European Journal of Medicinal Chemistry 124 (2016) 852–880

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

# Synthesis and biological evaluation of a series of *N*-alkylated imidazole alkanoic acids as mGAT3 selective GABA uptake inhibitors

Silke Kerscher-Hack, Thejavathi Renukappa-Gutke, Georg Höfner, Klaus T. Wanner*

*Ludwig-Maximilians-Universität München, Department für Pharmazie – Zentrum für Pharmaforschung, Butenandtstr. 5-13, 81377, Munich, Germany*

ARTICLE INFO

*Article history:*
Received 3 May 2016
Received in revised form
21 July 2016
Accepted 3 September 2016
Available online 7 September 2016

*Keywords:*
GABA uptake
mGAT3
*N*-alkylimidazolealkanoic acids

ABSTRACT

In this paper, we report the synthesis and biological evaluation of a series of 1,5- and 1,4- substituted derivatives of 1*H*-imidazol-4-ylacetic acid, a series of 1,2-substituted 3-(1*H*-imidazol-2-yl)propanoic acid and an *N*-substituted (2*E*)-3-(1*H*-imidazol-2-yl)prop-2-enoic acid as new mGAT3 inhibitors. The lipophilic moieties attached to the *N*-atom of the parent structures were delineated from the 2-[9-(4-methoxyphenyl)-9*H*-fluoren-9-yl]oxyethyl residue, known from a prototypic mGAT3 inhibitor. For the structure-activity-relationship studies, the spacer between the *N*-atom of the imidazole ring and the 2-[9-(4-methoxyphenyl)-9*H*-fluoren-9-yl] moiety was varied in length from three to six atoms, and in nature being either a pure saturated or unsaturated alkyl chain or an alkyl chain containing up to two ether functions. The compounds were characterized for inhibitory potencies at mouse GABA transporter proteins mGAT1–mGAT4. Among the 1,2-substituted compounds, the *N*-alkylated (2*E*)-3-(1*H*-imidazol-2-yl)prop-2-enoic acid **12e** containing a $C_5O$ spacer exhibits a $pIC_{50}$ value of 5.13 ± 0.04 at mGAT3, but is devoid of significant selectivity for this GABA transporter. However, the inhibitory potency displayed by **12e** at mGAT3 nominally surpasses that of SNAP-5294 reported as the most potent inhibitor of mGAT3 so far.



## 1. Introduction

A number of CNS disorders such as epilepsy [1], Morbus Parkinson [2], Huntington's chorea [3], and migraine [4] are associated with a reduced neurotransmission in the GABAergic system. Due to the high incidence of these diseases, the GABAergic system exhibits an important target in the development of new drugs. Apart from direct receptor agonism as well as allosteric activation, it has been shown that inhibition of GABA transport proteins, terminating GABAergic signalling by the uptake in surrounding glial cells as well as into presynaptic nerve terminals, augments the extracellular concentration of GABA (**1**, Fig. 1) in the synaptic cleft enhancing GABAergic neurotransmission [5–9]. To date, four distinct plasma membrane GABA transporter proteins (GATs) have been identified in different species including mice, rats, and humans by molecular cloning techniques [10,11]. The subtypes of GABA transporters originating from mouse cells are termed mGAT1, mGAT2, mGAT3, and mGAT4 (for transporters, originating from humans and rats, the nomenclature is different which is described in detail in Ref. [12]). Since the biological activity of the compounds described in this paper was evaluated using mouse transporters, the mouse nomenclature will preferably be used in this publication. If test results obtained for GABA transporters of other species are quoted, the nomenclature of the respective species will be given.

mGAT1 and mGAT4, the most prevalent GATs in the brain are responsible for neuronal and glial GABA uptake, respectively, thereby playing an important role in the termination of GABAergic neurotransmission [13,14]. mGAT2 and mGAT3 are predominant in liver and kidney [15,16]. While mGAT2 is expressed in low levels at the brain surface [15], the expression of mGAT3 is restricted to the leptomeninges and a subpopulation of blood-brain vessels [16]. Interestingly, recent experiments with mGAT3 knock out mouse indicated a taurine-exporting role at the blood-brain-barrier for mGAT3 [16]. Due to the affinity of mGAT3 to GABA, it may still play a role in the peripheral GABA uptake [16]. Selective targeting and modulation of GABA transporter subtypes is of fundamental importance. Compounds selectively addressing GABA transporter subtypes can provide essential information about the physiological function of the different GATs and, additionally, about their therapeutic potential.

