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Original article

# Synthesis of *N*-substituted acyclic β-amino acids and their investigation as GABA uptake inhibitors

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ABSTRACT

In this publication, we describe the synthesis of new inhibitors for the GABA transporter subtypes GAT1 and especially GAT3. We started with 3-aminopropanoic acid possessing a distinct preference for GAT3 in comparison to GAT1 and furthermore its homolog 3-aminobutanoic acid. A series of respective *N*-substituted amino acids was synthesized by selective *N*-monoalkylation of these parent structures with 6 different arylalkyl alcohols via a Mitsunobu-type reaction. The resulting compounds were investigated for their inhibitory potency GABA transporter subtypes. Among all tested compounds the 4,4-diphenylbut-3-enyl substituted 3-aminobutanoic acid (*rac*)-**6b** showed highest potency with a $pIC_{50}$ value of 5.34 at GAT1. Unfortunately, the expected GAT3 potency for 2-[tris(4-methoxyphenyl)methoxy] ethyl substituted derivatives was not as high as observed for the respective nipecotic acid derivatives.



## 1. Introduction

γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system (CNS). In the last four decades, several neuro-pathological and psychiatric diseases have been connected directly or indirectly with the GABAergic neurotransmission such as e.g. dyskinesia, epilepsy, anxiety states, depression, and several other behavioral disorders [1]. Interesting pharmacological targets in search for new drugs in this field are therefore the receptors, transporters, and metabolic enzymes that are involved in the GABAergic neurotransmission. Thus, a promising approach to the successful treatment of cerebral disorder is represented by drugs affecting GABA-uptake. GABA-uptake from the synaptic cleft into the glial cells and presynaptic neurons takes place by transmembrane proteins, the so called GABA transporters. Of the GABA transporters (GATs) for different subtypes are known [2–9]. These are termed mGAT1, mGAT2, mGAT3, and mGAT4 when originating from mice but are named GAT-1, GAT-2, GAT-3, and BGT1, respectively, for all other species, e.g. rats and humans whereby the species is indicated by a respective prefix (e.g. hGAT-1) (for a survey of different nomenclatures of GATs see Dalby et al. [10]). An additional nomenclature has been proposed by the Human Genome Organization (HUGO). Referring to the latter the GAT homologs are denoted as GAT1 (encoding gene: SLC6A1), BGT1 (SLC6A12), GAT2 (SLC6A13) and GAT3 (SLC6A11). For the sake of simplicity, the HUGO nomenclature is used in terms of a species independent nomenclature in the following, although it is – if taken accurately – restricted to human.

Substantial differences have been found with respect to the distribution of these four subtypes in the organism. GAT1 and GAT3 are located almost exclusively in the central nervous system, where GAT1 has been shown to be predominantly responsible for the transport of GABA into neurons and GAT3 into glial cells. BGT1 and GAT2 have repeatedly been reported to be widely distributed throughout the brain, too, though in low concentrations and in peripheral organs like the liver and the kidneys. However, according to recent studies from Danbolt et al. BGT1 and GAT2 are not detectable in brain parenchyma. In the brain, both proteins show distinct expressions in the leptomeninges and GAT2, in addition, in a subpopulation of brain blood vessels only [11,12]. Thus, only GAT1 and GAT3 but not BGT1 and GAT2 can be considered to play a role in neurotransmitter inactivation [13]. Accordingly, compounds addressing GAT1 and GAT3 with high potency and selectivity are of special interest when it comes to the development of CNS drugs

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enhancing GABA neurotransmission. This is especially true for potent and selective GAT3 inhibitors as those are lacking so far.

Nipecotic acid (**1**), which can be considered as a rigidified β-alanine, has been found to be an inhibitor of GABA uptake in neuronal and astroglial cell cultures [14]. But due to its low lipophilicity, nipecotic acid (**1**) lacks the capability to cross the blood–brain barrier in sufficient amount [15]. This obstacle was overcome by attaching a lipophilic side chain to the nipecotic acid nitrogen leading to GABA uptake inhibitors such as SK&F-89976-A [(*rac*)-**2**] [16,17], tiagabine [(*R*)-**3**] [18,19] and (*S*)-SNAP-5114 [(*S*)-**4**] [20]. SK&F-89976-A [(*rac*)-**2**] displays a 4,4-diphenylbut-3-enyl side chain whereas in case of tiagabine [(*R*)-**3**] a 4,4-bis(3-methyl thiophene-1-yl)but-3-enyl moiety is present, both of which not only enhance the potency of these compounds but also substantially improve the subtype selectivity in favor of GAT1 inhibition as compared to the basic compounds (*rac*)-**1** and (*R*)-**1**, respectively. For (*S*)-SNAP-5114 [(S)-**4**] this subtype selectivity is reversed, this compound possessing the highest inhibitory potency at GAT3 which has largely to be ascribed to the presence of the 2-[tris(4-methoxyphenyl)methoxy]ethyl residue. A similar effect, the rever sal of subtype selectivity from GAT1 to GAT3, has been observed for several other amino acids acting as GAT inhibitors when 4,4-diarylbutenyl moieties as in (*rac*)-**2** or (*R*)-**3** were replaced by the sterically more demanding *N*-substituent of (S)-SNAP-5114 [(*S*)-4] these residues were applied [21]. Interestingly, for GAT1 and GAT3 inhibitors like **3** and **4** and related compounds the change in subtype selectivity is commonly paralleled by a switch in biological enantioselectivity, the highest potency and subtype selectivity for GAT1 inhibitors residing in the (*R*)- and for GAT3 inhibitors in the (*S*)-enantiomer (or the corresponding homochiral compound) (Fig. 1).

β-Alanine (3-aminopropanoic acid, **5a**) is long known to inhibit GABA uptake into glial cells [22] and in the meantime it has been intensively studied on the four GABA transporter subtypes [23]. In the test system that has been established in our group and is based on HEK293 cells stably expressing the individual murine GABA transporters, β-alanine (**5a**) was found to possess a reasonable potency at and subtype selectivity for GAT3 ($pIC_{50} = 4.66 \pm 0.06$) as compared to GAT1 (GAT1: $pIC_{50} = 2.55 \pm 0.03$). Also the methyl substituted derivative 3-aminobutanoic acid [(*rac*)-**6a**] displays good inhibitory potency at GAT3 ($pIC_{50} = 4.08 \pm 0.03$) but this time also at GAT1 ($pIC_{50} = 4.30 \pm 0.10$) thus being, in contrast to β-alanine (**5a**), almost equally potent at both transporters. With the inhibitory potencies at GAT1 [for (*rac*)-**6a**] and at GAT3 [for **5a** and (*rac*)-**6a**] being in the range of (*rac*)-nipecotic acid [(*rac*)-**1a**] we considered these compounds suitable starting points for the development of new GABA uptake inhibitors for these GABA transporters, especially GAT3. Thereby it was hoped the subtype selectivity inherent to the parent compounds **5a** and (*rac*)-**6a** might also positively contribute to that of appropriately *N*-substituted compounds (Fig. 2).

In this context, it should be mentioned that attachment of lipophilic residues – known to enhance inhibitory potency at GAT1 and GAT3 – to the β-amino acids **5a** and (*rac*)-**6a** were expected to provide data for the establishment of structure activity relationships for the respective acyclic amino acid derivatives, yet unknown so far.

Though **5a** and (*rac*)-**6a** display also reasonable potencies at BGT1 and GAT2 no attention should be paid to the development of inhibitors of these GABA transporter subtypes as these transporters due to their low abundance in the brain are of no significant relevance for the development of CNS active compounds [12]. For our study the 4,4-diphenylbut-3-enyl (**b**), the 2-[2-(10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)ethoxy]ethyl (**c**), the 2-[2-(5*H*-dibenzo[*b*,*f*]azepin-5-yl)ethoxy]ethyl (**d**) and the 2-[2-(10*H*-phenothiazin-10-yl)ethoxy]ethyl (**e**) moiety were selected to be employed as *N*-substituents which according to the results published by Andersen et al. [24] improve the potency at GAT1 as well as the subtype selectivity for this transporter. With regard to the development of more potent GAT3 inhibitors from **5a** and (*rac*)-**6a** the 2-[tris(4-methoxyphenyl)methoxy]ethyl (**f**) and the (*E*)-2-[tris(4-methoxy phenyl)]but-2-en-1-yl (**g**) residue should be used as *N*-substituents, which are known to enhance potency and subtype selectivity in favor of this transporter as demonstrated by (*S*)-SNAP-5114 [(*S*)-**4**] and the recently introduced DDPM-1457 [25], two of the most potent inhibitors of this subtype of GABA transporters.

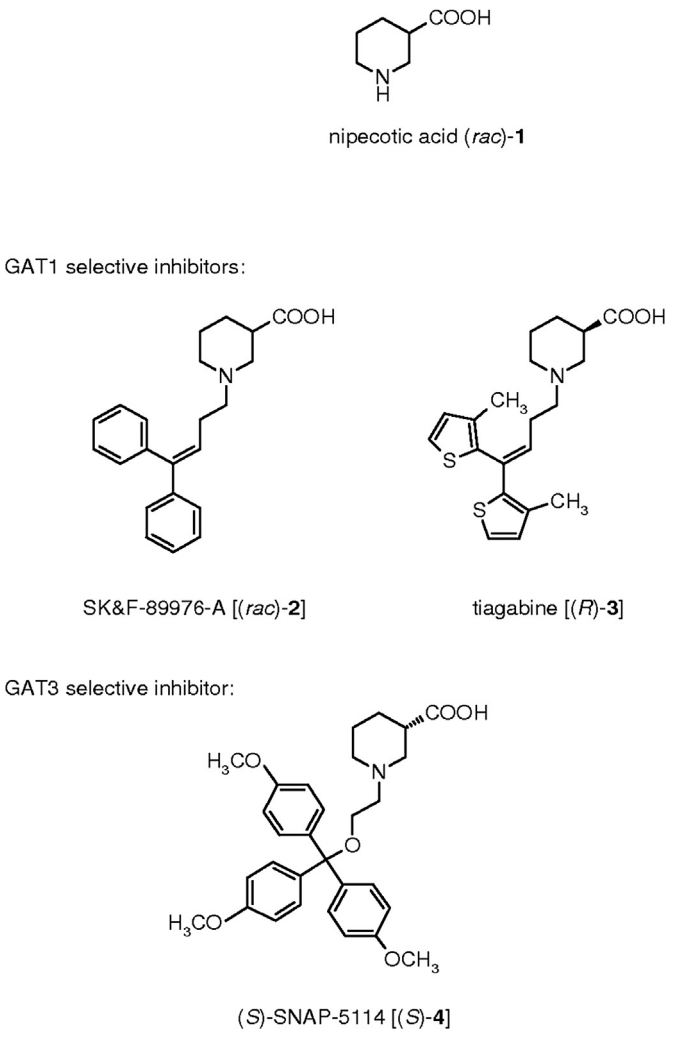



**Fig. 1.** Structures of GABA uptake inhibitors.

## 2. Chemistry

First attempts to synthesize the desired compounds were undertaken by reacting methyl 3-aminopropanoate hydrochloride (**9**) with the respective alkyl halides but resulted in yields that were not fully satisfying (Scheme 1). Thus, the exemplarily performed reaction of methyl 3-aminopropanoate (**7**) with the bromides **7b** and **7f** ($K_2CO_3$, KI, $CH_3CN$, 45 °C, 24 h) led to the corresponding *N*-alkylated ester derivatives **10b** and **10f** in moderate yields of 52% and 49% only.

Therefore, we decided to perform the synthesis of all other *N*-substituted amino acids by a variant of the Mitsunobu reaction

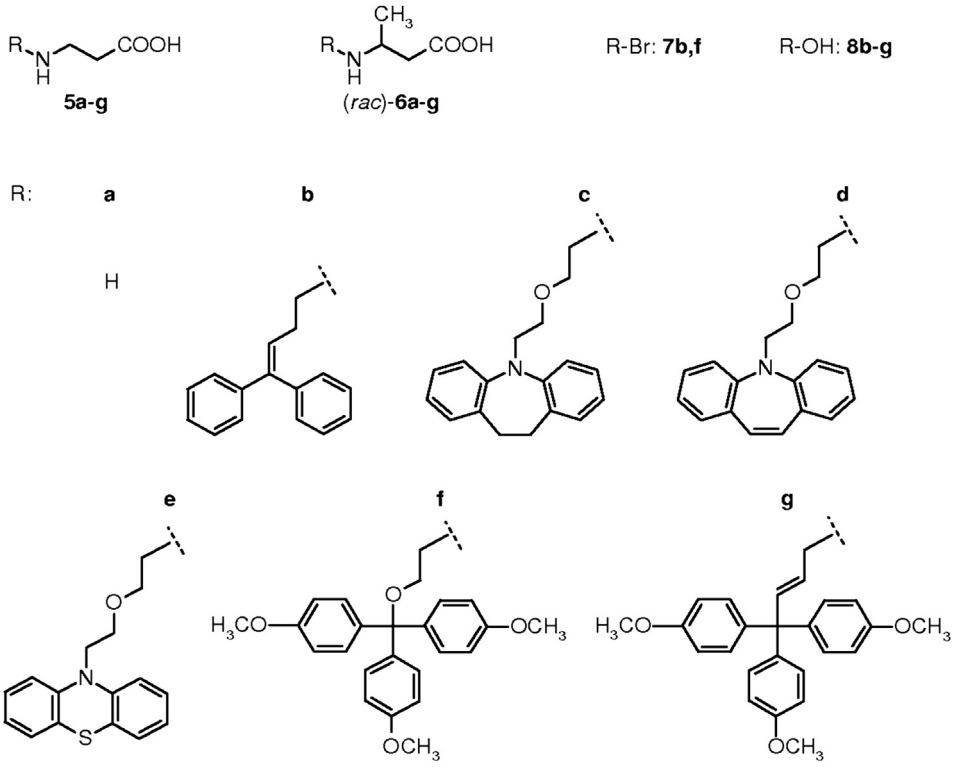


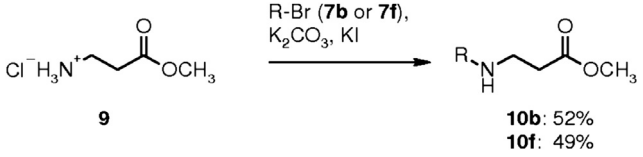

**Fig. 2.** β-Amino acid target structures.

following a procedure published by Fukuyama et al. [26] according to which amines were alkylated via their sulfonamides employing alcohols **8b**–**g** as alkylating agents. This approach appears also quite favorable as it avoids the preparation of alkyl bromides and thus an additional synthetic step, the formation of these alkylating agents commonly prepared from the respective alcohols.

