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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

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A series of GABA uptake inhibitors related to (*S*)-1-{2-[tris(4-methoxyphenyl)methoxy]ethyl}piperidine-3-carboxylic acid [(*S*)-SNAP-5114], the most potent mGAT4 inhibitor known so far, were synthesized and biologically evaluated for their inhibitory potency at the four GABA uptake transporters mGAT1–4 stably expressed in HEK-293 cell lines. New analogues were developed with potencies that are similar to or slightly higher than those of current mGAT4 inhibitors, but with distinctly improved chemical stability. (*S*)-Nipecotic acid derivatives possessing a 2-[1-(4-methoxy-2-methylphenyl)-1,1-bis(4-methoxyphenyl)methoxy]ethyl (DDPM-859) or a 4,4,4-tris(4-methoxyphenyl)but-2-en-1-yl moiety (DDPM-1457) were found to exhibit pIC_{50} values of 5.78 and 5.87, respectively. Thus, as mGAT4 inhibitors, these compounds compare well with (*S*)-SNAP-5114 ($pIC_{50} = 5.71$), but are far more stable than the latter. Moreover, DDPM-859 displays a more favorable subtype selectivity for mGAT4 versus mGAT3 than does (*S*)-SNAP-5114.

Introduction

γ-Aminobutyric acid (GABA, **1**, Figure 1) is the major inhibitory neurotransmitter in the central nervous system (CNS), with ~30–40% of synapses estimated to be GABAergic.[1] A dysregulation of GABA signaling is thought to play a key role in a number of different neurological disorders such as epilepsy, Parkinson's disease, Huntington's disease, schizophrenia, and Alzheimer's disease.[2] Targeting the individual stages of GABA signaling to positively modulate GABA neurotransmission has consequently become an important strategy for the potential therapy of these diseases. Barbiturates and benzodiazepines, for instance, which are among the most commonly used GABAergic drugs today, enhance GABA neurotransmission through allosteric modulation of $GABA_A$ receptors. The antiepileptic drug vigabatrine improves the GABA status by acting as a suicide inhibitor of GABA transaminase, an enzyme responsible for the metabolic degradation of GABA.

GABA signaling may be further controlled by manipulating the activity of GABA transporters that mediate the transport of synaptically released GABA from extra- to intracellular side of glial and neuronal cells. Inhibition of these transporters leads to an increase in extracellular GABA levels and thus to enhanced GABA signaling. There are four different GABA transporter subtypes belonging to the solute carrier 6 (SLC6) transporter that use the co-transport of sodium ions as a driving force for the translocation of their substrates against chemical gradients.[3] The GABA transporter subtypes cloned from murine brain are termed mGAT1, mGAT2, mGAT3, and mGAT4.[4] For all other species, including humans and rats, a different nomenclature, also adopted by the Human Genome Organization (HUGO) is used; these transporters are denoted as GAT1, GAT2, GAT3,[5] and BGT-1, respectively (see Ref. [6] for a detailed discussion).

mGAT1 and mGAT4 are the two most abundant GABA transporters in the brain, with the former being predominant. Both subtypes are almost exclusively expressed around the synaptic cleft; mGAT1 is primarily located in pre-synaptic neuronal membranes, whereas mGAT4 is mainly located on glial cells.

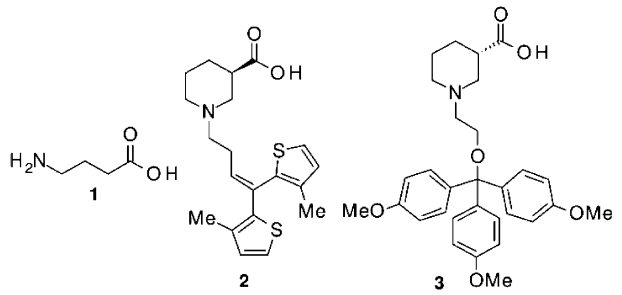

Figure 1. GABA (**1**), Tiagabine (**2**) and (*S*)-SNAP-5114 (**3**).

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mGAT1 is an approved drug target for the therapy of epilepsy. However, tiagabine (**2**, Figure 1), the only currently approved antiepileptic drug that addresses mGAT1 with high affinity and selectivity, has the disadvantage of occasionally observed side effects such as dizziness, asthenia, nervousness, tremor, diarrhea, and depression.[7,8] As these side effects seem to be inherently coupled with the function of mGAT1, other GAT subtypes have gained increasing research interest.[9–11] In particular, mGAT4, which is the second most abundant subtype in the brain and differs from mGAT1 not only with respect to its cellular localization but also to its distribution in different brain regions, shows great potential as a target for the development of antiepileptic drugs with an improved pharmacological profile.[9] Although a plethora of highly potent and subtype-selective inhibitors are available for mGAT1, only few inhibitors of mediocre potency are known for mGAT4. (*S*)-SNAP-5114 (**3**, Figure 1) represents the most potent and selective mGAT4 inhibitor so far.[12] It is characterized by a pIC_{50} value of 5.71[13,14] at mGAT4 (Figure 2 and Table 1 below). In in vivo studies, **3** has been found to significantly enhance GABA levels in rat thalamus but not in rat hippocampus, in contrast to the mGAT1-selective inhibitor tiagabine (**2**), which affects both brain regions.[9] In addition to underscoring the different pharmacological effects of mGAT4 versus mGAT1 inhibitors, this finding also highlights differences in the regional localization of these GABA transporters.

Unfortunately, the moderate potency at and selectivity for mGAT4 exhibited by **3** is also accompanied by poor chemical stability. Due to the trityloxy moiety present in the side chain capable of forming triarylcarbenium ions, compound **3** is susceptible to decomposition especially under acidic conditions. The aim of the study presented herein was to overcome this problem by developing new mGAT4-selective inhibitors related to (*S*)-SNAP-5114 (**3**) with structurally modified side chains of improved chemical stability.

Results and Discussion

Chemistry

To improve the chemical stability of the side chain of (*S*)-SNAP-5114, two strategies were followed. In each case, however, only small structural changes were envisaged to minimize the risk of a substantial loss in activity. One strategy was aimed at modifications of the trityl moiety, and the other at variation of the spacer connecting the nipecotic acid unit with the lipophilic moiety to decrease or even eliminate the risk of side chain destruction due to carbenium ion formation.

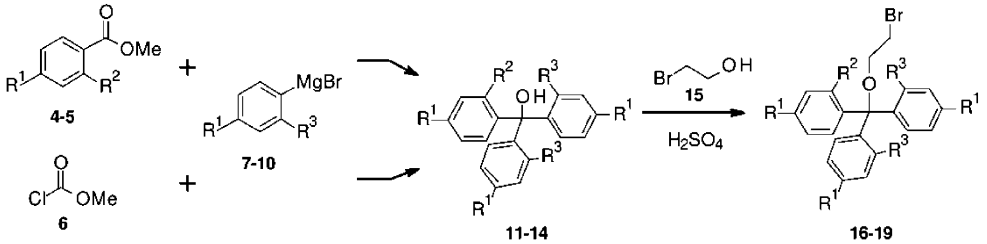
For the synthesis of test compounds, we adopted the synthetic route used by Dhar et al.[12] for the preparation of **3** and related compounds. Accordingly, to introduce the respective side chain, nipecotic acid ethyl ester (**30**) was allowed to react with the appropriate alkylating agents, and the resulting *N*-alkyl derivatives were finally subjected to hydrolysis to give the free amino acids. The alkylating agents required for preparation of the first set of test compounds with a structurally modified trityl moiety were synthesized as outlined in Scheme 1, again following a method used by Dhar et al.[12] The alkylating agents **16**–**19** were obtained by treating the carboxylic acid esters **4** and **5** or methyl chloroformate (**6**) with the appropriate Grignard reagents **7**–**10** (2.5 equiv **7** and **8**, and 4 equiv **9** and **10**) and subsequent treatment of the resulting alcohols **11**–**14** with 2-bromoethanol (**15**) in the presence of sulfuric acid to yield the alkyl bromides **16**–**19** in 15–65 % yield (Scheme 1).

The single *ortho*-methyl group present in **16** and even more so the two *ortho*-methyl groups in **17** were expected to impede planarization of the carbenium ions that would arise from heterolytic cleavage of the ether function in **16** and **17**, thus rendering the carbenium ions less stable, and consequently the ether functions more stable.

In **18** and **19**, the *para*-methoxy groups present in **3** were replaced by trifluoromethyl and trifluoromethoxy moieties, respectively. In this case, the electron-withdrawing nature of the substituents was expected to warrant the integrity of the trityloxy moiety by hampering the formation of the carbenium ion, responsible for the decomposition reaction.

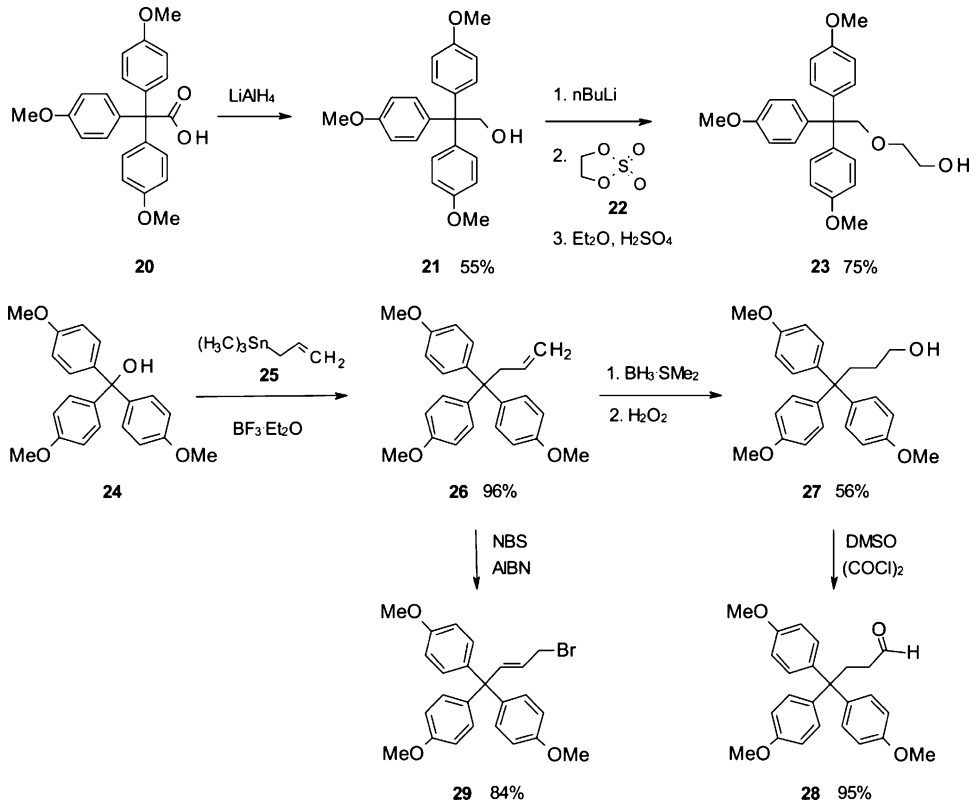
To overcome the chemical instability of the N-substituent of **3**, the structure of the spacer linking the trityl moiety to the nipecotic acid residue was modified. The residues represented by **23**, **28**, and **29**, respectively, seemed best suited for this purpose (Scheme 2). In each of these compounds the chemical instability of the side chain was eliminated by avoiding the critical ether function. This was reached either by insertion of a methylene moiety in the labile C–O bond (compound **23**) or by switching to a saturated (in **28**) or partially unsaturated all-carbon spacer (in **29**).

