2O_2$ (calcd. 349.2850).

rac-1-[3-(3,7-Diphenyl-10-azatricyclo[5.3.1.0^{3,8}]undecan-10-yl)propyl]piperidine-3-carboxylic acid *rac*-11f

According to **GP4**: Ester *rac*-**19f** (13 mg, 26 µmol, 1.0 equiv) and $Ba(OH)_2 \cdot 8\ H_2O$ (33 mg, 0.10 mmol, 4 equiv). The product was obtained as colorless oil (9 mg, 73%). IR (film) $\tilde{\nu} = 3398$, 2926, 2848, 2360, 2341, 1578, 1497, 1444, 1396, 1155, 1082, 1032, 758, 700 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): $\delta = 7.60$–7.51 (m, 4 H, CC*H*CH), 7.45–7.37 (m, 4 H, CCHC*H*), 7.27–7.20 (m, 2 H, CCHCHC*H*), 3.43 (s, 1 H, NCH), 3.12–2.90 (m, 4 H, C*H*CH$_2$NCH, CHNCH_2CH, OCCHCH_2^aN), 2.80 (d, $J =$ 11.6 Hz, 1 H, CHCH$_2$CH$_2$CH_2^a), 2.76–2.50 (m, 6 H, CHN(CH$_2$)$_2$CH_2, CHNCH_2CH$_2$, NCH(CH_2^a)$_2$), 2.32–2.12 (m, 3 H, NCH(CH_2^b)$_2$, OCCHCH_2^bN), 2.06–1.84 (m, 3 H, CCH$_2$CH_2^a, CHCH$_2$CH$_2$CH_2^b, OCCH), 1.71–1.42 (m, 8 H, CCH_2CH$_2$CH_2C, CCH$_2$CH_2^b, CHCH_2^aCH$_2$, CHNCH$_2$CH_2), 1.37–1.26 (m, 2 H, CHCH_2^bCH$_2$, CHCH$_2$CH_2^a), 0.74–0.53 (m, 1 H, CHCH$_2$CH_2^b) ppm; ^{13}C NMR (125 MHz, CD_3OD) $\delta = 180.7$ (CO), 151.1 (CH$_2$C*C*^{a}), 150.9 (CH$_2$C*C*^{b}), 130.0 (CCH*C*^{a}H), 129.9 (CCH*C*^{b}H), 127.3(CCHCH*C*H), 127.2 (C*C*^{a}HCH), 127.2 (C*C*^{b}HCH), 59.1 (CHN(CH$_2$)$_2$*C*H$_2$), 58.4 (CHN*C*H$_2$CH$_2$), 58.1 (OCCH*C*H$_2$N), 54.6 (NCH), 54.3 (CHCH$_2$CH$_2$*C*H$_2$), 50.0 (CHN*C*H$_2$CH), 45.0 (C*C*^{a}H$_2$CH$_2$), 45.0 (C*C*^{b}H$_2$CH$_2$), 44.9 (OC*C*H), 40.1 (*C*^{a}CH$_2$), 40.1 (*C*^{b}CH$_2$), 36.9 (CHNCH$_2$*C*H), 35.9 (NCH*C*^{a}H$_2$), 34.5 (NCH*C*^{b}H$_2$), 28.0 (CH$_2$*C*H$_2$CH), 24.3 (CHCH$_2$*C*H$_2$), 21.2 (CHNCH$_2$*C*H$_2$), 21.0 (CCH$_2$*C*H$_2$) ppm; HRESIMS *m/z* (pos): 473.3157 $C_{31}H_{41}N_2O_2$ (calcd. 473.3163).

rac-1-[4-(1,7-Dimethyl-4-azatricyclo[3.3.1.0^{2,7}]nonan-4-yl)butyl]piperidine-3-carboxylic acid *rac*-11g

According to **GP4**: Ester *rac*-**19g** (28 mg, 77 µmol, 1.0 equiv) and $Ba(OH)_2 \cdot 8\ H_2O$ (97 mg, 0.31 mmol, 4 equiv). The product was obtained as yellow oil (20 mg, 77%). IR (film) $\tilde{\nu} = 3408$, 2927, 2860, 2800, 1589, 1454, 1379, 1155, 1095, 1025, 939, 731 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): $\delta = 3.19$–3.09 (m, 1 H, OCCHCH_2^aN), 2.96–2.83 (m, 2 H, CHCH$_2$CH$_2$CH_2^a, CHN), 2.73 (d, $J = 2.4$ Hz, 2 H, CHNCH_2CH), 2.63–2.47 (m, 2 H, CHNCH_2CH$_2$), 2.46–2.29 (m, 3 H, CHN(CH$_2$)$_3$CH_2, OCCH), 2.09–1.96 (m, 2 H, CHCH_2^aCH$_2$, OCCHCH_2^bN), 1.92 (ddd, $J = 11.8/11.8/2.5$ Hz, 1 H, CHCH$_2$CH$_2$CH_2^b), 1.83 (d, $J = 13.3$ Hz, 2 H, NCH(CH_2^a)$_2$), 1.75–1.67 (m, 1 H, CHCH$_2$CH_2^a), 1.67–1.44 (m, 8 H, CHCH$_2$CH_2^b, NCH$_2$CH_2CH_2CH$_2$N, CCH$_2^a$C, NCH(CH_2^b)$_2$), 1.41 (s, 1 H, CHNCH$_2$C*H*), 1.40–1.31 (m, 2 H, CCH$_2^b$C, CHCH_2^bCH$_2$), 1.01 (s, 6 H, CH$_3$) ppm; ^{13}C NMR (125 MHz, CD_2Cl_2) $\delta = 182.6$ (CO), 60.1 (CHN(CH$_2$)$_3$*C*H$_2$), 58.2 (OCCH*C*H$_2$N), 57.8 (CHN*C*H$_2$CH$_2$), 55.0 (CHCH$_2$CH$_2$*C*H$_2$), 53.8 (NCH), 51.8 (C*C*H$_2$C), 48.1 (CHN*C*H$_2$CH), 46.3 (OC*C*H), 45.8 (CHNCH$_2$*C*H), 39.1 (NCH(*C*H$_2$)$_2$), 36.6 (*C*CH$_3$), 29.5 (CH*C*H$_2$CH$_2$), 26.9 (CHNCH$_2$CH$_2$*C*H$_2$), 26.0 (CHCH$_2$*C*H$_2$), 25.5 (CHNCH$_2$*C*H$_2$, CH$_3$) ppm; HRESIMS *m/z* (pos): 335.2695 $C_{20}H_{35}N_2O_2$ (calcd. 335.2693).

rac-1-[4-(1,7-Diphenyl-4-azatricyclo[3.3.1.0^{2,7}]nonan-4-yl)butyl]piperidine-3-carboxylic acid *rac*-11h

According to **GP4**: Ester *rac*-**19h** (14 mg, 29 µmol, 1.0 equiv) and $Ba(OH)_2 \cdot 8\ H_2O$ (36 mg, 0.12 mmol, 4 equiv).

The product was obtained as colorless viscous oil (13 mg, 98%). IR (KBr) $\tilde{\nu} = 3419$, 3057, 3024, 2933, 2858, 2800, 1601, 1495, 1446, 1387, 1155, 1030, 760, 700, 536 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): $\delta = 7.36–7.31$ (m, 4 H, CCHC*H*), 7.31–7.25 (m, 4 H, CC*H*CH), 7.23–7.17 (m, 2 H, CCHCHC*H*), 3.45 (br s, 1 H, CHN), 3.42 (d, $J =$ 2.2 Hz, 2 H, CHNCH_2CH), 3.11 (d, $J = 10.5$ Hz, 1 H, NCH_2^aCHCO), 3.08–2.78 (m, 7 H, NCH_2CH$_2$CH$_2$CH_2N, CHCH$_2$CH$_2$CH_2, NCH_2^bCHCO), 2.75 (s, 1 H, CHNCH$_2$C*H*), 2.60–2.52 (m, 1 H, CHCO), 2.44–2.33 (m, 3 H, CCH_2^aC, NCH(CH_2^a)$_2$), 2.29 (dd, $J = 14.0/$ 3.2 Hz, 2 H, NCH(CH_2^b)$_2$), 2.23 (d, $J = 8.9$ Hz, 1 H, CCH_2^bC), 1.93–1.81 (m, 2 H, CHCH$_2$CH_2^a, CHCH_2^aCH$_2$), 1.81–1.64 (m, 6 H, CHCH_2^bCH$_2$, CHCH$_2$CH_2^b, NCH$_2$CH_2CH_2CH$_2$N) ppm; ^{13}C NMR (125 MHz, CD_3OD) $\delta = 180.4$ (CO), 148.8 (*C*CHCH), 129.7 (CCH*C*H), 127.4 (CCHCH*C*H), 125.9 (C*C*HCH), 58.2 (CHN(CH$_2$)$_3$CH$_2$), 57.0 (CHN*C*H$_2$CH$_2$), 56.2 (OCCH*C*H$_2$N), 55.0 (NCH), 54.8 (CHCH$_2$CH$_2$*C*H$_2$), 50.3 (CHN*C*H$_2$CH), 50.0 (C*C*H$_2$C), 43.2 (OC*C*H), 43.0 (CHNCH$_2$*C*H), 42.9 (*C*CH$_2$*C*), 39.5 (NCH(*C*H$_2$)$_2$), 27.4 (CH*C*H$_2$CH$_2$), 25.1 (CHNCH$_2$CH$_2$*C*H$_2$)*, 23.5 (CHNCH$_2$*C*H$_2$)*, 23.5 (CHCH$_2$*C*H$_2$) ppm; Signals indicated by asterisk cannot be assigned unambiguously and are interchangeable. HRESIMS *m*/*z* (pos): 459.3008 $C_{30}H_{39}N_2O_2$ (calcd. 459.3006).

rac-1-[4-(3,6-Dimethyl-9-azatricyclo[4.3.1.0^{3,7}]decan-9-yl) butyl]piperidine-3-carboxylic acid *rac*-11j

According to **GP4**: Ester *rac*-**19j** (20 mg, 53 µmol, 1.0 equiv) and $Ba(OH)_2 \cdot 8\ H_2O$ (67 mg, 0.21 mmol, 4 equiv). The product was obtained as yellow oil (18 mg, 97%). IR (film) $\tilde{\nu} = 3398$, 2943, 2866, 2800, 1579, 1471, 1450, 1396, 1180, 1155, 1093 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2): $\delta = 10.77$ (br s, 1 H, COOH), 3.06–2.87 (m, 4 H, NCH, CHNCH_2CH, OCCHCH_2^aN), 2.78–2.63 (m, 3 H, CHNCH_2CH$_2$, CHCH$_2$CH$_2$CH_2^a), 2.47–2.31 (m, 3 H, CHN(CH$_2$)$_3$CH_2, OCCH), 2.26–2.07 (m, 2 H, CHCH$_2$CH$_2$CH_2^b, OCCHCH_2^bN), 1.97–1.81 (m, 3 H, NCH(CH_2^a)$_2$, CHCH_2^aCH$_2$), 1.75–1.65 (m, 1 H, CHCH$_2$CH_2^a), 1.65–1.39 (m, 10 H, CHCH_2^bCH$_2$, CHCH$_2$CH_2^b, NCH$_2$CH_2CH_2CH$_2$N, CCH_2CH_2C), 1.34 (dd, $J = 13.9/1.9$ Hz, 2 H, NCH(CH_2^b)$_2$), 1.13 (s, 6 H, CH$_3$), 1.00 (s, 1 H, CHNCH$_2$C*H*) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) $\delta = 178.8$ (CO), 58.3 (CHN(CH$_2$)$_3$*C*H$_2$), 56.7 (CHN*C*H$_2$CH$_2$), 54.9 (OCCH*C*H$_2$N), 54.3 (CHCH$_2$CH$_2$*C*H$_2$), 51.4 (NCH), 48.5 (CHNCH$_2$*C*H), 44.7 (CHN*C*H$_2$CH), 43.4 (OC*C*H), 40.6 (C*C*H$_2$C*H*$_2$C), 40.0 (NCH(*C*H$_2$)$_2$), 39.2 (*C*CH$_3$), 28.1 (CH*C*H$_2$CH$_2$), 26.1 (CH$_3$), 24.8 (CHCH$_2$*C*H$_2$), 24.2 (CHNCH$_2$*C*H$_2$), 24.0 (CHN(CH$_2$)$_2$*C*H$_2$) ppm; HRESIMS *m*/*z* (pos): 349.2850 $C_{21}H_{37}N_2O_2$ (calcd. 349.2850).

rac-1-[4-(3,6-Diphenyl-9-azatricyclo[4.3.1.0^{3,7}]decan-9-yl) butyl]piperidine-3-carboxylic acid *rac*-11k

According to **GP4**: Ester *rac*-**19k** (13 mg, 26 µmol, 1.0 equiv) and $Ba(OH)_2 \cdot 8\ H_2O$ (33 mg, 0.10 mmol, 4 equiv). The product was obtained as colorless viscous oil (8 mg, 65%). IR (film) $\tilde{\nu} = 3398$, 3054, 2943, 2866, 2802, 1651, 1587, 1495, 1444, 1394, 1153, 1105, 1032, 760, 702 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): $\delta = 7.49–7.43$ (m, 4 H, CC*H*CH), 7.39–7.33 (m, 4 H, CCHC*H*), 7.23–7.17 (m, 2 H, CCHCHC*H*), 3.02 (d, $J = 9.1$ Hz, 1 H, OCCHCH_2^aN), 2.98 (s, 1 H, NCH), 2.96–2.88 (m, 2 H, CHNCH_2CH), 2.85–2.77 (m, 2 H, CHCH$_2$CH$_2$CH_2^a, CHNCH$_2$C*H*), 2.56 (dt, $J =$ 13.9/2.6 Hz, 2 H, NCH(CH_2^a)$_2$), 2.53–2.44 (m, 2 H, CHN (CH$_2$)$_3$CH_2), 2.44–2.30 (m, 4 H, OCCHCH_2^bN, OCCH, CHNCH_2CH$_2$), 2.25–2.16 (m, 1 H, CHCH$_2$CH$_2$CH_2^b), 2.08 (dt, $J = 13.9/2.6$ Hz, 2 H, NCH(CH_2^b)$_2$), 2.01–1.84 (m, 5 H, CHCH_2^aCH$_2$, CCH_2CH_2C), 1.73–1.65 (m, 1 H, CHCH$_2$CH_2^a), 1.58–1.38 (m, 6 H, CHCH_2^bCH$_2$, NCH$_2$CH_2CH_2CH$_2$N, CHCH$_2$CH_2^b) ppm; ^{13}C NMR (125 MHz, CD_3OD) $\delta = 181.5$ (CO), 150.1 (*C*CHCH), 129.6 (CCH*C*H), 126.8 (C*C*HCH), 126.8 (CCHCH*C*H), 59.0 (CHN(CH$_2$)$_3$*C*H$_2$), 57.1 (OCCH*C*H$_2$N), 56.3 (CHN*C*H$_2$CH$_2$), 54.8 (CHCH$_2$CH$_2$*C*H$_2$), 52.4 (NCH), 47.6 (*C*^{a}CH$_2$), 47.5 (*C*^{b}CH$_2$), 47.4 (CHN*C*H$_2$CH), 44.8 (OC*C*H), 44.3 (C*C*H$_2$C*H*$_2$C), 43.0 (CHNCH$_2$*C*H), 42.3 (NCH*C*^{a}H$_2$), 42.2 (NCH*C*^{b}H$_2$), 28.5 (CH$_2$*C*H$_2$CH), 25.6 (CHNCH$_2$*C*H$_2$), 24.7 (CHNCH$_2$CH$_2$*C*H$_2$), 24.5 (CHCH$_2$*C*H$_2$) ppm; HRESIMS *m*/*z* (pos): 473.3164 $C_{31}H_{41}N_2O_2$ (calcd. 473.3163).

rac-1-[4-(3,7-Dimethyl-10-azatricyclo[5.3.1.0^{3,8}]undecan-10-yl)butyl]piperidine-3-carboxylic acid *rac*-11l

According to **GP4**: Ester *rac*-**19l** (17 mg, 44 µmol, 1.0 equiv) and $Ba(OH)_2 \cdot 8\ H_2O$ (55 mg, 0.17 mmol, 4 equiv). The product was obtained as colorless viscous oil (15 mg, 96%). IR (film) $\tilde{\nu} = 3398$, 2924, 2800, 1583, 1454, 1390, 1157, 1097, 1026, 953, 770 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2): $\delta = 9.02$ (br s, 1 H, COOH), 3.26–3.08 (m, 3 H, CHN, CHNCH_2CH), 2.97 (d, $J = 10.2$ Hz, 1 H, OCCH-CH_2^aN), 2.89–2.76 (m, 2 H, CHNCH_2CH$_2$), 2.76–2.64 (m, 1 H, CHCH$_2$CH$_2$CH_2^a), 2.48–2.31 (m, 3 H, OCCH, CHN(CH$_2$)$_3$CH_2), 2.27–2.03 (m, 2 H, CHCH$_2$CH$_2$CH_2^b, OCCHCH_2^bN), 1.94–1.83 (m, 1 H, CHCH_2^aCH$_2$), 1.75 (dd, $J = 13.9/2.7$ Hz, 2 H, NCH(CH_2^a)$_2$), 1.72–1.31 (m, 13 H, NCH(CH_2^b)$_2$, CCH_2^aCH$_2$CH_2^aC, CHCH_2^bCH$_2$, CHCH$_2$CH_2, NCH$_2$CH_2CH_2CH$_2$N, CCH$_2$CH_2), 1.14 (ddd, $J = 13.1/13.1/5.5$ Hz, 2 H, CCH_2^bCH$_2$CH_2^bC), 1.09 (s, 6 H, CH$_3$), 0.84 (s, 1 H, CHNCH$_2$C*H*) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) $\delta = 179.0$ (CO), 58.2 (CHN(CH$_2$)$_3$*C*H$_2$), 56.7 (OCCH*C*H$_2$N), 54.9 (CHN*C*H$_2$CH$_2$), 54.4 (CHCH$_2$CH$_2$*C*H$_2$), 52.4 (NCH), 46.3 (CHN*C*H$_2$CH), 44.9 (CHNCH$_2$*C*H), 43.5 (OC*C*H), 40.4 (C*C*H$_2$CH$_2$*C*H$_2$C), 34.0

(NCH(CH_2)$_2$), 30.6 (CCH_3), 30.1 (CH_3), 28.2 (CHCH_2CH$_2$), 24.9 (CHCH$_2$$CH_2$), 24.2 (CHN(CH$_2$)$_2$$CH_2$)*, 23.9 (CHNCH$_2$$CH_2$)*, 19.2 (CCH$_2$$CH_2$) ppm; Signals indicated by asterisk cannot be assigned unambiguously and are interchangeable; HRESIMS *m/z* (pos): 363.3006 $C_{22}H_{39}N_2O_2$ (calcd. 363.3006).