### 2.1. Synthesis of arylalkyl alcohols

The arylalkyl alcohols **8b**–**e** required for the preparation of the *N*-substituted β-amino acids **5c**–**e** and (*rac*)-**6b**–**e** by Mitsunobu reaction were synthesized by literature methods [24].

2-[Tris(4-methoxyphenyl)methoxy]ethyl alcohol (**8f**) was accessible by a two step procedure, i.e. by treating tertiary alcohol **11** with $SOCl_2$ followed by the reaction with ethylene glycol (Scheme 2). Unfortunately, the desired alcohol **8f** could only be isolated in moderate yield (32%), as the chlorinated derivative **12** had formed as side product, which to separate by column chromatography led to marked substance losses. For the synthesis of the triaryl allyl alcohol **8g** alcohol **13** was oxidized with IBX to afford aldehyde **14**. Treatment of **14** with triethyl phosphonoacetate and sodium hydride yielded the unsaturated ester **15** (96%). Subsequent reduction with lithium aluminum hydride afforded the desired alcohol **8g** in 71% yield.



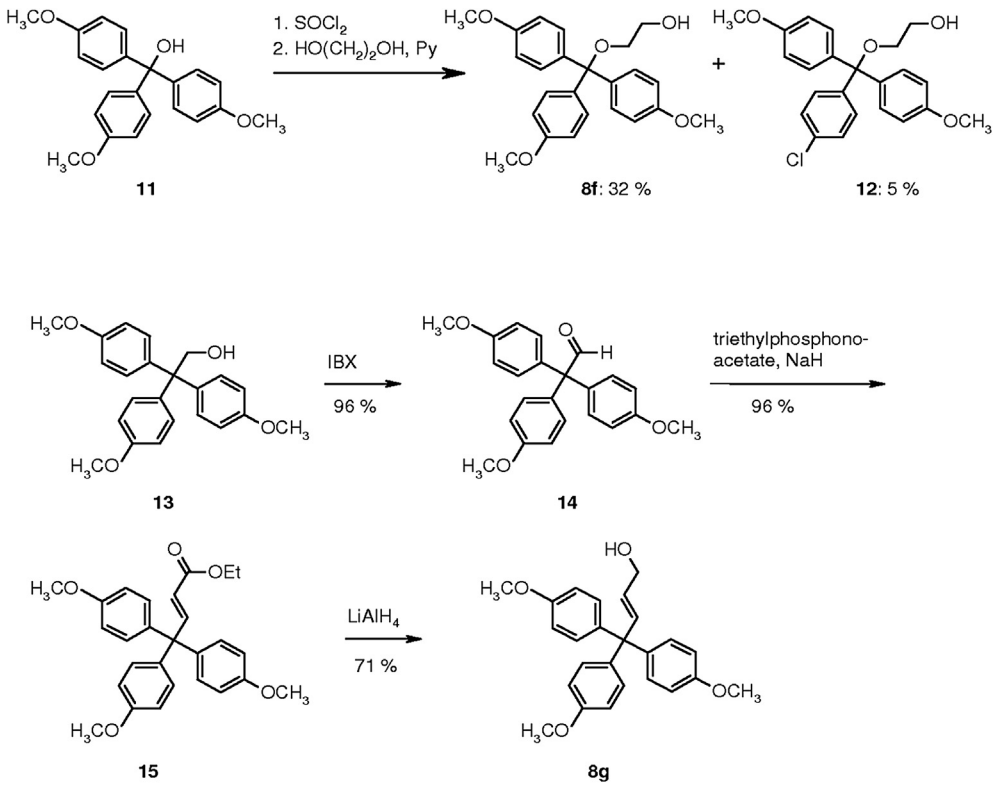

**Scheme 1.** *N*-Alkylation with bromides **7b** and **7f** under $S_N2$ condition.

### 2.2. Mitsunobu reaction

For the *N*-alkylation by Mitsunobu reaction the sulfonamides of the amino acid ester hydrochlorides **9** and (*rac*)-**16**, were required. Their synthesis was easily accomplished by treating **9** and (*rac*)-**16** with 2,4-dinitrophenylsulfonylchloride in the presence of pyridine to afford the desired sulfonamides **17** and (*rac*)-**18** in 91% and 53% yield, respectively (Scheme 3).

The *N*-alkylation of sulfonamides **17** and (*rac*)-**18** was performed in analogy to a procedure of Fukuyama et al. However, instead of diethyl azodicarboxylate (DEAD) diisopropyl azodicarboxylate (DIAD) was used, together with triphenylphosphane, for the activation of the alcohols, because at the time this work was performed DEAD was commercially unavailable in Germany due to safety problems [27]. Fortunately, DIAD proved to be suitable for this purpose as well. Thus, *N*-alkylation by Mitsunobu reactions proceeded smoothly, when mixtures of the sulfonamides **17** and (*rac*)-**18** (1 equiv.), the respective alcohol **8b**–**g** (2 equiv.) and $Ph_3P$ (2 equiv.) in benzene were treated with DIAD (2 equiv., addition at 10 °C, subsequent reaction at rt), providing the Mitsunobu products **19c**–**e**,**g** and **20b**–**g** in good to excellent yields (79–95%, see Table 1).

By aiming at the free amino acids in the last two steps of the synthetic sequence the removal of the 2,4-dinitrophenylsulfonyl moiety and the cleavage of the carboxylic acid ester function had to be accomplished. For the removal of the arylsulfonyl moiety we applied a mixture of mercaptoacetic acid and triethylamine following a protocol of Fukuyama et al. which resulted in the formation of the β-amino acid esters **9c**–**e**,**g** and **21b**–**g** in good yields (79–96%). The monoalkylated amino acid esters **9c**–**e**,**g** obtained via Mitsunobu reaction and **9b**,**f**, by direct *N*-alkylation as well as (*rac*)-**21b**–**g** were finally hydrolyzed with 2 M NaOH in MeOH at rt to give after workup and ion exchange chromatography – where necessary – the free amino acids **5b**–**g** and (*rac*)-**6b**–**g** in yields of




**Scheme 2.** Synthesis of alcohols **8f** and **8g**.

42–87%. Amino acid **5b** was further treated with HCl, to afford after recrystallization **5b**·HCl in 84% yield.

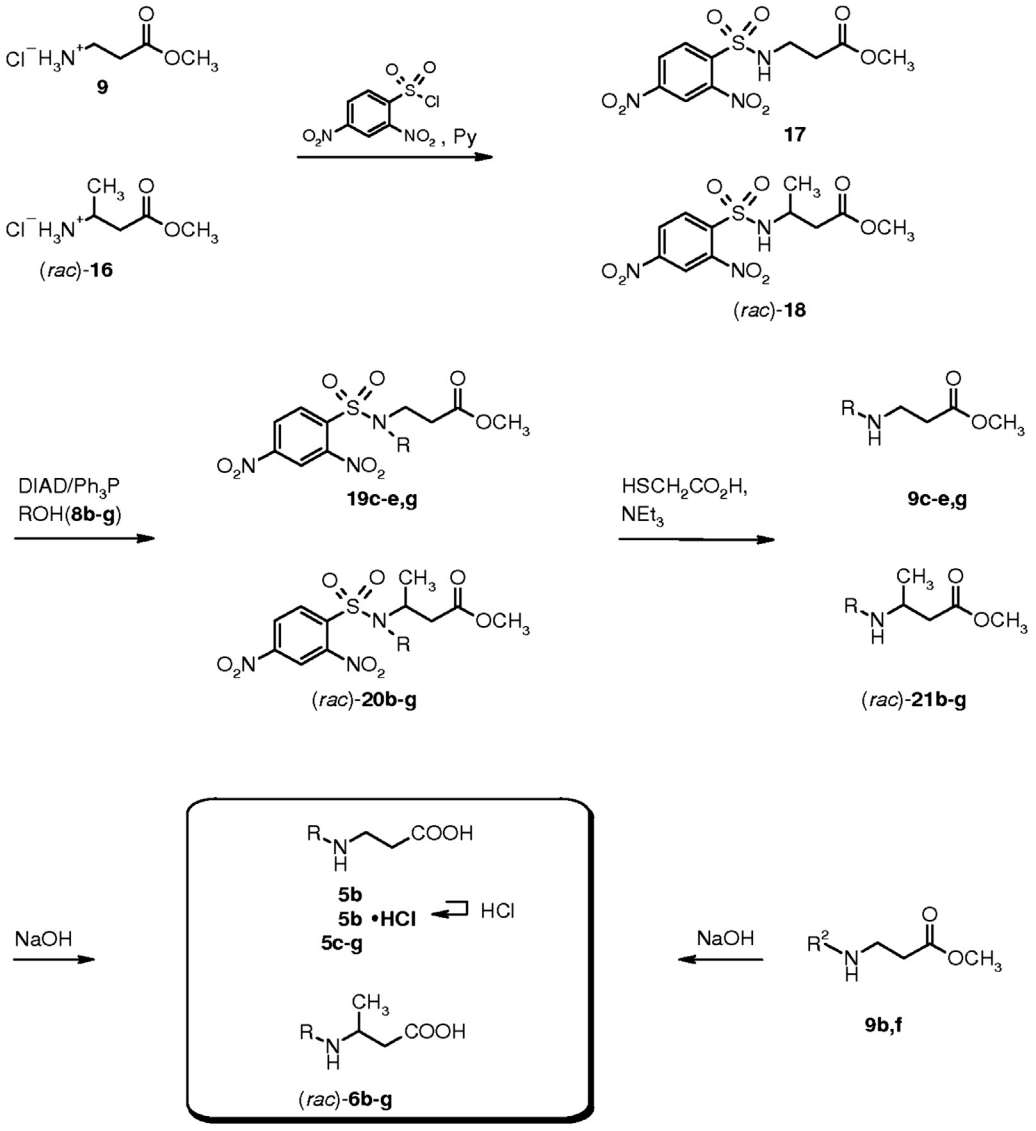
## 3. Biological studies

Like the parent structures **5a** and (*rac*)-**6a** before also the target compounds, the *N*-substituted β-amino acids **5b**–**g** and (*rac*)-**6b**–**g** were tested for their inhibitory potency at GAT1, BGT1, GAT2 and GAT3. The uptake assays were performed using HEK293 cell lines, each stably expressing one of the four murine GABA transporter subtypes [28].

Most of the new compounds that had been designed to address GAT1 showed moderate to good inhibitory activity with reasonable selectivity for this transporter subtype (Table 2). But attempts to improve GAT3 potency of the parent compounds **5a** and (*rac*)-**6a** met only little success. As already outlined in the introduction 3-aminopropanoic acid (**5a**) and 3-aminobutanoic acid [(*rac*)-**6a**] are distinctly different with respect to their potency at GAT1 the former possessing a far lower ($pIC_{50} = 2.55 \pm 0.03$) and the latter an almost similar potency (GAT1: $pIC_{50} = 4.30 \pm 0.10$) as nipecotic acid [(*rac*)-**1**] (GAT1: $pIC_{50} = 4.88 \pm 0.07$) which has been widely used as parent compound for the development of highly potent GAT inhibitors. In contrast, at GAT3 the potencies of all three compounds are similar [(*rac*)-**1**: $pIC_{50} = 4.70 \pm 0.07$; **5a**: $pIC_{50} = 4.46 \pm 0.06$; (*rac*)-**6a**: $pIC_{50} = 4.08 \pm 0.03$] (see Table 2).

Introduction of the 4,4-diphenylbut-3-enyl moiety as *N*-substituent known from SK&F-89976-A [(*rac*)-**2**] and many other examples to considerably enhance GAT1 potency improved uptake inhibition also for **5b** and (*rac*)-**6b**, but due to the low potency of the parent compounds no high GAT1 potencies were reached (**5b**: $pIC_{50} = 3.94 \pm 0.07$; (*rac*)-**6b**: $pIC_{50} = 5.34 \pm 0.06$). At the same time the GAT3 potencies of **5b** and (*rac*)-**6b** became lower, a phenomenon which is also quite common for this kind of substituents being displayed by (*rac*)-**2** as compared to (*rac*)-**1** as well (see Table 2). Curiously, while according to literature data the 3-[2-(10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)ethoxy]ethyl side chain leads to a slightly reduced GAT1 potency for (*R*)-**22** ($pIC_{50} = 4.40$) as compared to the parent compound (*R*)-**1** ($pIC_{50} = 5.07$), the opposite is true when the same residue is attached to **5a** and (*rac*)-**6a** [resulting in **5c** and (*rac*)-**6c**]. Here, the GAT1 potency raises for (*rac*)-**6a** from $pIC_{50} = 4.30$ to $pIC_{50} = 4.88$ ((*rac*)-**6c**) and for **5a** from $pIC_{50} = 2.55$ to $pIC_{50} = 4.69$ (**5c**), the latter equaling a difference of two log units. Here again in accord with a common trend observed for many other *N*-substituents enhancing GAT1 potency [see e.g. (*rac*)-**2**] at the same time the GAT3 potency was lowered for both compounds, **5c** and (*rac*)-**6c**. For nipecotic acid (*R*)-**1** the 3-[2-(5*H*-dibenzo[*b*,*f*]azepin-5-yl)ethoxy]ethyl and the 3-[2-(10*H*-phenothiazin-10-yl)ethoxy]ethyl residues when attached to the amino nitrogen give rise to highly potent GAT1 inhibitors, (*R*)-**23** and (*R*)-**24**. For **5a** the latter substituent leads to a clear improvement of GAT1 inhibitory potency (**5e**), too. This seems to be also the case for the former substituent (leading to **5d**), though the percentage of remaining GABA uptake determined for this compound provides only a rough estimate of its potency. Whatsoever, though the GAT1 potency of the parent compounds has increased due to the presence of the *N*-substituents it is still low for both compounds. Again the opposite effect was observed for the GAT3 potency for **5d**, **5e**, (*rac*)-**6d** and (*rac*)-**6e** due to the presence of these residues, **d** and **e**, their potency being lower than that of the parent compounds **5a** and (*rac*)-**6a**.

As the parent compounds **5a** and (*rac*)-**6a** display reasonable potencies at GAT3 they were considered promising starting points for the development of more potent inhibitors of this GABA transporter. It was expected that the 2-[tris(4-methoxyphenyl)methoxy]ethyl and the (*E*)-2-[tris(4-methoxyphenyl)]but-2-en-1-yl side chains which are known from (*S*)-SNAP-5114 [(*S*)-**4**] and DDPM-1457 [(*S*)-




**Scheme 3.** Synthesis of *N*-monoalkylated β-amino acids.

**25**], two of the most potent GAT3 inhibitors, should enhance their GAT3 potency and selectivity. But none of the derivatives **5f**, **5g**, (*rac*)-**6f** and (*rac*)-**6g** showed the expected improvements. Their inhibitory potencies at GAT3 were moderate, still in the range of the parent compounds (**5f** $pIC_{50} = 4.37 \pm 0.06$, **5g** 59%, at 100 μM; (*rac*)-**6f**; $pIC_{50} = 4.47 \pm 0.11$; (*rac*)-**6g**; $pIC_{50} = 4.22 \pm 0.01$), nor did they display a significant activity at GAT1.