For residue **23** the effect on the GAT inhibitory potency of an elongated side chain with the position of the ether function with respect to the amino function remaining unchanged should also be tested. The synthesis of **23** was accomplished in two steps. Reduction of **20** with lithium aluminum hydride



Educt				Product	
Compound No.	R^1	R^2	R^3	Compound No. + Yield	
4 and **7**	OMe	Me	H	**11** 68%	**16** 24%
5 and **8**	OMe	H	Me	**12** 78%	**17** 15%
6 and **9**	CF_3	H	H	**13** 52%	**18** 64%
6 and **10**	OCF_3	H	H	**14** 34%	**19** 65%

Scheme 1. Synthesis of lipophilic residues with ether function.



Scheme 2. Synthesis of the lipophilic residues **23**, **28**, and **29**.

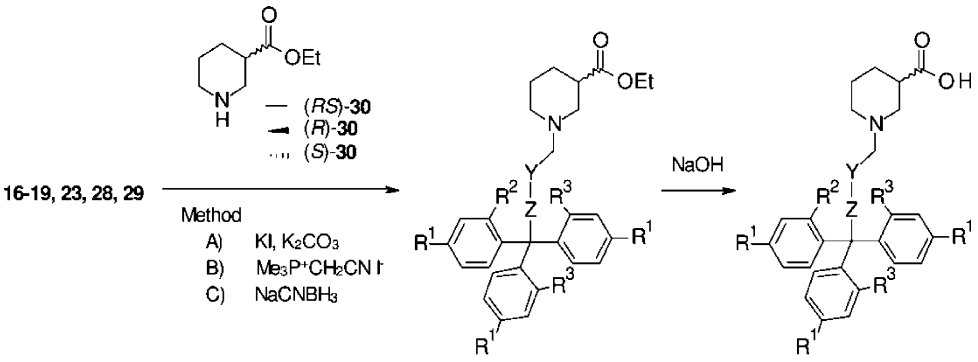
led to primary alcohol **21** (55%), which upon deprotonation with *n*-butyllithium at −78 °C, subsequent treatment with ethylene sulfate **22**, and hydrolysis of the resulting alkyl sulfate provided alcohol **23** in 75% yield.

For the synthesis of carba analogues **28** and **29**, the 4,4,4-triphenylbutene derivative **26** was required (Scheme 2). An attempt to prepare **26** by treatment of **24** with allyltrimethylsilane and catalytic amounts of tris(pentafluorophenyl)borane in analogy to a method reported by Rubin and Gevorgian,[15] however, failed to give product (Scheme 2). The transformation was finally successful by using allyl(tributyl)stannane (**25**) as nucleophile and boron trifluoride diethyl etherate as Lewis acid to provide **26** in 96% yield.

Hydroboration and oxidation of **26** with borane dimethyl sulfide and hydrogen peroxide, respectively, provided alcohol **27**, which, upon Swern oxidation, furnished aldehyde **28** in 95% yield (Scheme 2). Finally for the preparation of **29**, compound **26** was subjected to bromination with *N*-bromosuccinimide (NBS) and 2,2′-azobis(2-methylpropionitrile) (AIBN) by following a report for an analogous transformation of 4,4,4-triphenylbutene,[16] delivering the desired compound in 84% yield (Scheme 2).

In the next step of the synthetic sequence, the resulting lipophilic residues were used for the preparation of the N-substituted nipecotic acid ester derivatives **31**–**39**. Compounds **31**–**34** and **37**–**39** were prepared in reasonable yields by reacting nipecotic ester **30**, in racemic or in enantiopure form, with the respective alkyl halide in the presence of potassium iodide and potassium carbonate (method A, Scheme 3).

N-Alkylation of (*RS*)-**30** with alcohol **23** was performed by following a method reported by Zaragoza and Stephensen[17] based on (cyanomethyl)trimethylphosphonium iodide as activating agent (method B, Scheme 3). The yield of **35** amounted to 75%. Reductive amination of (*RS*)-**30** with aldehyde **28** finally yielded **36** in 82% yield (sodium cyanoborohydride, method C, Scheme 3). In the final step, the nipecotic acid esters **31**–**39** were subjected to alkaline hydrolysis to provide the target



starting materials	product	method	yield	conf.	R^1	R^2	R^3	–Y—Z–	product	yield
16 and (*S*)-**30**	**31**	A	84%	*S*	OMe	Me	H	$-CH_2O-$	**40**	80%
17 and (*RS*)-**30**	**32**	A	61%	*RS*	OMe	H	Me	$-CH_2O-$	**41**	51%
18 and (*RS*)-**30**	**33**	A	85%	*RS*	CF_3	H	H	$-CH_2O-$	**42**	62%
19 and (*RS*)-**30**	**34**	A	66%	*RS*	OCF_3	H	H	$-CH_2O-$	**43**	80%
23 and (*RS*)-**30**	**35**	B	75%	*RS*	OMe	H	H	$-CH_2OCH_2-$	**44**	92%
28 and (*RS*)-**30**	**36**	C	82%	*RS*	OMe	H	H	$-CH_2CH_2-$	**45**	67%
29 and (*RS*)-**30**	**37**	A	72%	*RS*	OMe	H	H	-CH=CH-	**46**	92%
29 and (*R*)-**30**	**38**	A	72%	*R*	OMe	H	H	-CH=CH-	**47**	95%
29 and (*S*)-**30**	**39**	A	86%	*S*	OMe	H	H	-CH=CH-	**48**	86%

Scheme 3. Synthesis of the esters and their hydrolysis.

compounds, the corresponding amino acid derivatives, **40**–**48** in good yields (Scheme 3).

Biological evaluation

Nipecotic acid derivatives **40**–**48** were evaluated for their inhibitory potency at the four GABA transporter subtypes mGAT1–mGAT4. The assay system used is based on [^{3}H]GABA uptake in HEK-293 cells stably expressing the individual GABA transporters.[13] The results are listed in Table 1. They are given as pIC_{50} values except for test compounds that are unable to decrease specific [^{3}H]GABA uptake to a value below 50% at a concentration of 100 μM. For these, only the percentage of the remaining specific [^{3}H]GABA uptake (at 100 μM) is reported. For comparison, Table 1 also includes the pIC_{50} values that (*S*)-SNAP-5114, the reference compound, exhibits in this test system.

As outlined above, compounds **40**–**43** (Table 1, Entry 2) had been modified with respect to their substitution pattern of the aromatic ring systems in order to improve their chemical stability over that of (*S*)-SNAP-5114 (**3**). Interestingly, the introduction of one *ortho*-methyl group in one of the three phenyl groups in **3** is well tolerated by the GABA transporters. Thus, the potencies of the resulting compound DDPM-859 (**40**) at the various GABA transporter subtypes are similar to those of **3**. Only for mGAT3 is the potency of compound **40** (pIC_{50} = 4.85, Table 1, Entry 2) somewhat lower than that of **3** (pIC_{50} = 5.29). Accordingly, **40** exhibits even a slightly improved subtype selectivity regarding mGAT3 and mGAT4. Moreover, ^{1}H NMR experiments revealed compound **40** to be distinctly less prone to decomposition reactions in acidic media than **3** (pH 4.5, **3**: $t_{1/2}$ ~ 4 h; **40**: $t_{1/2}$ ~ 270 h). Thus, DDPM-859 (**40**) surpasses **3** with respect to subtype selectivity and chemical stability.

mGAT4 cannot tolerate two phenyl rings substituted with an *ortho*-methyl group, as **41** is less active; its pIC_{50} value (5.07) is lower than that observed for **3** and compound **40**. Although **41** was tested as a racemic mixture, this would also be true if the biological activity were to reside in one enantiomer only. With potencies at mGAT1–mGAT3 ranging from pIC_{50} = 4.17 to pIC_{50} = 4.54, the subtype selectivity of **41** for mGAT4 (pIC_{50} = 5.07) is less pronounced.

Low potencies at mGAT4 are also observed for compounds **42** and **43** in which the methoxy groups in **3** are replaced by trifluoromethyl and trifluoromethoxy moieties, respectively, to stabilize the compounds by decreasing the electron-donating capacities of the aromatic ring systems. Thus, for **42** and **43**, pIC_{50} values of 4.63 and 4.95 at mGAT4 were observed. With the pIC_{50} values at mGAT4 being close to those of mGAT1–mGAT3, compounds **42** and **43** also lack any significant subtype selectivity (Table 1, Entries 4 and 5).

Extension of the spacer between nipecotic acid and the trityl moiety in **3** by insertion of a methylene group in the labile C–O bond or direct replacement of the ether function by carbon is even less tolerated by mGAT4. For compounds **44** and **45**, the pIC_{50} values at mGAT4 dropped to 4.06 and 4.21, respectively, and these compounds were devoid of any reasonable subtype selectivity (Table 1, Entries 6 and 7).

Interestingly, compound **45**, a weakly active mGAT4 inhibitor (pIC_{50} = 4.21), gains almost 1.5 log units in potency by replacement of the carbon–carbon single bond adjacent to the trityl moiety in **45** by a double bond, resulting in DDPM-1007 (**46**). Although compound **46** is still racemic, its potency at mGAT4 is nearly equal to the potency of (*S*)-SNAP-5114 (**3**) at this transporter. Additionally, DDPM-1007 (**46**) can be considered

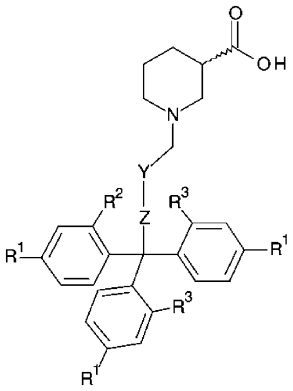


Figure 2. Synthesized GAT inhibitors.

Table 1. Structures of synthesized GAT inhibitors (see Figure 2) and their inhibitory potencies toward mGAT1–4.

Entry	Compd	Config.	R^1	R^2	R^3	-Y–Z-	pIC_{50} (mean ± SEM)[a]			
							mGAT1	mGAT2	mGAT3	mGAT4
1	(*S*)-SNAP-5114 (**3**)	*S*	OMe	H	H	$-CH_2-O-$	4.07 ± 0.09	56%	5.29 ± 0.04	5.71 ± 0.07
2	DDPM-859 (**40**)	*S*	OMe	Me	H	$-CH_2-O-$	4.19 ± 0.07	4.12 ± 0.08	4.85 ± 0.04	**5.78 ± 0.03**
3	**41**	*RS*	OMe	H	Me	$-CH_2-O-$	4.17 ± 0.02	4.49 ± 0.09	4.54 ± 0.10	5.07 ± 0.09
4	**42**	*RS*	CF_3	H	H	$-CH_2-O-$	4.88 ± 0.11	4.76 ± 0.02	4.82 ± 0.07	4.63 ± 0.03
5	**43**	*RS*	OCF_3	H	H	$-CH_2-O-$	4.87 ± 0.02	4.96 ± 0.07	4.75 ± 0.07	4.95 ± 0.12
6	**44**	*RS*	OMe	H	H	$-CH_2-O-CH_2-$	4.12 ± 0.07	4.10 ± 0.03	4.08 ± 0.14	4.06 ± 0.07
7	**45**	*RS*	OMe	H	H	$-CH_2-CH_2-$	3.94 ± 0.09	59%	4.34 ± 0.11	4.21 ± 0.07
8	DDPM-1007 (**46**)[b]	*RS*	OMe	H	H	-CH=CH-	4.32 ± 0.05	4.68 ± 0.09	5.19 ± 0.06	5.67 ± 0.06
9	**47**	*R*	OMe	H	H	-CH=CH-	4.19 ± 0.09	79%	61%	4.33 ± 0.05
10	DDPM-1457 (**48**)	*S*	OMe	H	H	-CH=CH-	4.40 ± 0.05	4.42 ± 0.11	5.47 ± 0.02	**5.87 ± 0.08**

[a] If not stated otherwise, the results are given as the mean ± SEM of three independent experiments, each performed in triplicate; percentages represent specific binding remaining in the presence of 100 μM inhibitor. [b] Compound **46** was tested as the hydrochloride.

chemically stable, as it lacks the critical ether function in (*S*)-SNAP-5114 (**3**) responsible for the chemical instability of this compound. This was indeed confirmed by ^{1}H NMR experiments with an aqueous solution of DDPM-1007 (**46**) at pH 4.5 and 1.5, for which no signs of decomposition could be detected (reaction time: 72 h).