Some representative inhibitors of GATs developed over the past

* Corresponding author.
*E-mail address:* klaus.wanner@cup.uni-muenchen.de (K.T. Wanner).

http://dx.doi.org/10.1016/j.ejmech.2016.09.012
0223-5234/

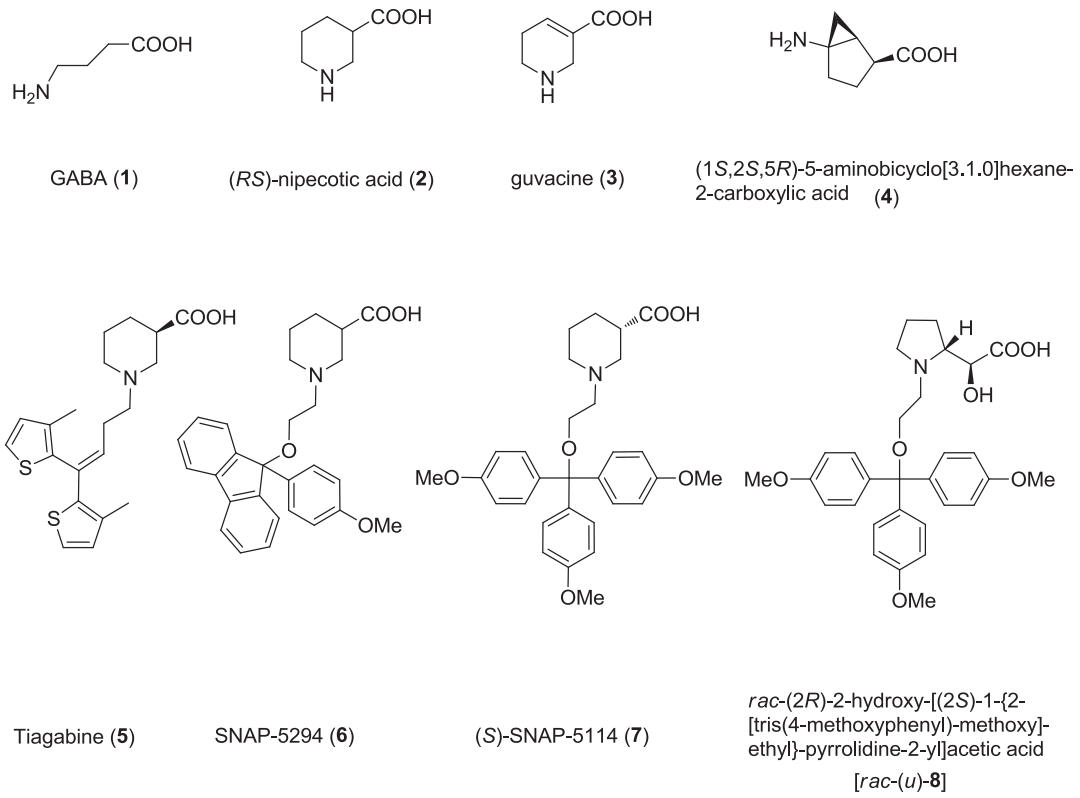



**Fig. 1.** Structures of GABA and representative GABA transporter inhibitors.

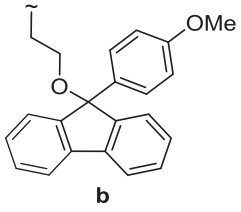


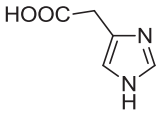

**Fig. 2.** Structure of the 2-[9-(4-methoxyphenyl)-9*H*-fluoren-9-yl]oxyethyl moiety (**b**).

decades are exemplified in Fig. 1 (compounds **2**–**8**) [17–24]. Although the conformationally restricted GABA analogs (*RS*)-nipecotic acid (**2**) and guvacine (**3**) show *in vitro* high GABA uptake inhibition without intrinsic activity at $GABA_A$ receptors, the pharmacological usefulness of these compounds is limited as they lack the capability to cross the blood-brain barrier [17]. However, the introduction of special lipophilic side chains resulted not only in an improved capability of these compounds to cross the blood-brain barrier, but also in the augmentation of their inhibitory potency at and selectivity for the different subtypes of GABA transporter [18–21]. Addition of the lipophilic moiety 4,4-bis-(3-methylthiophene-2-yl)but-3-en-1-yl to the nitrogen atom of (*R*)-nipecotic acid leads for example to the mGAT1 inhibitor tiagabine (**5**) which has been introduced successfully in the therapy of epilepsy validating mGAT1 as drug target [22]. The introduction of the 2-[9-(4-methoxyphenyl)-9*H*-fluoren-9-yl]oxyethyl moiety to the nitrogen atom of nipecotic acid [SNAP-5294 (**6**)] improves mGAT3 selectivity [21]. Nipecotic acid derivative *(S)*-SNAP-5114 (**7**) is a compound showing high inhibitory potency at mGAT4 compared to mGAT1, mGAT2, and mGAT3 [21], whereas compound *rac*-(*u*)-**8** with 2-hydroxy-2-pyrrolidine-2-ylacetic acid as core amino acid has comparatively better selectivity for mGAT4 than (*S*)-SNAP-5114 [23]. Similarly, varying the amino acid skeleton, the conformationally restricted GABA analogue **4** with a bicyclo[3.1.0]hexane backbone has been developed which is the most highly potent and selective inhibitor known to date for mGAT2 [24].