In addition, most of the newly synthesized compounds have also been studied with respect to their potency at BGT1 and GAT2. But no reasonable potencies were found.

## 4. Conclusion

A series of new *N*-monoalkylated derivatives of 3-aminopro panoic acid (**5a**) and 3-aminobutanoic acid (*rac*)-**6a** utilizing a variant of the Mitsunobu reaction as key step has been synthesized. The thus obtained *N*-substituted β-amino acids have been evaluated for their potency at GAT1, BGT1, GAT2 and GAT3. In general, the compounds derived from the 3-aminobutanoic acid [(*rac*)-**6a**] were more potent than those delineated from 3-aminopropanoic acid (**5a**). The most potent inhibitors were found for GAT1. Of all new compounds 3-aminobutanoic acid derivative (*rac*)-**6b** exhibiting a 4,4-diphenylbut-3-enyl moiety at the amino nitrogen displayed the highest inhibitory potency at this GABA transporter (GAT1: $pIC_{50} = 5.34 \pm 0.06$) along with a distinct subtype selectivity (BGT1: 86%, GAT2: 82% and GAT3: 98% remaining GABA uptake at a concentration of 100 μM of test compound). On the other hand, a potent and highly selective inhibitor for GAT3 could not be found. To finally conclude, the SAR established for nipecotic acid (**1**) is only partly reflected in the acyclic β-amino acids examined in this study. Nevertheless, the present study is the first systematic investigation providing SAR data for acyclic amino acids with lipophilic *N*-substituents.

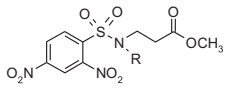
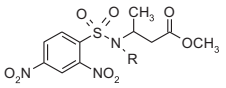
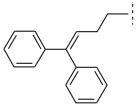
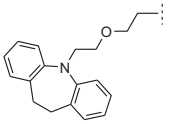
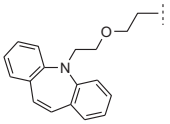
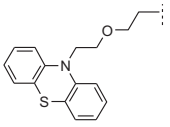
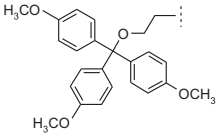
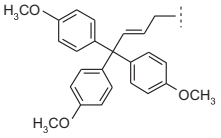
## 5. Experimental section

### 5.1. Chemistry

#### 5.1.1. General

Benzene, toluene, *n*-heptane, $NEt_3$ were distilled from sodium under nitrogen. $CH_3CN$, $CH_2Cl_2$ and $CHCl_3$ were distilled from $CaH_2$ under nitrogen. MeOH was distilled from Mg and acetone from

**Table 1**
Yields of the Mitsunobu reaction.

| R= |  |  |
|---|---|---|
|  | –[a] | 94% [(*rac*)-**20b**] |
|  | 92% (**19c**) | 85% [(*rac*)-**20c**] |
|  | 86% (**19d**) | 95% [(*rac*)-**20d**] |
|  | 83% (**19e**) | 87% [(*rac*)-**20e**] |
|  | –[a] | 89% [(*rac*)-**20f**] |
|  | 79% (**19g**) | l96% [(*rac*)-**20g**] |

[a] Compound not synthesized, see also text.

$CaCl_2$ under nitrogen. Ethylene glycol and pyridine were stored over mol sieve (3 Å and 4 Å, respectively) after distillation. Other common solvents for recrystallization, and column chromatography were distilled before use. Purchased chemical reagents were used without further purification. TLC was carried out on precoated silica gel F254 aluminum sheets (Merck). Compounds were stained either with 5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 0.2% $Ce(SO_4)_2\cdot 4H_2O$ and 5% conc. $H_2SO_4$ or with ninhydrin (0.3% in *n*-butanol + 3% HOAc). If nothing else is stated, Merck silica gel (mesh 230–400) was used as stationary phase for flash chromatography (CC). Melting points: m.p. (uncorrected) were determined with an Electrothermal IA9100MK1 Melting Point apparatus. Elementary analysis: Elementaranalysator Vario EL (Elementar). The results of elemental analyses for C, H, N, S were within ±0.4% of the theoretical values. IR spectroscopy: FT-IR Spectrometer 1600 and Paragon 1000 (Perkin Elmer), oils were measured as film, solid samples as KBr-pellets. Mass spectrometry: EI and CI, Mass Spectrometer 5989 A with 59980 B particle beam LC/MS interface (Hewlett Packard); ESI, API 2000 (Applied Biosystems). NMR spectroscopy: NMR spectra were recorded on JNMR-GX (JEOL, 400 MHz and 500 MHz) with TMS as internal standard and integrated with the NMR-software Nuts (2D Version 5.097, Acorn NMR, 1995).

*5.1.2. General procedure for the preparation of N-alkylated sulpho namides by Mitsunobu reaction (GP1)*

To a stirred solution of the respective sulphonamide (1 equiv.), $Ph_3P$ (2 equiv.) and alcohol (2 equiv.) in benzene at 10 °C DIAD (2 equiv.) was added drop wise. The reaction mixture was stirred at 10 °C for 5 min and at rt for the time given followed by concentration in vacuo. The residue was purified by CC.

*5.1.3. General procedure for the cleavage 2,4-dinitrophenylsulfonyl group (GP2)*

To a stirred solution of the respective sulfonamide (1 equiv.) in $CH_2Cl_2$ mercaptoacetic acid (1.3 equiv.) and finally $NEt_3$ (2 equiv.) was added. After the time given the reaction mixture was poured into a sat. $NaHCO_3$ solution followed by extraction of the aqueous layer with $Et_2O$. The combined organic layers were dried ($MgSO_4$) and concentration in vacuo. The residue was purified by CC.

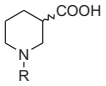
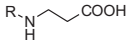
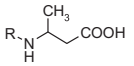
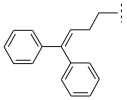
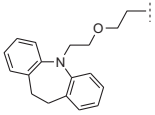
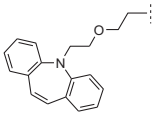
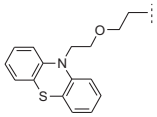
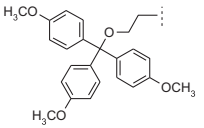
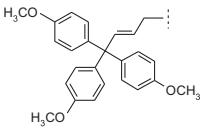
*5.1.4. General procedure for the saponification of the ester derivatives (GP3)*

The respective ester derivative (1 equiv.) in MeOH (0.4 M) was cooled to 0 °C followed by the drop wise addition of aqueous NaOH (2 M). The reaction mixture was stirred at rt for the time given and followed by concentrating in vacuo. Purification was accomplished as described.

*5.1.5. Methyl 3-(4,4-diphenylbut-3-en-1-ylamino)propanoate (**10b**)*

To a stirred suspension of methyl 3-aminopropanoate hydrochloride (209 mg, 1.50 mmol) $K_2CO_3$ (484 mg, 3.50 mmol) and KI (25 mg, 0.15 mmol) in $CH_3CN$ (1.5 ml) a solution of 4-bromo-1,1-diphenylbuten (431 mg, 1.50 mmol) in $CH_3CN$ (1.5 ml) was added.

**Table 2**
GABA uptake inhibition of β-amino acids and their derivatives at GAT1, BGT1, GAT2 and GAT3 compared to nipecotic acid and its derivatives.[I,II,III]

| R= |  | | | |  | | | |  | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $pIC_{50}$ ± S.E.M. | | | | $pIC_{50}$ ± S.E.M | | | | $pIC_{50}$ ± S.E.M | | | |
| | GAT1 | BGT1 | GAT2 | GAT3 | GAT1 | BGT1 | GAT2 | GAT3 | GAT1 | BGT1 | GAT2 | GAT3 |
| H | (*rac*)-**1**<br>4.88 ± 0.07[a] | 3.10 ± 0.09[a] | 4.64 ± 0.07[a] | 4.70 ± 0.07[a] | **5a**<br>2.55 ± 0.03[a] | 3.48 ± 0.11[a] | 4.66 ± 0.06[a] | 4.46 ± 0.13[a] | (*rac*)-**6a**<br>4.30 ± 0.10[a] | 3.09 ± 0.10[a] | 4.33 ± 0.03[a] | 4.08 ± 0.03[a] |
| H | (*R*)-**1**<br>5.07 ± 0.02[a] | 3.28 ± 0.05[a] | 4.71 ± 0.04[a] | 4.79 ± 0.05 | | | | | | | | |
| H | (*S*)-**1**<br>4.13 ± 0.05[a] | 3.12 ± 0.12[a] | 3.71 ± 0.04[a] | 3.51 ± 0.06[a] | | | | | | | | |
|  | SK&F-89976-A [(*rac*)-**2**]<br>6.16 ± 0.05[a] | 3.43 ± 0.07[a] | 3.71 ± 0.04[a] | 3.56 ± 0.06[a] | **5b**·HCl<br>3.94 ± 0.07[b] | | | 3.36 ± 0.04[c] | (*rac*)-**6b**<br>5.34 ± 0.06[a] | 100 μM: 86%[a] | 100 μM 82%[a] | 100 μM: 98%[a] |
|  | (*R*)-**22** [24]<br>4.40[d] | – | – | – | **5c**<br>4.69 ± 0.14[a] | 100 μM: 85%[a] | 100 μM: 55%[a] | 100 μM: 95%[a] | (*rac*)-**6c**<br>4.88 ± 0.05[a] | 1 mM: 69%[a] | 3.67 ± 0.07[a] | 3.47 ± 0.01[a] |
|  | (*R*)-**23** [24]<br>6.19[d] | – | – | – | **5d**<br>100 μM: 56%[a] | 100 μM: 85%[a] | 100 μM: 87%[a] | 100 μM: 78%[a] | (*rac*)-**6d**<br>4.76 ± 0.10[a] | 100 μM: 82%[a] | 100 μM: 84%[a] | 100 μM: 90%[a] |
|  | (*R*)-**24** [24]<br>6.51[d] | – | – | – | **5e**<br>4.45 ± 0.11[a] | 100 μM: 88%[a] | 100 μM: 50%[a] | 100 μM: 91%[a] | (*rac*)-**6e**<br>5.06 ± 0.11[a] | 100 μM: 74%[a] | 4.39 ± 0.13[a] | 100 μM: 68%[a] |
|  | (*S*)-SNAP-5114 [(*S*)-**4**]<br>4.07 ± 0.09[a] | 4.51 ± 0.15[a] | 5.29 ± 0.04[a] | 5.71 ± 0.20[a] | **5f**<br>100 μM: 57%[a] | 100 μM: 55%[a] | 100 μM: 40%[a] | 4.37 ± 0.06[a] | (*rac*)-**6f**<br>100 μM: 114%[a] | 100 μM: 73%[a] | 100 μM: 48%[a] | 4.47 ± 0.11[a] |
|  | DDPM-1457 (*S*)-**25** [25]<br>4.40 ± 0.05[a] | 4.42 ± 0.11[a] | 5.47 ± 0.02[a] | 5.87 ± 0.08[a] | **5g**<br>100 μM: 77%[a] | 100 μM: 47%[a] | 100 μM: 94%[a] | 100 μM: 59%[a] | (*rac*)-**6g**<br>100 μM: 52%[a] | 100 μM: 47%[a] | 4.20 ± 0.05[a] | 4.22 ± .01[a] |

[I] The compounds' inhibitory potencies are given as $pIC_{50}$ values (mean ± S.E.M., $N = 3$).
[II] The abbreviations a,b and c specify the employed biological material: [a]HEK293 stably expressing mGAT1-4 (i.e. GAT1, BGT1, GAT2 and GAT3, respectively, according to HUGO), [b]$pfcP_{2B}$ membrane preparation from porcine frontal cortex predominantly addressing the GAT1-subtype, [c]$pbsP_{2C}$ membrane preparation from porcine brainstem predominantly addressing the GAT3-subtype. [d]Refers to values from literature, for which the used material can be considered as to consist predominantly of GAT1. For the sake of clarity, the reported $IC_{50}$ values were converted into $pIC_{50}$ values.
[III] Percentages represent specific binding remaining in presence of inhibitor in the stated concentrations.

The reaction mixture was heated to 45 °C for 24 h. The solvent was removed in vacuo and the resulting residue was resolved in $H_2O$ which was subsequently extracted with $Et_2O$ (3×). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification was accomplished by CC ($Et_2O$/*n*-pentane, 80:20 + 2% $EtMe_2N$). Yield: 241 mg (52%), colorless oil. $^1H$ NMR (400 MHz; $CDCl_3$): $\delta = 2.31$ (q, $J = 7.3$ Hz, 2H, =CHC*H*$_2$CH$_2$), 2.49 (t, $J = 6.6$ Hz, 2H, $CH_2COO$), 2.73 (t, $J = 7.3$ Hz, 2H, 2H, =CHCH$_2$C*H*$_2$), 2.85 (t, $J = 6.6$ Hz, 2H, NCH$_2$C*H*$_2$COO), 3.67 (s, 3H, $OCH_3$), 6.07 (t, $J = 7.3$ Hz, 1H, C=CH), 7.15–7.40 (m, 10H, $H_{arom}$). IR (film): $\tilde{\nu} = 3055$ cm$^{-1}$, 3023, 2950, 2836, 1737, 1598. MS (CI, $CH_5^+$); *m*/*z* (%): 310 (100) $[M + H]^+$. Anal. Calcd. for $C_{20}H_{23}NO_2$; C, 77.64; H, 7.49; N, 4.53 Found: C, 77.61; H, 7.56; N, 4.49.