As for racemic (*RS*)-SNAP-5114[18] and also in the case of racemate **46**, the potency resides mainly in one of the two enantiomers, the *S* enantiomer. Thus, the *S* enantiomer DDPM-1457 (**48**) exhibits a pIC_{50} value of 5.87 (Table 1, Entry 8), whereas the potency of its enantiomer **47** is distinctly lower (pIC_{50} = 4.33, Table 1, Entry 9). The potency of DDPM-1457 (**48**) is slightly higher than that of (*S*)-SNAP-5114 (pIC_{50} = 5.71), but only to an extent that cannot be considered statistically significant. Also with respect to subtype selectivity, *S* enantiomer DDPM-1457 (**48**) compares well with (*S*)-SNAP-5114 (**3**). For both compounds, the preference for mGAT4 relative to mGAT3 is identical. With the potencies at mGAT4 being only slightly higher than those at mGAT3, however, both compounds can be considered mixed inhibitors of mGAT4 and mGAT3 with a preference of the former. Also with reference to mGAT1 and mGAT2, the subtype selectivities of (*S*)-SNAP-5114 (**3**) and DDPM-1457 (**48**) are similar, except that the potency of **48** at these transporters is slightly lower. The similarities in potencies and subtype selectivities displayed by compounds **48** and **3** are likely to reflect analogous binding modes of these compounds. Obviously, for a reasonably high potency at mGAT4 an ether oxygen atom as in (*S*)-SNAP-5114 (**3**) or a double bond as in DDPM-1457 (**48**) is essential, as the all-carbon spacer analogue **45** is only a weak mGAT4 inhibitor. Taking into account the aforementioned similarities in the pharmacological profile of **3** and **48**, and the fact that ether oxygen atoms commonly serve as hydrogen bond acceptors when interacting with proteins, it seems reasonable to assume that the double bond in DDPM-1457 (**48**) serves as a hydrogen bond acceptor[19] as well. Accordingly, the double bond in **48** may be considered a bioisosteric substitute for the O–CH_2 group present in **3**, avoiding the chemical lability associated with the trityloxy moiety.

For the newly synthesized compounds, log *D* values were calculated (clog *D*: calculated log *D* by MarvinSketch[20] and Pipeline Pilot[21]) to estimate the lipophilicity and the potential of **40**–**46** to cross the blood–brain barrier (BBB). For tiagabine (**2**) and (*S*)-SNAP-5114 (**3**) under the same methods, clog *D* values of ~2 were found (Table 2). It is generally accepted that log *D* values should lie within the range of 2–5,[22] ideally closer to 2,[23] to improve the potential for BBB penetration. The clog *D* calculated for tiagabine, which is as an approved drug known to enter the CNS,[24] nicely supports this rule. With clog *D* values amounting to ~5 and ~8, respectively, the fluoro-substituted compounds **42** and **43** (see Table 2) can be expected to possess only low to negligible potential for BBB penetration. In contrast, the remaining compounds, **40**, **41**, and **44**–**46** display distinctly lower clog *D* values ranging from 1.92–2.99, and meet the criteria defined for brain penetration reasonably well. For DDPM-859 (**40**) and DDPM-1457 (**48**, clog *D* identical to that of racemate **46**), which have been identified as the most efficacious substances at mGAT4 and which are also active at mGAT3 to some extent, the mean clog *D* values are 2.43 and 2.67, respectively (mean of MarvinSketch and Pipeline Pilot). Thus, these compounds possess clog *D* values close to optimal (log *D* 2), in which respect they also compare quite well with (*S*)-SNAP-5114 (**3**; mean clog *D* 1.95), which had so far been the most potent mGAT4 inhibitor known. With the clog *D* value in line with common requirements, compounds **40** and **48** should have reasonable potential for in vivo activity and might be a valuable lead for the development of more potent mGAT4 inhibitors.

Table 2. Logarithmic distribution coefficients calculated with MarvinSketch and Pipeline Pilot.

Compd	clog *D* (pH 7.4)	
	MarvinSketch[20]	Pipeline Pilot[21]
2	2.22	2.26
3	1.89	2.01
40	2.36	2.50
41	2.83	2.99
42	5.30	4.94
43	7.70	8.42
44	2.13	1.92
45	2.95	2.83
46	2.82	2.51

Conclusions

As clearly documented by the results described above, the linker and the triaryl moiety in compound **3** may be modified to some extent while retaining the potency at mGAT4 and simultaneously improving chemical stability. Compound DDPM-859 (**40**), with an additional methyl group at the *ortho* position of one of the aromatic rings of **3**, exhibits similar efficacy at mGAT4 (**40**: pIC_{50} = 5.78; **3**: pIC_{50} = 5.71) accompanied by a slight improvement in subtype selectivity and enhanced chemical stability over that of **3**. Thus, DDPM-859 could be a good lead molecule for the development of even more potent and selective mGAT4 inhibitors. A structurally different kind of mGAT4 inhibitor was found with compound DDPM-1457 (**48**), characterized by substitution of the ethyloxy spacer in **3** with a propenyl moiety. This carba analogue shows efficacy equal to that of **3** at mGAT4 (pIC_{50} = 5.87; **3**: pIC_{50} = 5.71) combined with substantially altered chemical characteristics of the lipophilic residue.

As the in vivo effect of (*S*)-SNAP-5114 in animals after intraperitoneal administration is unexpectedly poor,[9] the synthesized GAT inhibitors DDPM-859 (**40**) and DDPM-1457 (**48**) could serve as improved pharmacological tools to study mGAT4. Further efforts are certainly warranted to develop more potent and more selective GAT4 inhibitors.

Experimental Section

Solvents were p.a. quality and freshly distilled before use. Purchased reagents were used without further purification. As petroleum ether (PE) the fraction 40–80 °C was used. TLC plates were

made from silica gel 60 F_{254} on aluminum sheets (Merck). Flash chromatography was carried out using Merck silica gel 60 (mesh 0.040–0.063 mm) as stationary phase. Melting points: mp (uncorrected) were determined with a Büchi 512 Melting Point apparatus. NMR spectroscopy: ^{1}H NMR spectra were recorded at RT with a JNMR-GX (JEOL, 400 or 500 MHz) instrument using TMS as internal standard and integrated with the NMR software MestReNova. IR spectroscopy: FTIR Spectrometer 410 (Jasco); samples were measured as KBr pellets. Mass spectrometry (MS): Mass Spectrometer 5989A with 59980B particle beam LC–MS interface (Hewlett Packard) or Applied Biosystems LC–MS/MS Mass Spectrometer API 2000; analysis was carried out using chemical ionization (CH_5^+) or electron impact ionization. High-resolution mass spectrometry (HRMS): JEOL MS-Station JMS-700, FAB (Xenon, 6 kV, MBA, reference PEG), LTQ FT (Thermo Finnigan). Elementary analysis: Elementaranalysator Rapid (Heraeus) and Vario EL (Elementar).

General Procedure 1 (GP 1): Under argon atmosphere, magnesium turnings were suspended in THF, and the corresponding aryl halide was slowly added. After 2 h, the corresponding ester was added and stirred for the time given at the temperature stated. The reaction mixture was cooled to 0 °C and a saturated solution of NH_4Cl was added. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with a saturated NaCl solution, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography.

General Procedure 2 (GP 2): To a solution of the alcohol, conc. H_2SO_4 was added, and the resulting mixture was stirred for 5 min at 65 °C. After adding **15** at RT and stirring for the time given, H_2O and Et_2O were added. Extraction with Et_2O, drying of the combined organic layers over $MgSO_4$, and removing of the solvent in vacuo resulted in the crude product, which was purified by flash chromatography.

General Procedure 3 (GP 3): A solution of the alkyl bromide was added to a solution of the appropriate nipecotic acid. K_2CO_3 and KI were added, and the reaction mixture was stirred for the time given under N_2 atmosphere and under exclusion of light. The solvent was removed in vacuo. The crude product was resolved in H_2O and CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo.

General Procedure 4 (GP 4): The carboxylic acid ester was dissolved in NaOH and stirred for the given time at RT before adjusting the mixture to pH 6 with HCl.

1-(4-Methoxy-2-methylphenyl)-1,1-bis(4-methoxyphenyl)methanol (11): According to GP 1: 1-Bromo-4-methoxybenzene (935 mg, 5.00 mmol, 0.63 mL), magnesium (134 mg, 5.50 mmol) in THF (3.8 mL), **4**[25] (360 mg, 2.00 mmol) in THF (1 mL), 96 h at RT and flash chromatography (cyclohexane/EtOAc = 9:1). Colorless oil (566 mg, 78%): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.12 (s, 3H, CH_3), 2.81 (s, 1H, OH), 3.77 (s, 3H, OCH_3), 3.80 (s, 6H, OCH_3), 6.53 (dd, J = 8.6/2.7 Hz, 1H, CCHC*H*), 6.64 (d, J = 8.6 Hz, 1H, C*CH*CH), 6.73 (d, J = 2.6 Hz, 1H, CCH), 6.78–6.88 (m, 4H), 7.08–7.17 ppm (m, 4H); ^{13}C NMR (126 MHz, CD_2Cl_2): δ = 20.0 (CH_3), 53.1 (OCH_3), 53.2 (OCH3), 80.0 (*C*OCH_2), 107.0 (CHC*H*CCHC), 111.0 (OCCH), 116.1 (CHCHCC*H*C), 126.7 (*C*CH), 128.6 (*CH*CHCCHC), 135.5 (C_{ar}), 137.6 (C_{ar}), 156.5 (*C*OCH_3), 156.8 ppm (*C*OCH_3); IR (KBr): $\tilde{\nu}$ = 3506, 2933, 1606, 1508, 825 cm^{-1}; HRMS-EI+: m/z $[M]^+$ calcd for $C_{23}H_{24}O_4$: 364.1675, found: 364.1682.

1,1-Bis(4-methoxy-2-methylphenyl)-1-(4-methoxyphenyl)methanol (12): According to GP 1: 1-Bromo-4-methoxy-2-methylbenzene (1.0 g, 5.0 mmol, 0.71 mL), magnesium (134 mg, 5.50 mmol) in THF (3.8 mL), **5** (332 mg, 2.00 mmol) in THF (1 mL), 2 h at 80 °C and flash chromatography (pentane/EtOAc = 9:1 + 1% NEt_3). Colorless crystals (519 mg, 68%): mp: 50–55 °C; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 2.13 (s, 6H, CH_3), 2.88 (s, 1H, OH), 3.75 (s, 6H, OCH_3), 3.79 (s, 3H, OCH_3), 6.50 (dd, J = 8.7/2.6 Hz, 2H, CH_{ar}), 6.59 (d, J = 8.7 Hz, 2H, CH_{ar}), 6.73 (d, J = 2.4 Hz, 2H, CH_{ar}), 6.83 (d, J = 8.9 Hz, 2H, CH_{ar}), 7.07 ppm (d, J = 8.8 Hz, 2H, CH_{ar}); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 22.3 (CH_3), 55.1 (OCH_3), 55.2 (OCH_3), 83.3 (COH), 109.3 (CH_{ar}), 113.0 (CH_{ar}), 118.1 (CH_{ar}), 129.0 (CH_{ar}), 130.2 (CH_{ar}), 137.4 (C_{ar}), 139.2 (C_{ar}), 139.3 (C_{ar}), 158.6 (*C*OCH_3), 158.7 ppm (*C*OCH_3); IR (KBr): $\tilde{\nu}$ = = 3491, 2931, 1606, 1498, 809 cm^{-1}; HRMS-EI+: m/z $[M]^+$ calcd for $C_{24}H_{26}O_4$: 378.1831, found: 378.1831.