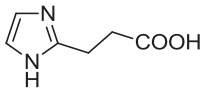
Up to date, many highly potent and selective mGAT1 inhibitors have been reported in the literature [25,26]. Currently, mGAT2 has also been in focus as exemplified through the development of the aforementioned mGAT2 inhibitor **4** [24,27], but only few selective inhibitors for mGAT3 are published [21,28,29], since compounds inhibiting this transporter are in the majority of cases also inhibitors of mGAT4 [21,28–30]. Therefore, the binding sites of the transporters mGAT3 and mGAT4 are thought to be closely related [8]. Due to the absence of compounds displaying high mGAT2, mGAT3, and mGAT4 inhibitory potency in combination with good subtype selectivity, the search for GABA uptake inhibitors continues.

Continuing our research in this field, we aimed to develop new and potent GABA uptake inhibitors of mGAT3. Hereto, we had previously reported the good inhibitory potency of 1*H*-imidazol-4-ylacetic acid (**9a**) at mGAT3 with a $pIC_{50}$ value of 4.76 ± 0.08 in combination with a reasonable preference for this transporter, especially when compared to mGAT1 (35:1, Table 1, entry 1) [29]. Hence, **9a** should make a promising starting point for the development of new mGAT3 inhibitors. *N*-alkylation of **9a** would lead to the possibility of obtaining both 1,4- and 1,5-regioisomers resulting from the substitution at either of the two non-equivalent nitrogen atoms of the imidazole ring in **9a** (formally delineated from structure **9a** and tautomer **10a**, Fig. 3) [31]. By contrast, the higher homologue and 2-substituted compound **11a** (Table 1, entry 2) [29] displays with a $pIC_{50}$ value of 4.54 ± 0.15 a slightly lower mGAT3 inhibitory potency than **9a**, but exhibits with $IC_{50}$ ratios between mGAT3:mGAT2 = 18:1 and mGAT3:mGAT4 = 7:1 an improved mGAT3 selectivity. Therefore, 3-(1*H*-imidazol-2-yl)propanoic acid

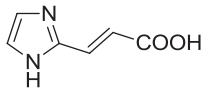
**Table 1**
Representative mGAT3 selective partial structures and their GABA uptake inhibition at mGAT1–4 [29].