rac-1-[4-(3,7-Diphenyl-10-azatricyclo[5.3.1.0^{3,8}]undecan-10-yl)butyl]piperidine-3-carboxylic acid *rac*-11m

According to **GP4**: Ester *rac*-**19m** (12 mg, 23 µmol, 1.0 equiv) and Ba(OH)$_2$ · 8 H$_2$O (29 mg, 92 µmol, 4 equiv). The product was obtained as colorless oil (6 mg, 53%). IR (film) $\tilde{\nu}$ = 3390, 3055, 2926, 2852, 2800, 1595, 1495, 1444, 1402, 1155, 1099, 1032, 756, 700 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ = 7.54 (d, J = 8.3 Hz, 4 H, CC*H*CH), 7.44–7.34 (m, 4 H, CCHC*H*), 7.21 (t, J = 7.3 Hz, 2 H, CCHCHC*H*), 3.23 (s, 1 H, NCH), 2.95 (d, J = 8.4 Hz, 1 H, OCCHCH_2^aN), 2.92–2.84 (m, 2 H, CHNCH_2CH), 2.82 (s, 1 H, C*H*CH$_2$NCH), 2.78–2.73 (m, 1 H, CHCH$_2$CH$_2$CH_2^a), 2.73–2.64 (m, 2 H, NCH(CH_2^a)$_2$), 2.52–2.28 (m, 6 H, OCCHCH_2^bN, CHN(CH$_2$)$_3$CH_2, CHNCH_2CH$_2$, OCCH), 2.28–2.18 (m, 1 H, CHCH$_2$CH$_2$CH_2^b), 2.14 (ddd, J = 14.6/5.6/2.3 Hz, 2 H, NCH(CH_2^b)$_2$), 1.99–1.90 (m, 1 H, CCH$_2$CH_2^a), 1.89–1.82 (m, 1 H, CHCH_2^aCH$_2$), 1.72–1.59 (m, 4 H, CHCH$_2$CH_2^a, CCH$_2$CH_2^b, CCH_2^aCH$_2$CH_2^aC), 1.56–1.33 (m, 8 H, CHCH_2^bCH$_2$, CHCH$_2$CH_2^b, CHNCH$_2$CH_2, CHN(CH$_2$)$_2$CH_2, CCH_2^bCH$_2$CH_2^bC) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ = 181.3 (CO), 151.5 (CH$_2$C*C*), 129.7 (CCH*C*H), 127.2 (C*C*HCH), 127.0 (CCHCH*C*H), 58.4 (CHN(CH$_2$)$_3$*C*H$_2$), 56.9 (OCCH*C*H$_2$N), 56.5 (CHN*C*H$_2$CH$_2$), 54.7 (CHCH$_2$CH$_2$*C*H$_2$), 53.0 (NCH), 50.0 (CHN*C*H$_2$CH), 45.0 (C*C*H$_2$CH$_2$*C*H$_2$C), 44.5 (OC*C*H), 40.3 (*C*CH$_2$), 37.5 (CHNCH$_2$*C*H), 35.3 (NCH*C*^{a}H$_2$), 35.1 (NCH*C*^{b}H$_2$), 28.3 (CH$_2$*C*H$_2$CH), 24.9 (CHNCH$_2$*C*H$_2$), 24.5 (CHCH$_2$*C*H$_2$), 24.1 (CHN(CH$_2$)$_2$*C*H$_2$), 21.1 (CCH$_2$*C*H$_2$) ppm; HRESIMS *m/z* (pos): 487.3315 $C_{32}H_{43}N_2O_2$ (calcd. 487.3319).

rac-Ethyl 1-(3-hydroxypropyl)piperidine-3-carboxylate *rac*-15a

Synthesis according to literature [39].

rac-Ethyl 1-(4-hydroxybutyl)piperidine-3-carboxylate *rac*-15b

According to **GP1**: Reaction under exclusion of oxygen and light with potassium carbonate (4.15 g, 30.0 mmol, 3.0 equiv), sodium iodide (19 mg, 0.13 mmol, 0.01 equiv), ethyl nipecotate *rac*-**16** (1.57 g, 10.0 mmol, 1.6 mL, 1.0 equiv) and 4-bromobutan-1-ol (2.30 g, 15.0 mmol, 1.5 equiv) (no solvent used; the mixture was cooled to 0 °C prior to the halide addition). The temperature was kept at 0 °C for 6 h, then at 20 °C for 42 h. FC (SiO_2, CH_2Cl_2/MeOH/NEt_3 93:5:2). The product was obtained as colorless oil (2.18 g, 95%). IR (film): $\tilde{\nu}$ = 3390, 2939, 2868, 2810, 2775, 1732, 1470, 1446, 1371, 1311, 1182, 1151, 1032, 862 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.11 (dq, J = 7.2/0.5 Hz, 2 H, CH_2CH$_3$), 3.59–3.50 (m, 2 H, CH_2OH), 3.08 (d, J = 11.3 Hz, 1 H, NCH_2^aCH), 2.86 (d, J = 11.3 Hz, 1 H, CHCH$_2$CH$_2$CH_2^a), 2.59 (tt, J = 11.1/3.9 Hz, 1 H, CHCO), 2.43–2.34 (m, 2 H, NCH_2(CH$_2$)$_3$OH), 2.13 (t, J = 11.1 Hz, 1 H, NCH_2^bCH), 2.03–1.92 (m, 2 H, NCH$_2$CHCH_2^a, CHCH$_2$CH$_2$CH_2^b), 1.77–1.54 (m, 6 H, CHCH$_2$CH_2, CH_2CH_2CH$_2$OH), 1.40 (dq, J = 12.0/4.3 Hz, 1 H, NCH$_2$CHCH_2^b), 1.23 (t, J = 7.2 Hz, 3 H, CH$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9 (CO), 62.8 (CH$_2$OH), 60.6 (*C*H$_2$CH$_3$), 59.0 (*C*H$_2$(CH$_2$)$_3$OH), 55.3 (CH*C*H$_2$N), 53.7 (CHCH$_2$CH$_2$*C*H$_2$), 41.5 (*C*HCO), 32.7 (*C*H$_2$CH$_2$OH), 27.1 (CH*C*H$_2$CH$_2$), 25.6 (*C*H$_2$CH$_2$CH$_2$OH), 24.4 (CHCH$_2$*C*H$_2$), 14.3 (CH_3) ppm; HREIMS *m/z* [M]$^+$: 229.1692 $C_{12}H_{23}NO_3$ (calcd. 229.1672).

rac-Ethyl 1-[2-(1,3-dioxolan-2-yl)ethyl]piperidine-3-carboxylate *rac*-15c

According to **GP1**: Potassium carbonate (9.12 g, 66.0 mmol, 3.3 equiv), sodium iodide (41 mg, 0.28 mmol, 0.01 equiv), ethyl nipecotate *rac*-**16** (3.14 g, 20.0 mmol, 3.1 mL, 1.0 equiv) and 2-(2-bromoethyl)-1,3-dioxolane (3.98 g, 22.0 mmol, 2.6 mL, 1.1 equiv) (no solvent used; the mixture was cooled to 0 °C prior to the halide addition). The temperature was kept at 0 °C for 3 h, then at 20 °C for 48 h. FC (SiO_2, CH_2Cl_2/MeOH/NEt_3 93:5:2). The product was obtained as yellow oil (4.79 g, 93%). IR (film) $\tilde{\nu}$ = 2943, 2885, 2773, 1730, 1470, 1373, 1309, 1180, 1140, 1032, 945, 912, 800 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.91 (t, J = 4.9 Hz, 1 H, OCH), 4.11 (q, J = 7.1 Hz, 2 H, CH_2CH$_3$), 4.00–3.76 (m, 4 H, OCH$_2$CH$_2$O), 3.03–2.91 (m, 1 H, NCH_2^aCH), 2.76 (dt, J = 11.2/3.6 Hz, 1 H, NCH_2^aCH$_2$CH$_2$), 2.59–2.45 (m, 3 H, NCH$_2$C*H*, OCHCH$_2$CH_2), 2.14 (t, J = 10.7 Hz, 1 H, NCH_2^bCH), 2.04–1.80 (m, 4 H, OCHCH_2, NCH_2^bCH$_2$CH$_2$, NCH$_2$CHCH_2^a), 1.76–1.65 (m, 1 H, NCH$_2$CH_2^aCH$_2$), 1.61–1.49 (m, 1 H, NCH$_2$CH_2^bCH$_2$), 1.42 (dq, J = 11.9/3.9 Hz, 1 H, NCH$_2$CHCH_2^b), 1.24 (t, J = 7.1 Hz, 3 H, CH$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3 (CO), 103.5 (OCH), 65.0 (OCH$_2$CH$_2$O), 60.4 (*C*H$_2$CH$_3$), 55.6 (N*C*H$_2$CH), 53.9 (N*C*H$_2$CH$_2$CH$_2$), 53.7 (OCHCH$_2$*C*H$_2$), 42.1 (NCH$_2$*C*H), 31.5 (OCH*C*H$_2$), 27.1 (NCH$_2$CH*C*H$_2$), 24.7 (NCH$_2$*C*H$_2$CH$_2$), 14.4 (CH_3) ppm; HREIMS *m/z* [M]$^+$: 257.1611 $C_{13}H_{23}NO_4$ (calcd. 257.1622).

rac-Ethyl 1-[3-(1,3-dioxolan-2-yl)propyl]piperidine-3-carboxylate *rac*-15d

According to **GP1**: Potassium carbonate (4.15 g, 30.0 mmol, 3.0 equiv), sodium iodide (19 mg, 0.13 mmol, 0.01 equiv), ethyl nipecotate *rac*-**16** (1.57 g, 10.0 mmol, 1.6 mL, 1.0 equiv) and 2-(3-chloropropyl)-1,3-dioxolane (1.66 g, 11.0 mmol, 1.45 mL, 1.1 equiv) in 1,4-dioxane (10 mL). The temperature was kept at 100 °C for 82 h. FC (SiO_2, CH_2Cl_2/MeOH/NEt_3 93:5:2). The product was obtained as yellow oil (2.15 g, 79%). IR (film) $\tilde{\nu} = 2945, 2877, 2806, 2769, 1730, 1470, 1446, 1371, 1309, 1209, 1180, 1151, 1034, 943, 862, 733\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.87$ (dt, $J =$ 4.4/0.8 Hz, 1 H, OCH), 4.11 (dq, $J = 7.1/0.6$ Hz, 2 H, CH_2CH_3), 4.01–3.77 (m, 4 H, OCH_2CH_2O), 2.98 (d, $J =$ 11.0 Hz, 1 H, NCH_2^aCH), 2.75 (d, $J = 11.2$ Hz, 1 H, $NCH_2^aCH_2CH_2$), 2.59–2.47 (m, 1 H, NCH_2CH), 2.44–2.31 (m, 2 H, $OCHCH_2CH_2CH_2$), 2.12 (t, $J = 10.7$ Hz, 1 H, NCH_2^bCH), 2.02–1.86 (m, 2 H, $NCH_2^bCH_2CH_2$, $NCH_2CHCH_2^a$), 1.75–1.49 (m, 6 H, $NCH_2CH_2CH_2$, $OCHCH_2$, $OCHCH_2CH_2$), 1.42 (dq, $J = 11.9/4.1$ Hz, 1 H, $NCH_2CHCH_2^b$), 1.24 (dt, $J = 7.1/0.9$ Hz, 3 H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.4$ (CO), 104.6 (OCH), 65.0 (OCH_2CH_2O), 60.4 (CH_2CH_3), 58.7 ($OCHCH_2CH_2CH_2$), 55.7 (NCH_2CH), 53.8 ($NCH_2CH_2CH_2$), 42.1 (NCH_2CH), 31.9 ($OCHCH_2CH_2$), 27.2 (NCH_2CHCH_2), 24.8 ($NCH_2CH_2CH_2$), 21.4 ($OCHCH_2$), 14.4 (CH_3) ppm; HREIMS *m/z* $[M]^+$: 271.1745 $C_{14}H_{25}NO_4$ (calcd. 271.1778).

rac-Ethyl 1-(3,3-dimethoxypropyl)piperidine-3-carboxylate *rac*-15e

According to **GP1**: Potassium carbonate (5.12 g, 37.0 mmol, 3.0 equiv), ethyl nipecotate *rac*-**16** (1.93 g, 12.3 mmol, 1.9 mL, 1.0 equiv) and 3-bromo-1,1-dimethoxypropane (2.49 g, 13.6 mmol, 1.9 mL, 1.1 equiv) in acetone (12 mL) (no sodium iodide was used). The temperature was kept at 70 °C for 18 h. FC (SiO_2, CH_2Cl_2/MeOH/NEt_3 93:5:2). The product was obtained as yellow oil (2.17 g, 68%). IR (film) $\tilde{\nu} = 2943, 2827, 2775, 1732, 1470, 1446, 1371, 1311, 1180, 1126, 1057, 964, 912, 862\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.43$ (t, $J = 5.7$ Hz, 1 H, OCH), 4.12 (q, $J = 7.1$ Hz, 2 H, CH_2CH_3), 3.31 (s, 6 H, OCH_3), 2.96 (d, $J = 11.2$ Hz, 1 H, NCH_2^aCH), 2.74 (d, $J =$ 11.0 Hz, 1 H, $NCH_2^aCH_2CH_2$), 2.60–2.49 (m, 1 H, NCH_2CH), 2.44–2.35 (m, 2 H, $OCHCH_2CH_2$), 2.15 (t, $J =$ 10.6 Hz, 1 H, NCH_2^bCH), 1.99 (dd, $J = 11.0/2.7$ Hz, 1 H, $NCH_2^bCH_2CH_2$), 1.95–1.87 (m, 1 H, $NCH_2CHCH_2^a$), 1.83–1.76 (m, 2 H, $OCHCH_2$), 1.76–1.67 (m, 1 H, $NCH_2CH_2^aCH_2$), 1.62–1.49 (m, 1 H, $NCH_2CH_2^bCH_2$), 1.49–1.37 (m, 1 H, $NCH_2CHCH_2^b$), 1.24 (t, $J = 7.1$ Hz, 3 H, CH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.3$ (CO), 103.5 (OCH), 60.4 (CH_2CH_3), 55.7 (NCH_2CH), 54.2 ($OCHCH_2CH_2$), 54.0 ($NCH_2CH_2CH_2$), 53.0 (OCH_3), 42.1 (NCH_2CH), 30.2 ($OCHCH_2$), 27.1 (NCH_2CHCH_2), 24.8 ($NCH_2CH_2CH_2$), 14.4 (CH_3) ppm; HRESIMS *m/z* (pos): 260.1856 $C_{13}H_{26}NO_4$ (calcd. 260.1856).

rac-Ethyl 1-(4,4-dimethoxybutyl)piperidine-3-carboxylate *rac*-15f

According to **GP1**: Potassium carbonate (4.15 g, 30.0 mmol, 3.0 equiv), sodium iodide (450 mg, 3.00 mmol, 0.3 equiv), ethyl nipecotate *rac*-**16** (1.57 g, 10.0 mmol, 1.6 mL, 1.0 equiv) and 4-chloro-1,1-dimethoxybutane (1.68 g, 11.0 mmol, 1.6 mL, 1.1 equiv) in acetone (10 mL). The temperature was kept at 70 °C for 62 h. FC (SiO_2, CH_2Cl_2/MeOH/NEt_3 94:5:1). The product was obtained as yellow oil (2.02 g, 74%). IR (film) $\tilde{\nu} = 2943, 2827, 2808, 2775, 1732, 1471, 1448, 1371, 1309, 1180, 1128, 1074, 1034, 962, 862, 794, 735\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.36$ (t, $J = 5.5$ Hz, 1 H, OCH), 4.11 (q, $J = 7.1$ Hz, 2 H, CH_2CH_3), 3.30 (s, 6 H, OCH_3), 2.97 (d, $J = 10.7$ Hz, 1 H, NCH_2^aCH), 2.75 (d, $J = 11.1$ Hz, 1 H, $CCHCH_2CH_2CH_2^a$), 2.53 (tt, $J =$ 10.7/3.8 Hz, 1 H, NCH_2CH), 2.36–2.30 (m, 2 H, $OCHCH_2CH_2CH_2$), 2.11 (t, $J = 10.7$ Hz, 1 H, NCH_2^bCH), 1.99–1.88 (m, 2 H, $CCHCH_2CH_2CH_2^b$, $NCH_2CHCH_2^a$), 1.74–1.67 (m, 1 H, $NCH_2CHCH_2CH_2^a$), 1.62–1.48 (m, 5 H, $NCH_2CHCH_2CH_2^b$, $OCHCH_2$, $OCHCH_2CH_2$), 1.42 (dq, $J =$ 13.3/3.8 Hz, 1 H, $NCH_2CHCH_2^b$), 1.24 (t, $J = 7.1$ Hz, 3 H, CH_2CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 174.4$ (CO), 104.6 (OCH), 60.4 (CH_2CH_3), 58.7 ($OCHCH_2CH_2CH_2$), 55.6 (NCH_2CH), 53.9 ($CCHCH_2CH_2CH_2$), 52.8 (OCH_3), 42.1 (NCH_2CH), 30.6 ($OCHCH_2$), 27.2 (NCH_2CHCH_2), 24.8 ($NCH_2CHCH_2CH_2$), 22.1 ($OCHCH_2CH_2$), 14.4 (CH_3) ppm; HREIMS *m/z* $[M]^+$: 273.1956 $C_{14}H_{27}NO_4$ (calcd. 273.1935).