Tris[4-(trifluoromethyl)phenyl]methanol (13):[26] According to GP 1: 1-Bromo-4-trifluoromethylbenzene (8.1 g, 36 mmol, 4.97 mL), magnesium (948 mg, 39.6 mmol) in THF (22 mL), **6** (851 mg, 9.00 mmol) in THF (1 mL), 1 h at RT and flash chromatography (pentane/EtOAc = 94:6). Yellow crystals (225 mg, 52%). Analytical data are in accordance with published data.[26]

Tris[4-(trifluoromethoxy)phenyl]methanol (14): According to GP 1: 1-Bromo-4-trifluoromethoxybenzene (3.9 g, 16 mmol, 2.6 mL), magnesium (430 mg, 17.6 mmol) in THF (30 mL), **6** (378 mg, 4.00 mmol), 3 h at RT and flash chromatography (PE/EtOAc = 95:5). Colorless oil (702 mg, 34%): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.16–7.21 (m, 6H), 7.28–7.32 ppm (m, 6H); IR (KBr): $\tilde{\nu}$ = 3474, 1509, 851 cm^{-1}; MS (EI, 70 eV): m/z (%): 512 (5) $[M]^+$, 351 (96), 189 (100); Anal. calcd for $C_{22}H_{13}O_4F_9$: C 51.58, H 2.56, found: C 51.75, H 2.41.

1-[1-(2-Bromoethoxy)-1,1-bis(4-methoxyphenyl)methyl]-4-methoxy-2-methylbenzene (16): According to GP 2: **11** (729 mg, 2.00 mmol) in toluene (3.3 mL), conc. H_2SO_4 (34 μL), **15** (3.75 g, 30.0 mmol, 2.13 mL), 3 h and flash chromatography (pentane/EtOAc = 92:8). Colorless oil (224 mg, 24%): ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.93 (s, 3H, CH_3), 3.39 (t, J = 6.0 Hz, 2H, CH_2O), 3.51 (t, J = 6.0 Hz, 2H, CH_2Br), 3.75 (s, 6H, OCH_3), 3.78 (s, 3H, OCH_3), 6.65 (dd, J = 8.6/2.7 Hz, 1H, CHC*H*CCHC), 6.71 (d, J = 2.6 Hz, 1H, CHCHCC*H*C), 6.75–6.85 (m, 4H, OCC*H*CH), 7.25–7.33 (m, 4H, OCCHC*H*), 7.35 ppm (d, J = 8.6 Hz, 1H, C*H*CHCCHC); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 22.1 (CH_3), 31.7 (CH_2Br), 55.1 (OCH_3), 55.2 (OCH_3), 64.3 (CH_2O), 86.8 (CO), 109.3 (CH*C*HCCHC), 113.2 (OC*C*H), 118.2 (CHCHC*C*HC), 128.5 (*C*CH), 131.8 (*C*HCHCCHC), 132.6 (C_{ar}), 137.6 (C_{ar}), 140.8 (C_{ar}), 158.1 (*C*OCH_3), 159.1 ppm (*C*OCH_3); IR (KBr): $\tilde{\nu}$ = 2931, 1606, 1507, 824 cm^{-1}; HRMS-FAB: m/z $[M]^+$ calcd for $C_{25}H_{27}BrO_4$: 470.1093, found: 470.1106.

1-[1-(2-Bromoethoxy)-1-(4-methoxy-2-methylphenyl)-1-(4-methoxyphenyl)methyl]-4-methoxy-2-methylbenzene (17): According to GP 2: **12** (253 mg, 0.669 mmol) in toluene (2 mL), conc. H_2SO_4 (12 μL), **15** (142 mg, 1.34 mmol, 95 μL), 2 h and flash chromatography (PE/EtOAc = 97:3 + 1% $NEtMe_2$). Colorless oil (49 mg, 15%): ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 2.13 (s, 6H, CH_3), 3.36 (t, J = 5.9 Hz, 2H, CH_2O), 3.57 (t, J = 5.9 Hz, 2H, CH_2Br), 3.75 (s, 6H, OCH_3), 3.77 (s, 3H, OCH_3), 6.58 (dd, J = 8.7/2.8 Hz, 2H, CHC*H*CCHC), 6.67 (d, J = 2.8 Hz, 2H, CHCHCC*H*C), 6.82 (d, J = 9.0 Hz, 2H, $OCCH_{ar}$), 7.05 (d, J = 8.8 Hz, 2H, C*H*CHCCHC), 7.26 ppm (d, J = 9.0 Hz, 2H, CCH_{ar}); ^{13}C NMR (126 MHz, CD_2Cl_2): δ = 20.3 (CH_3), 29.6 (CH_2Br), 53.0 (OCH_3), 53.2 (OCH_3), 62.9 (CH_2O), 86.9 (*C*OCH_2), 107.5 (CH*C*HCCHC), 110.7 (OC*C*H_{ar}), 115.9 (CHCHC*C*HC), 127.4 (*CC*H_{ar}), 128.1 (*C*HCHCCHC), 132.7 (C_{ar}), 132.8 (C_{ar}), 137.6 (C_{ar}), 156.0 (*C*OCH_3), 156.6 ppm (*C*OCH_3); IR (KBr): $\tilde{\nu}$ = 2928, 1605, 1497, 806 cm^{-1}; HRMS-EI+: m/z $[M]^+$ calcd for $C_{26}H_{29}BrO_4$: 484.1249, found: 484.1231.

1-{1-(2-Bromoethoxy)-1,1-bis[4-(trifluoromethyl)phenyl]methyl}-4-(trifluoromethyl)benzene (18): According to GP 2: **13** (219 mg,

0.471 mmol) in toluene (1.2 mL), conc. H_2SO_4 (8 μL), **15** (118 mg, 0.942 mmol, 67 μL), 19 h and flash chromatography (pentane/CH_2Cl_2 = 98:2). Colorless crystals (171 mg, 64%): mp: 139–143 °C; ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 3.41 (t, J = 5.7 Hz, 2H), 3.52 (t, J = 5.7 Hz, 2H), 7.61 ppm (q, J = 8.7 Hz, 12H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 30.9 (CH_2Br), 64.1 (OCH_2), 86.0 ($COCH_2$), 124.1 (q, J = 272 Hz, CF_3), 125.4 (q, J = 4 Hz, F_3CCCH), 129.0, 129.8 (q, J = 32 Hz, F_3CC), 146.4 ppm (CCH); IR (KBr): $\tilde{\nu}$ = 2910, 2866, 1616, 829 cm^{-1}; HRMS-EI+: m/z $[M]^+$ calcd for $C_{24}H_{16}BrF_9O$: 570.0241, found: 570.0257.

1-{1-(2-Bromoethoxy)-1,1-bis[4-(trifluoromethoxy)phenyl]methyl}-4-(trifluoromethoxy)benzene (19): According to GP 2: **14** (4.1 g, 8.0 mmol) in toluene (15 mL), conc. H_2SO_4 (0.15 mL), **15** (1.5 g, 12 mmol, 0.85 mL), 4 h and flash chromatography (PE/EtOAc = 95:5). Yellow oil (3.2 g, 65%): ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 3.38–3.42 (m, 2H, CH_2Br), 3.44–3.48 (m, 2H, CH_2O), 7.15–7.21 (m, 6H, $OCCH_{ar}$), 7.43–7.48 ppm (m, 6H, CCH_{ar}); IR (KBr): $\tilde{\nu}$ = 2868, 1594, 1504, 808 cm^{-1}; Anal. calcd for $C_{24}H_{16}BrO_4F_9$: C 46.55, H 2.60, found: C 47.09; H 2.10.

2,2,2-Tris(4-methoxyphenyl)ethanol (21): Under argon atmosphere, $LiAlH_4$ (0.56 g, 15 mmol) was suspended in THF (20 mL) and cooled to 0 °C. Then, a solution of **20**[27] (2.3 g, 6.2 mmol) in THF (20 mL) was added dropwise. The mixture was warmed up to RT, stirred for 14 h, again cooled to 0 °C, and quenched with 1 N HCl. After adding 2 N NaOH (pH > 12), the mixture was extracted with Et_2O. The combined organic layers were washed with a saturated NaCl solution (20 mL), dried over $MgSO_4$, and concentrated in vacuo. The product was obtained by flash chromatography (PE/EtOAc = 90:10) as colorless crystals (1.23 g, 55%): mp: 150 °C; ^{1}H NMR (500 MHz, CD_3OD): δ = 3.77 (s, 9H, OCH_3), 4.86 (s, 2H, CH_2OH), 6.78–6.82 (m, 6H, CH_{ar}), 7.02–7.07 ppm (m, 6H, CH_{ar}); ^{13}C NMR (125 MHz, CD_3OD): δ = 55.1 (OCH_3), 57.2 (CCH_2OH), 70.2 (CH_2OH), 113.6 (CH_{ar}), 131.1 (CH_{ar}), 139.4 (C_{ar}), 158.8 ppm ($COCH_3$); IR (KBr): $\tilde{\nu}$ = 3521, 3034, 2917, 2873, 2838, 2362, 2042, 1897, 1605, 1577, 835 cm^{-1}; MS (CI, CH_5^+): m/z (%): 365 $[M+H]^+$; Anal. calcd for $C_{23}H_{24}O_4$: C 75.80, H 6,64, found: C 76.03, H 6.82.

2-[2,2,2-Tris(4-methoxyphenyl)ethoxy]ethanol (23): **21** (1.12 g, 3.06 mmol) in THF (20 mL) was cooled to −78 °C. After 1.6 M nBuLi in hexane (3.06 mmol, 1.92 mL) was added dropwise, the mixture was stirred at −78 °C for 15 min. A solution of ethylene sulfate (**22**; 385 mg, 3.10 mmol) in THF (5 mL) was added. The mixture was stirred for 1 h at this temperature, additional 2 h at 0 °C and finally for 16 h at RT. After adding Et_2O (20 mL) and H_2SO_4 (20 mL), the mixture was stirred at RT for a further 24 h. The separated aqueous layer was extracted two times with Et_2O. The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. Compound **23** was obtained by flash chromatography (PE/EtOAc = 70:30) as colorless solid (945 mg, 75%): mp: 119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.58–3.60 (m, 2H, OCH_2CH_2O), 3.61–3.63 (m, 2H, OCH_2CH_2O), 3.80 (s, 9H, OCH_3), 4.38 (s, 2H, CCH_2O), 6.79–6.84 (m, 2H, $OCCH_{ar}$), 7.09–7.14 ppm ($OCCH_{ar}CH_{ar}$); IR (KBr): $\tilde{\nu}$ = 3549, 2932, 2904, 2835, 1607, 1579, 825 cm^{-1}; MS (CI, CH_5^+): m/z (%): 365 (9), 347 (72), 333 (100); Anal. calcd for $C_{25}H_{28}O_5$: C 73.51, H 6.91, found: C 73.71, H 7.02.