2-(1*H*-imidazol-4-yl)-acetic acid (**9a**)




3-(1*H*-imidazol-2-yl)-propanoic acid (**11a**) [29]




(2*E*)-3-(1*H*-imidazol-2-yl)-prop-2-enoic acid (**12a**) [29]

| Entry | Compound | Uptake inhibition $pIC_{50}$ (±SEM, n = 3) | | | |
|---|---|---|---|---|---|
| | | mGAT1 | mGAT2 | mGAT3 | mGAT4 |
| **1** | **9a**[a] | 3.21 ± 0.12 | 3.99 ± 0.05 | 4.76 ± 0.08 | 4.33 ± 0.01 |
| **2** | **11a**[a] | 62.8%[b] | 3.28 ± 0.19 | 4.54 ± 0.15 | 3.51 ± 0.03 |
| **3** | **12a**[a] | 73.7%[b] | 77.3%[b] | 3.71 ± 0.05 | 47.2%[b] |

[a] The $pIC_{50}$ values originate from literature [29].
[b] Percent inhibition at 100 μM.

(**11a**) [29] also represents, due to its good subtype selectivity, a promising lead structure for further development of mGAT3 inhibitors with high potency and subtype selectivity. Similarly, the unsaturated compound (2*E*)-3-(1*H*-imidazol-2-yl)prop-2-enoic acid (**12a**, Table 1, entry 3) [29] possesses a $pIC_{50}$ value of 3.71 ± 0.05 for mGAT3 combined with a reasonable subtype selectivity and could also serve as a promising lead structure.

Due to the fact that SNAP-5294 (**6**) exhibits, unlike nipecotic acid (**2**), moderate affinity at and a certain preference for mGAT3 [21], the 2-[9-(4-methoxyphenyl)-9*H*-fluoren-9-yl]oxyethyl moiety (**b**) (Fig. 2) seemed to be a promising side chain to be introduced at the *N*-atom of the parent compounds **9a**-**12a**.

In order to determine the influence of the distance as well as the spatial arrangement of the lipophilic and hydrophilic domain to the inhibitory potencies at the GABA transporters subtypes of the test compounds to be derived from **9a**–**12a**, the structure of the lipophilic moiety starting from **b** [21] was systematically varied (see Fig. 3). Thus, the spacer length between nitrogen and oxygen atom was first elongated from $OC_2$ to $OC_5$ (lipophilic moieties **b**–**e**). Based on the 4-[9-(4-methoxyphenyl)-9*H*-fluoren-9-yl]oxybutyl moiety (**d**), the lipophilic moieties **h** and **i** with a double bond forming *E*- and *Z*-configurational isomers, respectively, were designed to study the influence of unsaturation and side chain geometry on the biological activity. In addition, the ethoxy linker of moiety **b** was replaced by a prop-2-en-1-yl-group leading to moiety **f**. Due to positive effects of an additional oxygen atom within the spacer described in 2001 by Andersen et al. [32] also the ether bridge containing moieties **g** and **j** were included in this study. To summarize, the 1,4- (compounds **9b**–**9f**) and the 1,5-disubstituted imidazoles (compounds **10b**–**10f**) of 1*H*-imidazol-4-yl-acetic acid (**9a**), the 1,2-disubstituted imidazoles of 3-(1*H*-imidazol-2-yl)-propanoic acid (**11a**), the *N*-alkyl derivatives **11b**–**11j**, and of (2*E*)-3-(1*H*-imidazol-2-yl)prop-2-enoic acid (**12a**) compound **12e** were to be included in this study (Fig. 3). The synthesis and biological evaluation of these compounds forms the content of this publication.