### 5.1.6. Methyl 3-({2-[tris(4-methoxyphenyl)methoxy]ethyl}amino) butanoate (**10f**)

To a stirred suspension of methyl 3-aminopropionate hydrochloride (279 mg, 2.00 mmol) $K_2CO_3$ (622 mg, 4.50 mmol) and KI (33 mg, 0.20 mmol) in $CH_3CN$ (1.5 ml) a solution of 2-[tris(4-methoxyphenyl)methoxy]ethyl bromide (914 mg, 2.00 mmol) in $CH_3CN$ (1.5 ml) was added. The reaction mixture was heated to 45 °C for 24 h. The solvent was removed in vacuo and the residue was resolved in $H_2O$ which was subsequently extracted with $Et_2O$ (3×). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification was accomplished by CC ($Et_2O$/*n*-pentane, 40:60 + 2% $EtMe_2N$). Yield: 459 mg (48%), colorless oil. $^1H$ NMR (400 MHz; $CDCl_3$): $\delta = 2.53$ (t, $J = 6.6$ Hz, 2H, $CH_2COO$), 2.80 (t, $J = 5.4$ Hz, 2H, OCH$_2$C*H*$_2$N), 2.88 (t, $J = 6.6$ Hz, 2H, 2H, NC*H*$_2$CH$_2$COO), 3.21 (t, $J = 5.4$ Hz, 2H, OC*H*$_2$CH$_2$N), 3.69 (s, 3H, $OCH_3$), 3.78 (s, 9H, $OCH_3$), 6.78–6.84 (m, 6H, $H_{arom}$), 7.28–7.34 (m, 6H, $H_{arom}$). IR (film): $\tilde{\nu} = 3036$ cm$^{-1}$, 2999, 2951, 2836, 1737, 1608. MS (CI, $CH_5^+$); *m*/*z* (%): 355 (23) $[M + H]^+$, 334 (100). Anal. Calcd. for $C_{28}H_{33}NO_6$; C, 70.13; H, 6.94; N, 2.92 Found: C, 70.10; H, 6.94; N, 2.95.

### 5.1.7. 2-[Tris(4-methoxyphenyl)methoxy]ethanol (**8f**) and 2-[(4-chlorphenyl)bis(4-methoxyphenyl)methoxy]ethanol (**12**)

To tris(4-methoxyphenyl)methanol (7.50 g, 21.4 mmol) in toluene (15 ml) at 0 °C thionyl chloride (2.95 ml, 40.7 mmol) was added, followed by refluxing for 4.5 h. After cooling to rt *n*-heptane (40 ml) was added and the resulting precipitate was filtered off under $N_2$ and washed with *n*-heptane (30 ml). The residue was twice recrystallized from *n*-heptane/toluene to result in 6.0 g of yellow crystals. 526 mg thereof were added to a mixture of ethylene glycol (194 mg, 3.13 mmol) and pyridine (2.2 ml). After stirring at rt for 25 h phosphate buffer (pH 7, 50 ml) was added, followed by extraction with $Et_2O$. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification was accomplished by CC (EtOAc/*n*-pentane = 35:65 + 1% $EtMe_2N$). Yield: 235 mg (32%) of **8f** and 37 mg (5%) of **12**; **8f**: colorless oil. $^1H$ NMR (500 MHz, $C_6D_6$): $\delta = 1.60$ (t, $J = 6.1$ Hz, 1H, CH$_2$O*H*), 3.34–3.38 (m, 2H, C*H*$_2$CH$_2$OH), 3.42 (s, 9H, 3× $CH_3O$), 3.67–3.72 (m, 2H, CH$_2$C*H*$_2$OH), 6.87–6.92 (m, 6H, 6× $CH_3$OCC*H*CH), 7.57–7.63 (m, 6H, 6× $CH_3$OCCHC*H*). IR (film): $\tilde{\nu} = 3428$ cm$^{-1}$, 3001, 2933, 2836, 1607, 1582, 1505, 1463, 1302, 1249, 1175, 1034. MS (EI, 70 eV): *m*/*z* (%): 394 (7) $[M]^+$, 333 (100). Anal. Calcd. for $C_{24}H_{26}O_5$; C, 73.08; H, 6.64; Found C, 73.08; H, 6.78. **12**: colorless oil. $^1H$ NMR (500 MHz, $CD_2Cl_2$): $\delta = 1.84$ (t, $J = 6.2$ Hz, 1H, CH$_2$O*H*), 3.18 (t, $J = 4.8$ Hz, 2H, C*H*$_2$CH$_2$OH), 3.67–3.74 (m, 2H, CH$_2$C*H*$_2$OH), 3.78 (s, 6H, 2× $OCH_3$), 6.80–6.88 (m, 4H, 4× $CH_3$OCC*H*CH), 7.24–7.34 (m, 6H, 4× $CH_3$OCCHC*H*, 2× ClCC*H*CH), 7.38–7.44 (m, 2H, 2× ClCCHC*H*). IR (film): $\tilde{\nu} = 3426$ cm$^{-1}$, 3000, 2932, 2836, 1608, 1509, 1488, 1301, 1251. MS (EI, 70 eV): *m*/*z* (%): 398 (7) $[M]^+$, 337 (100). Anal. Calcd. for $C_{23}H_{23}O_4Cl$; C, 69.26; H, 5.81; Found: C, 68.99; H, 5.61.

### 5.1.8. 2,2,2-Tris(4-methoxyphenyl)acetaldehyde (**14**)

2,2,2-Tris(4-methoxyphenyl)ethanol (5.47 g, 15.0 mmol) was added to IBX (8.16 g, 29.1 mmol) in DMSO (26 ml) at rt. The reaction mixture was stirred for 20 h. Sat. NaCl solution (150 ml) was added and the aqueous layer was extracted with $Et_2O$. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification was accomplished by CC ($CH_2Cl_2$/*n*-pentane, 60:40). Yield: 5.24 g (96%); colorless solid, m.p.: 129 °C. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 3.81$ (s, 9H, 3× $OCH_3$), 6.84–6.90 (m, 6H, 6× OCC*H*CH), 6.94–7.00 (m, 6H, 6× OCCHC*H*), 10.19–10.21 (m, 1H, C*H*O). IR (KBr): $\tilde{\nu} = 2932$ cm$^{-1}$, 2837, 1724, 1607, 1578, 1509, 1461, 1290, 1252, 1181. MS (CI, $CH_5^+$); *m*/*z* (%): 363 $[M + H]^+$ (39), 255 (100). Anal. Calcd. for $C_{23}H_{22}O_4$; C, 76.22; H, 6.12; Found: C, 76.06; H, 6.24.

### 5.1.9. (E)-Ethyl 4,4,4-tris(4-methoxyphenyl)but-2-enoate (**15**)

Triethyl phosphonoacetate (3.8 ml, 18.4 mmol) was added to NaH (538 mg, 21.3 mmol) in benzene (14 ml) at rt. The reaction mixture was stirred for 30 min at rt, and then 1 h at 60 °C. 2,2,2-Tris(4-methoxyphenyl)acetaldehyde (5.09 g, 14.0 mmol) in benzene (39 ml) was added at rt. The reaction mixture was stirred for 13 h. $H_2O$ (150 ml) was added and the aqueous layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification was accomplished by CC ($CH_2Cl_2$/*n*-pentane, 60:40) and recrystallized from EtOH Yield: 5.82 g (96%); colorless solid, m.p.: 132–133 °C. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta = 1.28$ (t, $J = 7.2$ Hz, 3H, CH$_2$C*H*$_3$), 3.80 (s, 9H, 3× $OCH_3$), 4.20 (q, $J = 7.2$ Hz, 2H, C*H*$_2$CH$_3$), 5.64 (d, $J = 15.8$ Hz, 1H, COC*H*CH), 6.78–6.84 (m, 6H, 6× OCC*H*CH), 6.93–7.00 (m, 6H, 6× OCCHC*H*), 7.89 (d, $J = 15.8$ Hz, 1H, COCHC*H*). IR (KBr): $\tilde{\nu} = 3432$ cm$^{-1}$, 2959, 2834, 1709, 1645, 1606, 1508, 1292, 1250. MS (CI, $CH_5^+$); *m*/*z* (%): 433 $[M + H]^+$ (30), 325 (100). Anal. Calcd. for $C_{27}H_{28}O_5$: C, 74.98; H, 6.53; Found: C, 74.78; H, 6.50.

### 5.1.10. (E)-4,4,4-Tris(4-methoxyphenyl)but-2-en-1-ol (**8g**)

A solution of $LiAlH_4$ (11 ml, 1.0 M in THF, 11 mmol) was added to a solution of **15** (4.33 g, 10.0 mmol) in THF (12 ml). The reaction mixture was stirred 46 h at 40 °C. Potassium sodium tartrate solution (1 M, 165 ml) was added and the aqueous layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification was accomplished by CC (EtOAc/*n*-pentane, 30:70) and recrystallized from EtOAc and *n*-pentane. Yield: 2.76 g (71%); colorless solid, m.p.: 137–138 °C. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 1.32$ (t, $J = 5.9$ Hz, 1H, CH$_2$O*H*), 3.80 (s, 9H, 3× $OCH_3$), 4.26 (td, $J = 1.5/5.9$ Hz, 2H, C*H*$_2$OH), 5.45 (dt, $J = 5.7/15.6$ Hz, 1H, CH$_2$CHC*H*), 6.67 (dt, $J = 1.5/15.6$ Hz, 1H, CH$_2$C*H*CH), 6.77–6.83 (m, 6H, 6× $CH_3$OCC*H*CH), 6.96–7.01 (m, 6H, 6× $CH_3$OCCHC*H*). IR (KBr): $\tilde{\nu} = 3517$ cm$^{-1}$, 3008, 2933, 2835, 1606, 1580, 1507, 1462, 1296, 1247. MS (CI, $CH_5^+$); *m*/*z* (%): 390 $[M + H]^+$ (9), 373 (100). Anal. Calcd. for $C_{25}H_{26}O_4$: C, 76.90; H, 6.71; Found: C, 76.64; H, 6.79.

### 5.1.11. Methyl 3-(2,4-dinitrophenylsulfonylamino)propanoate (**17**)

Pyridine (830 μl, 10.3 mmol) was added to 2,4-dinitrophenyl sulfonylchloride (313 mg, 1.15 mmol) and **9** (120 mg, 0.976 mmol) in $CH_3CN$ (6 ml) at 0 °C. The reaction mixture was stirred for 2 h, than warmed to rt and stirred for additional 62.5 h. Phosphate buffer (pH 3, 40 ml) was added and the aqueous layer was extracted with $Et_2O$. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification was accomplished by CC ($CH_2Cl_2$) and recrystallized from $CH_2Cl_2$ and *n*-pentane. Yield: 259 mg (91%); colorless solid, m.p.: 100 °C. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta = 2.63$ (t, $J = 6.0$ Hz, 2H, $COCH_2$), 3.42 (q, $J = 6.0$ Hz, 2H, $NHCH_2$), 3.70 (s, 3H, $OCH_3$), 6.10 (t, $J = 6.0$ Hz, 1H, NH), 8.37 (d, $J = 8.6$ Hz, 1H, $SO_2CCH$), 8.56 (dd, $J = 8.6/2.2$ Hz, 1H, $SO_2CCHCH$),

8.69 (d, $J$ = 2.2 Hz, 1H, C($NO_2$)CHC$NO_2$). IR (KBr): $\tilde{\nu}$ = 3301 $cm^{-1}$, 3103, 1732, 1605, 1558, 1538, 1367, 1349, 1165. MS (CI, $CH_5^+$); $m/z$ (%): 334 (36) $[M + H]^+$, 302 (100). Anal. Calcd. for $C_{10}H_{11}N_3O_8S$; C, 36.04; H, 3.33; N, 12.61; S, 9.62; Found: C, 35.79; H, 3.25; N, 12.61; S, 9.33.

### 5.1.12. Methyl (rac)-3-(2,4-dinitrophenylsulfonylamino)butanoate [(rac)-**18**]

Pyridine (13.8 ml, 170.62 mmol) was added to 2,4-dinitrophenyl sulfonylchloride (5.19 g, 19.1 mmol) and (*rac*)-**16** (2.19 g, 14.3 mmol) in $CH_3CN$ (100 ml) at 0 °C. The reaction mixture was stirred for 2 h, then warmed to rt and stirred for additional 65.5 h. Phosphate buffer (pH 2, 600 ml) was added and the aqueous layer was extracted with $Et_2O$. The combined org. layers were dried ($MgSO_4$) and concentrated in vacuo. Purification was accomplished by CC ($CH_2Cl_2$) and recrystallized from $CH_2Cl_2$ and *n*-heptane. Yield: 2.65 g (53%); colorless solid, m.p.: 65–66 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.26 (t, $J$ = 6.8 Hz, 3H, CHC$H_3$), 2.56 (dd, $J$ = 5.5/0.8 Hz, 2H, $COCH_2$), 3.63 (s, 3H, $OCH_3$), 3.99 (dqt, $J$ = 8.2/6.8/5.5 Hz, 1H, $CH_2CH$), 6.00 (d, $J$ = 8.2 Hz, 1H, NH), 8.40 (d, $J$ = 8.7 Hz, 1H, $SO_2CCH$), 8.56 (dd, $J$ = 8.7/2.2 Hz, 1H, $SO_2CCHCH$), 8.69 (d, $J$ = 2.2 Hz, 1H, C($NO_2$)CHC$NO_2$). IR (KBr): $\tilde{\nu}$ = 3333 $cm^{-1}$, 3107, 1725, 1605, 1535, 1350, 1169. MS (CI, $CH_5^+$): $m/z$ (%): 348 (4) $[M + H]^+$, 118 (100). Anal. Calcd. for $C_{11}H_{13}N_3O_8S$; C, 38.04; H, 3.77; N, 12.10; S 9.23; Found: C, 37.89; H, 3.79; N, 12.15; S, 9.47.

### 5.1.13. Methyl (rac)-3-[(2,4-dinitrophenylsulfonyl)(4,4-diphenylbut-3-en-1-yl)amino]butanoate [(rac)-**20b**]

According to GP1 starting from (*rac*)-**18** (425 mg, 1.22 mmol), $Ph_3P$ (645 mg, 2.46 mmol), **8b** (549 mg, 2.45 mmol) and DIAD (500 µl, 2.45 mmol) in benzene (3.7 ml); reaction time: 45 min. Purification was accomplished by CC (first $CH_2Cl_2$ then $Et_2O$/*n*-pentane, 30:70). Yield: 635 mg (94%); yellow solid, m.p.: 46–49 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.13 (d, $J$ = 6.8 Hz, 3H, NCHC$H_3$), 2.28 (dd, $J$ = 15.7/7.9 Hz, 1H, $COCH_2$), 2.37–2.44 (m, 2H, $NCH_2CH_2CH$), 2.48 (dd, $J$ = 15.7/6.6 Hz, 1H, $COCH_2$), 3.28–3.36 (m, 1H, $NCH_2$), 3.38–3.47 (m, 1H, $NCH_2$), 3.58 (s, 3H, $CH_3O$), 4.22–4.30 (m, 1H, $COCH_2CH$), 6.05 (t, $J$ = 7.6 Hz, $(C_6H_5)_2CCH$), 7.15–7.18 (m, 2H, $H_{arom}$), 7.20–7.23 (m, 2H, $H_{arom}$), 7.23–7.29 (m, 3H, $H_{arom}$), 7.32–7.36 (m, 1H, $H_{arom}$), 7.37–7.42 (m, 2H, $H_{arom}$), 8.19 (d, $J$ = 8.7 Hz, 1H, $SO_2CCH$), 8.38 (dd, $J$ = 8.7/2.2 Hz, 1H, $SO_2CCHCH$), 8.41 (d, $J$ = 2.2 Hz, 1H, C($NO_2$)CHC$NO_2$). IR (KBr): $\tilde{\nu}$ = 3101 $cm^{-1}$, 2952, 1736, 1604, 1555, 1538, 1495, 1442, 1351, 1302, 1205, 1166. MS (ESI+) $m/z$: 592 $[M + K]^+$, 576 $[M + Na]^+$. Anal. Calcd. for $C_{27}H_{27}N_3O_8S$; C, 58.58; H, 4.92; N, 7.59; S, 5.79; Found: C, 58.69; H, 4.87; N, 7.59; S, 6.08.