4,4,4-Tris(4-methoxyphenyl)butene (26): **24** (168 mg, 0.479 mmol) and **25** (205 mg, 1.00 mmol, 0.310 mL) dissolved in CH_2Cl_2 (1 mL) were slowly treated with $BF_3{\cdot}OEt_2$ (142 mg, 1.00 mmol) and stirred at RT for 4 h. The reaction was stopped by adding saturated $NaHCO_3$ solution. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The raw product was purified by flash chromatography (PE/EtOAc = 9:1). Colorless crystals (171.6 mg, 95.6%): mp: 101 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.36 (dt, J = 6.6/1.4 Hz, 2H, $CHCH_2C$), 3.79 (s, 9H, OCH_3), 4.95 (dq, J = 10.3/1.8 Hz, 1H, CH_2CH), 5.03 (dq, J = 17.3/1.8 Hz, 1H, CH_2CH), 5.65–5.72 (m, 1H, CH_2CH), 6.78–6.81 (m, 6H, CH_{ar}), 7.09–7.12 ppm (m, 6H, CH_{ar}); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 46.0 ($CHCH_2C$), 54.3 (OCH_3), 55.2 ($C(C_6H_5)_3$), 113.0 (CH_{ar}), 117.0 (CH_2CH), 130.3 (CH_{ar}), 136.3 (CH_2CH), 140.1 (C_q), 157.5 ppm (C_q); IR (KBr): $\tilde{\nu}$ = 3057, 3035, 3005, 2655, 2931, 2899, 2835, 1606 cm^{-1}; MS (CI, CH_5^+): m/z (%): 375 (71) $[M+H]^+$, 333 (37), 267 (100); Anal. calcd for $C_{25}H_{26}O_3$ (374.48): C 80.18, H 7.00, found, C 79.92, H 7.03.

4,4,4-[Tris(4-methoxyphenyl)]butan-1-ol (27): Under N_2 atmosphere and ice cooling, **26** (1.87 g, 5.00 mmol) was dissolved in abs. THF (20 mL) and abs. pentane (20 mL) and treated with 2 M $BH_3{\cdot}S(CH_3)_2$ solution in THF (5.0 mmol, 2.5 mL). The reaction mixture was stirred at RT for 5 h. To oxidize the boron compound, first ethanol (30 mL) and 3 N NaOH (30 mL) and then, under ice cooling, a 30% solution of H_2O_2 (20 mL) was added dropwise. The resulting mixture was held at reflux for 2 h and stirred at RT until the boron compound was completely oxidized. The mixture was poured in ice water, the aqueous layer saturated with NaCl, and extracted with Et_2O. The combined organic layers were washed with saturated Na_2HSO_3 solution, dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by flash chromatography (PE/EtOAc = 3:1). Colorless oil (1.1 g, 56%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (m, 2H, CH_2CH_2OH), 2.55 (m, 2H, CCH_2), 3.61 (t, J = 6.4 Hz, 2H, CH_2OH), 3.77 (s, 9H, OCH_3), 6.77–6.80 (m, 6H, H_{ar}), 7.15–7.18 ppm (m, 6H, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.28 (CH_2CHOH), 36.98 (CCH_2), 54.30 (CCH_2), 55.18 (OCH_3), 63.39 (CH_2OH), 113.08 (CH_{ar}), 130.04 (CH_{ar}), 140.03 (C_{ar}), 157.41 ppm ($COCH_3$); IR (KBr): $\tilde{\nu}$ = 3380, 2951, 2835, 1607, 1508 cm^{-1}; HRMS-EI+: m/z $[M]^+$ calcd for $C_{25}H_{28}O_4$: 392.1988, found: 392.1976.

4,4,4-[Tris(4-methoxyphenyl)]butanal (28): Oxalyl chloride (57 mg, 0.45 mmol) in CH_2Cl_2 (3.5 mL) was cooled to −78 °C and during 5 min DMSO (76 mg, 0.98 mmol, 69 μL) was added dropwise. After stirring at −78 °C for 15 min, **27** (136 mg, 0.346 mmol) was added over a period of 45 min. The mixture was stirred for further 15 min before NEt_3 (210 mg, 2.08 mmol, 288 μL) was added over a period of 5 min. After stirring for 5 min at −78 °C and 1 h at RT, the mixtures was poured in $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2, the combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. Yellow oil (130 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (t, J = 7.9 Hz, 2H, CH_2CHO), 2.83 (t, J = 7.9 Hz, 2H, CCH_2), 3.78 (s, 9H, OCH_3), 6.78–6.81 (m, 6H, H_{ar}), 7.14–7.17 (m, 6H, H_{ar}), 9.63 ppm (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.24 (CCH_2), 41.17 (CH_2CHO), 53.83 (CCH_2), 55.16 (OCH_3), 113.25 (CH_{ar}), 129.85 (CH_{ar}), 139.17 (C_{ar}), 157.55 ($COCH_3$), 201.91 ppm (CHO); IR (KBr): $\tilde{\nu}$ = 2952, 2830, 1728, 1607, 1509 cm^{-1}; HRMS-EI+: m/z $[M]^+$ calcd for $C_{25}H_{26}O_4$: 390.1831, found: 390.1848.

1-Bromo-4,4,4-tris(4-methoxyphenyl)but-2-ene (29): **26** (374 mg, 1.00 mmol) dissolved in CCl_4 was treated with NBS (178 mg, 1.00 mmol) and 2-[(1-cyano-1-methylethyl)azo]-2-methylpropanenitrile (10 mg, 0.06 mmol) and heated at reflux for 16 h. The precipitate was separated and the solvent was removed in vacuo. The residue was purified by crystallization from EtOH. Colorless crystals (265.9 mg, 58.6%): mp: 104 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.81 (s, 9H, OCH_3), 4.10 (d, J = 7.7 Hz, 2H, $CHCH_2$), 5.54 (dt, J = 15.4/7.7 Hz, 1H, $CHCH_2$), 6.73 (d, J = 15.4 Hz, 1H, $CHCHCH_2$), 6.81–6.83 (m, 6H, CH_{ar}), 6.96–6.98 ppm (m, 6H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.4 (CH_2), 55.2 (OCH_3), 58.4 ($C(C_6H_4OCH_3)_3$)), 113.0 (CH_{ar}), 127.3 ($CHCH_2$), 131.0 (CH_{ar}), 138.0 (C_q), 143.1 ($CHCHCH_2$),

157.9 ppm (C_q); MS (CI, CH_5^+): *m/z* (%): 339 (64) $[M+H]^+$, 297 (70), 243 (38), 123 (100); Anal. calcd for $C_{25}H_{25}O_3Br$: C 66.23, H 5.56. found: C 65.56, H 5.41.

Ethyl (3*S*)-1-{2-[1-(4-methoxy-2-methylphenyl)-1,1-bis(4-methoxyphenyl)methoxy]ethyl}piperidine-3-carboxylate (31): According to GP 3: **16** (19.5 mg, 0.414 mmol) in MeCN (1.0 mL), (*S*)-**30**·HCl (12 mg, 0.062 mmol) in MeCN (0.2 mL), KI (0.7 mg, 0.04 mmol) and K_2CO_3 (30 mg, 0.22 mmol), 13 days and flash chromatography (pentane/EtOAc = 85:15 + 1% $NEtMe_2$). Colorless oil (19 mg, 84%): $[\alpha]_D^{20}$ + 11.5 (*c* = 0.8, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 1.19 (t, *J* = 7.1 Hz, CH_2CH_3), 1.40 (ddd, *J* = 24.2/11.8/4.0 Hz, 1H, $NCH_2CH_2CH_2$), 1.47–1.61 (m, 1H, $NCH_2CH_2CH_2$), 1.63–1.75 (m, 1H, $NCH_2CH_2CH_2$), 1.83–1.91 (m, 1H, $NCH_2CH_2CH_2$), 1.93 (s, 3H, CH_3), 2.05 (td, *J* = 10.9/2.2 Hz, 1H, $NCH_2CH_2CH_2$), 2.19 (t, *J* = 10.7 Hz, 1H, NCH_2CH), 2.51 (tt, *J* = 10.4/3.7, 1H, NCH_2CH), 2.62 (t, *J* = 5.9 Hz, 2H, NCH_2CH_2O), 2.73 (d, *J* = 11.0 Hz, 1H, $NCH_2CH_2CH_2$), 2.98 (d_{br}, *J* = 10.5 Hz, 1H, NCH_2CH), 3.05–3.16 (m, 2H, NCH_2CH_2O), 3.74 (s, 6H, OCH_3), 3.77 (s, 3H, OCH_3), 4.05 (q, *J* = 7.1 Hz, CH_2CH_3), 6.64 (dd, *J* = 8.7/2.8 Hz, 1H, CHCHCCHC), 6.70 (d, *J* = 2.7 Hz, 1H, CHCHCCHC), 6.73–6.84 (m, 4H, $OCCH_{ar}$), 7.24–7.36 ppm (m, 5H, CCH_{ar}, CHCHCCHC); ^{13}C NMR (126 MHz, CD_2Cl_2): δ = 14.1 (CH_2CH_3) 21.9 (CH_3), 24.8 ($NCH_2CH_2CH_2$), 26.9 ($NCH_2CH_2CH_2$), 42.2 (NCH_2CH), 54.4 ($NCH_2CH_2CH_2$), 55.1 (OCH_3), 55.2 (OCH_3), 56.5 (NCH_2CH), 58.7 (NCH_2CH_2O), 60.2 (CH_2CH_3) 62.6 (NCH_2CH_2O), 86.4 ($COCH_2$), 109.1 (CHCHCCHC), 113.0 (CHCOCH$_3$), 118.0 (CHCHCCHC), 128.5 (CCH_{ar}), 128.6 (CCH_{ar}), 131.8 (CHCHCCHC), 133.0 (C_{ar}), 138.3 (C_{ar}), 140.9 (C_{ar}), 138.8 (C_{ar}), 158.0 ($COCH_3$), 158.9 ($COCH_3$), 174.1 ppm ($COOCH_3$); IR (KBr): $\tilde{\nu}$ = 2934, 1730, 1606, 1506, 824 cm^{-1}; HRMS-ESI+: *m/z* $[M+H]^+$ calcd for $C_{33}H_{42}NO_6$: 548.3007, found: 548.3012.

Ethyl 1-{2-[1,1-Bis(4-methoxy-2-methylphenyl)-1-(4-methoxyphenyl)methoxy]ethyl}piperidine-3-carboxylate (32): According to GP 3: **17** (19 mg, 0.038 mmol) in acetone (0.5 mL), (*RS*)-**30** (9.0 mg, 0.057 mmol) in acetone (0.5 mL), KI (0.6 mg, 0.004 mmol) and K_2CO_3 (19.7 mg, 0.143 mmol), 96 h and flash chromatography (pentane/EtOAc = 9:1 + 1% $NEtMe_2$). Colorless oil (14 mg, 66%): ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 1.19 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.40 (ddd, *J* = 15.0/12.1/3.6 Hz, 1H, $NCH_2CH_2CH_2$), 1.47–1.74 (m, 2H, $NCH_2CH_2CH_2$), 1.83–1.95 (m, 1H, $NCH_2CH_2CH_2$), 2.05 (td, *J* = 10.7/2.4 Hz, 1H, $NCH_2CH_2CH_2$), 2.11 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.18 (t, *J* = 10.5 Hz, 1H, NCH_2CH), 2.52 (tt, *J* = 10.5/3.8 Hz, 1H, NCH_2CH), 2.65 (t, *J* = 5.9 Hz, 2H, NCH_2CH_2O), 2.72 (d, *J* = 11.0 Hz, 1H, $NCH_2CH_2CH_2$), 2.97 (d_{br}, *J* = 10.5 Hz, 1H, NCH_2CH), 3.01–3.12 (m, 2H, NCH_2CH_2O), 3.75 (s, 6H, OCH_3), 3.77 (s, 3H, OCH_3), 3.96–4.18 (m, 2H, CH_2CH_3), 6.50–6.61 (m, 2H, CHCHCCHC), 6.66 (s, 2H, CHCHCCHC), 6.81 (d, *J* = 8.9 Hz, 2H, OCCH), 7.01–7.12 (m, 2H, CHCHCCHC), 7.32 ppm (d, *J* = 8.8 Hz, 2H, CCH); ^{13}C NMR (126 MHz, CD_2Cl_2): δ = 12.0 (CH_2CH_3), 20.1 (CH_3), 22.8 ($NCH_2CH_2CH_2$), 24.8 ($NCH_2CH_2CH_2$), 40.1 (NCH_2CH), 52.4 ($NCH_2CH_2CH_2$), 53.0 (OCH_3), 53.1 (OCH_3), 54.4 (NCH_2CH), 56.6 (NCH_2CH_2O), 58.1 (CH_2CH_3), 61.0 (NCH_2CH_2O), 86.3 ($COCH_2$), 107.3 (CHCHCCHC), 110.5 (OCCH), 115.7 (CHCHCCHC), 127.7 (CCH), 128.0 (CHCHCCHC), 133.1 (C_{ar}), 137.6 (C_{ar}), 137.7 (C_{ar}), 155.8 ($COCH_3$), 156.3 ppm ($COCH_3$), 172.0 (CO); IR (KBr): $\tilde{\nu}$ = 2937, 1730, 1606, 806 cm^{-1}; HRMS-ESI+: *m/z* $[M+H]^+$ calcd for $C_{34}H_{44}NO_6$: 562.3163, found: 562.3164.