## 2. Chemistry

### 2.1. Synthesis of alkylating agents

The arylalkyl structures required for the modification of the core structures **9a**, **11a**, and **12a** were prepared as their halides (**20** [21], **21**–**25**, **30**), alcohols (**26**, **31**), and mesylates (**32**–**34**) as described in Table 1, and Schemes 1–3. Alkylating agents **21**–**26** were prepared analogous to literature procedures [21] by treating 9-(4-methoxyphenyl)-9*H*-fluoren-9-ol (**13**) [21] with conc. $H_2SO_4$ in toluene followed by addition of the alcohols **14**–**19** at rt to afford **21**–**26** in 20%–92% yield (Table 2, entries 1–6). Only a maximum of 20% yield could be achieved for compound **26** (Table 2, entry 6), which is to be accounted to the formation of a disubstituted side product resulting from reaction of both hydroxyl groups of diol **19** with fluorenyl derivative **13**. The alcohols **14**–**19** employed in the etherification of **13** [21] were either prepared according to literature procedures (**16** [33], **17** [34], **18** [35]) or obtained from commercial sources (**14**, **15**, **19**).

The alcohol **27** required for the preparation of the mesylate **33** comprising two ether functions in the side chain was prepared from **21** and sodium ethylene glycolate in 68% yield via *Williamson ether synthesis* (Scheme 1). The preparation of **30** and its chain-extended derivative **31** was realized starting from 9-(4-methoxyphenyl)-9*H*-fluoren-9-ol (**13**) [21]. The fluorene derivative **13** was treated with allytributylstannane (**28**) and $BF_3 \cdot Et_2O$ in $CH_2Cl_2$ analogous to a literature procedure [36] to yield the allyl derivative **29** quantitatively. Subsequent chemoselective bromination of **29** according to the Wohl-Ziegler-method using AIBN as a radical starter in analogy to a literature procedure [37] afforded bromide **30** in 78% yield. Upon subjection of **30** to a *Williamson ether synthesis* analogous to that employed in the preparation of **27**, the alcohol **31** was obtained in 51% yield (Scheme 2).

The mesylates **32**–**34** were obtained analogous to a standard procedure [38] by, as shown in Scheme 3, treating the corresponding alcohols **26**, **27**, and **31**, with methanesulfonylchloride and $NEt_3$ at 0 °C for 2 h (yield: 73%–97%).

### 2.2. Synthesis of N-alkylated 2-(1H-imidazol-5-yl)acetic acids

The regioselective synthesis of 1,5-disubstituted imidazole derivatives **10b**–**10f** was performed based on the methods described in the literature [39–42]. In order to ascertain a regioselective *N*-alkylation of 1*H*-imidazol-4-yl-acetic acid (**9a**), the trityl derivative **35** was used in which *N*(1) is protected and which was synthesized by a literature procedure. Initially, **35** [42] was first reacted with 1.0 equiv. of 9-(2-bromoethoxy)-9-methoxyphenyl-9*H*-fluorene (**20**) [21] in $CH_3CN$ at 55 °C for a period of 3 days. The residue obtained after evaporation containing the putative 1,3,4-trisubstituted imidazolium derivative **36b** was not isolated, but immediately subjected to methanolysis under reflux conditions to remove the trityl