### 5.1.14. Methyl 3-({2-[2-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)ethoxy]ethyl}(2,4-dinitrophenylsulfonyl)amino)propanoate (**19c**)

According to GP1 starting from **17** (345 mg, 1.04 mmol), $Ph_3P$ (545 mg, 2.08 mmol), **8c** (586 mg, 2.07 mmol) and DIAD (430 µl, 2.11 mmol) in benzene (3.1 ml), reaction time: 20 min. Purification was accomplished by twice CC ($CH_2Cl_2$ then EtOAc/*n*-pentane, 25:75). Yield: 570 mg (92%), brown oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 2.65 (t, $J$ = 7.2 Hz, 2H, $COCH_2$), 3.11 (s, 4H, $CCH_2CH_2C$), 3.43–3.50 (m, 4H, $CH_2OCH_2CH_2NSO_2$), 3.53 (t, $J$ = 5.1 Hz, 2H, $OCH_2CH_2NSO_2$), 3.60–3.66 (m, 2H, $COCH_2CH_2N$), 3.63 (s, 3H, $CH_3O$), 3.82 (t, $J$ = 5.9 Hz, 2H, $(C_{arom})_2NCH_2CH_2O$), 6.92 (td, $J$ = 7.4/1.1 Hz, 2H, 2× NCCCHCH), 7.01 (dd, $J$ = 8.1/1.1 Hz, 2H, 2× NCCHCH), 7.05–7.15 (m, 4H, 2× NCCHCH, 2× NCCCHCH), 8.19–8.22 (m, 2H, $SO_2CCHCH$), 8.36–8.38 (m, 1H, C($NO_2$)CHC$NO_2$). IR (film): $\tilde{\nu}$ = 3443 $cm^{-1}$, 3101, 2920, 1735, 1602, 1553, 1537, 1486, 1351, 1163. MS (CI, $CH_5^+$); $m/z$ (%): 599 (14) $[M + H]^+$, 123 (100). Anal. Calcd. for $C_{28}H_{30}N_4O_9S$; C, 56.18; H, 5.05; N, 9.36; S, 5.36; Found: C, 56.20; H, 5.38; N, 9.06; S, 5.58.

### 5.1.15. Methyl (rac)-3-({2-[2-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)ethoxy]ethyl}(2,4-dinitrophenylsulfonyl)amino)butanoate [(rac)-**20c**]

According to GP1 starting from (*rac*)-**18** (339 mg, 0.977 mmol), $Ph_3P$ (511 mg, 1.95 mmol), **8d** (551 mg, 1.94 mmol) and DIAD (400 µl, 1.96 mmol), in benzene (2.9 ml); reaction time: 45 min. Purification by twice CC ($CH_2Cl_2$ then EtOAc/*n*-pentane, 20:80) Yield: 506 mg (85%); red brown solid, m.p.: 44–49 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.23 (d, $J$ = 6.8 Hz, 3H, NCHC$H_3$), 2.44 (dd, $J$ = 15.8/7.7 Hz, 1H, $COCH_2$), 2.68 (dd, $J$ = 15.8/6.5 Hz, 1H, $COCH_2$), 3.14 (s, 4H, $CCH_2CH_2C$), 3.36–3.53 (m, 4H, $OCH_2CH_2NSO_2$), 3.50 (t, $J$ = 6.1 Hz, 2H, $(C_{Ar})_2NCH_2CH_2O$), 3.58 (s, 3H, $CH_3O$), 3.88–3.95 (m, 2H, $(C_{arom})_2NCH_2CH_2O$), 4.25–4.34 (m, 1H, $COCH_2CHCH_3$), 6.93 (td, $J$ = 7.4/1.3 Hz, 2H, 2× NCCCHCH), 7.07 (dd, $J$ = 8.1/1.1 Hz, 2H, 2× NCCHCH), 7.09 (dd, $J$ = 7.4/1.6 Hz, 2H, NCCCHCH), 7.11–7.15 (m, 2H, NCCHCH), 8.26 (d, $J$ = 8.7 Hz, 1H, $SO_2CCHCH$), 8.33 (dd, $J$ = 8.7/2.2 Hz, 1H, $SO_2CCHCH$), 8.41 (d, $J$ = 2.2 Hz, 1H, C($NO_2$)CHC$NO_2$). IR (KBr): $\tilde{\nu}$ = 3441 $cm^{-1}$, 3099, 2948, 1736, 1553, 1537, 1487, 1350, 1207, 1166, 1108. MS (ESI+) $m/z$: 613 $[M + H]^+$. Anal. Calcd. for $C_{29}H_{32}N_4O_9S$; C, 56.85; H, 5.27; N, 9.15; S, 5.23; Found: C, 56.63; H, 5.25; N, 9.08; S, 5.72.

### 5.1.16. Methyl 3-({2-[2-(5H-dibenzo[b,f]azepin-5-yl)ethoxy]ethyl}(2,4-dinitrophenylsulfonyl)amino)propanoate (**19d**)

According to GP1 starting from **17** (261 mg, 0.784 mmol), $Ph_3P$ (409 mg, 1.56 mmol), **8d** (436 mg, 1.55 mmol) and DIAD (315 µl, 1.55 mmol) in benzene (2.4 ml); reaction time: 45 min. Purification by CC ($CH_2Cl_2$ then $Et_2O$/*n*-pentane, 60:40). Yield: 402 mg (86%); orange solid, m.p.: 44–56 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 2.66 (t, $J$ = 7.3 Hz, 2H, $COCH_2$), 3.48–3.54 (m, 6H, $CH_2OCH_2CH_2NSO_2$), 3.63 (s, 3H, $CH_3O$), 3.66 (t, $J$ = 7.3 Hz, 2H, $COCH_2CH_2N$), 3.78 (t, $J$ = 5.8 Hz, 2H, $(C_{arom})_2NCH_2CH_2O$), 6.70 (s, 2H, CCHCHC), 6.91 (dd, $J$ = 8.1/0.9 Hz, 2H, 2× NCCHCH), 6.99–7.03 (m, 2H, 2× NCCCHCH), 7.06 (dd, $J$ = 7.6/1.8 Hz, 2H, 2× NCCCHCH), 7.27 (ddd, $J$ = 8.1/7.2/1.8 Hz, 2H, NCCHCH), 8.11 (dd, $J$ = 8.7/2.2 Hz, 1H, $SO_2CCHCH$), 8.21 (dd, $J$ = 8.7/0.3 Hz, 1H, $SO_2CCHCH$), 8.37 (dd, $J$ = 2.2/0.3 Hz, 1H, C($NO_2$)CHC$NO_2$). IR (KBr): $\tilde{\nu}$ = 3097 $cm^{-1}$, 2948, 2868, 1735, 1604, 1553, 1537, 1484, 1458, 1437, 1351, 1202, 1163, 1130, 1116. MS (ESI+) $m/z$: 597 $[M + H]^+$. Anal. Calcd. for $C_{28}H_{28}N_4O_9S$; C, 56.37; H, 4.73; N, 9.39; S, 5.38; Found: C, 56.36; H, 4.78; N, 9.14; S, 5.65.

### 5.1.17. Methyl (rac)-3-({2-[2-(5H-dibenzo[b,f]azepin-5-yl)ethoxy]ethyl}(2,4-dinitrophenylsulfonyl)amino)butanoate [(rac)-**20d**]

According to GP1 starting from (*rac*)-**18** (412 mg, 1.19 mmol), $Ph_3P$ (626 mg, 2.39 mmol), **8d** (668 mg, 2.37 mmol) and DIAD (485 µl, 2.38 mmol) in benzene (3.6 ml); reaction time 45 min. Purification by CC ($CH_2Cl_2$).Yield: 686 mg (95%); orange solid, m.p.: 45–52 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.24 (d, $J$ = 6.8 Hz, 3H, $COCH_2CHCH_3$), 2.46 (dd, $J$ = 15.9/7.9 Hz, 1H, $COCH_2CH$), 2.72 (dd, $J$ = 15.9/6.4 Hz, 1H, $COCH_2CH$), 3.42–3.46 (m, 2H, $OCH_2CH_2NSO_2$), 3.52–3.57 (m, 2H, $OCH_2CH_2NSO_2$), 3.55 (t, $J$ = 6.1 Hz, 2H, $(C_{arom})_2NCH_2CH_2O$), 3.58 (s, 3H, $CH_3O$), 3.88 (t, $J$ = 6.1 Hz, 2H, $(C_{arom})_2NCH_2CH_2O$), 4.25–4.33 (m, 1H, $COCH_2CH$), 6.70 (s, 2H, CCHCHC), 6.98–7.03 (m, 4H, 2× NCCCHCH, 2× NCCHCH), 7.06 (dd, $J$ = 7.9/1.7 Hz, 2H, NCCCHCH), 7.24–7.29 (m, 2H, NCCHCH), 8.28 (d, $J$ = 8.7 Hz, 1H, $SO_2CCHCH$), 8.31 (dd, $J$ = 8.7/2.2 Hz, 1H, $SO_2CCHCH$), 8.41 (d, $J$ = 2.2 Hz, 1H, C($NO_2$)CHC$NO_2$). IR (KBr): $\tilde{\nu}$ = 3099 $cm^{-1}$, 2951, 2869, 1735, 1604, 1553, 1538, 1484, 1458, 1436, 1350, 1207, 1165, 1130, 1116. MS (ESI+) $m/z$: 611 $[M + H]^+$. Anal. Calcd. for $C_{29}H_{30}N_4O_9S$; C, 57.04; H, 4.95; N, 9.18; S, 5.25; Found: C, 56.76; H, 4.92; N, 9.19; S, 5.58.

### 5.1.18. Methyl 3-[(2,4-dinitrophenylsulfonyl){2-[2-(10H-phenothiazin-10-yl)-ethoxy]ethyl}amino]propanoate (**19e**)

According to GP1 starting from **17** (258 mg, 0.775 mmol), $Ph_3P$ (408 mg, 1.56 mmol), **8e** (442 mg, 1.54 mmol) and DIAD (315 µl,

1.55 mmol) in benzene (2.3 ml), reaction time: 20 min. Purification by CC ($Et_2O$/*n*-pentane 60:40). Yield: 386 mg (83%) red brown, solid melting range 43–50 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 2.61 (t, $J$ = 7.1 Hz, 2H, $COCH_2$), 3.53–3.57 (m, 2H, $OCH_2CH_2NSO_2$), 3.57–3.60 (m, 2H, $OCH_2CH_2NSO_2$), 3.62 (s, 3H, $CH_3O$), 3.64 (t, $J$ = 7.1 Hz, 2H, $COCH_2CH_2$), 3.74 (t, $J$ = 5.7 Hz, 2H, $(C_{arom})_2NCH_2CH_2O$), 4.02 (t, $J$ = 5.7 Hz, 2H, $(C_{arom})_2NCH_2CH_2O$), 6.84 (d, $J$ = 8.1 Hz, 2H, 2× NCCHCH), 6.94 (t, $J$ = 7.5 Hz, 2H, 2× NCCCHCH), 7.14 (dd, $J$ = 7.7/1.4 Hz, 2H, 2× NCCCHCH), 7.12–7.19 (m, 2H, 2× NCCHCH), 8.23–8.25 (m, 2H, $SO_2CCHCH$), 8.40–8.42 (m, 1H, $C(NO_2)CHCNO_2$). IR (KBr): $\tilde{\nu}$ = 3448 cm$^{-1}$, 3097, 2871, 1735, 1594, 1552, 1537, 1463, 1350, 1162. MS (ESI+) *m*/*z*: 603 $[M + H]^+$. Anal. Calcd. for $C_{26}H_{26}N_4O_9S_2$: C, 51.82; H, 4.35, N, 9.30; Found: C, 51.63; H, 4.23; N 9.05.

### 5.1.19. Methyl (rac)-3-[(2,4-dinitrophenylsulfonyl){2-[2-(10H-phenothiazin-10-yl)ethoxy]ethyl}amino]butanoate [(rac)-**20e**]

According to GP1 starting from (*rac*)-**18** (389 mg, 1.12 mmol), $Ph_3P$ (587 mg, 2.24 mmol), **8e** (642 mg, 2.23 mmol) and DIAD (455 µl, 2.23 mmol) in benzene (3.4 ml); reaction time: 45 min. Purification by CC ($Et_2O$/*n*-pentane, 60:40). Yield: 386 mg (87%); brown solid, m.p.: 43–49 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.21 (d, $J$ = 6.8 Hz, 3H, $COCH_2CHCH_3$), 2.43 (dd, $J$ = 15.8/7.7 Hz, 1H, $COCH_2CH$), 2.70 (dd, $J$ = 15.8/6.6 Hz, 1H, $COCH_2CH$), 3.45–3.51 (m, 2H, $OCH_2CH_2NSO_2$), 3.58 (s, 3H, $CH_3O$), 3.59–3.64 (m, 2H, $OCH_2CH_2NSO_2$), 3.76–3.81 (m, 2H, $(C_{Ar})_2NCH_2CH_2O$), 4.08 (t, $J$ = 5.8 Hz, 2H, $(C_{Ar})_2NCH_2CH_2O$), 4.23–4.31 (m, 1H, $COCH_2CHCH_3$), 6.87 (dd, $J$ = 8.1/0.9 Hz, 2H, 2× NCCHCH), 6.93 (td, $J$ = 7.5/1.1 Hz, 2H, 2× NCCCHCH), 7.13 (dd, $J$ = 7.6/1.5 Hz, 2H, 2× NCCCHCH), 7.15 (ddd, $J$ = 8.1/7.5/1.5 Hz, 2H, 2× NCCHCH), 8.28 (d, $J$ = 8.7 Hz, 1H, $SO_2CCHCH$), 8.37 (dd, $J$ = 8.7/2.2 Hz, 1H, $SO_2CCHCH$), 8.42 (d, $J$ = 2.2 Hz, 1H, $C(NO_2)CHCNO_2$). IR (KBr): $\tilde{\nu}$ = 3097 cm$^{-1}$, 2950, 2872, 1734, 1552, 1537, 1463, 1350, 1255, 1208, 1165, 1130, 1105. MS (ESI+) *m*/*z*: 617 $[M + H]^+$. Anal. Calcd. for $C_{27}H_{28}N_4O_9S_2$; C, 52.59; H, 4.58; N, 9.09; S, 10.40; Found: C, 52.47; H, 4.55; N, 8.89; S, 10.72.