rac-1-(3-Hydroxypropyl)piperidine-3-carboxylic acid *rac*-18a

According to **GP4**: Ester *rac*-**15a** (150 mg, 0.697 mmol, 1.0 equiv) and $Ba(OH)_2 \cdot 8\ H_2O$ (880 mg, 2.79 mmol, 4 equiv). The product was obtained as colorless viscous oil (109 mg, 84%). IR (KBr) $\tilde{\nu} = 3394, 2951, 2871, 1589, 1450, 1392, 1068, 935, 773\ cm^{-1}$; ^1H NMR (400 MHz, CD_3OD/1 M NaOD in D_2O 6:1): $\delta = 3.60$ (t, $J = 6.3$ Hz, 2 H, CH_2OH), 3.16–3.05 (m, 1 H, NCH_2^aCH), 2.91 (d, $J = 11.0$ Hz, 1 H, $CHCH_2CH_2CH_2^a$), 2.50–2.41 (m, 2 H, $NCH_2(CH_2)_2OH$), 2.36 (tt, $J = 11.8/3.7$ Hz, 1 H, CHCO), 2.06–1.87 (m, 3 H, $CHCH_2^aCH_2$, $CHCH_2CH_2CH_2^b$, NCH_2^bCH), 1.83–1.65 (m, 3 H, $CHCH_2CH_2^a$, CH_2CH_2OH), 1.57 (tq, $J = 12.9/3.8$ Hz, 1 H, $CHCH_2CH_2^b$), 1.34 (dq, $J = 12.7/4.0$ Hz, 1 H, $CHCH_2^bCH_2$) ppm; ^{13}C NMR (100 MHz, CD_3OD/1 M NaOD in D_2O 6:1): $\delta = 183.0$ (CO), 61.8 (CH_2OH), 58.0 ($CHCH_2N$), 57.1 ($CH_2(CH_2)_2OH$), 54.8 ($CHCH_2CH_2CH_2$), 46.3 (CHCO), 29.9 (CH_2CH_2OH), 29.3 ($CHCH_2CH_2$), 25.8

($CHCH_2CH_2$) ppm; HRESIMS *m/z* (pos): 188.1279 $C_9H_{18}NO_3$ (calcd. 188.1281).

rac-1-(4-Hydroxybutyl)piperidine-3-carboxylic acid *rac*-18b

According to **GP4**: Ester *rac*-**15b** (80 mg, 0.35 mmol, 1.0 equiv) and $Ba(OH)_2 \cdot 8\ H_2O$ (442 mg, 1.40 mmol, 4 equiv). The product was obtained as yellow viscous oil (50 mg, 71%). IR (film) $\tilde{\nu} = 3348, 2940, 2868, 1714, 1589, 1448, 1392, 1061, 1026, 771\ cm^{-1}$; ^1H NMR (400 MHz, CD_3OD/1 M NaOD in D_2O 6:1): $\delta = 3.56$ (t, $J = 6.0$ Hz, 2 H, CH_2OH), 3.17–3.08 (m, 1 H, NCH_2^aCH), 2.91 (d, $J =$ 11.1 Hz, 1 H, $CHCH_2CH_2CH_2^a$), 2.43–2.30 (m, 3 H, CHCO, $NCH_2(CH_2)_3OH$), 2.05–1.86 (m, 3 H, $CHCH_2^aCH_2$, $CHCH_2CH_2CH_2^b$, NCH_2^bCH), 1.75–1.66 (m, 1 H, $CHCH_2CH_2^a$), 1.66–1.50 (m, 5 H, $CHCH_2CH_2^b$, $CH_2CH_2CH_2OH$), 1.34 (dq, $J = 12.6/4.1$ Hz, 1 H, $CHCH_2^bCH_2$) ppm; ^{13}C NMR (100 MHz, CD_3OD/1 M NaOD in D_2O 6:1): $\delta = 182.9$ (CO), 62.8 (CH_2OH), 59.9 ($CH_2(CH_2)_3OH$), 57.9 ($CHCH_2N$), 54.8 ($CHCH_2CH_2CH_2$), 46.2 (*C*HCO), 32.0 (CH_2CH_2OH), 29.4 ($CHCH_2CH_2$), 25.8 ($CHCH_2CH_2$), 24.3 ($CH_2(CH_2)_2OH$) ppm; HRESIMS *m/z* (pos): 202.1436 $C_{10}H_{20}NO_3$ (calcd. 202.1438).

rac-1-[2-(1,3-Dioxolan-2-yl)ethyl]piperidine-3-carboxylic acid *rac*-18c

According to **GP4**: Ester *rac*-**15c** (150 mg, 0.583 mmol, 1.0 equiv) and $Ba(OH)_2 \cdot 8\ H_2O$ (735 mg, 2.33 mmol, 4 equiv). The product was obtained as colorless viscous oil (118 mg, 88%). IR (KBr) $\tilde{\nu} = 3419, 2954, 2893, 1589, 1450, 1390, 1140, 1030, 651, 771\ cm^{-1}$; ^1H NMR (400 MHz, CD_3OD/1 M NaOD in D_2O 6:1): $\delta = 4.91–4.85$ (m, 1 H, OCHO), 4.00–3.81 (m, 4 H, OCH_2CH_2O), 3.13–3.03 (m, 1 H, NCH_2^aCH), 2.88 (d, $J = 11.0$ Hz, 1 H, $CHCH_2CH_2CH_2^a$), 2.54–2.41 (m, 2 H, CH_2CH_2CHO), 2.36 (tt, $J = 11.8/3.7$ Hz, 1 H, CHCO), 2.06–1.81 (m, 5 H, $CCHCH_2^aCH_2$, $CHCH_2CH_2CH_2^b$, NCH_2^bCH, CH_2CHO), 1.75–1.66 (m, 1 H, $CCHCH_2CH_2^a$), 1.57 (tq, $J = 12.9/3.8$ Hz, 1 H, $CCHCH_2CH_2^b$), 1.33 (dq, $J = 12.7/4.1$ Hz, 1 H, $CCHCH_2^bCH_2$) ppm; ^{13}C NMR (100 MHz, CD_3OD/1 M NaOD in D_2O 6:1): $\delta = 182.9$ (CO), 104.3 (OCHO), 65.9 (OCH_2CH_2O), 57.9 ($CHCH_2N$), 54.7 ($CHCH_2CH_2CH_2$), 54.4 (CH_2CH_2CHO), 46.2 (*C*HCO), 31.6 (CH_2CH_2CHO), 29.3 ($CHCH_2CH_2$), 25.7 ($CHCH_2CH_2$) ppm; HRESIMS *m/z* (pos): 230.1385 $C_{11}H_{20}NO_4$ (calcd. 230.1387).

rac-1-[3-(1,3-Dioxolan-2-yl)propyl]piperidine-3-carboxylic acid *rac*-18d

According to **GP4**: Ester *rac*-**15d** (150 mg, 0.553 mmol, 1.0 equiv) and $Ba(OH)_2 \cdot 8\ H_2O$ (697 mg, 2.21 mmol, 4 equiv). The product was obtained as colorless solid (124 mg, 92%). Mp 132 °C; IR (KBr) $\tilde{\nu} = 3429, 2954, 2887, 1610, 1483, 1387, 1140, 1041, 962, 912, 822, 768, 700, 530\ cm^{-1}$; ^1H NMR (400 MHz, CD_3OD/1 M NaOD in D_2O 6:1): $\delta =$ 4.88–4.84 (m, 1 H, OCHO), 4.00–3.80 (m, 4 H, OCH_2CH_2O), 3.15–3.06 (m, 1 H, NCH_2^aCH), 2.89 (d, $J =$ 11.1 Hz, 1 H, $CCH(CH_2)_2CH_2^a$), 2.44–2.31 (m, 3 H, $CH_2(CH_2)_2CHO$, CHCO), 2.05–1.94 (m, 2 H, $CCHCH_2^aCH_2$, NCH_2^bCH), 1.91 (ddd, $J = 11.8/11.8/2.8$ Hz, 1 H, $CCH(CH_2)_2CH_2^b$), 1.75–1.51 (m, 6 H, $CCHCH_2CH_2$, $NCH_2CH_2CH_2CHO$), 1.33 (dq, $J = 12.6/4.1$ Hz, 1 H, $CCHCH_2^bCH_2$) ppm; ^{13}C NMR (100 MHz, CD_3OD/1 M NaOD in D_2O 6:1): $\delta = 183.0$ (CO), 105.3 (OCHO), 65.9 (OCH_2CH_2O), 59.9 ($CH_2(CH_2)_2CHO$), 58.0 ($CHCH_2N$), 54.7 ($CCH(CH_2)_2CH_2$), 46.2 (*C*HCO), 32.8 (CH_2CH_2CHO), 29.4 ($CCHCH_2CH_2$), 25.8 ($CCHCH_2CH_2$), 21.7 (CH_2CHO) ppm; HRESIMS *m/z* (pos): 244.1541 $C_{12}H_{22}NO_4$ (calcd. 244.1543).

rac-1-(3,3-Dimethoxypropyl)piperidine-3-carboxylic acid *rac*-18e

According to **GP4**: Ester *rac*-**15e** (150 mg, 0.578 mmol, 1.0 equiv) and $Ba(OH)_2 \cdot 8\ H_2O$ (729 mg, 2.31 mmol, 4 equiv). The product was obtained as colorless solid (57 mg, 43%). Mp 124 °C; IR (KBr) $\tilde{\nu} = 3435, 2951, 2834, 1601, 1450, 1385, 1192, 1128, 1053, 997, 947, 770, 704, 525\ cm^{-1}$; ^1H NMR (400 MHz, CD_3OD/1 M NaOD in D_2O 6:1): $\delta =$ 4.44 (t, $J = 5.6$ Hz, 1 H, OCHO), 3.34 (s, 6 H, OCH_3), 3.12–3.04 (m, 1 H, NCH_2^aCH), 2.87 (d, $J = 11.0$ Hz, 1 H, $CHCH_2CH_2CH_2^a$), 2.46–2.30 (m, 3 H, CHCO, CH_2CH_2CHO), 2.06–1.88 (m, 3 H, $CCHCH_2^aCH_2$, $CHCH_2CH_2CH_2^b$, NCH_2^bCH), 1.88–1.78 (m, 2 H, CH_2CHO), 1.75–1.66 (m, 1 H, $CCHCH_2CH_2^a$), 1.57 (tq, $J = 12.9/3.8$ Hz, 1 H, $CCHCH_2CH_2^b$), 1.33 (dq, $J = 12.6/4.1$ Hz, 1 H, $CCHCH_2^bCH_2$) ppm; ^{13}C NMR (100 MHz, CD_3OD/1 M NaOD in D_2O 6:1): $\delta = 182.9$ (CO), 105.0 (OCHO), 58.0 ($CHCH_2N$), 55.1 (CH_2CH_2CHO), 54.8 ($CHCH_2CH_2CH_2$), 53.7 (OCH_3), 46.2 (*C*HCO), 30.6 (CH_2CHO), 29.3 ($CCHCH_2CH_2$), 25.8 ($CCHCH_2CH_2$) ppm; HRESIMS *m/z* (pos): 232.1541 $C_{11}H_{22}NO_4$ (calcd. 232.1543).

rac-1-(4,4-Dimethoxybutyl)piperidine-3-carboxylic acid *rac*-18f

According to **GP4**: Ester *rac*-**15f** (150 mg, 0.549 mmol, 1.0 equiv) and $Ba(OH)_2 \cdot 8\ H_2O$ (691 mg, 2.19 mmol, 4 equiv). The product was obtained as colorless solid (85 mg, 63%). Mp 99 °C; IR (KBr) $\tilde{\nu} = 3433, 2945, 2831, 1601, 1456, 1385, 1126, 1072, 1049, 960, 768, 706\ cm^{-1}$; ^1H NMR (400 MHz, CD_3OD/1 M NaOD in D_2O 6:1): $\delta = 4.46–4.37$ (m, 1 H, OCHO), 3.34 (s, 6 H, OCH_3), 3.14–3.05 (m, 1 H, NCH_2^aCH), 2.89 (d, $J = 11.0$ Hz, 1 H, $CCH(CH_2)_2CH_2^a$),

2.43–2.29 (m, 3 H, CHCO, CH_2CH$_2$CH$_2$CHO), 2.05–1.85 (m, 3 H, CCHCH_2^aCH$_2$, CCH(CH$_2$)$_2$CH_2^b, NCH_2^bCH), 1.75–1.65 (m, 1 H, CCHCH$_2$CH_2^a), 1.65–1.50 (m, 5 H, CCHCH$_2$CH_2^b, CH_2CH$_2$CHO), 1.33 (dq, J = 12.7/4.0 Hz, 1 H, CCHCH_2^bCH$_2$) ppm; ^{13}C NMR (100 MHz, CD$_3$OD/1 M NaOD in D$_2$O 6:1): δ = 183.0 (CO), 106.1 (OCHO), 59.7 (*C*H$_2$(CH$_2$)$_2$CHO), 57.9 (CH*C*H$_2$N), 54.7 (CCH(CH$_2$)$_2$*C*H$_2$), 53.8 (OCH$_3$), 46.2 (*C*HCO), 31.7 (*C*H$_2$CHO), 29.3 (CCH*C*H$_2$CH$_2$), 25.7 (CCHCH$_2$*C*H$_2$), 22.3 (*C*H$_2$CH$_2$CHO) ppm; HRESIMS *m/z* (pos): 246.1698 C$_{12}$H$_{24}$NO$_4$ (calcd. 246.1700).

rac-Ethyl 1-[3-(1,7-dimethyl-4-azatricyclo[3.3.1.0^{2,7}]nonan-4-yl)propyl]piperidine-3-carboxylate *rac*-19a

According to **GP2**: Tricyclic imine **10a** (30 mg, 0.20 mmol, 1 equiv), sodium triacetoxyborohydride (106 mg, 0.500 mmol, 2.5 equiv), acetic acid (25 mg, 0.42 mmol, 24 µL, 2.1 equiv), ethyl 1-(3,3-dimethoxypropyl) piperidine-3-carboxylate *rac*-**15e** (104 mg, 0.400 mmol, 2 equiv) and FeCl$_3$ · 6H$_2$O (303 mg, 1.12 mmol, 5.6 equiv). The reaction was kept at 40 °C for 18 h. The crude product was purified by FC and RP-MPLC. The product was obtained as yellow oil (19 mg, 27%). IR (film) $\tilde{\nu}$ = 2939, 2858, 2800, 1734, 1450, 1373, 1309, 1223, 1205, 1178, 1151, 1099, 1032 cm^{-1}; ^{1}H NMR (400 MHz, CD$_2$Cl$_2$): δ = 4.08 (q, J = 7.1 Hz, 2 H, CH_2CH$_3$), 2.91 (d, J = 11.0 Hz, 1 H, OCCHCH_2^aN,), 2.77–2.68 (m, 2 H, CHCH$_2$CH$_2$CH_2^a, CHN), 2.67 (d, J = 2.5 Hz, 2 H, CHNCH_2CH), 2.49 (tt, J = 10.3/3.8 Hz, 1 H, OCCH), 2.45–2.38 (m, 2 H, CHNCH_2CH$_2$), 2.37–2.28 (m, 2 H, CHN(CH$_2$)$_2$CH_2), 2.11 (t, J = 10.4 Hz, 1 H, OCCHCH_2^bN), 1.95 (ddd, J = 10.8/10.8/2.6 Hz, 1 H, CHCH$_2$CH$_2$CH_2^b), 1.91–1.81 (m, 1 H, CHCH_2^aCH$_2$), 1.78–1.63 (m, 3 H, CHCH$_2$CH_2^a, NCH(CH_2^a)$_2$), 1.61–1.38 (m, 7 H, CHCH_2^bCH$_2$, CHCH$_2$CH_2^b, NCH$_2$CH_2CH$_2$N, CCH$_2^a$C, NCH(CH_2^b)$_2$), 1.36 (s, 1 H, CHNCH$_2$C*H*), 1.33 (d, J = 8.6 Hz, 1 H, CCH$_2^b$C), 1.23 (t, J = 7.1 Hz, 3 H, CH$_2$CH_3), 0.98 (s, 6 H, CCH_3) ppm; ^{13}C NMR (100 MHz, CD$_2$Cl$_2$) δ = 174.5 (CO), 60.5 (*C*H$_2$CH$_3$), 57.3 (CHN(CH$_2$)$_2$*C*H$_2$), 56.1 (OCCH*C*H$_2$N), 55.5 (CHN*C*H$_2$CH$_2$), 54.3 (CHCH$_2$CH$_2$*C*H$_2$), 53.4 (NCH), 51.3 (C*C*H$_2$C), 47.7 (CHN*C*H$_2$CH), 45.6 (CHNCH$_2$*C*H), 42.4 (OC*C*H), 39.6 (NCH(*C*H$_2$)$_2$), 36.0 (*C*CH$_3$), 27.5 (CH*C*H$_2$CH$_2$), 26.5 (CHNCH$_2$*C*H$_2$), 25.5 (C*C*H$_3$), 25.1 (CHCH$_2$*C*H$_2$), 14.4 (CH$_2$*C*H$_3$) ppm; HRESIMS *m/z* (pos): 349.2848 C$_{21}$H$_{37}$N$_2$O$_2$ (calcd. 349.2850).

rac-Ethyl 1-[3-(1,7-diphenyl-4-azatricyclo[3.3.1.0^{2,7}]nonan-4-yl)propyl]piperidine-3-carboxylate *rac*-19b

According to **GP2**: Tricyclic imine **10b** (27 mg, 0.10 mmol, 1 equiv), sodium triacetoxyborohydride (53 mg, 0.25 mmol, 2.5 equiv), acetic acid (13 mg, 0.21 mmol, 12 µL, 2.1 equiv), ethyl 1-(3,3-dimethoxypropyl)piperidine-3-carboxylate *rac*-**15e** (52 mg, 0.20 mmol, 2 equiv) and FeCl$_3$ · 6H$_2$O (541 mg, 2.00 mmol, 20 equiv). The reaction was kept at 40 °C for 12 h. The crude product was purified by FC and RP-MPLC. The product was obtained as yellow oil (11 mg, 23%). IR (film) $\tilde{\nu}$ = 3056, 3024, 2935, 2854, 2804, 1730, 1603, 1495, 1444, 1367, 1309, 1178, 1151, 1030, 758, 698 cm^{-1}; ^{1}H NMR (500 MHz, CD$_2$Cl$_2$): δ = 7.34–7.29 (m, 4 H, CCHC*H*), 7.29–7.24 (m, 4 H, CC*H*CH), 7.18 (tt, J = 7.1/1.4 Hz, 2 H, CCHCHC*H*), 4.09 (q, J = 7.1 Hz, 2 H, CH_2CH$_3$), 3.17 (d, J = 2.4 Hz, 2 H, CHNCH_2CH), 3.02 (p, J = 1.6 Hz, 1 H, CHN), 2.95 (d, J = 10.5 Hz, 1 H, OCCHCH_2^aN), 2.73 (d, J = 10.9 Hz, 1 H, CHCH$_2$CH$_2$CH_2^a), 2.58 (dd, J = 7.3/7.3 Hz, 2 H, CHNCH_2CH$_2$), 2.55 (s, 1 H, CCHC), 2.51 (tt, J = 10.3/3.9 Hz, 1 H, OCCH), 2.44 (dt, J = 8.7/2.0 Hz, 1 H, CCH$_2^a$C), 2.41–2.36 (m, 2 H, CHN(CH$_2$)$_2$CH_2,), 2.27 (d, J = 13.1 Hz, 2 H, NCH(CH_2^a)$_2$), 2.14 (t, J = 10.4 Hz, 1 H, OCCHCH_2^bN,), 2.11–2.05 (m, 3 H, CCH$_2^b$C, NCH(CH_2^b)$_2$), 1.99 (ddd, J = 10.9/10.9/2.1 Hz, 1 H, CHCH$_2$CH$_2$CH_2^b), 1.92–1.85 (m, 1 H, CHCH_2^aCH$_2$), 1.74–1.67 (m, 1 H, CHCH$_2$CH_2^a), 1.65 (p, J = 7.3 Hz, 2 H, NCH$_2$CH_2CH$_2$N), 1.58–1.48 (m, 1 H, CHCH$_2$CH_2^b), 1.48–1.38 (m, 1 H, CHCH_2^bCH$_2$), 1.23 (t, J = 7.1 Hz, 3 H, CH$_2$CH_3) ppm; ^{13}C NMR (125 MHz, CD$_2$Cl$_2$) δ = 174.5 (CO), 149.4 (*C*CHCH), 128.7 (CCH*C*H), 126.1 (CCHCH*C*H), 125.4 (C*C*HCH), 60.5 (*C*H$_2$CH$_3$), 57.2 (CHN(CH$_2$)$_2$*C*H$_2$), 56.1 (OCCH*C*H$_2$N), 55.6 (CHN*C*H$_2$CH$_2$), 54.3 (CHCH$_2$CH$_2$*C*H$_2$), 53.6 (NCH), 49.9 (CHN*C*H$_2$CH), 49.1 (C*C*H$_2$C), 44.1 (CHNCH$_2$*C*H), 42.5 (*C*CH$_2$*C*), 42.4 (OC*C*H), 40.8 (NCH(*C*H$_2$)$_2$), 27.5 (CH*C*H$_2$CH$_2$), 26.6 (NCH$_2$*C*H$_2$CH$_2$N), 25.1 (CHCH$_2$*C*H$_2$), 14.5 (CH$_2$*C*H$_3$) ppm; HRESIMS *m/z* (pos): 473.3165 C$_{31}$H$_{41}$N$_2$O$_2$ (calcd. 473.3163).