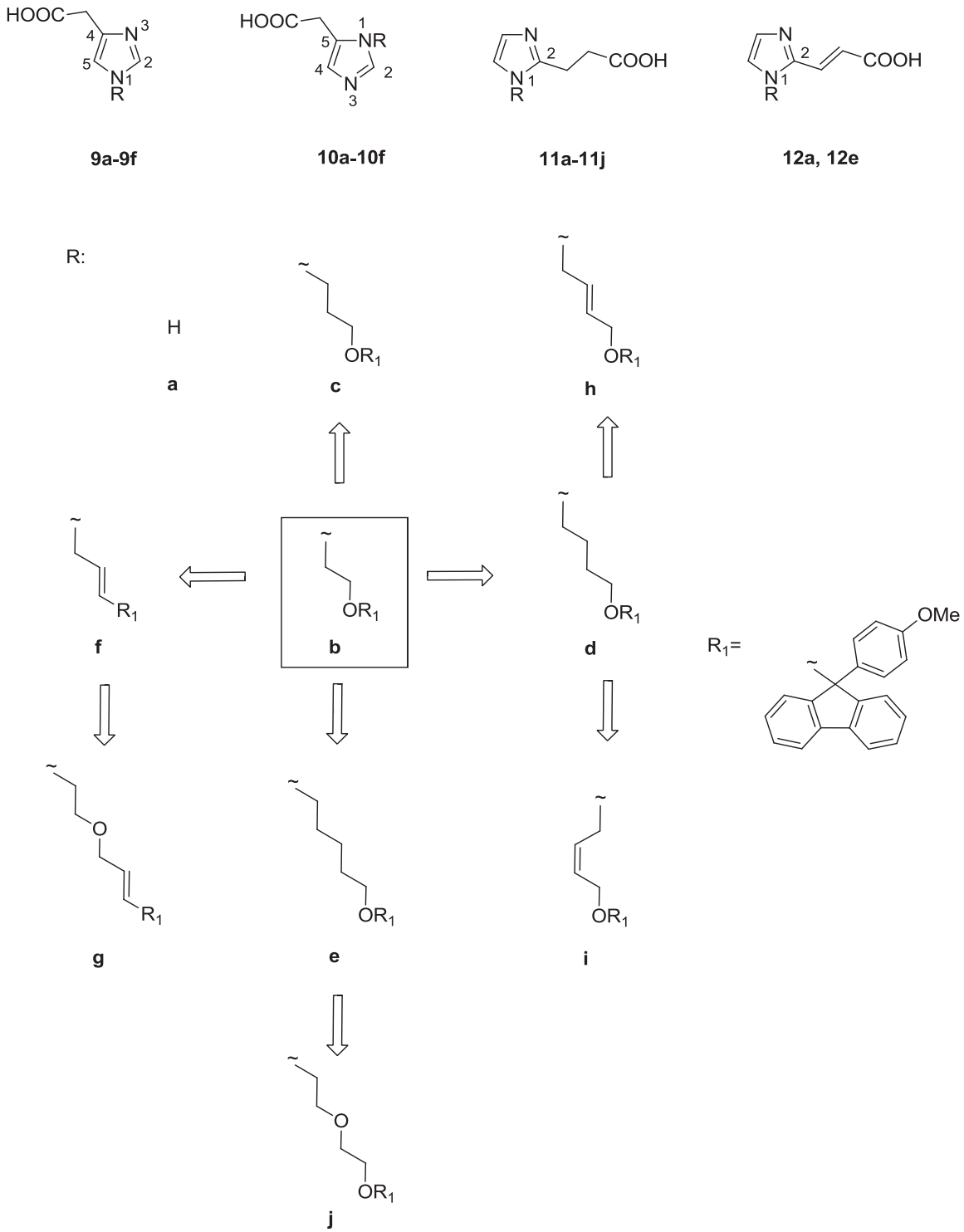
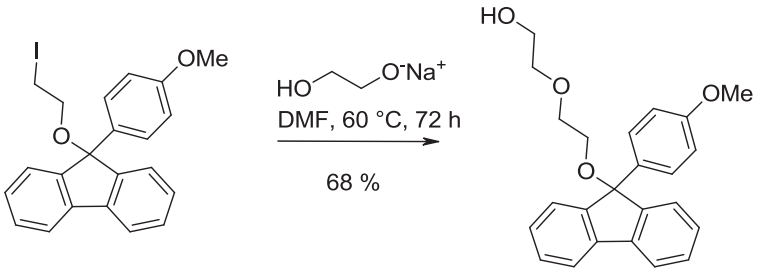


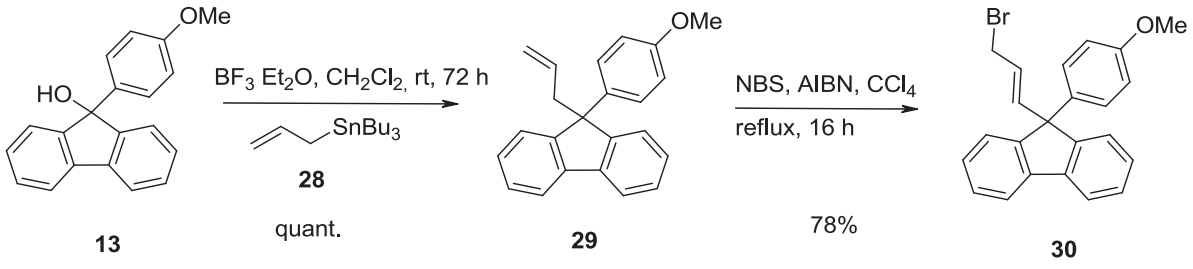

**Fig. 3.** Core structures, their 1,4-, 1,5-, and 1,2-disubstituted derivatives and the design of the lipophilic moieties **c**–**j**.