### 5.1.20. Methyl (rac)-3-[(2,4-dinitrophenylsulfonyl){2-[tris(4-methoxyphenyl)methoxy]ethyl}amino]butanoate [(rac)-**20f**]

According to GP1 starting from (*rac*)-**18** (108 mg, 0.311 mmol), $Ph_3P$ (159 mg, 0.606 mmol), **8f** (238 mg, 0.604 mmol) and DIAD (125 µl, 0.61 mmol) in benzene (0.9 ml); reaction time: 45 min. Purification by CC ($Et_2O$/*n*-pentane 40:60 + 5% $EtMe_2N$); Yield: 200 mg (89%); yellow solid, m.p.: 67–72 °C. $^1$H NMR (500 MHz, $CD_2Cl_2$): $\delta$ = 1.14 (d, $J$ = 6.8 Hz, 3H, $COCH_2CHCH_3$), 2.36 (dd, $J$ = 15.7/8.2 Hz, 1H, $COCH_2CH$), 2.54 (dd, $J$ = 15.7/6.1 Hz, 1H, $COCH_2CH$), 3.27 (t, $J$ = 6.4 Hz, 2H, $OCH_2CH_2NSO_2$), 3.42–3.51 (m, 2H, $OCH_2CH_2NSO_2$), 3.55 (s, 3H, $CH_3O$), 3.78 (s, 9H, 3× $CH_3OC_6H_4$), 4.22–4.30 (m, 1H, $COCH_2CH$), 6.80–6.85 (m, 6H, 6× $CH_3OCCHCH$), 7.27–7.31 (m, 6H, 6× $CH_3OCCHCH$), 8.19 (d, $J$ = 8.7 Hz, 1H, $SO_2CCHCH$), 8.35 (dd, $J$ = 8.7/2.2 Hz, 1H, $SO_2CCHCH$), 8.43 (d, $J$ = 2.2 Hz, 1H, $C(NO_2)CHCNO_2$). IR (KBr): $\tilde{\nu}$ = 3100 cm$^{-1}$, 2953, 2837, 1736, 1607, 1555, 1540, 1508, 1463, 1440, 1351, 1302, 1250. MS (ESI+) *m*/*z*: 762 $[M + K]^+$, 746 $[M + Na]^+$. Anal. Calcd. for $C_{35}H_{37}N_3O_{12}S$; C, 58.08; H, 5.15; N, 5.81; S, 4.43; Found: C, 57.99; H, 5.22; N, 5.56; S, 4.87.

### 5.1.21. Methyl (rac)-3-(4,4-diphenylbut-3-en-1-ylamino)butanoate [(rac)-**21b**]

According to GP2 starting from (*rac*)-**20b** (549 mg, 0.993 mmol), mercaptoacetic acid (92 µl, 1.30 mmol) and $NEt_3$ (280 µl, 2.01 mmol) in $CH_2Cl_2$ (9.9 ml); reaction time: 5.5 h; work-up: sat. $NaHCO_3$ solution (100 ml) and $Et_2O$. Purification by CC ($Et_2O$/*n*-pentane 80:20 + 2% $EtMe_2N$). Yield: 288 mg (89%), colorless oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.09 (d, $J$ = 6.4 Hz, 3H, $NHCHCH_3$), 2.30 (q, $J$ = 7.3 Hz, 2H, $NCH_2CH_2CH$), 2.32 (dd, $J$ = 15.2/6.1 Hz, 1H, $COCH_2$), 2.44 (dd, $J$ = 15.2/6.7 Hz, 1H, $COCH_2$), 2.64–2.78 (m, 2H, $NCH_2CH_2CH$), 3.08 (sext., $J$ = 6.4 Hz, 1H, $NHCHCH_3$), 3.65 (s, 3H, $CH_3O$), 6.07 (t, $J$ = 7.4 Hz, 1H, $NCH_2CH_2CH$), 7.16–7.39 (m, 10H, $H_{arom}$), 7.34–7.39 (m, 2H, $H_{arom}$). IR (film): $\tilde{\nu}$ = 2951 cm$^{-1}$, 1733, 1493, 1442, 1360, 1294. MS (CI, $CH_5^+$); *m*/*z* (%): 324 (100) $[M + H]^+$. Anal. Calcd. for $C_{21}H_{25}N_1O_2$; C, 77.99; H, 7.79; N, 4.33; Found: C, 77.83; H, 7.92; N, 4.34.

### 5.1.22. Methyl 3-({2-[2-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)ethoxy]ethyl}amino)propanoate (**9c**)

According to GP2 starting from **19c** (386 mg, 0.645 mmol), mercaptoacetic acid (58 µl, 0.83 mmol) and $NEt_3$ (180 µl, 1.29 mmol) in $CH_2Cl_2$ (6.5 ml); reaction time: 3 h; work-up: sat. $NaHCO_3$ solution (50 ml) and. Purification by CC (EtOAc/*n*-pentane 40:60 + 2% $EtMe_2N$). Yield: 220 mg (92%), yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 2.49 (t, $J$ = 6.8 Hz, 2H, $COCH_2$), 2.69–2.74 (m, 2H, $NHCH_2CH_2OCH_2$), 2.86 (t, $J$ = 6.8 Hz, 2H, $COCH_2CH_2NH$), 3.15 (s, 4H, $CCH_2CH_2C$), 3.42–3.47 (m, 2H, $NHCH_2CH_2OCH_2$), 3.56 (t, $J$ = 6.3 Hz, 2H, $(C_{arom})_2NCH_2CH_2O$), 3.67 (s, 3H, $CH_3O$), 3.97 (t, $J$ = 6.3 Hz, 2H, $(C_{arom})_2NCH_2CH_2O$), 6.89–6.94 (m, 2H, 2× NCCCHCH), 7.06–7.15 (m, 6H, 2× NCCCHCH, 2× NCCHCH). IR (film): $\tilde{\nu}$ = 2889 cm$^{-1}$, 2846, 1735, 1486, 1457, 1337, 1236, 1175, 1127, 1109. MS (CI, $CH_5^+$); *m*/*z* (%): 369 (98) $[M + H]^+$, 221 (100). Anal. Calcd. for $C_{22}H_{28}N_2O_3$; C, 71.71; H, 7.66; N, 7.60; Found: C, 71.27; H, 7.51; N, 7.53.

### 5.1.23. Methyl (rac)-3-({2-[2-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)ethoxy]ethyl}amino)butanoate [(rac)-**21c**]

According to GP2 starting from (*rac*)-**20c** (374 mg, 0.611 mmol), mercaptoacetic acid (56 µl, 0.81 mmol) and $NEt_3$ (170 µl, 1.22 mmol) in $CH_2Cl_2$ (6.1 ml); reaction time: 6 h; work-up: sat. $NaHCO_3$ solution (50 ml) and $Et_2O$. Purification by CC (EtOAc/*n*-pentane 20:80 + 2% $EtMe_2N$). Yield: 206 mg (88%), yellow oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.09 (d, $J$ = 6.4 Hz, 3H, $NHCHCH_3$), 2.28 (dd, $J$ = 15.1/6.9 Hz, 1H, $COCH_2$), 2.46 (dd, $J$ = 15.1/6.1 Hz, 1H, $COCH_2$), 2.67 (dt, $J$ = 12.0/5.3 Hz, 1H, $NHCH_2CH_2OCH_2$), 2.73 (dt, $J$ = 12.0/5.3 Hz, 1H, $NHCH_2CH_2OCH_2$), 3.02–3.10 (m, 1H, $NHCHCH_3$), 3.15 (s, 4H, $CCH_2CH_2C$), 3.44 (t, $J$ = 5.3 Hz, 2H, $NHCH_2CH_2OCH_2$), 3.56 (t, $J$ = 6.3 Hz, 2H, $(C_{arom})_2NCH_2CH_2O$), 3.65 (s, 3H, $CH_3O$), 3.97 (t, $J$ = 6.3 Hz, 2H, $(C_{arom})_2NCH_2CH_2O$), 6.89–6.94 (m, 2H, 2× NCCCHCH), 7.07–7.14 (m, 6H, 2× NCCCHCH, 2× NCCHCH). IR (film): $\tilde{\nu}$ = 2859 cm$^{-1}$, 1734, 1595, 1572, 1487, 1457, 1336, 1294, 1236. MS (CI, $CH_5^+$); *m*/*z* (%): 383 (100) $[M + H]^+$. Anal. Calcd. for $C_{23}H_{30}N_2O_3$; C, 72.22; H, 7.91; N, 7.33; Found: C, 72.10; H, 7.77; N, 7.31.

### 5.1.24. Methyl 3-({2-[2-(5H-dibenzo[b,f]azepin-5-yl)ethoxy]ethyl}amino)propanoate (**9d**)

According GP2 starting from **19d** (304 mg, 0.510 mmol), mercaptoacetic acid (47 µl, 0.66 mmol) and $NEt_3$ (145 µl, 1.04 mmol) in $CH_2Cl_2$ (5.1 ml), reaction time: 5.5 h; work-up: sat. $NaHCO_3$ solution (50 ml) and $Et_2O$. Purification by CC (Et2O/*n*-pentane 80:20 + 2% $EtMe_2N$). Yield: 171 mg (92%), yellow oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 2.49 (t, $J$ = 6.8 Hz, 2H, $COCH_2$), 2.69–2.72 (m, 2H, $NHCH_2CH_2OCH_2$), 2.86 (t, $J$ = 6.8 Hz, 2H, $COCH_2CH_2NH$), 3.47–3.50 (m, 2H, $NHCH_2CH_2OCH_2$), 3.59 (t, $J$ = 6.5 Hz, 2H, $(C_{Ar})_2NCH_2CH_2O$), 3.68 (s, 3H, $CH_3O$), 3.94 (t, $J$ = 6.5 Hz, 2H, $(C_{Ar})_2NCH_2CH_2O$), 6.72 (s, 2H, CCHCHC), 6.96–7.01 (m, 2H, 2× NCCCHCHCH), 7.03–7.07 (m, 4H, 2× NCCHCH, 2× NCCCHCHCH), 7.25 (ddd, $J$ = 8.2/7.2/1.6 Hz, 2H, 2× NCCHCH). IR (film): $\tilde{\nu}$ = 3018 cm$^{-1}$, 2856, 1735, 1592, 1570, 1483, 1458, 1436, 1238, 1195. MS (CI, $CH_5^+$); *m*/*z* (%): 367 (100) $[M + H]^+$. Anal. Calcd. for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64; Found: C, 71.69; H, 7.20; N, 7.51.

### 5.1.25. Methyl (rac)-3-({2-[2(5H-dibenzo[b,f]azepin-5-yl)-ethoxy]ethyl}amino)butanoate [(rac)-**21d**]

According to GP2 starting from (*rac*)-**20d** (603 mg, 0.989 mmol), mercaptoacetic acid (92 µl, 1.30 mmol) and $NEt_3$ (275 µl, 1.98 mmol)

in $CH_2Cl_2$ (9.9 ml); reaction time 5.5 h; work-up: sat. $NaHCO_3$ solution (100 ml) and $Et_2O$. Purification by CC ($Et_2O$/*n*-pentane 80:20 + 2% $EtMe_2N$). Yield: 332 mg (88%), yellow oil. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 1.10 (d, *J* = 6.4 Hz, 3H, NHCHC*H*$_3$), 2.29 (dd, *J* = 15.1/6.9 Hz, 1H, COC*H*$_2$CH), 2.47 (dd, *J* = 15.1/6.1 Hz, 1H, COC*H*$_2$CH), 2.64–2.76 (m, 2H, NHC*H*$_2$CH$_2$OCH$_2$), 3.07 (sext., *J* = 6.4 Hz, 1H, COCH$_2$C*H*), 3.49 (t, *J* = 5.2 Hz, 2H, NHCH$_2$C*H*$_2$OCH$_2$), 3.59 (t, *J* = 6.6 Hz, 2H, (C$_{Ar}$)$_2$NCH$_2$C*H*$_2$O), 3.66 (s, 3H, CH$_3$O), 3.94 (t, *J* = 6.6 Hz, 2H, (C$_{Ar}$)$_2$NC*H*$_2$CH$_2$O), 6.72 (s, 2H, C*CHCH*C), 6.99 (td, *J* = 7.4/1.1 Hz, 2H, 2× NCCCHC*H*CH), 7.05 (dd, *J* = 8.1/0.8 Hz, 2H, 2× NCC*H*CH), 7.06 (dd, *J* = 7.6/1.7 Hz, 2H, 2× NCCC*H*CHCH), 7.25 (ddd, *J* = 8.1/7.3/1.7 Hz, 2H, 2× NCCHC*H*). IR (film): $\tilde{\nu}$ = 3019 cm$^{-1}$, 2950, 2860, 1732, 1593, 1571, 1483, 1459, 1435, 1297, 1239, 1195. MS (CI, $CH_5^+$); *m*/*z* (%): 381 (100) [M + H]$^+$. Anal. Calcd. for $C_{23}H_{28}N_2O_3$; C, 72.61; H, 7.42; N, 7.36; Found: C, 72.27; H, 7.34; N, 7.33.