rac-Ethyl 1-[3-(3,6-dimethyl-9-azatricyclo[4.3.1.0^{3,7}]decan-9-yl)propyl]piperidine-3-carboxylate *rac*-19c

According to **GP2**: Tricyclic imine **10c** (33 mg, 0.20 mmol, 1 equiv), sodium triacetoxyborohydride (106 mg, 0.500 mmol, 2.5 equiv), acetic acid (25 mg, 0.42 mmol, 24 µL, 2.1 equiv), ethyl 1-(3,3-dimethoxypropyl)piperidine-3-carboxylate *rac*-**15e** (104 mg, 0.400 mmol, 2 equiv) and FeCl$_3$ · 6H$_2$O (303 mg, 1.12 mmol, 5.6 equiv). The reaction was kept at 20 °C for 12 h. The crude product was purified by FC. The product was obtained as yellow oil (19 mg, 26%). IR (film) $\tilde{\nu}$ = 2942, 2864, 2804, 1732, 1450, 1371, 1311, 1209, 1180, 1153, 1099, 1032 cm^{-1}; ^{1}H NMR (500 MHz, CD$_2$Cl$_2$): δ = 4.08 (q, J = 7.1 Hz, 2 H, OCH_2CH$_3$), 2.90 (d, J = 10.5 Hz, 1 H, OCCHCH_2^aN), 2.74 (s, 2 H, CHNCH_2CH), 2.70 (d, J = 10.9 Hz, 1 H, CHCH$_2$CH$_2$CH_2^a), 2.56–2.39 (m, 4 H, CHNCH_2CH$_2$, NCH, OCCH), 2.37–2.29 (m, 2 H, CHN(CH$_2$)$_2$CH_2), 2.13 (t, J = 10.3 Hz, 1 H,

OCCHCH_2^bN), 1.97 (ddd, $J = 10.6/10.6/2.2$ Hz, 1 H, CHCH$_2$CH$_2$CH_2^b), 1.91–1.82 (m, 1 H, CHCH_2^aCH$_2$), 1.76 (d, $J = 12.8$ Hz, 2 H, NCH(CH_2^a)$_2$), 1.72–1.65 (m, 1 H, CHCH$_2$CH_2^a), 1.61 (p, $J = 7.3$ Hz, 2 H, NCH$_2$CH_2CH$_2$), 1.56–1.36 (m, 6 H, CHCH_2^bCH$_2$, CHCH$_2$CH_2^b, CCH_2CH_2C), 1.29–1.19 (m, 5 H, NCH(CH_2^b)$_2$, CH$_2$CH_3), 1.10 (s, 6 H, CCH_3), 0.88 (s, 1 H, CHNCH$_2$C*H*) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) $\delta =$ 174.5 (CO), 60.5 (*C*H$_2$CH$_3$), 57.0 (CHN(CH$_2$)$_2$*C*H$_2$), 56.1 (OCCH*C*H$_2$N), 54.5 (CHN*C*H$_2$CH$_2$), 54.3 (CHCH$_2$CH$_2$*C*H$_2$), 52.0 (NCH), 49.6 (CHNCH$_2$*C*H), 46.1 (CHN*C*H$_2$CH), 42.6 (OC*C*H), 41.9 (NCH(*C*H$_2$)$_2$), 40.8 (C*C*H$_2$CH$_2$C), 39.6 (*C*CH$_3$), 27.8 (CCH*C*H$_2$CH$_2$), 26.6 (C*C*H$_3$), 25.7 (CHNCH$_2$*C*H$_2$), 25.1 (CHCH$_2$*C*H$_2$), 14.5 (CH$_2$*C*H$_3$) ppm; HRESIMS *m/z* (pos): 363.3006 $C_{22}H_{39}N_2O_2$ (calcd. 363.3006).

rac-Ethyl 1-[3-(3,6-diphenyl-9-azatricyclo[4.3.1.0^{3,7}]decan-9-yl)propyl]piperidine-3-carboxylate *rac*-19d

According to **GP2**: Tricyclic imine **10d** (29 mg, 0.10 mmol, 1 equiv), sodium triacetoxyborohydride (53 mg, 0.25 mmol, 2.5 equiv), acetic acid (13 mg, 0.21 mmol, 12 µL, 2.1 equiv), ethyl 1-(3,3-dimethoxypropyl)piperidine-3-carboxylate *rac*-**15e** (52 mg, 0.20 mmol, 2 equiv) and $FeCl_3 \cdot 6H_2O$ (151 mg, 0.560 mmol, 5.6 equiv). The reaction was kept at 20 °C for 12 h. The crude product was purified by FC and RP-MPLC. The product was obtained as yellow oil (12 mg, 25%). IR (film) $\tilde{\nu} = 3055$, 3022, 2943, 2868, 2804, 1730, 1601, 1495, 1470, 1444, 1369, 1309, 1178, 1151, 1032, 760, 700 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 7.52$–7.42 (m, 4 H, CC*H*CH), 7.40–7.30 (m, 4 H, CCHC*H*), 7.24–7.17 (m, 2 H, CCHCHC*H*), 4.07 (q, $J = 7.1$ Hz, 2 H, OCH_2), 2.87 (d, $J = 11.3$ Hz, 1 H, OCCHCH_2^aN), 2.82 (s, 1 H, NCH), 2.71 (d, $J = 1.6$ Hz, 2 H, CHNCH_2CH), 2.66 (d, $J = 11.5$ Hz, 1 H, CHCH$_2$CH$_2$CH_2^a), 2.53–2.38 (m, 4 H, C*H*CH$_2$NCH, OCCH, NCH(CH_2^a)$_2$), 2.38–2.25 (m, 4 H, NCH_2CH$_2$CH_2N), 2.08 (t, $J = 10.5$ Hz, 1 H, OCCHCH_2^bN), 2.05–1.79 (m, 8 H, CHCH_2^aCH$_2$, CHCH$_2$CH$_2$CH_2^b, NCH(CH_2^b)$_2$, CCH_2CH_2C), 1.70–1.61 (m, 1 H, CHCH$_2$CH_2^a), 1.58–1.33 (m, 4 H, CHCH_2^bCH$_2$, NCH$_2$CH_2CH$_2$N, CHCH$_2$CH_2^b), 1.21 (t, $J = 7.1$ Hz, 3 H, CH_3) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) $\delta = 174.5$ (CO), 149.9 (CH$_2$C*C*), 128.6 (CCH*C*H), 126.5 (C*C*HCH), 125.8 (CCHCH*C*H), 60.5 (OCH$_2$), 57.2 (CHN(CH$_2$)$_2$*C*H$_2$), 56.1 (OCCH*C*H$_2$N), 54.3 (CHCH$_2$CH$_2$*C*H$_2$), 54.1 (CHN*C*H$_2$CH$_2$), 51.7 (NCH), 47.3 (*C*CH$_2$), 46.7 (CHN*C*H$_2$CH), 44.9 (CHNCH$_2$*C*H), 42.5 (C*C*H$_2$*C*H$_2$C), 42.4 (OC*C*H), 42.3 (NCH(*C*H$_2$)$_2$), 27.4 (CH$_2$*C*H$_2$CH), 26.0 (CHNCH$_2$*C*H$_2$), 25.1 (CHCH$_2$*C*H$_2$), 14.4 (CH$_3$) ppm; HRESIMS *m/z* (pos): 487.3318 $C_{32}H_{43}N_2O_2$ (calcd. 487.3319).

rac-Ethyl 1-[3-(3,7-dimethyl-10-azatricyclo[5.3.1.0^{3,8}]undecan-10-yl)propyl]piperidine-3-carboxylate *rac*-19e

According to **GP3**: Tricyclic imine **10e** (36 mg, 0.20 mmol, 1 equiv), sodium cyanoborohydride (66 mg, 1.0 mmol, 5 equiv), hydrochloric acid (73 mg, 2.0 mmol, 2.0 mL, 10 equiv), sodium triacetoxyborohydride (106 mg, 0.500 mmol, 2.5 equiv), acetic acid (25 mg, 0.42 mmol, 24 µL, 2.1 equiv), ethyl 1-(3,3-dimethoxypropyl)piperidine-3-carboxylate *rac*-**15e** (104 mg, 0.400 mmol, 2 equiv) and $FeCl_3 \cdot 6H_2O$ (1.08 g, 4.00 mmol, 20 equiv). The reaction was stirred at 40 °C for 12 h. The crude product was purified by FC. The product was obtained as yellow oil (28 mg, 37%). IR (film) $\tilde{\nu} = 2922$, 2802, 1732, 1497, 1471, 1446, 1373, 1306, 1180, 1151, 1103, 1034, 862 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2): $\delta = 4.08$ (q, $J = 7.1$ Hz, 2 H, CH_2CH$_3$), 2.96–2.84 (m, 3 H, CHNCH_2CH, OCCHCH_2^aN), 2.71 (d, $J = 11.2$ Hz, 1 H, CHCH$_2$CH$_2$CH_2^a), 2.61 (br s, 1 H, CHN), 2.56–2.45 (m, 3 H, CHNCH_2CH$_2$, OCCH), 2.33 (dd, $J = 7.4/7.4$ Hz, 2 H, CHN(CH$_2$)$_2$CH_2), 2.11 (t, $J =$ 10.5 Hz, 1 H, OCCHCH_2^bN), 1.96 (ddd, $J = 10.9/10.9/$ 2.4 Hz, CHCH$_2$CH$_2$CH_2^b), 1.90–1.82 (m, 1 H, CHCH_2^aCH$_2$), 1.73–1.65 (m, 1 H, CHCH$_2$CH_2^a), 1.64–1.47 (m, 6 H, CHCH$_2$CH_2^b, CHNCH$_2$CH_2, NCH(CH_2^a)$_2$, CCH$_2$CH_2^a), 1.46–1.36 (m, 2 H, CHCH_2^bCH$_2$, CCH$_2$CH_2^b), 1.32–1.25 (m, 4 H, NCH(CH_2^b)$_2$, CCH_2^aCH$_2$CH_2^aC), 1.23 (t, $J = 7.1$ Hz, 3 H, CH$_2$CH_3), 1.10 (dd, $J = 13.5/4.6$ Hz, 2 H, CCH_2^bCH$_2$CH_2^bC), 1.05 (s, 6 H, CCH_3), 0.68 (s, 1 H, CHNCH$_2$C*H*) ppm; ^{13}C NMR (125 MHz, CD_2Cl_2) $\delta =$ 174.5 (CO), 60.5 (*C*H$_2$CH$_3$), 57.1 (CHN(CH$_2$)$_2$*C*H$_2$), 56.1 (OCCH*C*H$_2$N), 54.8 (CHN*C*H$_2$CH$_2$), 54.3 (CHCH$_2$CH$_2$*C*H$_2$), 52.9 (NCH), 47.6 (CHN*C*H$_2$CH), 46.3 (CHNCH$_2$*C*H), 42.5 (OC*C*H), 40.8 (C*C*H$_2$CH$_2$*C*H$_2$C), 36.8 (NCH(*C*H$_2$)$_2$), 31.0 (*C*CH$_3$, C*C*H$_3$), 27.5 (CCH*C*H$_2$CH$_2$), 26.4 (CHNCH$_2$*C*H$_2$), 25.1 (CHCH$_2$*C*H$_2$), 19.6 (CCH$_2$*C*H$_2$), 14.5 (CH$_2$*C*H$_3$) ppm; HRESIMS *m/z* (pos): 377.3164 $C_{23}H_{41}N_2O_2$ (calcd. 377.3163).

rac-Ethyl 1-[3-(3,7-diphenyl-10-azatricyclo[5.3.1.0^{3,8}]undecan-10-yl)propyl]piperidine-3-carboxylate *rac*-19f

According to **GP3**: Tricyclic imine **10f** (30 mg, 0.10 mmol, 1 equiv), sodium cyanoborohydride (33 mg, 0.50 mmol, 5 equiv), hydrochloric acid (36 mg, 1.0 mmol, 1.0 mL, 10 equiv), sodium triacetoxyborohydride (53 mg, 0.25 mmol, 2.5 equiv), acetic acid (13 mg, 0.21 mmol, 12 µL, 2.1 equiv), ethyl 1-(3,3-dimethoxypropyl)piperidine-3-carboxylate *rac*-**15e** (52 mg, 0.20 mmol, 2 equiv) and $FeCl_3 \cdot 6H_2O$ (541 mg, 2.00 mmol, 20 equiv). The reaction was stirred at 40 °C for 12 h. The crude product was purified by FC and RP-MPLC. The product was obtained as colorless viscous oil (17 mg, 34%). IR (film) $\tilde{\nu} = 3057$, 2926, 2852, 2802, 1730, 1597, 1495, 1444, 1369, 1306, 1180, 1151,

1032, 758, 700 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2): δ = 7.52–7.47 (m, 4 H, CC*H*CH), 7.37–7.31 (m, 4 H, CCHC*H*), 7.19 (t, J = 7.3 Hz, 2 H, CCHCHC*H*), 4.06 (q, J = 7.2 Hz, 2 H, OCH_2), 2.88 (s, 1 H, NCH), 2.81 (d, J = 11.0 Hz, 1 H, OCCHCH_2^aN), 2.63–2.53 (m, 3 H, NCH(CH_2^a)$_2$, $CHCH_2CH_2CH_2^a$), 2.50 (d, J = 2.1 Hz, 2 H, CHNCH_2CH), 2.39 (tt, J = 10.4/3.8 Hz, 1 H, OCCH), 2.35 (s, 1 H, C*H*CH_2NCH), 2.22–2.11 (m, 4 H, CHN$(CH_2)_2$CH_2, CHNCH_2CH_2), 1.99 (t, J = 10.4 Hz, 1 H, OCCHCH_2^bN), 1.94–1.79 (m, 5 H, CHC$H_2^a$$CH_2$, $CHCH_2CH_2CH_2^b$, NCH(CH_2^b)$_2$, $CCH_2CH_2^a$), 1.65–1.37 (m, 8 H, CHC$H_2^b$$CH_2$, $CHCH_2CH_2$, $CCH_2CH_2^b$, CC$H_2CH_2CH_2$C), 1.37–1.32 (m, 2 H, CHNCH_2CH_2), 1.21 (t, J = 7.2 Hz, 3 H, CH_3) ppm; ^{13}C NMR (125 MHz, CD_2Cl_2) δ = 174.5 (CO), 151.9 (CH_2CC), 128.5 (CCH*C*H), 126.7 (C*C*HCH), 125.7 (CCHCH*C*H), 60.5 (OCH_2), 56.9 (CHN$(CH_2)_2$CH_2), 56.0 (OCCHCH_2N), 54.5 (CHNCH_2CH_2), 54.1 ($CHCH_2CH_2CH_2$), 51.5 (NCH), 49.3 (CHNCH_2CH), 43.7 ($CCH_2CH_2CH_2C$), 42.4 (OC*C*H), 40.2 (*C*CH_2), 39.1 (CHNCH$_2$*C*H), 36.0 (NCH(*C*$H_2)_2$), 27.4 (CH_2CH_2CH), 26.2 ($CHNCH_2CH_2$), 25.0 ($CHCH_2CH_2$), 20.6 (CCH_2CH_2), 14.4 (CH_3) ppm; HRESIMS *m*/*z* (pos): 501.3476 $C_{33}H_{45}N_2O_2$ (calcd. 501.3476).

rac-Ethyl 1-[4-(1,7-dimethyl-4-azatricyclo[3.3.1.0^{2,7}]nonan-4-yl)butyl]piperidine-3-carboxylate *rac*-19g