Ethyl 1-(2-{1,1,1-tris[4-(trifluoromethyl)phenyl]methoxy}ethyl)piperidine-3-carboxylate (33): According to GP 3: **18** (171 mg, 0.300 mmol) in acetone (1.2 mL), (*RS*)-**30** (70 mg, 0.45 mmol) in acetone (0.5 mL), KI (5 mg, 0.03 mmol) and K_2CO_3 (156 mg, 1.13 mmol), 5 days and flash chromatography (pentane/EtOAc = 95:5 + 0.5% $NEtMe_2$). Colorless oil (165 mg, 85%): ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.18 (t, *J* = 7.1 Hz, 3H, CH_3), 1.33–1.62 (m, 2H, $NCH_2CH_2CH_2$), 1.64–1.78 (m, 1H, $NCH_2CH_2CH_2$), 1.81–1.94 (m, 1H, $NCH_2CH_2CH_2$), 2.08 (t, *J* = 9.6 Hz, 1H, $NCH_2CH_2CH_2$), 2.24 (t, *J* = 10.3 Hz, 1H, NCH_2CH), 2.48–2.75 (m, 4H, $NCH_2CH_2CH_2$, NCH_2CH_2O, NCH_2CH), 2.95 (d, *J* = 9.8 Hz, 1H, NCH_2CH), 3.02–3.21 (m, 2H, NCH_2CH_2O), 3.97–4.14 (m, 2H, CH_2CH_3), 7.61 ppm (s, 12H, CH_{ar}); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 14.1 (CH_3), 24.8 ($NCH_2CH_2CH_2$), 26.8 ($NCH_2CH_2CH_2$), 42.1 (NCH_2CH), 54.4 ($NCH_2CH_2CH_2$), 56.4 (NCH_2CH), 58.3 (NCH_2CH_2O), 60.2 (CH_2CH_3), 62.6 (NCH_2CH_2O), 85.8 ($COCH_2$), 124.2 (q, *J* = 271 Hz, CF_3), 125.2 (F_3CCCH), 129.0 (CCH), 129.6 (q, *J* = 32 Hz, CCF_3), 147.1 (CCH), 173.9 ppm (CO); IR (KBr): $\tilde{\nu}$ = 2941, 1731, 1615, 831 cm^{-1}; HRMS-EI+: *m/z* $[M]^+$ calcd for $C_{32}H_{30}F_9NO_3$: 647.2082, found: 647.2082.

Ethyl 1-(2-{1,1,1-tris[4-(trifluoromethoxy)phenyl]methoxy}ethyl)-piperidine-3-carboxylate (34): According to GP 3: **19** (620 mg, 1.00 mmol) in acetone (1 mL), (*RS*)-**30** (157 mg, 1.00 mmol) in acetone (1.5 mL), KI (15 mg, 0.09 mmol), and K_2CO_3 (277 mg, 2.00 mmol), 65 h and flash chromatography (PE/EtOAc = 85:15). Colorless oil (482 mg, 69%): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.44 (ddd, *J* = 15.4/11.6/4.3 Hz, 1H, $NCH_2CH_2CH_2$), 1.50–1.62 (m, 1H, $NCH_2CH_2CH_2$), 1.68–1.78 (m, 1H, $NCH_2CH_2CH_2$), 1.93 (dd, *J* = 8.9/4.0 Hz, 1H, $NCH_2CH_2CH_2$), 2.02–2.12 (m, 1H, $NCH_2CH_2CH_2$), 2.23 (t, *J* = 10.7 Hz, 1H, NCH_2CH), 2.54 (tt, *J* = 10.5/3.8 Hz, 1H, NCH_2CH), 2.58–2.66 (m, 2H, NCH_2CH_2O), 2.70 (d, *J* = 11.0 Hz, 1H, $NCH_2CH_2CH_2$), 2.97 (d, *J* = 11.3 Hz, 1H, NCH_2CH), 3.09–3.19 (m, 2H, NCH_2CH_2O), 4.03–4.18 (m, 2H, CH_2CH_3), 7.09–7.23 (m, 6H, $OCCH_{ar}$), 7.38–7.52 ppm (m, 6H, CCH_{ar}); IR (KBr): $\tilde{\nu}$ = 2945, 1732, 1505, 847 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 685 (1) $[M]^+$, 495 (100), 190 (23); Anal. calcd for $C_{32}H_{30}NO_6F_9$: C 55.26, H 4.35, N 2.01, found: C 55.24, H 4.56, N 2.02.

Ethyl 1-{2-[2,2,2-tris(4-methoxyphenyl)ethoxy]ethyl}piperidine-3-carboxylate (35): To a mixture of **23** (481 mg, 1.18 mmol), (*RS*)-**30** (176 mg, 1.12 mmol, 172 μL), *N*,*N*-diisopropylethylamine (190 mg, 1.47 mmol, 251 μL) and propionitrile (2.4 mL), (cyanomethyl)trimethylphosphonium iodide[17] (329 mg, 1.35 mmol) was added and the mixture was heated at 90 °C for 2 h. After cooling to RT, addition of 1.28 M solution K_2CO_3 (12 mL) and extraction with CH_2Cl_2 the resulting organic layer was washed with saturated NaCl solution, dried over $MgSO_4$, and concentrated in vacuo. Compound **35** was obtained by flash chromatography (PE/EtOAc = 60:40). Colorless oil (482 mg, 75% based on **23**): ^{1}H NMR (400 MHz, C_6D_6): δ = 0.97 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.35–1.55 (m, 3H, $NCH_2CH_2CH_2$, $NCH_2CH_2CH_2$), 1.74–1.89 (m, 2H, $NCH_2CH_2CH_2$, $NCH_2CH_2CH_2$), 2.26–2.36 (m, 1H, NCH_2CH), 2.40 (dt, *J* = 5.7/1.2 Hz, 2H, NCH_2CH_2O), 2.36–2.48 (m, 1H, $NCH_2CH_2CH_2$), 2.50–2.59 (m, 1H, NCH_2CH), 2.87–2.96 (m, 1H, NCH_2CH), 3.37 (s, 9H, OCH_3), 3.43 (t, *J* = 5.7 Hz, 2H, NCH_2CH_2O), 3.97 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 4.27–4.33 (m, 2H, CCH_2O), 6.78–6.88 (m, 6H, $OCCH_{ar}$), 7.26–7.33 ppm (m, 6H, $OCCH_{ar}CH_{ar}$); ^{13}C NMR (100 MHz, C_6D_6): δ = 11.2 (CH_2CH_3), 22.0 ($NCH_2CH_2CH_2$), 24.1 ($NCH_2CH_2CH_2$), 39.4 (NCH_2CH), 51.0 ($NCH_2CH_2CH_2$), 51.7 (OCH_3), 53.3 (NCH_2CH), 55.1 (NCH_2CH_2O), 56.9 (CH_2CH_3), 66.9 (NCH_2CH_2O), 76.3 (OCH_2C), 110.4 ($OCCH_{ar}$), 127.9 ($OCCH_{ar}CH_{ar}$), 136.3 (OC_{ar}), 155.4 (CC_{ar}), 170.5 ppm (CO); IR (KBr): $\tilde{\nu}$ = 2936, 2834, 1729, 1607, 1509, 824 cm^{-1}; MS (CI, CH_5^+): *m/z* (%): 548 (42) $[M+H]^+$, 333 (94), 214 (100), 170 (75); Anal. calcd for $C_{33}H_{41}NO_6$: C 72.37, H 7.55, N 2.56, found: C 72.13, H 7.49, N 2.50.

Ethyl 1-[4,4,4-Tris(4-methoxyphenyl)butyl]piperidine-3-carboxylate (36): Under N_2 atmosphere, a solution of **28** (130 mg 0.333 mmol) in abs. MeOH (4 mL) and (*RS*)-**30** (57.6 mg, 0.366 mmol) was stirred at RT for 30 min before $NaCNBH_3$ (105 mg, 1.67 mmol) was added. The mixture was stirred over night at RT, then cooled to 0 °C, and quenched with 2 N HCl. The aqueous layer was extracted with CH_2Cl_2, the combined organic layers were dried over Na_2SO_4, and the solvent was removed in vacuo. The raw prod-

uct was purified by flash chromatography (PE/EtOAc = 9:1). Colorless oil (147 mg, 82%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85–0.95 (m, 3H, CH_2CH_3), 1.15–1.40 (m, 12H), 2.47–2.51 (m, 3H, NCH_2CH, CCH_2), 3.78 (s, 9H, OCH_3), 4.12–4.15 (m, 2H, OCH_2CH_3), 6.78–6.80 (m, 6H, H_{ar}), 7.13–7.16 ppm (m, 6H, H_{ar}); IR (KBr): $\tilde{\nu}$ = 2927, 2360, 1731, 1608, 1509 cm^{-1}; HRMS-EI+: *m/z* $[M]^+$ calcd for $C_{33}H_{41}NO_5$: 531.2985, found: 531.2995.

Ethyl 1-[4,4,4-tris(4-methoxyphenyl)but-2-en-1-yl]piperidine-3-carboxylate (37): According to GP 3: **29** (190 mg, 0.420 mmol) in acetone (1.6 mL), (*RS*)-**30** (99 mg, 0.63 mmol, 98 μL) in acetone (0.6 mL), KI (7.0 mg, 0.042 mmol), and K_2CO_3 (218 mg, 1.58 mmol), 48 h. The crude product was purified by flash chromatography (pentane/EtOAc = 9:1 + 1% $NEtMe_2$). Colorless oil (160 mg, 72%): ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.18 (t, *J* = 7.1 Hz, 3H), 1.36–1.55 (m, 2H, $NCH_2CH_2CH_2$), 1.63–1.72 (m, 1H, $NCH_2CH_2CH_2$), 1.85 (d_{br}, *J* = 12.4 Hz, 1H, $NCH_2CH_2CH_2$), 1.98 (t_{br}, *J* = 10.5 Hz, 1H, $NCH_2CH_2CH_2$), 2.09–2.17 (m, 1H, NCH_2CH), 2.47 (tt, *J* = 10.0/3.8 Hz, 1H, NCH_2CH), 2.68 (d_{br}, *J* = 11.0 Hz, 1H, $NCH_2CH_2CH_2$), 2.89 (d_{br}, *J* = 10.4 Hz, 1H, NCH_2CH), 2.96–3.20 (m, 2H, NCH_2CHCH), 3.76 (s, 9H, OCH_3), 3.99–4.12 (m, 2H, OCH_2), 5.23 (dt, *J* = 15.5/6.6 Hz, 1H, NCH_2CHCH), 6.54 (d, *J* = 15.5 Hz, 1H, NCH_2CHCH), 6.72–6.81 (m, 6H, H_{ar}), 6.90–7.00 ppm (m, 6H, H_{ar}); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 14.3 (CH_3), 24.9 ($NCH_2CH_2CH_2$), 27.1 ($NCH_2CH_2CH_2$), 42.2 (NCH_2CH), 53.9 ($NCH_2CH_2CH_2$), 55.4 (OCH_3), 55.8 (NCH_2CH), 60.4 (OCH_2), 61.5 (NCH_2CHCH), 113.1 (CH_{ar}), 128.8 (NCH_2CHCH), 131.3 (CH_{ar}), 139.1 (C_{ar}), 140.6 (NCH_2CHCH), 158.2 ($COCH_3$), 174.1 ppm (CO); IR (KBr): $\tilde{\nu}$ = 2932, 1729, 1606, 1507, 827 cm^{-1}; HRMS-EI+: *m/z* $[M]^+$ calcd for $C_{33}H_{39}NO_5$: 529.2828, found: 529.2795.