group which provided the methyl ester **37b** in 17% yield [39]. To optimize the reaction, it was repeated under identical conditions except that 1.3 equiv. of **20** was used. This increased the yield of **37b** to 22%. When in addition, the reaction time for the alkylation step was extended from 3 to 8 days 40% of **37b** could be isolated. The optimal conditions were finally reached when the reaction temperature was increased from 55 °C to 60 °C affording **37b** in 58% yield (Table 3, entry 1). In contrast, usage of 2.0 equiv. (instead of 1.3 equiv.) of **20** was counter productive, since then only 43% of **37b** could be isolated. The optimum reaction conditions for **37b** (Scheme 4) were then also used for the synthesis of the methyl esters **37c** and **37f** which could be obtained in acceptable yields of 44% and 60%, respectively, by using the bromides **22** and **30** as alkylating agents (Table 3, entry 2 and 5). For the *N*-alkylated 2-(1*H*-imidazol-5-yl)acetic acid methyl esters **37d** and **37e** with a $C_4O$ and a $C_5O$ spacer, generated by reacting **35** with the respective alkyl

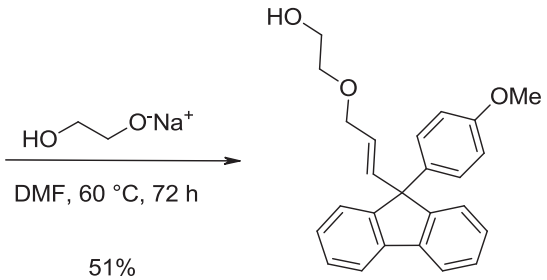



**21** **27**

**Scheme 1.** Synthesis of **27.**

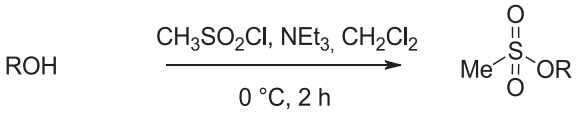



**13** **29** **30**




**31**

**Scheme 2.** Synthesis of **30** and **31.**




| | | | Ra: |
|---|---|---|---|
| **26** | 73% | **32** | i |
| **27** | 77% | **33** | j |
| **31** | 97% | **34** | g |

**Scheme 3.** Mesylation of alcohols **26**, **27**, and **31;** [a]: see Fig. 3.

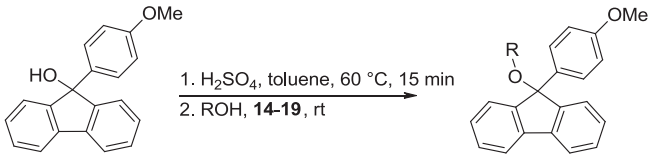
halides **23** and **24**, the subsequent deprotection under reflux in MeOH required the presence of 5% AcOH in analogy to a literature procedure [41] to yield compounds **37d** and **37e** in 55% and 42% yields (Table 3, entry 3 and 4). In absence of acid in case of compound **37d**, the yield amounted to only 17% (Table 3, entry 3).

Subsequent saponification of the esters **37b**–**37f** afforded the target compounds **10b**–**10f** in 65–100% yield (Scheme 4 and Table 3, entries 1–5).