According to **GP2**: Tricyclic imine **10a** (30 mg, 0.20 mmol, 1 equiv), sodium triacetoxyborohydride (106 mg, 0.500 mmol, 2.5 equiv), acetic acid (25 mg, 0.42 mmol, 24 µL, 2.1 equiv), ethyl 1-(4,4-dimethoxybutyl)piperidine-3-carboxylate *rac*-**15f** (109 mg, 0.400 mmol, 2 equiv) and $FeCl_3 \cdot 6H_2O$ (303 mg, 1.12 mmol, 5.6 equiv). The reaction was kept at 40 °C for 20 h. The crude product was purified by FC. The product was obtained as viscous yellow oil (32 mg, 44%). IR (film) $\tilde{\nu}$ = 2937, 2858, 2802, 1732, 1660, 1450, 1373, 1309, 1180, 1151, 1093, 1032 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2): δ = 4.08 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 2.95–2.83 (m, 2 H, OCCHCH_2^aN, CHN), 2.76 (d, J = 1.2 Hz, 2 H, CHNCH_2CH), 2.72 – 2.65 (m, 1 H, $CHCH_2CH_2CH_2^a$), 2.56–2.44 (m, 3 H, CHNCH_2CH_2, OCCH), 2.35–2.25 (m, 2 H, CHN$(CH_2)_3$CH_2), 2.10 (t, J = 10.6 Hz, 1 H, OCCHCH_2^bN), 1.95 (ddd, J = 10.8/10.8/2.6 Hz, 1 H, $CHCH_2CH_2CH_2^b$), 1.91–1.78 (m, 3 H, CHC$H_2^a$$CH_2$, NCH(C$H_2^a$)$_2$), 1.72–1.64 (m, 1 H, $CHCH_2CH_2^a$), 1.59 (dd, J = 13.1/3.5 Hz, 2 H, NCH(CH_2^b)$_2$), 1.56–1.37 (m, 8 H, CHC$H_2^b$$CH_2$, $CHCH_2CH_2^b$, $NCH_2CH_2CH_2CH_2N$, CCH_2^aC, CCHC), 1.35 (d, J = 8.7 Hz, 1 H, CCH_2^bC), 1.22 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.00 (s, 6 H, CCH_3) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) δ = 174.5 (CO), 60.5 (CH_2CH_3), 58.9 (CHN$(CH_2)_3CH_2$), 56.9 ($CHNCH_2CH_2$), 56.0 (OCCHCH_2N), 54.2 ($CHCH_2CH_2CH_2$), 53.4 (NCH), 51.1 (CCH_2C), 47.5 ($CHNCH_2CH$), 45.1 ($CHNCH_2CH$), 42.4 (OC*C*H), 38.8 (NCH(*C*$H_2)_2$), 36.0 (*C*CH_3), 27.5 (CH*C*H_2CH_2), 26.1 ($CHNCH_2CH_2CH_2$), 25.4 (C*C*H_3), 25.1 ($CHCH_2CH_2$), 25.0 ($CHNCH_2CH_2$), 14.4 (CH_2CH_3) ppm; HRESIMS *m*/*z* (pos): 363.3006 $C_{22}H_{39}N_2O_2$ (calcd. 363.3006).

rac-Ethyl 1-[4-(1,7-diphenyl-4-azatricyclo[3.3.1.0^{2,7}]nonan-4-yl)butyl]piperidine-3-carboxylate *rac*-19h

According to **GP2**: Tricyclic imine **10b** (27 mg, 0.10 mmol, 1 equiv), sodium triacetoxyborohydride (53 mg, 0.25 mmol, 2.5 equiv), acetic acid (13 mg, 0.21 mmol, 12 µL, 2.1 equiv), ethyl 1-(4,4-dimethoxybutyl)piperidine-3-carboxylate *rac*-**15f** (55 mg, 0.20 mmol, 2 equiv) and $FeCl_3 \cdot 6H_2O$ (151 mg, 0.560 mmol, 5.6 equiv). The reaction was kept at 40 °C for 20 h. The crude product was purified by FC and RP-MPLC. The product was obtained as yellow oil (23 mg, 47%). IR (film) $\tilde{\nu}$ = 3057, 3026, 2935, 2856, 2802, 1730, 1603, 1495, 1446, 1367, 1309, 1178, 1153, 1030, 758, 700 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2): δ = 7.35–7.24 (m, 8 H, CCHC*H*, CC*H*CH), 7.22–7.16 (m, 2 H, CCHCHC*H*), 4.09 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 3.19 (d, J = 1.8 Hz, 2 H, CHNCH_2CH), 3.07 (s, 1 H, CHN), 2.93 (d, J = 10.7 Hz, 1 H, OCCHCH_2^aN), 2.72 (d, J = 11.1 Hz, 1 H, $CHCH_2CH_2CH_2^a$), 2.60 (t, J = 3.1 Hz, 2 H, CHNCH_2CH_2), 2.56 (s, 1 H, CCHC), 2.51 (tt, J = 10.3/3.9 Hz, 1 H, OCCH), 2.45 (dt, J = 8.8/2.3 Hz, 1 H, CCH_2^aC), 2.38–2.25 (m, 4 H, CHN$(CH_2)_3$CH_2, NCH(CH_2^a)$_2$), 2.17–2.05 (m, 4 H, OCCHCH_2^bN, CCH_2^bC, NCH(CH_2^b)$_2$), 1.97 (ddd, J = 10.8/10.8/2.6 Hz, 1 H, $CHCH_2CH_2CH_2^b$), 1.92–1.85 (m, 1 H, CHC$H_2^a$$CH_2$), 1.74–1.65 (m, 1 H, $CHCH_2CH_2^a$), 1.60–1.37 (m, 6 H, CHC$H_2^b$$CH_2$, $CHCH_2CH_2^b$, $NCH_2CH_2CH_2CH_2N$), 1.23 (t, J = 7.1 Hz, 3 H, CH_2CH_3) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) δ = 174.5 (CO), 149.2 (*C*CHCH), 128.7 (CCH*C*H), 126.2 (CCHCH*C*H), 125.4 (C*C*HCH), 60.5 (CH_2CH_3), 59.1 (CHN$(CH_2)_3CH_2$), 57.3 ($CHNCH_2CH_2$), 56.0 (OCCHCH_2N), 54.2 ($CHCH_2CH_2CH_2$), 53.6 (NCH), 49.8 ($CHNCH_2CH$), 48.9 (CCH_2C), 44.0 ($CHNCH_2CH$), 42.5 (CCH_2C), 42.4 (OC*C*H), 40.6 (NCH(*C*$H_2)_2$), 27.5 (CH*C*H_2CH_2), 26.7 ($CHNCH_2CH_2CH_2$), 25.1 ($CHCH_2CH_2$), 25.0 ($CHNCH_2CH_2$), 14.4 (CH_2CH_3) ppm; HRESIMS *m*/*z* (pos): 487.3317 $C_{32}H_{43}N_2O_2$ (calcd. 487.3319).

rac-Ethyl 1-[4-(3,6-dimethyl-9-azatricyclo[4.3.1.0^{3,7}]decan-9-yl)butyl]piperidine-3-carboxylate *rac*-19j

According to **GP2**: Tricyclic imine **10c** (50 mg, 0.31 mmol, 1 equiv), sodium triacetoxyborohydride (162 mg, 0.766 mmol, 2.5 equiv), acetic acid (39 mg, 0.64 mmol, 37 µL, 2.1 equiv), ethyl 1-(4,4-dimethoxybutyl)piperidine-3-carboxylate *rac*-**15f** (167 mg, 0.613 mmol, 2 equiv) and $FeCl_3 \cdot 6H_2O$ (464 mg, 1.72 mmol, 5.6 equiv). The reaction was kept at 20 °C for 2 h. The crude product was purified by

FC. The product was obtained as yellow oil (84 mg, 73%). IR (film) $\tilde{\nu} = 2941$, 2864, 2802, 1734, 1468, 1452, 1371, 1311, 1178, 1153, 1101, 1034, 862 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2): $\delta = 4.08$ (q, $J = 7.2$ Hz, 2 H, OCH_2CH_3), 2.91 (d, $J = 10.3$ Hz, 1 H, $OCCHCH_2^aN$), 2.78–2.63 (m, 3 H, $CHCH_2CH_2CH_2^a$, $CHNCH_2CH$), 2.49 (tt, $J = 10.4/3.8$ Hz, 1 H, OCCH), 2.44 (br s, 1 H, NCH), 2.39 (t, $J = 7.2$ Hz, 2 H, $CHNCH_2CH_2$), 2.34–2.27 (m, 2 H, $CHN(CH_2)_3CH_2$), 2.09 (t, $J = 10.4$ Hz, 1 H, $OCCHCH_2^bN$), 1.95 (dt, $J = 10.9/2.4$ Hz, 1 H, $CHCH_2CH_2CH_2^b$), 1.91–1.83 (m, 1 H, $CHCH_2^aCH_2$), 1.78–1.64 (m, 3 H, $CHCH_2CH_2^a$, $NCH(CH_2^a)_2$), 1.58–1.33 (m, 10 H, $CHCH_2^bCH_2$, $CHCH_2CH_2^b$, $NCH_2CH_2CH_2CH_2N$, CCH_2CH_2C), 1.28–1.18 (m, 5 H, $NCH(CH_2^b)_2$, CH_2CH_3), 1.09 (s, 6 H, CCH_3), 0.85 (t, $J = 2.3$ Hz, 1 H, $CHNCH_2CH$) ppm; ^{13}C NMR (125 MHz, CD_2Cl_2) $\delta = 174.6$ (CO), 60.5 (CH_2CH_3), 59.2 ($CHN(CH_2)_3CH_2$), 56.4 ($CHNCH_2CH_2$), 56.0 ($OCCHCH_2N$), 54.2 ($CHCH_2CH_2CH_2$), 51.8 (NCH), 49.9 ($CHNCH_2CH$), 46.2 ($CHNCH_2CH$), 42.4 ($NCH(CH_2)_2$, OCCH), 40.8 (CCH_2CH_2C), 39.7 (CCH_3), 27.5 ($CCHCH_2CH_2$), 26.7 (CCH_3), 26.6 ($CHNCH_2CH_2CH_2$), 25.1 ($CHNCH_2CH_2$, $CHCH_2CH_2$), 14.4 (CH_2CH_3) ppm; HRESIMS *m/z* (pos): 377.3161 $C_{23}H_{41}N_2O_2$ (calcd. 377.3163).

rac-Ethyl 1-[4-(3,6-diphenyl-9-azatricyclo[4.3.1.0^{3,7}]decan-9-yl)butyl]piperidine-3-carboxylate *rac*-19k

According to **GP2**: Tricyclic imine **10d** (50 mg, 0.17 mmol, 1 equiv), sodium triacetoxyborohydride (92 mg, 0.44 mmol, 2.5 equiv), acetic acid (22 mg, 0.37 mmol, 21 µL, 2.1 equiv), ethyl 1-(4,4-dimethoxybutyl)piperidine-3-carboxylate *rac*-**15f** (116 mg, 0.348 mmol, 2 equiv) and $FeCl_3 \cdot 6H_2O$ (263 mg, 0.974 mmol, 5.6 equiv). The reaction was kept at 20 °C for 2 h. The crude product was purified by FC. The product was obtained as brown oil (63 mg, 72%). IR (film) $\tilde{\nu} = 2939$, 2804, 2360, 1730, 1601, 1495, 1444, 1369, 1309, 1178, 1151, 1032, 910, 760, 733, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.50–7.40$ (m, 4 H, $CCHCH$), 7.39–7.30 (m, 4 H, $CCHCH$), 7.21 (tt, $J = 7.3/1.3$ Hz, 2 H, $CCHCHCH$), 4.11 (q, $J = 7.1$ Hz, 2 H, OCH_2), 2.94 (d, $J = 11.2$ Hz, 1 H, $OCCHCH_2^aN$), 2.87 (s, 1 H, NCH), 2.75 (d, $J = 2.3$ Hz, 2 H, $CHNCH_2CH$), 2.71 (d, $J = 11.1$ Hz, 1 H, $CHCH_2CH_2CH_2^a$), 2.61–2.46 (m, 3 H, OCCH, NCH ($CH_2^a)_2$), 2.41 (s, 1 H, $CHCH_2NCH$), 2.33 (t, $J = 7.1$ Hz, 2 H, $CHNCH_2CH_2$), 2.30–2.24 (m, 2 H, $CHN(CH_2)_3CH_2$), 2.14−2.00 (m, 3 H, $OCCHCH_2^bN$, $CCH_2^aCH_2^aC$), 2.00–1.80 (m, 6 H, $CHCH_2^aCH_2$, $CHCH_2CH_2CH_2^b$, NCH ($CH_2^b)_2$, $CCH_2^bCH_2^bC$), 1.73–1.64 (m, 1 H, $CHCH_2CH_2^a$), 1.60–1.51 (m, 1 H, $CHCH_2CH_2^b$), 1.51–1.34 (m, 5 H, $CHCH_2^bCH_2$, $NCH_2CH_2CH_2CH_2N$), 1.23 (t, $J = 7.1$ Hz, 3 H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 174.4$ (CO), 149.0 (CH_2CC), 128.5 ($CCHCH$), 126.1 ($CCHCH$), 125.7 ($CCHCHCH$), 60.4 (OCH_2), 58.8 ($CHN(CH_2)_3CH_2$), 55.6 ($OCCHCH_2N$, $CHNCH_2CH_2$), 53.8 ($CHCH_2CH_2CH_2$), 51.4 (NCH), 46.9 (CCH_2), 46.2 ($CHNCH_2CH$), 44.6 ($CHNCH_2CH$), 42.2 (CCH_2CH_2C), 42.0 (OCCH), 41.8 ($NCH(CH_2)_2$), 27.2 (CH_2CH_2CH), 25.8 ($CHN(CH_2)_2CH_2$), 24.7 ($CHNCH_2CH_2$), 24.7 ($CHCH_2CH_2$), 14.3 (CH_3) ppm; HRESIMS *m/z* (pos): 501.3470 $C_{33}H_{45}N_2O_2$ (calcd. 501.3476).

rac-Ethyl 1-[4-(3,7-dimethyl-10-azatricyclo[5.3.1.0^{3,8}]undecan-10-yl)butyl]piperidine-3-carboxylate *rac*-19l

According to **GP3**: Tricyclic imine **10e** (32 mg, 0.18 mmol, 1 equiv), sodium cyanoborohydride (30 mg, 0.45 mmol, 2.5 equiv), hydrochloric acid (33 mg, 0.90 mmol, 0.9 mL, 5 equiv), sodium triacetoxyborohydride (95 mg, 0.45 mmol, 2.5 equiv), acetic acid (23 mg, 0.38 mmol, 22 µL, 2.1 equiv), ethyl 1-(4,4-dimethoxybutyl)piperidine-3-carboxylate *rac*-**15f** (98 mg, 0.36 mmol, 2 equiv) and $FeCl_3 \cdot 6H_2O$ (272 mg, 1.01 mmol, 5.6 equiv). Deviating from GP3 only 2.5 equiv $NaCNBH_3$ and 5 equiv HCl were used. The reaction was kept at 20 °C for 2 h. The crude product was purified by FC. The product was obtained as yellow oil (25 mg, 36%). IR (film) $\tilde{\nu} = 2924$, 2800, 1734, 1497, 1452, 1373, 1304, 1178, 1151, 1103, 1034, 862 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.11$ (q, $J = 7.1$ Hz, 2 H, CH_2CH_3), 2.97 (dd, $J = 11.2/2.9$ Hz, 1 H, $OCCHCH_2^aN$), 2.91 (d, $J = 1.7$ Hz, 2 H, $CHNCH_2CH$), 2.76 (d, $J = 11.2$ Hz, 1 H, $CHCH_2CH_2CH_2^a$), 2.69 (br s, 1 H, CHN), 2.58–2.48 (m, 3 H, $CHNCH_2CH_2$, OCCH), 2.37–2.28 (m, 2 H, $CHN(CH_2)_3CH_2$), 2.08 (t, $J = 10.8$ Hz, 1 H, $OCCHCH_2^bN$), 1.98–1.87 (m, 2 H, $CHCH_2^aCH_2$, $CHCH_2CH_2CH_2^b$), 1.70 (dp, $J = 13.4/3.7$ Hz, 1 H, $CHCH_2CH_2^a$), 1.64–1.35 (m, 10 H, $CHCH_2^bCH_2$, $CHCH_2CH_2^b$, $NCH_2(CH_2)_2CH_2N$, NCH ($CH_2^a)_2$, CCH_2CH_2), 1.32–1.25 (m, 4 H, $NCH(CH_2^b)_2$, $CCH_2^aCH_2CH_2^aC$), 1.23 (t, $J = 7.1$ Hz, 3 H, CH_2CH_3), 1.10 (dd, $J = 13.4/4.7$ Hz, 2 H, $CCH_2^bCH_2CH_2^bC$), 1.05 (s, 6 H, CCH_3), 0.68 (t, $J = 2.3$ Hz, 1 H, $CHNCH_2CH$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 174.4$ (CO), 60.4 (CH_2CH_3), 58.9 ($CHN(CH_2)_3CH_2$), 56.2 ($CHNCH_2CH_2$), 55.6 ($OCCHCH_2N$), 53.9 ($CHCH_2CH_2CH_2$), 52.3 (NCH), 47.3 ($CHNCH_2CH$), 45.7 ($CHNCH_2CH$), 42.1 (OCCH), 40.5 ($CCH_2CH_2CH_2C$), 36.1 ($NCH(CH_2)_2$), 30.9 (CCH_3), 30.7 (CCH_3), 27.2 ($CCHCH_2CH_2$), 26.3 ($CHNCH_2CH_2$), 24.8 ($CHN(CH_2)_2CH_2$, $CHCH_2CH_2$), 19.2 (CCH_2CH_2), 14.3 (CH_2CH_3) ppm; HRESIMS *m/z* (pos): 391.3317 $C_{24}H_{43}N_2O_2$ (calcd. 391.3319).

rac-Ethyl 1-[4-(3,7-diphenyl-10-azatricyclo[5.3.1.0^{3,8}]undecan-10-yl)butyl]piperidine-3-carboxylate *rac*-19m

According to **GP3**: Tricyclic imine **10f** (30 mg, 0.10 mmol, 1 equiv), sodium cyanoborohydride (33 mg, 0.50 mmol, 5 equiv), hydrochloric acid (36 mg, 1.0 mmol,

1.0 mL, 10 equiv), sodium triacetoxyborohydride (53 mg, 0.25 mmol, 2.5 equiv), acetic acid (13 mg, 0.21 mmol, 12 µL, 2.1 equiv), ethyl 1-(4,4-dimethoxybutyl)piperidine-3-carboxylate *rac*-**15f** (55 mg, 0.20 mmol, 2 equiv) and $FeCl_3 \cdot 6H_2O$ (151 mg, 0.560 mmol, 5.6 equiv). The reaction was stirred at 40 °C for 12 h. The crude product was purified by FC and RP-MPLC. The product was obtained as colorless oil (18 mg, 35%). IR (film) $\tilde{\nu} =$ 3055, 2933, 2854, 2802, 1730, 1597, 1495, 1444, 1369, 1304, 1178, 1151, 1031, 758, 700 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2): $\delta = 7.50$ (d, $J = 8.2$ Hz, 4 H, CC*H*CH), 7.41–7.30 (m, 4 H, CCHC*H*), 7.19 (t, $J =$ 7.3 Hz, 2 H, CCHCHC*H*), 4.07 (q, $J = 7.1$ Hz, 2 H, OCH_2), 2.89–2.85 (m, 1 H, NCH), 2.82 (d, $J = 10.2$ Hz, 1 H, OCCHCH_2^aN), 2.60 (d, $J = 11.0$ Hz, 1 H, $CHCH_2CH_2CH_2^a$), 2.56 (dd, $J = 13.0/3.0$ Hz, 2 H, NCH (CH_2^a)$_2$), 2.49 (d, $J = 2.4$ Hz, 2 H, $CHNCH_2CH$), 2.44 (tt, $J = 10.4/3.8$ Hz, 1 H, OCCH), 2.35 (s, 1 H, C*H*CH_2NCH), 2.21–2.10 (m, 4 H, $CHN(CH_2)_3CH_2$, $CHNCH_2CH_2$), 2.01 (t, $J = 10.3$ Hz, 1 H, OCCHCH_2^bN), 1.93–1.78 (m, 5 H, CHC$H_2^a$$CH_2$, $CHCH_2CH_2CH_2^b$, NCH (CH_2^b)$_2$, $CCH_2CH_2^a$), 1.67–1.33 (m, 8 H, CHC$H_2^b$$CH_2$, $CHCH_2CH_2$, $CCH_2CH_2^b$, $CCH_2CH_2CH_2C$), 1.33–1.25 (m, 2 H, $CHNCH_2CH_2$), 1.25–1.12 (m, 5 H, CH_3, CHN $(CH_2)_2CH_2$) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) $\delta =$ 174.5 (CO), 152.0 (CH_2CC), 128.5 (CCH*C*H), 126.7 (C*C*HCH), 125.6 (CCHCH*C*H), 60.5 (OCH_2), 59.0 (CHN $(CH_2)_3CH_2$), 56.3 ($CHNCH_2CH_2$), 56.0 (OCCHCH_2N), 54.1 ($CHCH_2CH_2CH_2$), 51.5 (NCH), 49.3 ($CHNCH_2CH$), 43.8 ($CCH_2CH_2CH_2C$), 42.4 (OC*C*H), 40.2 (CCH_2), 39.1 ($CHNCH_2CH$), 36.0 (NCH(CH_2)$_2$), 27.5 (CH_2CH_2CH), 26.8 ($CHN(CH_2)_2CH_2$), 25.1 ($CHCH_2CH_2$), 24.9 ($CHNCH_2CH_2$), 20.6 (CCH_2CH_2), 14.4 (CH_3) ppm; HRESIMS *m/z* (pos): 515.3632 $C_{34}H_{47}N_2O_2$ (calcd. 515.3632).