### 5.1.26. Methyl 3-({2-[2-(10H-phenothiazin-10-y)ethoxy]ethyl}amino) propanoate (**9e**)

According to GP2 starting **19e** (331 mg, 0.550 mmol), mercaptoacetic acid (50 µl, 0.71 mmol) and $NEt_3$ (155 µl, 1.12 mmol) in $CH_2Cl_2$ (5.5 ml); reaction time: 4.5 h; work-up: sat. $NaHCO_3$ solution (50 ml) and $Et_2O$. Purification was accomplished by CC (EtOAc/*n*-pentane 70:30 + 2% $EtMe_2N$). Yield: 182 mg (87%), yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 2.51 (t, *J* = 6.8 Hz, 2H, COCH$_2$), 2.78 (t, *J* = 5.2 Hz, 2H, NHC*H*$_2$CH$_2$OCH$_2$), 2.88 (t, *J* = 6.8 Hz, 2H, COCH$_2$C*H*$_2$), 3.54–3.59 (m, 2H, NHCH$_2$C*H*$_2$OCH$_2$), 3.68 (s, 3H, CH$_3$O), 3.81 (t, *J* = 6.2 Hz, 2H, (C$_{Ar}$)$_2$NCH$_2$C*H*$_2$O), 4.10 (t, *J* = 6.2 Hz, 2H, (C$_{Ar}$)$_2$NC*H*$_2$CH$_2$O), 6.87–6.96 (m, 4H, 2× NCCCHC*H*, 2× NCC*H*CH), 7.10–7.18 (m, 4H, 2× NCCHC*H*, 2× NCCC*H*CH). IR (film): $\tilde{\nu}$ = 3059 cm$^{-1}$, 2942, 2866, 1734, 1593, 1571, 1462, 1362, 1254, 1129. MS (CI, $CH_5^+$); *m*/*z* (%): 373 (100) [M + H]$^+$. Anal. Calcd. for $C_{20}H_{24}N_2O_3S$; C, 64.49; H, 6.50; N, 7.52; S, 8.61; Found: C, 64.21; H, 6.49; N, 7.51; S 8.52.

### 5.1.27. Methyl (rac)-3-({2-[2-(10H-phenothiazin-10-yl)ethoxy] ethyl}amino)butanoate [(rac)-**21e**]

According to GP2 starting (*rac*)-**20e** (548 mg, 0.890 mmol), mercaptoacetic acid (82 µl, 1.16 mmol) and $NEt_3$ (250 µl, 1.80 mmol) in $CH_2Cl_2$ (8.9 ml); reaction time 5.5 h; work-up: sat. $NaHCO_3$ solution (100 ml) and $Et_2O$. Purification by CC ($Et_2O$/*n*-pentane 80:20 + 2% $EtMe_2N$). Yield: 317 mg (93%), yellow oil. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 1.11 (d, *J* = 6.4 Hz, 3H, NHCHC*H*$_3$), 2.31 (dd, *J* = 15.2/6.6 Hz, 1H, COC*H*$_2$CH), 2.48 (dd, *J* = 15.2/6.3 Hz, 1H, COC*H*$_2$CH), 2.74 (dt, *J* = 12.3/5.3 Hz, 1H, NHC*H*$_2$CH$_2$OCH$_2$), 2.79 (dt, *J* = 12.3/5.2 Hz, 1H, NHC*H*$_2$CH$_2$OCH$_2$), 3.10 (sext., *J* = 6.4 Hz, 1H, NHC*H*CH$_3$), 3.58 (t, *J* = 5.2 Hz, 2H, NHCH$_2$C*H*$_2$OCH$_2$), 3.67 (s, 3H, CH$_3$O), 3.77–3.85 (m, 2H, (C$_{Ar}$)$_2$NCH$_2$C*H*$_2$O), 4.10 (t, *J* = 6.3 Hz, 2H, (C$_{Ar}$)$_2$NC*H*$_2$CH$_2$O), 6.88–6.94 (m, 4H, 2× NCCCHC*H*, 2× NCC*H*CH), 7.10–7.17 (m, 4H, 2× NCCC*H*CH, 2× NCCHC*H*). IR (film): $\tilde{\nu}$ = 3331 cm$^{-1}$, 3059, 2955, 2867, 1733, 1594, 1570, 1463, 1362, 1286, 1253, 1196, 1129. MS (CI, $CH_5^+$); *m*/*z* (%): 387 (100) [M + H]$^+$. Anal. Calcd. for $C_{21}H_{26}N_2O_3S$; C, 65.26; H, 6.78; N, 7.25; S, 8.30; Found: C, 65.15; H, 6.85; N, 7.25; S, 8.66.

### 5.1.28. Methyl (rac)-3-({2-[tris(4-methoxyphenyl)methoxy]ethyl} amino)butanoate [(rac)-**21f**]

According to GP2 starting from (*rac*)-**20f** (153 mg, 0.212 mmol) in $CH_2Cl_2$ (1.1 ml). Differing to the general procedure, the addition of mercaptoacetic acid (20 µl, 0.28 mmol) and $NEt_3$ (60 µl, 0.43 mmol) was carried out as a solution in $CH_2Cl_2$ (1.1 ml); reaction time 5.5 h; work-up: sat. $NaHCO_3$ solution (50 ml) and $Et_2O$. Purification by CC ($Et_2O$/*n*-pentane, 40:60 + 2% $EtMe_2N$). Yield: 65 mg (63%), colorless oil. $^1H$ NMR (500 MHz, $CD_2Cl_2$): $\delta$ = 1.07 (d, *J* = 6.4 Hz, 3H, NHCHC*H*$_3$), 2.31 (dd, *J* = 15.1/6.1 Hz, 1H, COC*H*$_2$CH), 2.43 (dd, *J* = 15.1/6.8 Hz, 1H, COC*H*$_2$CH), 2.69–2.81 (m, 2H, NHC*H*$_2$CH$_2$O), 3.06 (sext., *J* = 6.4 Hz, 1H, NHC*H*CH$_3$), 3.12 (t, *J* = 5.5 Hz, 2H, NHCH$_2$C*H*$_2$O), 3.64 (s, 3H, CH$_3$O), 3.77 (s, 9H, 9H, 3× C*H*$_3$OC$_6$H$_4$), 6.80–6.84 (m, 6H, 6× CH$_3$OCC*H*CH), 7.29–7.33 (m, 6H, 6× CH$_3$OCCHC*H*). IR (film): $\tilde{\nu}$ = 2952 cm$^{-1}$, 2836, 1733, 1607, 1555, 1539, 1507, 1462, 1301, 1249, 1175. MS (CI, $CH_5^+$); *m*/*z* (%): 333 (100) [M + H]$^+$. Anal. Calcd. for $C_{29}H_{35}NO_6$; C, 70.57; H, 7.15; N, 2.84; Found: C, 70.32; H, 6.66; N, 2.72.

### 5.1.29. (4,4-Diphenylbut-3en-1-yl)aminopropanoic acid **5b**

NaOH solution (12 M, 98 µl, 1.17 mmol) was added drop wise at 0 °C to **9b** (181 mg, 0.585 mmol) in EtOH (1.2 ml). The ice bath was removed and the reaction mixture was stirred for additional 4 h at rt. The reaction mixture was adjusted to pH ~ 1 by addition of aqueous HCl (4 M) at 0 °C and subsequently extracted 5 times with $CH_2Cl_2$. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The resulting hydrochloride was finally recrystallized from EtOH. Yield 163 mg (84%); colorless crystals, m.p.: 174 °C. $^1H$ NMR (400 MHz, $CD_3OD$): $\delta$ = 2.48 (t, *J* = 6.6 Hz, 2H, CH$_2$COO), 2.52 (q, *J* = 7.4 Hz, 2H, =CHC*H*$_2$CH$_2$), 3.11 (t, *J* = 7.4 Hz, 1H, =CHCH$_2$C*H*$_2$), 3.30–3.32 (m, 2H, NC*H*$_2$CH$_2$COO), 6.09 (t, *J* = 7.4 Hz, 1H, C=CH), 7.17–7.45 (m, 10H, H$_{arom}$). IR (KBr): $\tilde{\nu}$ = 3432 cm$^{-1}$, 3023, 2791, 1637, 1574. MS (CI, $CH_5^+$); *m*/*z* (%): 296 (100) [M + H]$^+$. Anal. Calcd. for $C_{19}H_{22}ClN_2O$; C, 68.77; H, 6.68; N, 4.22; Found: C, 68.79; H, 6.67; N, 4.13.

### 5.1.30. (rac)-3-[(4,4-Diphenylbut-3-enyl)amino]butanoic acid [(rac)-**6b**]

According to GP3 starting from (*rac*)-**21b** (218 mg, 0.675 mmol), MeOH (1.7 ml), NaOH (2 M, 1.01 ml, 2.02 mmol); reaction time 15 h; purification was accomplished as follows: the residue was dissolved in $H_2O$ and Phosphate buffer pH 6 (0.45 M, 6 ml) was added followed by extraction of the aqueous layer with $CH_2Cl_2$. The combined organic layers were washed with $H_2O$ and concentrated in vacuo. Yield: 167 mg (80%); colorless solid, m.p.: 197 °C. $^1H$ NMR (500 MHz, $CD_3OD$): $\delta$ = 1.27 (d, *J* = 6.6 Hz, 3H, NHCHC*H*$_3$), 2.31 (dd, *J* = 16.8/8.2 Hz, 1H, COCH$_2$), 2.48 (dd, *J* = 16.8/4.5 Hz, 1H, COCH$_2$), 2.48–2.57 (m, 2H, NHCH$_2$C*H*$_2$CH), 3.06 (dt, *J* = 12.3/7.6 Hz, 1H, NHC*H*$_2$CH$_2$CH), 3.15 (ddd, *J* = 12.3/7.9/6.6 Hz, 1H, NHC*H*$_2$CH$_2$CH), 3.33–3.41 (m, 1H, NHC*H*CH$_3$), 6.10 (t, *J* = 7.3 Hz, 1H, NHCH$_2$CH$_2$C*H*), 7.17–7.29 (m, 7H, H$_{arom}$), 7.32–7.37 (m, 1H, H$_{arom}$), 7.39–7.44 (m, 2H, H$_{arom}$). IR (KBr): $\tilde{\nu}$ = 3448 cm$^{-1}$, 3055, 2638, 2381, 1594, 1495, 1424, 1408, 1384, 1323, 1268, 1073. MS (CI, $CH_5^+$); *m*/*z* (%): 310 (100) [M + H]$^+$. Anal. Calcd. for $C_{20}H_{23}NO_2$; C, 77.64; H, 7.49; N, 4.53; Found: C, 77.13; H, 7.58; N, 4.49.

### 5.1.31. 3-({2-[2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)ethoxy] ethyl}amino)propanoic acid (**5c**)

According to GP3 starting from **9c** (141 mg, 0.383 mmol), MeOH (0.95 ml), NaOH (2 M, 580 µl, 1.16 mmol); reaction time 50 h; purification was accomplished by basic anion exchange chromatography (Amberlite IRA-410 elution with 0.15 M HCl) followed by an acidic cation exchange chromatography (DOWEX 50 WX8, elution with sat. aqueous $NH_3$ solution). The resulting residue was dissolved in $CH_2Cl_2$ and subsequently filtered. The filtrate was finally concentrated in vacuo. Yield: 58 mg (42%); light brown solid, m.p.: 160–162 °C. $^1H$ NMR (400 MHz, $CD_3OD$): $\delta$ = 2.45 (t, *J* = 6.3 Hz, 2H, COCH$_2$), 3.08–3.16 (m, 8H, C*H*$_2$NHC*H*$_2$, CCH$_2$CH$_2$C), 3.57–3.61 (m, 2H, NHCH$_2$C*H*$_2$OCH$_2$), 3.63 (t, *J* = 5.9 Hz, 2H, (C$_{Ar}$)$_2$NCH$_2$C*H*$_2$O), 4.02 (t, *J* = 5.9 Hz, 2H, (C$_{Ar}$)$_2$NC*H*$_2$CH$_2$O), 6.90 (ddd, *J* = 7.6/6.6/1.8 Hz, 2H, 2× NCCCHC*H*), 7.06–7.16 (m, 6H, 2× NCCC*H*CH, 2× NCC*HCH*). IR (KBr): $\tilde{\nu}$ = 3447 cm$^{-1}$, 3013, 2912, 1616, 1485, 1464, 1394, 1341, 1253, 1235, 1211, 1134. MS (CI, $CH_5^+$); *m*/*z* (%): 355 (18) [M + H]$^+$, 283 (100). Anal. Calcd. for $C_{21}H_{26}N_2O_3 \times 0.5H_2O$; C, 69.40; H, 7.49; N, 7.71; Found: C, 69.81; H, 7.37; N, 7.78.

*5.1.32. (rac)-3-({2-[2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl) ethoxy]ethyl}amino)butanoic acid [(rac)-**6c**]*

According to GP3 starting from (*rac*)-**21c** (133 mg, 0.348 mmol), MeOH (0.87 ml), NaOH (2 M, 520 μl, 1.04 mmol); reaction time: 43 h; purification was accomplished by basic anion exchange chromatography (Amberlite IRA-410 elution with 0.15 M HCl) followed by an acidic cation exchange chromatography (DOWEX 50 WX8, elution with sat. aqueous $NH_3$ solution). The resulting residue was dissolved in $CHCl_3$ and subsequently filtered. The filtrate was finally concentrated in vacuo. Yield: 53 mg (47%); rufous, amorphous solid, m.p.: 53–57 °C. $^1$H NMR (400 MHz, $CD_3OD$): $\delta = 1.27$ (d, $J = 6.6$ Hz, 3H, NHCHC$H_3$), 2.31 (dd, $J = 16.9/8.7$ Hz, 1H, COC$H_2$CH), 2.47 (dd, $J = 16.9/4.3$ Hz, 1H, COC$H_2$CH), 3.04–3.21 (m, 2H, NHC$H_2$C$H_2$O), 3.13 (s, 4H, CC$H_2$C$H_2$C), 3.35–3.44 (m, 1H, NHC*H*CH$_3$), 3.55–3.68 (m, 4H, NHCH$_2$C$H_2$OC$H_2$), 4.02 (t, $J = 6.0$ Hz, 2H, ($C_{arom}$)$_2$NC$H_2$CH$_2$O), 6.90 (ddd, $J = 7.6/6.9/1.6$ Hz, 2H, 2× NCCCHC*H*), 7.05–7.17 (m, 6H, 2× NCCC*H*CH, 2× NCC*HCH*). IR (KBr): $\tilde{\nu} = 3422$ cm$^{-1}$, 3055, 3013, 2919, 1595, 1487, 1458, 1419, 1337, 1323, 1264, 1237, 1131. MS (CI, $CH_5^+$); *m/z* (%): 369 (100) [M + H]$^+$, 222 (100). Anal. Calcd. for $C_{22}H_{28}N_2O_3 \times 0.75H_2O$; C, 69.18; H, 7.78; N, 7.33; Found: C, 68.92; H, 7.88; N, 7.08.