Ethyl (3*R*)-1-[4,4,4-tris(4-methoxyphenyl)but-2-en-1-yl]piperidine-3-carboxylate (38): According to GP 3: **29** (213 mg, 0.47 mmol) in acetone (0.7 mL), (*R*)-**30** (111 mg, 0.705 mmol) in acetone (0.7 mL), KI (7.8 mg, 0.047 mmol), and K_2CO_3 (244 mg, 1.763 mmol), 72 h. The crude product was purified by flash chromatography (pentane/EtOAc = 8:2 + 1% $NEtMe_2$). Colorless oil (114 mg, 86%). Analytical data correspond to those of **37** except $[\alpha]_D^{20}$ −12.6 (*c* = 0.5, CH_2Cl_2).

Ethyl (3*S*)-1-[4,4,4-tris(4-methoxyphenyl)but-2-en-1-yl]piperidine-3-carboxylate (39): According to GP 3: **29** (195 mg, 0.430 mmol) in MeCN (1.6 mL), (*S*)-**30**·HCl (125 mg, 0.645 mmol) in MeCN (1.5 mL), KI (7.1 mg, 0.043 mmol), and K_2CO_3 (312 mg, 2.26 mmol), 72 h. The crude product was purified by flash chromatography (*n*-pentane/EtOAc = 86:14 + 1% $NEtMe_2$). Colorless oil (165 mg, 72%). Analytical data correspond to those of **37** except $[\alpha]_D^{20}$ +13.2 (*c* = 0.5, CH_2Cl_2).

(3*S*)-1-[2-[1-(4-Methoxy-2-methylphenyl)-1,1-bis(4-methoxyphenyl)methoxy]ethyl]piperidine-3-carboxylic acid (40): According to GP 4: **31** (16 mg, 0.026 mmol) in EtOH (0.1 mL), 12 N NaOH (0.052 mmol, 4.5 μL), 72 h and 0.25 N HCl. The resulting solution was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified by flash chromatography (CH_2Cl_2/EtOH = 1:1). Colorless crystals (12 mg, 80%): mp: 88–94 °C; $[\alpha]_D^{22}$ −6.7 (*c* = 0.36); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.49–1.70 (m, 2H, $NCH_2CH_2CH_2$), 1.70–1.85 (m, 1H, $NCH_2CH_2CH_2$), 1.90 (s, 3H, CH_3), 1.92–2.05 (m, 1H, $NCH_2CH_2CH_2$), 2.08–2.20 (m, 1H, $NCH_2CH_2CH_2$), 2.38 (d, *J* = 10.8 Hz, 1H, NCH_2CH), 2.65 (m, 2H, NCH_2CH, NCH_2CH_2O), 2.74–2.85 (m, 1H, NCH_2CH_2O), 2.93–3.07 (m, 1H, $NCH_2CH_2CH_2$), 3.08–3.26 (m, 3H, NCH_2CH, NCH_2CH_2O), 3.74 (s, 6H, OCH_3), 3.77 (s, 3H, OCH_3), 6.65 (dd, *J* = 8.7/2.5 Hz, 1H, $CHCHCCHC$), 6.70 (d, *J* = 2.4 Hz, 1H, $CHCHCCHC$), 6.79 (d, *J* = 8.3 Hz, 4H, $OCCH_{ar}$), 7.22–7.31 (m, 4H, CCH_{ar}), 7.37 ppm (d, *J* = 8.7 Hz, 1H, $CHCHCCHC$); ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 22.0 (CH_3), 22.2 ($NCH_2CH_2CH_2$), 26.5 ($NCH_2CH_2CH_2$), 40.6 (NCH_2CH), 52.9 ($NCH_2CH_2CH_2$), 55.1 (OCH_3), 55.2 (OCH_3), 56.0 (NCH_2CH), 57.4 (NCH_2CH_2O), 60.2 (NCH_2CH_2O), 86.9 (CH_2OC), 109.3 ($CHCHCCHC$), 113.2 ($OCCH_{ar}$), 118.2 ($CHCHCCHC$), 128.4 (CCH_{ar}), 128.5 (CCH_{ar}), 131.8 ($CHCHCCHC$), 132.5 (C_{ar}), 137.6 (C_{ar}), 137.7 (C_{ar}), 140.6 (C_{ar}), 158.1 (H_3COC), 159.0 (H_3COC), 176.5 ppm (COO); IR (KBr): $\tilde{\nu}$ = 2926, 1606, 1508, 823; HRMS-ESI-: *m/z* $[M-H]^-$ calcd for $C_{31}H_{36}NO_6$: 518.2548, found: 518.2550.

1-{2-[1,1-Bis(4-methoxy-2-methylphenyl)-1-(4-methoxyphenyl)-methoxy]ethyl}piperidine-3-carboxylic acid (41): According to GP 4: **32** (56 mg, 0.10 mmol) in EtOH (0.4 mL), 12 N NaOH (0.2 mmol, 17 μL), 27 h and 0.25 N HCl. The resulting solution was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified by flash chromatography (CH_2Cl_2/EtOH = 8:2 + 1% $NEtMe_2$). Colorless crystals (27 mg, 51%): mp: 100–120 °C dec.; ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 1.53–1.63 (m, 1H, $NCH_2CH_2CH_2$), 1.66 (d, *J* = 14.2 Hz, 1H, $NCH_2CH_2CH_2$), 1.72–1.83 (m, 1H, $NCH_2CH_2CH_2$), 1.94 (d, *J* = 10.8 Hz, 1H, $NCH_2CH_2CH_2$), 2.08 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.12–2.22 (m, 1H, $NCH_2CH_2CH_2$), 2.38 (d, *J* = 10.9 Hz, 1H, NCH_2CH), 2.65 (s, 1H, NCH_2CH), 2.74 (dt, *J* = 12.2/6.0 Hz, 1H, NCH_2CH_2O), 2.85 (dt, *J* = 12.3/6.0 Hz, 1H, NCH_2CH_2O), 3.02 (d, *J* = 10.0 Hz, 1H, $NCH_2CH_2CH_2$), 3.12 (d, *J* = 10.9 Hz, 1H, NCH_2CH), 3.20 (t, *J* = 5.7 Hz, 2H, NCH_2CH_2O), 3.76 (s, 6H, OCH_3), 3.77 (s, 3H, OCH_3), 6.58–6.63 (m, 2H, CH_{ar}), 6.66–6.70 (m, 2H, CH_{ar}), 6.78–6.85 (m, 2H, CH_{ar}), 7.09–7.14 (m, 2H, CH_{ar}), 7.18–7.24 ppm (m, 2H, CH_{ar}); ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 22.1 ($NCH_2CH_2CH_2$), 22.2 (CH_3), 26.5 ($NCH_2CH_2CH_2$), 40.4 (NCH_2CH), 53.5 ($NCH_2CH_2CH_2$), 55.1 (OCH_3), 55.2 (OCH_3), 55.9 (NCH_2CH), 57.6 (NCH_2CH_2O), 61.2 (NCH_2CH_2O), 88.8 (CH_2OC), 109.6 (CH_{ar}), 112.8 (CH_{ar}), 117.8 (CH_{ar}), 117.9 (CH_{ar}), 129.5 (CH_{ar}), 130.2 (CH_{ar}), 130.3 (CH_{ar}), 134.4 (C_{ar}), 134.5 (C_{ar}), 134.9 (C_{ar}), 139.5 (C_{ar}), 139.6 (C_{ar}), 158.0 (C_{ar}), 158.6 (C_{ar}), 176.1 ppm (CO); IR (KBr): $\tilde{\nu}$ = 2934, 1606, 1508, 1497, 811 cm^{-1}; HRMS-ESI-: *m/z* $[M-H]^-$ calcd for $C_{32}H_{38}NO_6$: 532.2704, found: 532.2704.

1-(2-{1,1,1-Tris[4-(trifluoromethyl)phenyl]methoxy}ethyl)piperidine-3-carboxylic acid (42): According to GP 4: **33** (100 mg, 0.155 mmol) in EtOH (0.5 mL), 12 N NaOH (0.31 mmol, 26 μL), 22 h and 0.25 N HCl. The resulting solution was extracted with Et_2O. Colorless crystals (59 mg, 62%): mp: 78–90 °C; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.48–1.82 (m, 3H, $NCH_2CH_2CH_2$), 1.84–2.03 (m, 1H, $NCH_2CH_2CH_2$), 2.05–2.24 (m, 1H, $NCH_2CH_2CH_2$), 2.27–2.47 (m, 1H, NCH_2CH), 2.51–2.88 (m, 4H, $NCH_2CH_2CH_2$, NCH_2CH, NCH_2CH_2O), 2.91–3.10 (m, 1H, NCH_2CH), 3.11–3.35 (m, 2H, NCH_2CH_2O), 7.49–7.69 ppm (m, 12H, CH_{ar}); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 22.1 ($NCH_2CH_2CH_2$), 26.5 ($NCH_2CH_2CH_2$), 40.4 (NCH_2CH), 54.4 ($NCH_2CH_2CH_2$), 55.6 (NCH_2CH), 57.1 (NCH_2CH_2O), 60.1 (NCH_2CH_2O), 86.4 ($COCH_2$), 124.1 (q, *J* = 237 Hz, CF_3), 125.2 (m, F_3CCCH_{ar}), 128.9 (CH_{ar}), 129.8 (q, *J* = 32 Hz, CCF_3), 146.5 (C_{ar}), 176.2 ppm (COO); IR (KBr): $\tilde{\nu}$ = 2938, 1616, 830 cm^{-1}; HRMS-ESI+: *m/z* $[M+H]^+$ calcd for $C_{30}H_{27}F_9NO_3$:620.1842, found: 620.1841.

1-(2-{1,1,1-Tris[4-(trifluoromethoxy)phenyl]methoxy}ethyl)piperidine-3-carboxylic acid (43): According to GP 4: **34** (312 mg, 0.450 mmol) in EtOH (0.5 mL), 2 N NaOH (0.31 mmol, 10 mL), 20 h and 0.2 N HCl. The resulting precipitate was isolated. Colorless crystals (253 mg, 80%): mp: 45–63 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.52–1.72 (m, 3H, $NCH_2CH_2CH_2$), 1.72–1.89 (m, 2H, $NCH_2CH_2CH_2$), 2.04 (d, *J* = 11.6 Hz, 1H, $NCH_2CH_2CH_2$), 2.08–2.18 (m, 1H, $NCH_2CH_2CH_2$), 2.34 (d, *J* = 10.7 Hz, 1H, NCH_2CH), 2.63 (dt, *J* = 13.3/4.6 Hz, 1H, NCH_2CH), 2.67–2.77 (m, 2H, NCH_2CH_2O), 2.86 (d, *J* = 8.1 Hz, 1H, $NCH_2CH_2CH_2$), 3.05 (d, *J* = 8.9 Hz, 1H, NCH_2CH), 3.17–3.33 (m, 2H, NCH_2CH_2O), 7.18 (d, *J* = 8.1 Hz, 6H, CH_{ar}), 7.42 ppm (d,

J=8.6 Hz, 6H, CH_{ar}); IR (KBr): $\tilde{\nu}$=3425, 2948, 1606, 1508, 846 cm^{-1}; HRMS-ESI+: m/z $[M+H]^+$ calcd for $C_{30}H_{27}NO_6F_9$: 668.1689, found: 668.1690.