Biological evaluation

[^{3}H]GABA uptake assays

The [^{3}H]GABA uptake assays were performed as previously described with intact HEK293 cells stably expressing mGAT1, mGAT2, mGAT3, mGAT4 in a 96-well plate format [55].

MS binding assays

For the MS binding assays mGAT1 membrane preparations, obtained from a stable HEK293 cell line, and NO711 as native MS marker were employed in competitive binding experiments as described earlier [56].

Results and discussion

Synthesis

As direct precursors for the preparation of the target compounds *rac*-**11** their carboxylic acid esters *rac*-**19** should be employed. Their synthesis should be accomplished by linking of the tricyclic amines **14** with suitable *N*-substituted nipecotic acid derivatives via reductive amination (Fig. 4). Accordingly, besides the tricyclic amines **14**, which should be accessible from the tricyclic imines **10** by reduction, nipecotic acid derivatives carrying *N*-alkyl substituents with an aldehyde function at the terminal position of the *N*-alkyl chain were needed. These nipecotic acid derivatives with *N*-alkyl chains of different lengths between the amino nitrogen and the terminal aldehyde function, *rac*-**12** and *rac*-**13**, should be generated from suitable precursors, *rac*-**15**, in which the aldehyde function is present in masked form, for instance as alcohol or acetal group.

Preparation of the aldehyde precursors *rac*-15a–f and generation of the aldehydes *rac*-12–13

The required nipecotic acid derivatives with an *N*-alkyl residue with a terminal alcohol or acetal function,

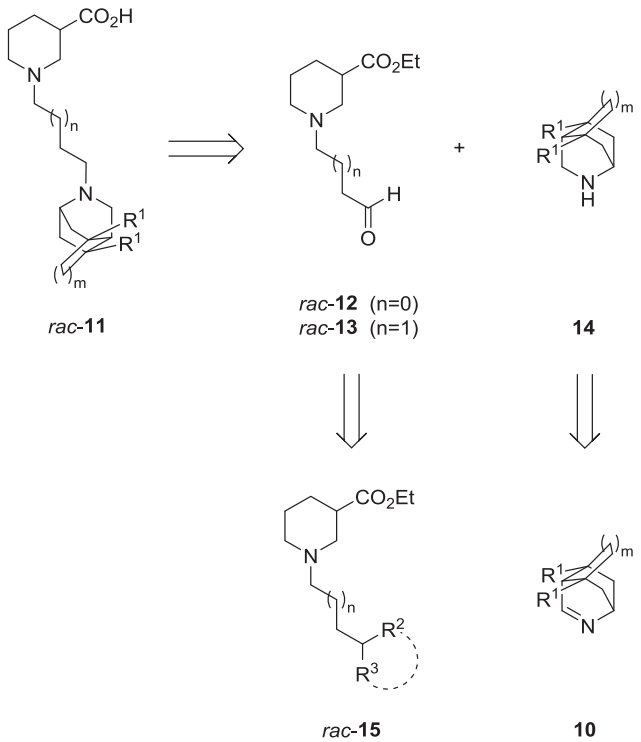
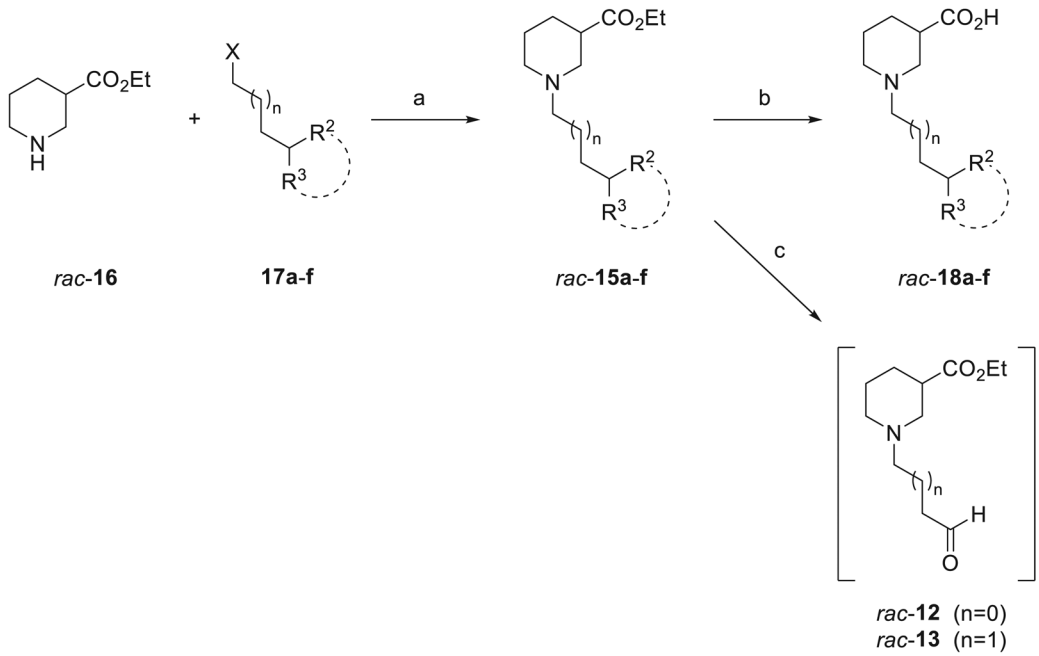


Fig. 4 Retrosynthetic analysis of the targeted *N*-substituted nipecotic acid derivatives *rac*-**11**

rac-**15a–f**, were obtained by *N*-alkylation of racemic ethyl nipecotate *rac*-**16** with ω-hydroxy and ω-dimethoxy substituted *n*-propyl- and *n*-butlyhalides **17a–b** and **17e–f** and the ω-(1,3-dioxolane-2-yl) substituted ethyl- and *n*-propylhalides **17c–d**, respectively, in good to excellent yields (Table 1, entries 1–6). The synthesis of alcohol *rac*-**15a** was performed according to a procedure described by Dhar et al. [39], which method was also used for the construction of *rac*-**15b–f**. As besides the aldehyde precursors *rac*-**15a–f** also the corresponding free carboxylic acids *rac*-**18a–f** should be evaluated for their inhibitory potency at mGAT1–mGAT4 the later were synthesized as well. This was accomplished by treating *rac*-**15a–f** with $Ba(OH)_2 \cdot 8\ H_2O$ in analogy to a literature procedure [33], which led to *rac*-**18a–f** in moderate to excellent yields (43–92%, Table 1, entries 1–6).

With the aldehyde precursors *rac*-**15a–f** in hand, the synthesis of the aldehydes *rac*-**12–13** was studied. Attempts to access the aldehydes *rac*-**12–13** by oxidation of the alcohols *rac*-**15a–b** showed, that even using mild oxidation conditions, e.g. Swern-, Parikh-Doering or Dess-Martin periodinane oxidation, the desired aldehydes were not formed or only in traces. As, in addition, the starting material had been completely consumed and a multitude of side products appeared, this approach was dismissed. Instead attempts to deprotect the acetals *rac*-

Table 1 Synthesis of the nipecotic acid derived aldehyde precursors *rac*-**15a–f** and their hydrolysis to the carboxylic acids *rac*-**18a–f**



Entry	Halide	X	n	R^2---------R^3		Ester	Yield	Acid	Yield
1	**17a**	Br	0	OH	H	*rac*-**15a**[(a)]	95	*rac*-**18a**	84
2	**17b**	Br	1	OH	H	*rac*-**15b**	95	*rac*-**18b**	71
3	**17c**	Br	0	OCH_2CH_2O		*rac*-**15c**	93	*rac*-**18c**	88
4	**17d**	Cl	1	OCH_2CH_2O		*rac*-**15d**	79	*rac*-**18d**	92
5	**17e**	Br	0	OMe	OMe	*rac*-**15e**	68	*rac*-**18e**	63
6	**17f**	Cl	1	OMe	OMe	*rac*-**15f**	74	*rac*-**18f**	43

Reagents and conditions: (a) K_2CO_3, NaI, neat, acetone or 1,4-dioxane; (b) $Ba(OH)_2 \cdot 8\ H_2O$, $MeOH/H_2O$; (c) various conditions tested, for *rac*-**15e-f**: $FeCl_3 \cdot 6\ H_2O$, CH_2Cl_2

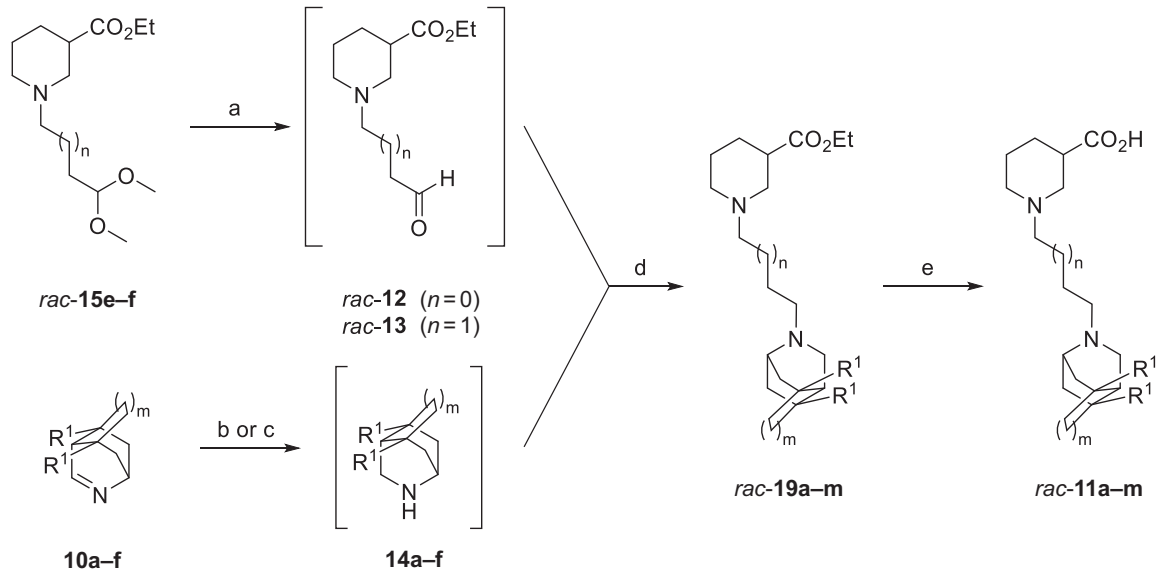
[a]Synthesis according to literature [39]

15c–f were undertaken. In this regard, only reaction conditions that should allow to deprotect the acetals without affecting the ester function were taken into account. Although several deprotection protocols were tested (I_2, acetone [57]; TMSOTf, 2,6-lutidine, CH_2Cl_2 [58]; pyridinium *p*-toluenesulfonate, THF/H_2O [59]; $FeCl_3 \cdot 6\ H_2O$, CH_2Cl_2 [60]; HCl, MeCN/H_2O [61]), the cyclic acetals *rac*-**15c–d** proofed to be too stable and showed only marginal or no aldehyde formation. In contrast, the dimethyl acetals *rac*-**15e–f** were easily deprotected by treatment with $FeCl_3 \cdot 6\ H_2O$ in CH_2Cl_2 according to a procedure of Sen et al. Analysis of the crude product from the cleavage reaction of dimethyl acetal *rac*-**15f** directly after aqueous workup by ^{1}H NMR spectroscopy showed predominant formation of aldehyde **13** ($n = 1$) and only low amounts of remaining dimethyl acetal *rac*-**15f**. However, the crude aldehyde *rac*-**13** was contaminated with unknown side products, resulting from decomposition most likely, which in addition to the dimethyl acetal *rac*-**15f** could not be separated from the desired compound *rac*-**13**. A similar situation was observed when the deprotection of dimethyl acetal *rac*-**15e** to aldehyde *rac*-**12** was attempted. In consequence, the crude aldehydes *rac*-**12–13** should be directly used for the subsequent reductive amination without prior chromatographic purification and without any delay.

Reduction of the imines 10a–f and synthesis of the target compounds *rac*-11a–m

The amines **14a–f**, required for the reductive amination of *rac*-**12** and *rac*-**13**, were synthesized by reduction of the

Table 2 Synthesis of the target compounds *rac*-**11a–m** with tricyclic amines as lipophilic residues



Entry	Imine	R^1	*m*	Acetal	*n*	Ester	Yield	Acid	Yield
1	**10a**	Me	0	*rac*-**15e**	0	*rac*-**19a**	27	*rac*-**11a**	87
2	**10b**	Ph	0	*rac*-**15e**	0	*rac*-**19b**	23	*rac*-**11b**	91
3	**10c**	Me	1	*rac*-**15e**	0	*rac*-**19c**	26	*rac*-**11c**	70
4	**10d**	Ph	1	*rac*-**15e**	0	*rac*-**19d**	25	*rac*-**11d**	84
5	**10e**	Me	2	*rac*-**15e**	0	*rac*-**19e**	37	*rac*-**11e**	81
6	**10f**	Ph	2	*rac*-**15e**	0	*rac*-**19f**	34	*rac*-**11f**	73
7	**10a**	Me	0	*rac*-**15f**	1	*rac*-**19g**	44	*rac*-**11g**	77
8	**10b**	Ph	0	*rac*-**15f**	1	*rac*-**19h**	47	*rac*-**11h**	98
9	**10c**	Me	1	*rac*-**15f**	1	*rac*-**19j**	73	*rac*-**11j**	97
10	**10d**	Ph	1	*rac*-**15f**	1	*rac*-**19k**	72	*rac*-**11k**	65
11	**10e**	Me	2	*rac*-**15f**	1	*rac*-**19l**	36	*rac*-**11l**	96
12	**10f**	Ph	2	*rac*-**15f**	1	*rac*-**19m**	35	*rac*-**11m**	53

Reagents and conditions: (a) $FeCl_3 \cdot 6\ H_2O$, CH_2Cl_2; (b) Reduction of **10a–d**: $NaBH(OAc)_3$, AcOH, CH_2Cl_2; (c) Reduction of **10e–f**: $NaBH_3CN$, HCl, MeOH; (d) $NaBH(OAc)_3$, AcOH, CH_2Cl_2; (e) $BaOH_2 \cdot 8\ H_2O$, MeOH/H_2O

tricyclic imines **10a–f**. The use of $NaBH_3CN$ under acidic conditions seemed well suited for this purpose as it had been successfully applied for the reduction of related tricyclic imines with an 2-azabicyclo[2.2.2]octane scaffold [50]. Indeed, when imines **10a–f** were treated with $NaBH_3CN$ and HCl in methanol the corresponding amines **14a–f** were formed. Unfortunately, amines **14a–b** (bridge size $m = 0$) were found to be instable and to decompose quickly, whereas amines **14c–f** did not show such a behavior. Hence, in addition to the aldehydes *rac*-**12–13**, it seemed best to use also amines **14a–f** directly after their formation without prior purification and isolation.

Considering that both, the aldehydes *rac*-**12–13** and amines **14a–f** had appeared to be labile to some extent, we intended to generate and directly subject them to the next reaction step, the reductive amination to give the respective esters *rac*-**19**. Thus, for the overall reaction sequence first acetals *rac*-**15e–f** should be cleaved by treatment with $FeCl_3 \cdot 6\ H_2O$ in CH_2Cl_2. Then the respective aldehyde should be added to a mixture of imine and reducing agent, which was premixed to mediate imine reduction and to allow subsequent reductive amination of the aldehyde function of *rac*-**12** or *rac*-**13** with the formed amine. When in a test reaction aldehyde **13** was added to a mixture of an imine, structurally similar to imine **10c** but with one of the methyl residues substituted by hydrogen (for a depiction of the structure see compound *rac*-14a in [49]), and $NaBH_3CN$, that had proven well suited for the reduction of the imines **10** to the corresponding amines **14**, besides the reductive amination product also the alcohol *rac*-**15b** resulting from the reduction of aldehyde *rac*-**13** was obtained. However, when the mild reducing agent $NaBH(OAc)_3$ [62, 63] in combination with acetic acid was used instead of $NaBH_3CN$ no such unfavorable reaction occurred. Thus, starting from dimethyl acetal *rac*-**15f** and the imines **10a–d** the esters *rac*-**19g–k** were obtained in moderate to good yields (Table 2, entries 7–10). This method could also successfully be applied to the reductive coupling of dimethyl acetal *rac*-**15e**—via the corresponding aldehyde *rac*-**12**—with the imines **10a–d** to give the desired esters *rac*-**19a–d**. However, in these cases the yields were poor (Table 2, entries 1–4), which is likely to be attributed to the instability of the intermediate aldehyde *rac*-**12** and its propensity to undergo a retro-Michael addition leading to further side reactions.