*5.1.33. 3-({2-[2-(5H-Dibenzo[b,f]azepin-5-yl)ethoxy]ethyl}amino) propanoic acid (**5d**)*

According to GP3 starting from **9d** (105 mg, 0.287 mmol), MeOH (0.72 ml), NaOH (2 M, 430 μl, 0.86 mmol); reaction time: 64 h; purification was accomplished as follows: the residue was dissolved in $H_2O$ (2 ml) and the pH was adjusted to 2 with aqueous HCl (1 M) at 0 °C. $CH_2Cl_2$ (200 ml) was added and the entire aqueous layer was bound by addition of $MgSO_4$. After filtration and concentration in vacuo the remaining viscous oil was dissolved in $H_2O$ and sat. aqueous $NH_3$ solution was added until pH 12 was reached. Concentration in vacuo, subsequent dissolving in $H_2O$ and extraction with $CH_2Cl_2$ which was washed with $H_2O$ resulted after concentration ion vacuo in a residue which was suspended in $Et_2O$. The remaining yellowish crystals were finally obtained by filtration. Yield: 73 mg (72%); yellow crystals, m.p.: 162–163 °C. $^1$H NMR (400 MHz, $CD_3OD$): $\delta = 2.44$ (t, $J = 6.3$ Hz, 2H, COC$H_2$), 3.09–3.14 (m, 4H, C$H_2$NHC$H_2$), 3.63–3.69 (m, 4H, C$H_2$OC$H_2$), 3.99 [t, $J = 5.8$ Hz, 2H, ($C_{arom}$)$_2$NC$H_2$CH$_2$O], 6.74 (s, 2H, CCHCHC), 6.97–7.03 (m, 2H, 2× NCCCHC*H*CH), 7.06–7.13 (m, 4H, 2× NCCC*H*CHCH, 2× NCC*H*CH), 7.28 (ddd, $J = 8.1/7.2/1.7$ Hz, 2H, 2× NCCHC*H*). IR (KBr): $\tilde{\nu} = 3448$ cm$^{-1}$, 3019, 2958, 2902, 2875, 1589, 1483, 1458, 1406, 1356, 1341, 1232, 1213, 1116. MS (CI, $CH_5^+$); *m/z* (%): 353 (91) [M + H]$^+$, 116 (100). Anal. Calcd. for $C_{21}H_{24}N_2O_3 \times 0.25H_2O$; C, 70.67; H, 6.92; N, 7.85; Found: C, 70.47; H, 6.77; N, 7.79.

*5.1.34. (rac)-3-({2-[2-(5H-Dibenzo[b,f]azepin-5-yl)ethoxy]ethyl} amino)butanoic acid [(rac)-**6d**]*

According to GP3 starting from (*rac*)-**21d** (267 mg, 0.703 mmol), MeOH (1.75 ml), NaOH (2 M, 1.05 ml, 2.10 mmol); reaction time. 16 h; purification was accomplished as follows: the residue was dissolved in $H_2O$ (10 ml) and the pH was adjusted to 1 with aqueous HCl (1 M). $CH_2Cl_2$ (100 ml) was added and the entire aqueous layer was bound by addition of $MgSO_4$. After filtration and concentration in vacuo the remaining viscous oil was dissolved in $H_2O$ and sat. aqueous $NH_3$ solution was added until pH 12 was reached. Concentration in vacuo, subsequent dissolving in $H_2O$ and extraction with $CH_2Cl_2$ which was washed with $H_2O$ resulted, after concentration in vacuo, in a residue which was suspended in $Et_2O$. The remaining yellowish crystals were finally obtained by filtration. Yield: 195 mg (74%); pale yellow crystals, m.p.: 125–127 °C. $^1$H NMR (400 MHz, $CD_3OD$): $\delta = 1.26$ (d, $J = 6.6$ Hz, 3H, NHCHC$H_3$), 2.30 (dd, $J = 16.9/8.6$ Hz, 1H, COC$H_2$), 2.46 (dd, $J = 16.9/4.3$ Hz, 1H, COC$H_2$), 3.06 (ddd, $J = 13.1/7.1/3.7$ Hz, 1H, NHC$H_2$CH$_2$O), 3.16 (ddd, $J = 13.1/6.0/3.5$ Hz, 1H, NHC$H_2$CH$_2$O), 3.34–3.44 (m, 1H, NHC*H*CH$_3$), 3.61–3.73 (m, 4H, CH$_2$OCH$_2$), 3.95–4.04 (m, 2H, ($C_{arom}$)$_2$NC$H_2$CH$_2$O), 6.73 (s, 2H, CCHCHC), 6.97–7.03 (m, 2H, 2× NCCCHC*H*CH), 7.08 (dd, $J = 7.6/1.7$ Hz, 2H, 2× NCCC*H*CHCH), 7.11 (dd, $J = 8.2/1.0$ Hz, 2H, 2× NCC*H*CH), 7.27 (ddd, $J = 8.2/7.2/1.7$ Hz, 2H, 2× NCCHC*H*). IR (KBr): $\tilde{\nu} = 3423$ cm$^{-1}$, 3018, 2870, 2729, 2414, 1593, 1483, 1458, 1406, 1127. MS (CI, $CH_5^+$); *m/z* (%): 367 (100) [M + H]$^+$. Anal. Cacd. for $C_{22}H_{26}N_2O_2 \times 0.5H_2O$; C, 70.38; H, 7.25; N, 7.46; Found: C, 70.64; H, 7.24; N, 7.43.

*5.1.35. 3-({2-[2-(10H-Phenothiazin-10-yl)ethoxy]ethyl}amino)pro panoic acid (**5e**)*

According to GP3 starting from **9e** (126 mg, 0.339 mmol), MeOH (0.85 ml), NaOH (2 M, 510 μl, 1.02 mmol); reaction time: 18 h; purification was accomplished by acidic cation exchange chromatography (DOWEX 50 WX 8, elution with sat. aqueous $NH_3$ solution). The resulting residue was dissolved in MeOH and the desired product was precipitated by addition of $Et_2O$. This procedure was repeated two times. Yield: 56 mg (45%); colorless solid, m.p.: 164–165 °C. $^1$H NMR (500 MHz, $CD_3OD$): $\delta = 2.40$ (t, $J = 6.4$ Hz, 2H, COCH$_2$), 3.04 (t, $J = 6.4$ Hz, 2H, COCH$_2$C$H_2$NH), 3.07 (t, $J = 5.1$ Hz, 2H, NHC$H_2$CH$_2$O), 3.69 (t, $J = 5.1$ Hz, 2H, NHCH$_2$C$H_2$O), 3.86 (t, $J = 5.6$ Hz, 2H, ($C_{arom}$)$_2$NCH$_2$C$H_2$O), 4.17 (t, $J = 5.6$ Hz, 2H, ($C_{arom}$)$_2$NC$H_2$CH$_2$O), 6.93 (td, $J = 7.5/1.1$ Hz, 2H, 2× NCCCHC*H*), 7.01 (dd, $J = 8.2/1.0$ Hz, 2H, 2× NCC*H*CH), 7.12 (dd, $J = 7.6/1.5$ Hz, 2H, 2× NCCC*H*CH), 7.19 (ddd, $J = 8.2/7.4/1.5$ Hz, 2H, 2× NCCHC*H*). IR (KBr): $\tilde{\nu} = 3442$ cm$^{-1}$, 3057, 2877, 1590, 1458, 1355, 1288, 1256, 1222, 1109, 1075, 1037. MS (CI, $CH_5^+$); *m/z* (%): 359 (100) [M + H]$^+$. Anal. Calcd. for $C_{19}H_{22}N_2O_3S$ 0.25$H_2O$; C, 62.87; H, 6.25; N, 7.72, S, 8.83; Found: C, 62.88; H, 6.13; N, 7.72; S, 9.07.

*5.1.36. 3-({2-[Tris(4-methoxyphenyl)methoxy]ethyl}amino) propanoic acid **5f***

To a stirred solution of **9f** (333 mg, 0.694 mmol) in EtOH (1.4 ml) was added drop wise a NaOH solution (12 M, 116 μl, 1.39 mmol) at 0 °C. The ice bath was removed and the reaction mixture was stirred for additional 4 h at rt. The reaction mixture was adjusted to pH ~ 6 by addition of aqueous HCl (0.25 M) at 0 °C and subsequently extracted with $CH_2Cl_2$. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The resulting residue was recrystallized from $Et_2O$/*n*-pentane (1:1). Yield 261 mg (81%); colorless crystals, m.p.: 87 °C. 1H NMR (400 MHz, $CDCl_3$): $\delta = 2.49$ (t, $J = 5.8$ Hz, 2H, CH$_2$COO), 2.89 (t, $J = 5.0$ Hz, 2H, OCH$_2$C$H_2$N), 2.94 (t, $J = 5.8$ Hz, 2H, NC$H_2$CH$_2$COO), 3.39 (t, $J = 5.0$ Hz, 2H, OC$H_2$CH$_2$N), 3.75 (s, 9H, OCH$_3$), 6.78–6.83 (m, 6H, $H_{arom}$), 7.27–7.32 (m, 6H, $H_{arom}$). IR (KBr): $\tilde{\nu} = 3428$ cm$^{-1}$, 2945, 2835, 1607, 1582. MS (CI, $CH_5^+$); *m/z* (%): 335 (100) [M-$C_5H_{10}NO_2$+H]$^+$. Anal. Calcd. for $C_{27}H_{31}NO_6$; C, 69.66; H, 6.71; N, 3.01; Found: C, 69.43; H, 7.00; N, 2.95.

*5.1.37. (rac)-3-({2-[2-(10H-Phenothiazin-10-yl)ethoxy]ethyl}amino) butanoic acid [(rac)-**6e**]*

According to GP3 starting from (*rac*)-**21e** (263 mg, 0.681 mmol), MeOH (1.7 ml), NaOH (2 M, 1.02 ml, 2.04 mmol); reaction time: 15 h; purification was accomplished as follows: the residue was dissolved in $H_2O$ (10 ml) and the pH was adjusted to 1 with aqueous HCl (2 M). $CH_2Cl_2$ (100 ml) was added and the entire aqueous layer was bound by addition of $MgSO_4$. After filtration and concentration in vacuo the remaining viscous oil was dissolved in $H_2O$ and sat. aqueous $NH_3$ solution was added until pH 12 was reached. Concentration in vacuo, subsequent dissolving in $H_2O$, extraction with $CH_2Cl_2$ which was washed with $H_2O$ resulted, after concentration in vacuo, in a residue which was dissolved in MeOH. The desired product was precipitated by addition of $Et_2O$. Yield: 176 mg (70%); colorless solid, m.p.: 142 °C. $^1$H NMR (500 MHz, $CD_3OD$): $\delta = 1.24$ (d,

$J = 6.6$ Hz, 3H, NHCHC$H_3$), 2.28 (dd, $J = 16.9/8.7$ Hz, 1H, $COCH_2$), 2.44 (dd, $J = 16.9/4.2$ Hz, 1H, $COCH_2$), 3.11 (ddd, $J = 13.1/7.2/3.6$ Hz, 1H, NHC$H_2$CH$_2$O), 3.20 (ddd, $J = 13.1/6.0/3.4$ Hz, 1H, NHC$H_2$CH$_2$O), 3.35–343 (m, 1H, NHC$H$CH$_3$), 3.71 (ddd, $J = 10.9/7.2/3.4$ Hz, 1H, NHCH$_2$C$H_2$O), 3.76 (ddd, $J = 10.9/6.0/3.6$ Hz, 1H, NHCH$_2$C$H_2$O), 3.83–3.91 (m, 2H, $(C_{arom})_2$NCH$_2$C$H_2$O), 4.14–4.24 (m, 2H, $(C_{arom})_2$NC$H_2$CH$_2$O), 6.94 (td, $J = 7,5/1.1$ Hz, 2H, 2× NCCCHC$H$), 7.02 (d, $J = 8.2$ Hz, 2H, 2× NCC$H$CH), 7.12 (dd, $J = 7.7/1.5$ Hz, 2H, 2× NCCC$H$CH), 7.19 (ddd, $J = 8.2/7.4/1.5$ Hz, 2H, 2× NCCHC$H$). IR (KBr): $\tilde{\nu} = 3423$ cm$^{-1}$, 3059, 2883, 2685, 2399, 1595, 1571, 1464, 1407, 1355, 1311, 1262, 1112. MS (CI, $CH_5^+$); $m/z$ (%): 373 (100) $[M + H]^+$, Anal. Calcd. for $C_{20}H_{24}N_2O_3S$; C, 64.49; H, 6.49; N, 7.52; Found: C, 64.27; H, 6.47; N, 7.50.

### 5.1.38. *(rac)-3-({2-[Tris(4-methoxyphenyl)methoxy]ethyl}amino) butanoic acid [(rac)-**6f**]*

According to GP3 starting from (*rac*)-**21f** (51 mg, 0.10 mmol), MeOH (0.26 ml), NaOH (2 M, 160 μl, 0.32 mmol); reaction time 9 h; purification was accomplished as follows: the residue was dissolved in $H_2O$ (7 ml) followed by addition of aqueous phosphate buffer pH 6 (0.45 M, 20 ml) at 0 °C. After extraction with $CH_2Cl_2$, the combined organic layers were washed with $H_2O$ and concentrated in vacuo. The residue was recrystallized from acetone/$H_2O$. Yield: 44 mg (87%); light brown crystals, m.p.: 142 °C. $^1$H NMR (500 MHz, $CD_2Cl_2$): $\delta = 1.20$ (d, $J = 6.5$ Hz, 3H, NHCHC$H_3$), 2.17 (dd, $J = 16.8/7.9$ Hz, 1H, COC$H_2$CH), 2.46 (dd, $J = 16.8/3.9$ Hz, 1H, COC$H_2$CH), 2.72–2.78 (m, 1H, NHC$H_2$CH$_2$O), 2.85–2.91 (m, 1H, NHC$H_2$CH$_2$O), 2.97–3.05 (m, 1H, NHC$H$CH$_3$), 3.25–3.34 (m, 2H, NHCH$_2$C$H_2$O), 3.78 (s, 9H, 3× $CH_3$O), 6.81–6.86 (m, 6H, 6× $CH_3$OCC$H$CH), 7.28–7.32 (m, 6H, 6× $CH_3$OCCHC$H$). IR (KBr): $\tilde{\nu} = 3422$ cm$^{-1}$, 2934, 2836, 1607, 1582, 1508, 1459, 1440, 1404, 1302, 1250, 1175. MS (ESI+) $m/z$ (%): 502 $[M + Na]^+$, 480 $[M + H]^+$. Anal. Calcd. for $C_{28}H_{33}NO_6 \times 0.25H_2O$; C, 69.47; H, 6.98; N, 2.89; Found: C, 69.37; H, 6.81; N, 2.82.

### 5.2. Inhibition of GABA uptake

GABA uptake assays based on porcine brain material employing $pfcP_{2B}$ (GAT1) and $pbsP_{2C}$ membrane fraction (GAT3) were performed as previously described [29]. GABA uptake assays employing HEK293 cells stably expressing mGAT1-4 (i.e. GAT1, BGT1, GAT2 and GAT3, respectively, according to HUGO) were performed as described [25].

## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.04.063.

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