1-{2-[2,2,2-Tris(4-methoxyphenyl)ethoxy]ethyl}piperidine-3-carboxylic acid (44): According to GP 4: **35** (103 mg, 0.187 mmol) in EtOH (2 mL), 2 N NaOH (0.468 mmol, 235 μL), 16 h and 0.01 N HCl. The resulting solution was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. Colorless solid (89.5 mg, 92%): mp: 72 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.19–1.42 (m, 2H, $NCH_2CH_2CH_2$, $NCH_2CH_2CH_2$), 1.45–1.57 (m, 1H, $NCH_2CH_2CH_2$), 1.68–1.78 (m, 1H, $NCH_2CH_2CH_2$), 1.87–2.00 (m, 1H, $NCH_2CH_2CH_2$), 2.08–2.21 (m, 1H, NCH_2CH), 2.29–2.39 (m, 1H, NCH_2CH), 2.50–2.60 (m, 3H, NCH_2CH_2O, $NCH_2CH_2CH_2$), 2.75–2.86 (m, 1H, NCH_2CH), 3.46–3.56 (m, 2H, NCH_2CH_2O), 3.71 (s, 9H, OCH_3), 4.27 (dd, 2H, J=16.5/9.4, OCH_2C_q), 6.76–6.83 (m, 6H, CH_{ar}), 6.95–7.10 ppm (m, 6H, CH_{ar}); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=22.3 ($NCH_2CH_2CH_2$), 24.7 ($NCH_2CH_2CH_2$), 39.5 (NCH_2CH), 51.4 ($NCH_2CH_2CH_2$), 53.3 (OCH_3), 53.8 (NCH_2CH), 55.3 (NCH_2CH_2O), 70.7 (NCH_2CH_2O), 76.2 (OCH_2C), 111.3 ($OCCH_{ar}$), 128.4 ($OCCH_{ar}CH_{ar}$), 136.7 (OC), 155.6 (CC), 173.4 ppm (CO); IR (KBr): $\tilde{\nu}$= 3399, 2951, 2834, 1717, 1607, 824 cm^{-1}; MS (CI, CH_5^+): m/z (%): 520 (12) $[M+H]^+$, 333 (100), 142 (34); Anal. calcd for $C_{31}H_{37}NO_6$: C 71.65, H 7.18, N 2.70, found: C 71.38, H 7.11, N 2.40.

1-[4,4,4-Tris(4-methoxyphenyl)butyl]piperidine-3-carboxylic acid (45): According to GP 4: **36** (42 mg, 0.084 mmol) in EtOH (1 mL), 2 N NaOH (0.2 mmol, 0.1 mL), 5 days and 2 N HCl. The resulting solution was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. Colorless crystals (28.6 mg, 67%): mp: 101–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.85 (m, 3H), 1.21 (m, 9H), 2.19 (m, 1H), 2.50 (m, 1H, CH), 3.26 (m, 1H), 3.77 (s, 9H, OCH_3), 6.80 (d, J=8.6 Hz, 6H, H_{ar}), 7.14 (d, J=8.6 Hz, 6H, H_{ar}), 11.15 ppm (s, 1H, COOH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.01 ($CH_{2,piperidine}$), 25.32 ($CH_{2,piperidine}$), 29.68 (CCH_2CH_2), 37.44 (CCH_2), 38.62 (CH), 51.71 (NCH_2), 53.40 (NCH_2), 54.52 (CCH_2), 55.22 (OCH_3), 57.98 (NCH_2), 113.36 (CH_{ar}), 129.89 (CH_{ar}), 139.06 (C_{ar}), 157.57 ($COCH_3$), 172.83 ppm (COOH); IR (KBr): $\tilde{\nu}$=3436, 2931, 2734, 1726, 1606, 1508 cm^{-1}; HRMS-ESI+: m/z $[M+H]^+$ calcd for $C_{31}H_{38}NO_5$: 504.2744, found: 504.2742.

1-[4,4,4-Tris(4-methoxyphenyl)but-2-en-1-yl]piperidine-3-carboxylic acid (46): According to GP 4: **37** (93 mg, 0.17 mmol) in EtOH (0.6 mL), 12 N NaOH (0.35 mmol, 30 μL), 72 h and 0.25 N HCl (1.2 mL). The resulting solution was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. Colorless crystals (83 mg, 95%): mp: 98–102 °C; ^{1}H NMR (400 MHz, CD_2Cl_2): δ=1.56 (tt, J=13.1/4.7 Hz, 1H, $NCH_2CH_2CH_2$), 1.64 (d, J=14.1 Hz, 1H, $NCH_2CH_2CH_2$), 1.70–1.85 (m, 1H, $NCH_2CH_2CH_2$), 1.93 (d, J=12.6 Hz, 1H, $NCH_2CH_2CH_2$), 2.14–2.31 (m, 2H, $NCH_2CH_2CH_2$, NCH_2CH), 2.57–2.65 (m, 1H, NCH_2CH), 2.96 (d, J=9.7 Hz, 1H, $NCH_2CH_2CH_2$), 3.08 (d, J=10.6 Hz, 1H, NCH_2CH), 3.17–3.31 (m, 2H, NCH_2CHCH), 3.76 (s, 10H), 5.23–5.36 (m, 1H, NCH_2CHCH), 6.64 (d, J=15.5 Hz, 1H, NCH_2CHCH), 6.78 (d, J= 8.8 Hz, 6H), 6.94 ppm (d, J=8.8 Hz, 6H); ^{13}C NMR (126 MHz, CD_2Cl_2): δ=20.5 ($NCH_2CH_2CH_2$), 24.9 ($NCH_2CH_2CH_2$), 38.7 (NCH_2CH), 51.5 ($NCH_2CH_2CH_2$), 52.9 (NCH_2CH), 53.7 (OCH_3), 57.3 ($C(C_6H_5)_3$), 58.2 (NCH_2CHCH), 111.5 (CH_{ar}), 123.1 (NCH_2CHCH), 129.4 (CH_{ar}), 136.7 (C_{ar}), 142.5 (NCH_2CHCH), 156.5 ($COCH_3$), 174.4 ppm (CO); IR (KBr): $\tilde{\nu}$=3433, 2933, 1606, 1507, 828 cm^{-1}; HRMS-ESI+: m/z $[M+H]^+$ calcd for $C_{31}H_{36}NO_5$: 502.2588, found: 502.2585.

(*R*)-1-[4,4,4-Tris(4-methoxyphenyl)but-2-en-1-yl]piperidine-3-carboxylic acid (47): According to GP 4: **38** (164 mg, 0.327 mmol) in EtOH (1.5 mL), 12 N NaOH (0.62 mmol, 52 μL), 96 h and 0.25 N HCl (6.6 mL). The resulting solution was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo; **47** was obtained as colorless crystals (133 mg, 86%). Analytical data correspond to those of **46** except $[\alpha]_D^{22}$ +18.7 (c=0.33).

(3*S*)-1-[4,4,4-Tris(4-methoxyphenyl)but-2-en-1-yl]piperidine-3-carboxylic acid (48): According to GP 4: **39** (96 mg, 0.18 mmol) in EtOH (1 mL), 12 N NaOH (0.36 mmol, 30 μL), 72 h and 0.25 N HCl (1.2 mL). The resulting solution was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo; **48** was obtained as colorless crystals (84 mg, 92%). Analytical data correspond to those of **46** except $[\alpha]_D^{22}$ −19.5 (c=0.33).

Pharmacological methods

[^{3}H]GABA uptake

Cells grown in 145 cm^2 plates to a confluence of 70–90% were treated with 4 mL trypsin/EDTA for ~30 s. Afterward normal medium was added (8 mL), and the resulting cell suspension was centrifuged for 5 min at 500 *g*. The cells were washed three times in phosphate-buffered saline (PBS; 137 mM NaCl, 2.7 mM KCl, 8 mM Na_2HPO_4, 1.75 mM KH_2PO_4, pH 7.4) by centrifugation as described above and finally resuspended in Krebs buffer (2.5 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 4.7 mM KCl, 11 mM glucose, 25 mM Tris, 119 mM NaCl, pH 7.2). The uptake assays were performed with aliquots of the resulting cell suspension (~100 000 cells per well for mGAT1, mGAT3, mGAT4, and ~200 000 cells per well for mGAT2) in a total volume of 250 μL in 96-well 2.2 mL polyethylene deep-well plates (Abgene, Epsom, UK). The cells were equilibrated for 25 min in Krebs buffer in the presence of the test compound at 37 °C in a gently shaking water bath. Due to the poor solubility of the test compounds, all samples contained 1% DMSO. (The highest concentration investigated was 100 μM. Because many of the test compounds tend to precipitate at this concentration, it cannot be absolutely ruled out that the inhibition assays are affected by precipitation at a test compound concentration for 100 μM. However, the inhibition curves obtained gave no indication of any distortion effects. After addition of 25 μL of a solution containing [^{3}H]GABA (3 TBq $mmol^{-1}$, Amersham Biosciences, Freiburg, Germany) and unlabeled GABA in Krebs (final concentration 8 nM [^{3}H]GABA and 32 nM unlabeled GABA for mGAT1, mGAT3, mGAT4, and 20 nM [^{3}H]GABA and 20 nM unlabeled GABA for mGAT2), cells were incubated for a further 4 min (mGAT1, mGAT3, mGAT4) or 10 min (mGAT2). The incubation was stopped by filtration through Whatman GF/C filters pre-soaked for 1 h in 0.9% NaCl by means of a Brandell MWXR-96TI cell harvester (Brandell, Gaithersburg, MD, USA) under reduced pressure (not <250 mbar). The filters were rinsed four times with cold 0.9% NaCl and subsequently transferred to 96-well sample plates (PerkinElmer LAS, Boston, MA, USA). After addition of Rotiszint Eco Plus (Roth, Karlsruhe, Germany; 200 μL per well), the radioactivity was determined in a microbeta liquid scintillation counter (PerkinElmer LAS, Boston, MA, USA). Nonspecific uptake was defined in parallel experiments with 10 μM NO 711 (mGAT1) or 1 mM GABA (mGAT2, mGAT3, mGAT4) and was subtracted from total uptake (no inhibitor) to yield specific uptake. IC_{50} values were determined by nonlinear regression using GraphPad Prism 4 ("one site competition"; bottom and top were fixed to 0 and 100%, respectively). The results are expressed as means ± SEM of at least three separate experiments, each carried out in triplicate. Protein concentration was

determined in an aliquot of the final cell suspension according to Bradford[28] using BSA as a standard.

Keywords: biological activity · GABA · GAT · inhibitors · mGAT1–4

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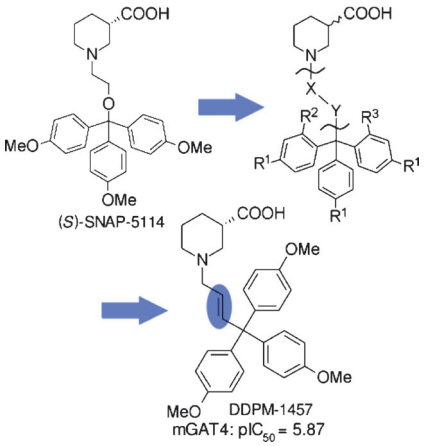
Development of an (*S*)-1-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}piperidine-3-carboxylic acid [(*S*)-SNAP-5114] Carba Analogue Inhibitor for Murine γ-Aminobutyric Acid Transporter Type 4



Stability is a snap! We developed a series of analogues of (*S*)-SNAP-5114, the most potent inhibitor of murine γ-aminobutyric acid transporter type 4 (mGAT4) known thus far. These analogues have potencies that are similar to or slightly higher than that of (*S*)-SNAP-5114 toward mGAT4 (DDPM-1457: $pIC_{50} = 5.87$), but with distinctly improved chemical stability.