Unfortunately, the reaction of imines **10e–f** with in situ generated aldehydes *rac*-**12** and *rac*-**13** did not lead to the desired products, the nipecotic acid esters *rac*-**19e–f** and *rac*-**19l–m** under the aforementioned reaction conditions. Actually, despite treatment with $NaBH(OAc)_3$ imines **10e–f** remained unchanged, indicating that they are less reactive than compounds **10a–d**. This is likely to be due to a more severe shielding of the imine function by the adjacent R^1 groups as a result of the larger "upper" bridge ($m = 2$) in **10e–f** as it was claimed before in cycloaddition reactions performed with these compounds [51]. To overcome this problem the aforementioned procedure was changed as follows: Instead of $NaBH(OAc)_3$ $NaBH_3CN$ was employed for the reduction of imines **10e–f** to the amines **14e–f**. Then, when the conversion to the amines **14e–f** had gone to completion according to TLC, excess reducing agent was removed by basic-aqueous workup and the crude amines were reacted with $NaBH(OAc)_3$ and the aldehydes *rac*-**12–13** in analogy to the original procedure. That way, the remaining esters *rac*-**19e–f** and *rac*-**19l–m** could finally be obtained in yields of 34–37% (Table 2, entries 5–6 and 11–12). Basic hydrolysis of the esters *rac*-**19a–m** with $Ba(OH)_2 \cdot 8\ H_2O$ according to a literature procedure [33] provided finally the desired carboxylic acids *rac*-**11a–m** in moderate to excellent yields (53–98%).

Biological evaluation

For the evaluation of the inhibitory potencies of the nipecotic acid derivatives *rac*-**11a–m** exhibiting a free carboxylic acid function and a fully established lipophilic domain, as well as of *rac*-**18a–f** possessing only small *N*-substituents and their corresponding esters *rac*-**15a–f** and *rac*-**19a–m** at the different GAT subtypes mGAT1–mGAT4 a standardized [^{3}H]GABA uptake assay was used [55]. HEK293 cell lines, each stably expressing one individual subtype of the GATs, represent the basis of this assay. Additionally, with a MS Binding Assay the binding affinities towards mGAT1 were determined using NO711 as native MS marker. If the tested compounds did not reduce the [^{3}H]GABA uptake or NO711 marker binding significantly below 50% in preliminary experiments at a concentration of 100 µM, which corresponds to a pIC_{50} of ≤ 4.0 and a pK_i of ≤ 4.0 respectively, only percent values of the remaining [^{3}H]GABA uptake or NO711 marker binding are given. In case of a significant reduction of the [^{3}H]GABA uptake or NO711 marker binding below 50% at an inhibitor concentration of 100 µM, the inhibitory potency (pIC_{50}) and the binding affinity (pK_i), respectively, were determined in a single experiment performed in triplicates.

As Tiagabine (**6**), NO711 (**7**), (*S*)-SNAP-5114 (**8**), or Deramciclane (*rac*-**9**) represent prototypic GAT inhibitors, they provide important reference values for the estimation of the biological activities of the newly synthesized and tested compounds described in this paper, despite the marked differences in their chemical structures. When considering the values of these reference compounds (see Fig. 2), it must be noted that these were partially obtained for enantiomerically pure [Tiagabine, (*S*)-SNAP-5114] or achiral (NO711) GAT inhibitors, whereas the substances displayed in this work are racemic mixtures.

The initially tested nipecotic acid esters *rac*-**15a–f**, that had been synthesized to serve as synthetic intermediates for the introduction of the tricyclic cage unit, and the corresponding carboxylic acids *rac*-**18a–f** displayed only very weak to negligible inhibitory potency and affinity. Only the dimethoxy substituted nipecotic acid derivatives *rac*-**18e** and *rac*-**18f** showed weak inhibitory potency at mGAT1 the remaining [^{3}H]GABA uptake amounting to 50% and 46%, respectively, at a test compound concentration of 100 µM. In addition, these compounds displayed inhibitory potency at mGAT3 and mGAT4, though this was even lower than that at mGAT1 with values for the remaining [^{3}H]GABA uptake in the range of 61–75% (Table 3, entries 10 and 12).

Due to their structural similarity it seemed appropriate to compare the test results for the synthesized carboxylic acids *rac*-**11a–m** and carboxylic acid esters *rac*-**19a–m** exhibiting a tricyclic residue as lipophilic domain among each other as this should provide insight on the influence of the spacer length (n), the bridge size (m) and the residues (R) on the biological activity. The comparison of test results of carboxylic acids of identical structure varying only in their spacer lengths ($n = 0$ or $n = 1$) among each other showed no significant impact of the spacer length on the biological activity for most structures. Only for the two nipecotic acid derivatives *rac*-**11g** and *rac*-**11k** with a butyl spacer improved inhibitory potencies were observed compared to their analogs with a propyl spacer *rac*-**11a** and *rac*-**11d**. For compound *rac*-**11g** a pIC_{50} of 4.25 at mGAT1 was determined, whereas the structurally related carboxylic acid *rac*-**11a** with a propyl spacer could only reduce the [^{3}H]GABA uptake to 66%. Even more pronounced was the effect for carboxylic acid *rac*-**11k** for which a pIC_{50} of 4.40 at mGAT1 and a remaining [^{3}H]GABA uptake of 45% at mGAT2 was found. The corresponding nipecotic acid derivate *rac*-**11d** with a propyl spacer merely reduced the [^{3}H]GABA uptake to 66% at mGAT1 and to 79% at mGAT2.

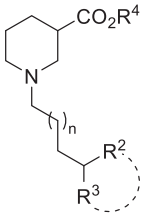
A comparative analysis of the biological activity of carboxylic acid esters *rac*-**19a–m** among each other to study the influence of the spacer length led to diverging results. For some esters of otherwise identical structure the variation of the spacer length did not seem to affect the results of the biological testing (compare: *rac*-**19a** and *rac*-**19g**; *rac*-**19e** and *rac*-**19l**). However, most nipecotic acid ester derivatives showed differences in the biological activity at the different GAT subtypes when the spacer length was altered. The carboxylic ester *rac*-**19b** substituted with phenyl residues and equipped with a methylene bridge ($m = 0$) and a propyl spacer ($n = 0$) exhibited higher inhibitory potencies at mGAT2 and mGAT3 with pIC_{50} values of 4.53 and 4.43, respectively, compared to its analog *rac*-**19h** with a butyl spacer. Yet this analog *rac*-**19h** displayed a higher inhibitory potency at mGAT4 with a pIC_{50} value of 4.89, whereas the potencies at mGAT1 were almost identical. Nipecotic acid ester derivative *rac*-**19c** with a C_3-spacer reached lower remaining [^{3}H]GABA uptake with values ranging from 50 to 60% at mGAT2–mGAT4 as compared to its structural analog *rac*-**19j** with a C_4-spacer. For the phenyl substituted ester *rac*-**19k** with a butyl spacer ($n = 1$) and a C_2-bridge ($m = 1$) at mGAT1–mGAT3 inhibitory potencies with pIC_{50} values ranging from 4.60 to 4.65 were observed, whereas the related ester *rac*-**19d** with a propyl spacer proofed to be less biologically active at mGAT1–mGAT3 and to have an identical activity at mGAT4. Finally, compound *rac*-**19f** displaying phenyl residues, a C_3-bridge ($m = 2$) and a propyl spacer ($n = 0$) had a considerably higher activity at mGAT2 and mGAT3 with pIC_{50} values of 4.28 and 4.97, respectively, but also a lower one at mGAT4 as compared to the analogous ester *rac*-**19m** with a butyl spacer, who had pIC_{50} of 4.33 at mGAT4. Unfortunately, these results did not indicate a universal trend for the inhibitory potency at mGAT1–mGAT4 when the spacer length was altered.

Further analysis of the biological activity of carboxylic acids *rac*-**11a–m** by comparing structures deviating only in their attached residues R^1, being either methyl or phenyl residues, showed that for most of the carboxylic acids the residue had a very small to negligible effect on the inhibitory potency at mGAT1–mGAT4 (compare *rac*-**11a** and *rac*-**11b**; *rac*-**11c** and *rac*-**11d**; *rac*-**11e** and *rac*-**11f**; *rac*-**11l** and *rac*-**11m**). Exceptions are the methyl-substituted nipecotic acid derivative *rac*-**11g** with a butyl spacer ($n = 1$) and a methylene bridge ($m = 0$), which had an improved inhibitory potency at mGAT1 with a pIC_{50} of 4.25 as compared to its phenyl substituted analog *rac*-**11h**, and the phenyl substituted nipecotic acid derivative *rac*-**11k** with a butyl spacer ($n = 1$) and a C_2-bridge ($m = 1$), that had a higher biological activity at mGAT1 and mGAT2 with a pIC_{50} of 4.40 and a remaining [^{3}H]GABA uptake of 45%, respectively, as compared to its related methyl-substituted carboxylic acid *rac*-**11j**.

When taking a look at the carboxylic acid esters *rac*-**19a–m** it became evident that almost always the phenyl substituted esters had higher inhibitory potencies at mGAT1–mGAT4 than their otherwise identical methyl-substituted analogs. This observation is nicely highlighted by ester *rac*-**19k** with pIC_{50} values in a range of 4.60–4.65 at mGAT1–mGAT4, which are in strong contrast to the biological results obtained for the related, basically inactive methyl-substituted ester *rac*-**19j**. Obviously, the aromatic phenyl residue in the nipecotic acid ester derived GAT inhibitors seems to be necessary as structural element to achieve a reasonable activity at all GAT subtypes.

The examination of the influence of the bridge size (m) on the biological activity of the carboxylic acids *rac*-**11a–m** at mGAT1–mGAT4 led to contradictory results. For the

Table 3 Binding affinities and inhibitory potencies of nipecotic acid derivatives *rac*-**15a–f** and *rac*-**18a–f**



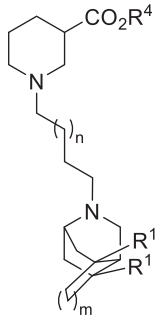
Entry	Compound	R^2---------R^3		n	R^4	pK_i [a]	pIC_{50} [a]			
						mGAT1	mGAT1	mGAT2	mGAT3	mGAT4
1	*rac*-**15a**	OH	H	0	Et	91%	113%	89%	110%	99%
2	*rac*-**18a**	OH	H	0	H	82%	67%	82%	81%	87%
3	*rac*-**15b**	OH	H	1	Et	91%	111%	97%	103%	89%
4	*rac*-**18b**	OH	H	1	H	96%	87%	93%	80%	96%
5	*rac*-**15c**	OCH_2CH_2O		0	Et	82%	104%	72%	92%	96%
6	*rac*-**18c**	OCH_2CH_2O		0	H	104%	71%	76%	70%	83%
7	*rac*-**15d**	OCH_2CH_2O		1	Et	86%	95%	88%	103%	85%
8	*rac*-**18d**	OCH_2CH_2O		1	H	103%	87%	92%	81%	89%
9	*rac*-**15e**	OMe	OMe	0	Et	90%	93%	82%	106%	96%
10	*rac*-**18e**	OMe	OMe	0	H	98%	**50%**	89%	61%	69%
11	*rac*-**15f**	OMe	OMe	1	Et	87%	100%	89%	89%	100%
12	*rac*-**18f**	OMe	OMe	1	H	97%	**46%**	97%	74%	75%

[a]All values were determined in one experiment performed in triplicate. The results of the MS binding assay are given as pK_i, the results of the [^{3}H]GABA uptake assay as pIC_{50}. Percent values indicate remaining specific NO711 binding or remaining [^{3}H]GABA uptake, respectively, in presence of 100 μM test compound

methyl-substituted nipecotic acid derivatives *rac*-**11a**, *rac*-**11c**, and *rac*-**11e** with a propyl spacer ($n = 0$) no significant effect of the bridge size on the inhibitory potencies at mGAT1–mGAT4 could be observed. Also, the methyl-substituted carboxylic acids *rac*-**11g**, *rac*-**11j**, and *rac*-**11l** with a butyl spacer ($n = 1$) showed similar biological activities at mGAT2–mGAT4 despite their varying bridge size ($m = 0$–2) and only at mGAT1 a preference for the carboxylic acid *rac*-**11g** with the smallest bridge size ($m = 0$), for which a pIC_{50} of 4.25 was found, could be noticed. The comparison of the phenyl substituted carboxylic acids *rac*-**11b**, *rac*-**11d**, and *rac*-**11f** with a propyl spacer ($n = 0$) among each other indicated a preference for structures with smaller bridge sizes with regard to biological activity at mGAT1 and mGAT3 as the remaining [^{3}H]GABA uptake declined from 82 to 52% at mGAT1 and from 90 to 67% at mGAT3 with decreasing bridge size. For these structures at mGAT4 no influence of the bridge size on the biological activity was observed and at mGAT2 only a weak preference for carboxylic acid *rac*-**11f** with a C_3-bridge was recognized. The comparative analysis of the phenyl substituted carboxylic acids *rac*-**11h**, *rac*-**11k**, and *rac*-**11m** with a butyl spacer ($n = 1$), in contrast, showed a preference for the medium-sized bridge ($m = 1$) for the biological activity at mGAT1–mGAT3, as the best inhibitory potencies with a pIC_{50} value of 4.40 at mGAT1 and remaining [^{3}H]GABA uptakes of 45–58% at mGAT2–mGAT3 were determined for carboxylic acid *rac*-**11k**.

In addition, the influence of the bridge size (m) on the biological activity was studied for the carboxylic acid esters *rac*-**19a–m**. When the esters *rac*-**19a**, *rac*-**19c**, and *rac*-**19e**, all equipped with methyl residues and a propyl spacer ($n =$

Table 4 Nipecotic acid derivatives possessing various tricyclic amines as substituents and their binding affinities and inhibitory potencies



Entry	Compound	R^1	m	n	R^4	pK_i [a]	pIC_{50} [a]			
						mGAT1	mGAT1	mGAT2	mGAT3	mGAT4
1	*rac*-**19a**	Me	0	0	Et	95%	66%	61%	81%	69%
2	*rac*-**11a**	Me	0	0	H	82%	66%	78%	73%	81%
3	*rac*-**19b**	Ph	0	0	Et	**4.62**	**4.32**	**4.53**	**4.46**	**4.59**
4	*rac*-**11b**	Ph	0	0	H	68%	52%	79%	67%	68%
5	*rac*-**19c**	Me	1	0	Et	72%	86%	50%	60%	54%
6	*rac*-**11c**	Me	1	0	H	76%	50%	83%	75%	77%
7	*rac*-**19d**	Ph	1	0	Et	60%	**4.37**	58%	**4.29**	**4.65**
8	*rac*-**11d**	Ph	1	0	H	104%	66%	79%	79%	69%
9	*rac*-**19e**	Me	2	0	Et	89%	69%	76%	77%	89%
10	*rac*-**11e**	Me	2	0	H	88%	62%	72%	74%	87%
11	*rac*-**19f**	Ph	2	0	Et	78%	**4.14**	**4.28**	**4.97**	62%
12	*rac*-**11f**	Ph	2	0	H	98%	83%	57%	90%	71%
13	*rac*-**19g**	Me	0	1	Et	95%	59%	60%	77%	62%
14	*rac*-**11g**	Me	0	1	H	84%	**4.25**	80%	61%	71%
15	*rac*-**19h**	Ph	0	1	Et	81%	**4.35**	**4.00**	**4.13**	**4.89**
16	*rac*-**11h**	Ph	0	1	H	82%	67%	79%	77%	80%
17	*rac*-**19j**	Me	1	1	Et	106%	88%	81%	90%	86%
18	*rac*-**11j**	Me	1	1	H	84%	74%	102%	71%	96%
19	*rac*-**19k**	Ph	1	1	Et	84%	**4.60**	**4.61**	**4.65**	**4.64**
20	*rac*-**11k**	Ph	1	1	H	71%	**4.40**	45%	58%	83%
21	*rac*-**19l**	Me	2	1	Et	101%	83%	73%	86%	74%
22	*rac*-**11l**	Me	2	1	H	89%	78%	85%	79%	86%
23	*rac*-**19m**	Ph	2	1	Et	72%	**4.18**	59%	53%	**4.33**
24	*rac*-**11m**	Ph	2	1	H	104%	83%	76%	105%	76%

[a]All values were determined in one experiment performed in triplicate. The results of the MS binding assay are given as pK_i, the results of the [^{3}H]GABA uptake assay as pIC_{50}. Percent values indicate remaining specific NO711 binding or remaining [^{3}H]GABA uptake, respectively, in presence of 100 µM test compound

0), were compared among each other, only for the inhibitory potency at mGAT4 the bridge size seemed to be important to some extent. Here ester *rac*-**19c** with a medium-sized C_2-bridge ($m = 1$) reducing the remaining [^{3}H]GABA uptake to 54% at a test compound concentration of 100 µM proofed to be best. Also, the biological activity of the methyl-substituted esters *rac*-**19g**, *rac*-**19j**, and *rac*-**19l** with a butyl spacer ($n = 1$) at mGAT2–mGAT4 appeared to be rather unaffected by the bridge size of these compounds. Solely, according to the results of the inhibitory potencies at mGAT1, a methylene bridge ($m = 0$) mediates a slightly higher potency at this GAT subtype (see ester *rac*-**19g**). The comparative analysis of the test results of the phenyl substituted esters *rac*-**19b**, *rac*-**19d**, and *rac*-**19f** with a C_3-spacer ($n = 0$) showed, that ester *rac*-**19f** with the largest bridge size ($m = 2$) turned out best to address mGAT3, with a pIC_{50} value of 4.97, whereas, in order to address mGAT2, ester *rac*-**19b** with the smallest bridge size ($m = 0$) led to the best result (pIC_{50} of 4.53). The esters *rac*-**19b**, *rac*-**19d** with a small or medium-sized bridge were equally suited to address mGAT4. As the esters *rac*-**19b**, *rac*-**19d**, and *rac*-**19f** displayed almost equal inhibitory potencies at mGAT1, no effect of the bridge size on the biological activity at this GAT subtype could be noticed. Finally, the structurally related phenyl substituted esters *rac*-**19h**, *rac*-**19k**, and *rac*-**19m** with a butyl spacer ($n = 1$) were compared among each other to study the influence of the bridge size on the biological activity for these compounds. Ester *rac*-**19k** with a medium-sized bridge ($m = 1$) demonstrated to be superior as compared to esters *rac*-**19h** and *rac*-**19m** with regard to inhibitory activities at mGAT1–mGAT3. Since at mGAT4 the inhibitory potency of esters *rac*-**19h**, *rac*-**19k**, and *rac*-**19m** was decreasing with an increase in bridge size, the ester *rac*-**19h** led with a pIC_{50} value of 4.89 to the best result. However, by the above obtained results no general correlation between the biological activity at a certain GAT subtype and the bridge size (m) in the lipophilic domain of the tested carboxylic acids *rac*-**11a–m** or their corresponding esters *rac*-**19a–m** could be concluded.

Interestingly, all phenyl substituted nipecotic acid ester derivatives, i.e., *rac*-**19b**, *rac*-**19d**, *rac*-**19f**, *rac*-**19h**, *rac*-**19k**, and *rac*-**19m** exhibited higher inhibitory potencies at mGAT1–mGAT4 than their corresponding carboxylic acids. For the methyl-substituted nipecotic acid ester derivatives no such universal effect was observed. The former phenyl substituted nipecotic acid derivatives showed rather equal inhibitory potencies at all four GAT subtypes (Table 4, see entries for compounds *rac*-**19b**, *rac*-**19d**, *rac*-**19k**, and *rac*-**19m**), but also a weak subtype selectivity for mGAT3 and for mGAT4 was achieved with ester *rac*-**19f** (pIC_{50} value of 4.97 at mGAT3; Table 4, entry 11) and ester *rac*-**19h** (pIC_{50} value of 4.89 at mGAT4; Table 4, entry 15), respectively. These esters, *rac*-**19f** and *rac*-**19h**, represent the first subtype selective GAT inhibitors carrying a cage unit in the lipophilic domain.

Still to be mentioned is the fact, that the binding affinities at mGAT1 determined in binding assays often do not correlate with the inhibitory potencies from mGAT1 uptake assays. This phenomenon, the cause of which is still to be clarified, can be seen for example in case of ester *rac*-**19k**. This compound, *rac*-**19k**, exhibits a pIC_{50} value of 4.60 at mGAT1 in the uptake assay, but a reduction of remaining NO711 marker binding in the binding assay to 84% only (at a test compound concentration of 100 µM).

Conclusion

Inspired by the drug Deramciclane (*rac*-**9**), a new class of GABA uptake inhibitors with bulky and highly rigid tricyclic subunits in the lipophilic domain delineated from the 2-azabicyclo[2.2.2]octane scaffold by the presence of an additional carbon bridge was developed. The polycyclic subunits are connected via a plain hydrocarbon spacer with the amino nitrogen of nipecotic acid or that of the corresponding ethyl ester. For the synthesis of the new compounds, nipecotic acid derivates with an *N*-alkyl residue displaying a terminal aldehyde function, were connected with symmetric tricyclic amines by reductive amination. The tricyclic amines used were either generated in situ from tricyclic imines serving as precursors directly before the reductive amination by the same reducing agent or they were generated from the tricyclic imines in a separate reaction step. The new GAT inhibitors varied in regard to the spacer length, the size of one of the bridges of the tricyclic skeleton of the lipophilic domain and the substituents attached to the latter. Whereas the nipecotic acid derived GAT inhibitors displayed only weak inhibitory potencies and binding affinities at the four different GAT subtypes, all phenyl substituted nipecotic acid ethyl ester derivatives exhibited moderate biological activity at mGAT1–mGAT4. The structure activity relationship of these GAT inhibitors demonstrated the importance of the phenyl residues and the ester function for the biological activity. Two of the phenyl substituted nipecotic acid ethyl ester derivates, *rac*-**19f** and *rac*-**19h**, being equipped with either a propyl spacer and a C_3-bridge (*rac*-**19f**) or a butyl spacer and a methylene bridge (*rac*-**19h**), showed even moderate subtype selectivity at mGAT3 and mGAT4 respectively. As demonstrated by the obtained results tricyclic cage structures represent promising subunits for the construction of novel GAT inhibitors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

1. Guzmán BCF, Vinnakota C, Govindpani K, Waldvogel HJ, Faull RLM, Kwakowsky A. The GABAergic system as a therapeutic target for Alzheimer's disease. J Neurochem. 2018;146:649–69.
2. Lanctot KL, Herrmann N, Mazzotta P, Khan LR, Ingber N. GABAergic function in Alzheimer's disease: evidence for dysfunction and potential as a therapeutic target for the treatment of behavioural and psychological symptoms of dementia. Can J Psychiatry. 2004;49:439–53.
3. Kalueff AV, Nutt DJ. Role of GABA in anxiety and depression. Depression Anxiety. 2007;24:495–517.
4. Kleppner SR, Tobin AJ. GABA signalling: therapeutic targets for epilepsy, Parkinson's disease and Huntington's disease. Expert Opin Ther Targets. 2001;5:219–39.
5. Treimann DM. GABAergic mechanisms in epilepsy. Epilepsia. 2001;42:8–12.
6. Firbank MJ, Parikh J, Murphy N, Killen A, Allan CL, Collerton D, et al. Reduced occipital GABA in Parkinson disease with visual hallucinations. Neurology. 2018;91:675–85.
7. van Nuland AJM, den Ouden HEM, Zach H, Dirkx MFM, van Asten JJA, Scheenen TWJ, et al. GABAergic changes in the thalamocortical circuit in Parkinson's disease. Hum Brain Mapp. 2020;41:1017–29.
8. Błaszczyk JW. Parkinson's disease and neurodegeneration: GABA-collapse hypothesis. Front Neurosci. 2016;10:269.
9. Krogsgaard-Larsen P. GABA synaptic mechanisms: stereochemical and conformational requirements. Med Res Rev. 1988;8:27–56.
10. Lüllmann H, Mohr K, Hein L. Pharmakologie und Toxikologie. Stuttgart: Georg Thieme Verlag; 2010.
11. Scheschonka A, Betz H, Becker CM. Chemische Signalübertragung zwischen Neuronen. In: Löffler G, Petrides PE, Heinrich PC, (ed). Biochemie und Pathobiochemie. Heidelberg: Springer; 2007. p. 1036–45.
12. Sałat K, Podkowa A, Kowalczyk P, Kulig K, Dziubina A, Filipek B, et al. Anticonvulsant active inhibitor of GABA transporter subtype 1, tiagabine, with activity in mouse models of anxiety, pain and depression. Pharm Rep. 2015;67:465–72.
13. Schousboe A, Madsen KK, Barker-Haliski ML, White HS. The GABA synapse as a target for antiepileptic drugs: a historical overview focused on GABA transporters. Neurochem Res. 2014;39:1980–7.
14. Borden LA. GABA transporter heterogeneity: pharmacology and cellular localization. Neurochem Int. 1996;29:335–56.
15. Gether U, Andersen PH, Larsson OM, Schousboe A. Neurotransmitter transporters: molecular function of important drug targets. Trends Pharm Sci. 2006;27:375–83.
16. Kristensen AS, Andersen J, Jorgensen TN, Sorensen L, Eriksen J, Loland CJ, et al. SLC6 neurotransmitter transporters: structure, function, and regulation. Pharm Rev. 2011;63:585–640.
17. Willford SL, Anderson CM, Spencer SR, Eskandari S. Evidence for a revised ion/substrate coupling stoichiometry of GABA transporters. J Membr Biol. 2015;248:795–810.
18. Conti F, Minelli A, Melone M. GABA transporters in the mammalian cerebral cortex: localization, development and pathological implications. Brain Res Rev. 2004;45:196–212.
19. Liu QR, López-Corcuera B, Mandiyan S, Nelson H, Nelson N. Molecular characterization of four pharmacologically distinct α-aminobutyric acid transporters in mouse brain. J Biol Chem. 1993;268:2106–12.
20. Madsen KK, Clausen RP, Larsson OM, Krogsgaard-Larsen P, Schousboe A, White HS. Synaptic and extrasynaptic GABA transporters as targets for anti-epileptic drugs. J Neurochem. 2009;109:139–44.
21. Christiansen B, Meinild AK, Jensen AA, Bräuner-Osborne H. Cloning and characterization of a functional human γ-aminobutyric acid (GABA) transporter, human GAT-2. J Biol Chem. 2007;282:19331–41.
22. Palacín M, Estévez R, Bertran J, Zorzano A. Molecular biology of mammalian plasma membrane amino acid transporters. Physiol Rev. 1998;78:969–1054.
23. Jin XT, Galvan A, Wichmann T, Smith Y. Localization and function of GABA transporters GAT-1 and GAT-3 in the basal ganglia. Front Syst Neurosci. 2011;5:63.
24. Minelli A, DeBiasi S, Brecha NC, Zuccarello LV, Conti F. GAT-3, a high-affinity GABA plasma membrane transporter, is localized to astrocytic processes, and it is not confined to the vicinity of GABAergic synapses in the cerebral cortex. J Neurosci. 1996;16:6255–64.
25. Zhou Y, Holmseth S, Guo C, Hassel B, Höfner G, Huitfeldt HS, et al. Deletion of the γ-aminobutyric acid transporter 2 (GAT2 and SLC6A13) gene in mice leads to changes in liver and brain taurine contents. J Biol Chem. 2012;287:35733–46.
26. Zhou Y, Holmseth S, Hua R, Lehre AC, Olofsson AM, Poblete-Naredo I, et al. The betaine-GABA transporter (BGT1, slc6a12) is predominantly expressed in the liver and at lower levels in the kidneys and at the brain surface. Am J Physiol Ren Physiol. 2012;302:316–28.
27. Knutsen LJS, Andersen KE, Lau J, Lundt BF, Henry RF, Morton HE, et al. Synthesis of novel GABA uptake inhibitors. 3. diaryloxime and diarylvinyl ether derivatives of nipecotic acid and guvacine as anticonvulsant agents. J Med Chem. 1999;42:3447–62.
28. Andersen KE, Lau J, Lundt BF, Petersen H, Huusfeldt PO, Suzdak PD, et al. Synthesis of novel GABA uptake inhibitors. Part 6: preparation and evaluation of *N*-Ω asymmetrically substituted nipecotic acid derivatives. Bioorg Med Chem. 2001;9:2773–85.
29. Schaarschmidt M, Höfner G, Wanner KT. Synthesis and biological evaluation of nipecotic acid and guvacine derived 1,3-disubstituted allenes as inhibitors of murine GABA transporter mGAT1. ChemMedChem. 2019;14:1135–51.
30. Andersen KE, Sørensen JL, Huusfeldt PO, Knutsen LJS, Lau J, Lundt BF, et al. Synthesis of novel GABA uptake inhibitors. 4. bioisosteric transformation and successive optimization of known GABA uptake inhibitors leading to a series of potent anticonvulsant drug candidates. J Med Chem. 1999;42:4281–91.
31. Tóth K, Höfner G, Wanner KT. Synthesis and biological evaluation of novel N-substituted nipecotic acid derivatives with a

trans-alkene spacer as potent GABA uptake inhibitors. Bioorg Med Chem. 2018a;26:5944–61.
32. Tóth K, Höfner G, Wanner KT. Synthesis and biological evaluation of novel N-substituted nipecotic acid derivatives with an alkyne spacer as GABA uptake inhibitors. Bioorg Med Chem. 2018b;26:3668–87.
33. Böck MC, Höfner G, Wanner KT. N-substituted nipecotic acids as (*S*)-SNAP-5114 analogues with modified lipophilic domains. ChemMedChem. 2020;15:1–17.
34. Andersen KE, Braestrup C, Grønwald FC, Jørgensen AS, Nielsen EB, Sonnewald U.et al. The synthesis of novel GABA uptake inhibitors. 1. Elucidation of the structure-activity studies leading to the choice of (*R*)-1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic acid (tiagabine) as an anticonvulsant drug candidate. J Med Chem. 1993;36:1716–25.
35. Madsen KK, White HS, Schousboe A. Neuronal and non-neuronal GABA transporters as targets for antiepileptic drugs. Pharm Ther. 2010;125:394–401.
36. Skovstrup S, Taboureau O, Bräuner-Osborne H, Jørgenson FS. Homology modelling of the GABA transporter and analysis of tiagabine binding. ChemMedChem. 2010;5:968–1000.
37. Wein T, Petrera M, Allmendinger L, Höfner G, Pabel J, Wanner KT. Different binding modes of small and large binders of GAT1. ChemMedChem. 2016;11:509–18.
38. Zafar S, Jabeen I. Structure, function, and modulation of γ-aminobutyric acid transporter 1 (GAT1) in neurological disorders: a pharmacoinformatic prospective. Front Chem. 2018;6:397.
39. Dhar TGM, Borden LA, Tyagarajan S, Smith KE, Branchek TA, Weinshank RL, et al. Design, synthesis and evaluation of substituted triarylnipecotic acid derivatives as GABA uptake inhibitors: identification of a ligand with moderate affinity and selectivity for the cloned human GABA transporter GAT-3. J Med Chem. 1994;37:2334–42.
40. Leppik IE, Gram L, Deaton R, Sommerville KW. Safety of tiagabine: summary of 53 trials. Epilepsy Res. 1999;33:235–46.
41. Kerscher-Hack S, Renukappa-Gutke T, Höfner G, Wanner KT. Synthesis and biological evaluation of a series of N-alkylated imidazole alkanoic acids as mGAT3 selective GABA uptake inhibitors. Eur J Med Chem. 2016;124:852–80.
42. Andersen KE, Sørensen JL, Lau J, Lundt BF, Petersen H, Huusfeldt PO, et al. Synthesis of novel γ-aminobutyric acid (GABA) uptake inhibitors. 5. Preparation and structure-activity studies of tricyclic analogues of known GABA uptake inhibitors. J Med Chem. 2001;44:2152–63.
43. Wipf P, Skoda EM, Mann A. The practice of medicinal chemistry. London, San Diego, Waltham, Oxford: Academic Press; 2015.
44. Zheng Y, Tice CM, Singh SB. The use of spirocyclic scaffolds in drug discovery. Bioorg Med Chem Lett. 2014;24:3673–82.
45. Joubert J, Geldenhuys WJ, van der Schyf CJ, Oliver DW, Kruger HG, Govender T, et al. Polycyclic cage structures as lipophilic scaffolds for neuroactive drugs. ChemMedChem. 2012;7:375–84.
46. Stockdale TP, Williams CM. Pharmaceuticals that contain polycyclic hydrocarbon scaffolds. Chem Soc Rev. 2015;44:7737–63.
47. Brookes KB, Hickmott PW, Jutle KK, Schreyer CA. Introduction of pharmacophoric groups into polycyclic systems. Part 4. Aziridine, oxiran and tertiary β-hydroxyethylamine derivatives of adamantane. S Afr J Chem. 1992;45:8–11.
48. Kovács I, Maksay G, Simonyi M. Inhibition of high-affinity synaptosomal uptake of gamma-aminobutyric acid by a bicycloheptane derivative. Arzneimittelforschung. 1989;39:295–297.
49. Rudy HKA, Wanner KT. Accessing tricyclic imines comprising a 2-azabicyclo[2.2.2]octane scaffold by intramolecular hetero-diels–alder reaction of 4-alkenyl-substituted *N*-silyl-1,4-dihydropyridines. Synthesis. 2019;51:4296–310.
50. Schmaunz CE, Mayer P, Wanner KT. Inter- and intramolecular [4 +2]-cycloaddition reactions with 4,4-disubstituted *N*-silyl-1,4-dihydropyridines as precursors for N-protonated 2-azabutadiene intermediates. Synthesis. 2014;46:1630–8.
51. Rudy HKA, Mayer P, Wanner KT. Synthesis of 1,5-Ring fused imidazoles from cyclic imines and TosMIC—identification of in situ generated N-methyleneformamide as a catalyst in the van leusen imidazole synthesis. Eur J Org Chem. 2020;51:3599–11.
52. Perrin DD, Armarego WLF. Purification of Laboratory Chemicals. New York: Pergamon; 1988.
53. Fulmer GR, Miller AJM, Sherden NH, Gottlieb HE, Nudelman A, Stoltz BM, et al. NMR chemical shifts of trace impurities: common laboratory solvents, organics, and gases in deuterated solvents relevant to the organometallic chemist. Organometallics. 2010;29:2176–9.
54. Pauli GF, Chen S-N, Simmler C, Lankin DC, Gödecke T, Jaki BU, et al. Importance of purity evaluation and the potential of quantitative ^{1}H NMR as a purity assay. J Med Chem. 2014;57:9220–31.
55. Kragler A, Höfner G, Wanner KT. Synthesis and biological evaluation of aminomethylphenol derivatives as inhibitors of the murine GABA transporters mGAT1-GAT4. Eur J Med Chem. 2008;43:2404–11.
56. Zepperitz C, Höfner G, Wanner KT. MS-binding assays: kinetic, saturation, and competitive experiments based on quantitation of bound marker as exemplified by the GABA transporter mGAT1. ChemMedChem. 2006;1:208–17.
57. Sun J, Dong Y, Cao L, Wang X, Wang S, Hu Y. Highly efficient chemoselective deprotection of O,O-acetals and O,O-ketals catalyzed by molecular iodine in acetone. J Org Chem. 2004;69:8932–4.
58. Fujioka H, Sawama Y, Murata N, Okitsu T, Kubo O, Matsuda S, et al. Unexpected highly chemoselective deprotection of the acetals from aldehydes and not ketones: TESOTf-2,6-lutidine combination. J Am Chem Soc. 2004;126:11800–1.
59. Denmark SE, Gomez L. Tandem double intramolecular [4+2]/[3 +2] cycloadditions of nitroalkenes. The fused/bridged mode. J Org Chem. 2003;68:8015–24.
60. Sen SE, Roach SL, Boggs JK, Ewing GJ, Magrath J. Ferric chloride hexahydrate: a mild hydrolytic agent for the deprotection of acetals. J Org Chem. 1997;62:6684–6.
61. Rancati F, Rizzi A, Carzaniga L, Linney I, Walden S, Knight C, et al. Compounds having muscarinic receptor antagonist and beta2 adrenergic receptor agonst activity. US Patent 2016-0235734. 2016.
62. Abdel-Magid AF, Carson KG, Harris BD, Maryanoff CA, Shah RD. Reductive amination of aldehydes and ketones with sodium triacetoxyborohydride. Studies on direct and indirect reductive amination procedures. J Org Chem. 1996;61:3849–62.
63. Abdel-Magid AF, Mehrman SJ. A review on the use of sodium triacetoxyborohydride in the reductive amination of ketones and aldehydes. Org Proc Res Dev. 2006;10:971–1031.
64. Pabel J, Faust M, Prehn C, Wörlein B, Allmendinger L, Höfner G, et al. Development of an (*S*)-1-{2-[tris(4-methoxyphenyl)methoxy]ethyl}piperidine-3-carboxylic acid [(*S*)-SNAP-5114] carba analogue inhibitor for murine γ-aminobutyric acid transporter type 4. ChemMedChem. 2012;7:1245–55.