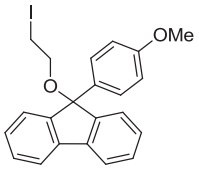
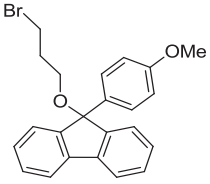
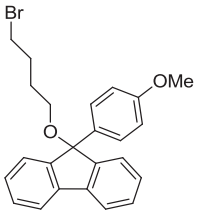
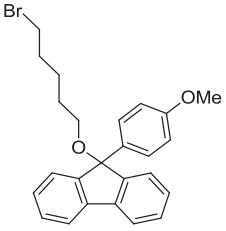
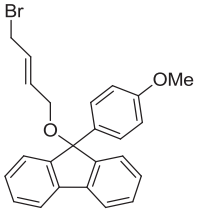
### 2.3. Synthesis of N-alkylated 2-(1H-imidazol-4-yl)acetic acids

According to literature, 1,4-disubstituted imidazole derivatives such as **38b**–**38f** can be synthesized in a regioselective manner [41]. The synthetic route, however, which in this case would

**Table 2**
Synthesis of the alkylating agents **21**–**26**.

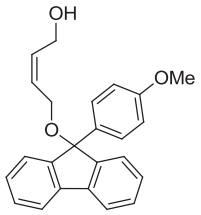



**13** [21] **21-26**

| Entry | ROH | Product | Time [h] | Isolated yield [%] |
|---|---|---|---|---|
| 1 | $I(CH_2)_2OH$ |  | 20 | 92 |
| | **14** | **21** | | |
| 2 | $Br(CH_2)_3OH$ |  | 20 | 90 |
| | **15** | **22** | | |
| 3 | $Br(CH_2)_4OH$ |  | 20 | 79 |
| | **16** [33] | **23** | | |
| 4 | $Br(CH_2)_5OH$ |  | 20 | 74 |
| | **17** [34] | **24** | | |
| 5 | $BrCH_2CH{=}CHCH_2OH_{(E)}$ |  | 18 | 60 |
| | **18** [35] | **25** | | |

(*continued on next page*)

**Table 2** (*continued*)

| Entry | ROH | Product | Time [h] | Isolated yield [%] |
|---|---|---|---|---|
| 6 | $HOCH_2CH{=}CHCH_2OH_{(Z)}$ |  | 18 | 20 |
| | **19** | **26** | | |

commence with the *N*-trityl protected imidazole derivative **35**, requires multiple steps including selective protection and deprotection of the *N*(1)- and *N*(3)-imidazol nitrogens in compound **35**. Therefore, we opted for an alternative, the synthesis of the *N*-alkylated 2-(1*H*-imidazol-4-yl)acetic acids **9b**–**9f** by non-regioselective alkylation of 1*H*-imidazol-4-ylacetic acid methyl ester · HCl (**38a**·**HCl**) [43,44] to first give the respective esters **38b**–**38f** as a mixture with the regioisomers **37b**–**37f** of which the former after separation should be transformed to the desired target compounds **9b**–**9f** by hydrolysis as shown in Scheme 5. As described in Scheme 5, the regioisomeric mixture of *N*-alkylated compounds **38b** and **37b** was obtained by treatment of **38a**·**HCl** [44] with 2.2 equiv. *t*BuOK in DMF and subsequent reaction with 1.3 equiv. of the alkyl bromide **20** [21] at 40 °C for 72 h. Though the reaction had been carried out in analogy to literature conditions, the yield was low (45%) [45]. In order to optimize the reaction, it was repeated at elevated temperature of 60 °C and 80 °C which yielded 57% and 51% of the isomeric mixture of **38b** and **37b**, respectively. When the amount of *t*BuOK was reduced from 2.2 equiv. to 2.05 equiv. keeping the reaction temperature at 60 °C, the yield decreased from 57% to 51% (regioisomeric mixture of **38b** and **37b**). The best yield of the 1,4- and 1,5-disubstituted imidazole derivatives **38b** and **37b** was finally obtained when at the beginning 2.2 equiv of *t*BuOK were applied, but the amount of alkylating agent **20** was raised from 1.3 to 2.0 equiv., then amounting to 64% (mixture of **38b** and **37b**). The thus optimized conditions were then also used for the alkylation of imidazole derivative, **38a**·**HCl** [44] with the alkylating agents **22**, **23**, and **30** which afforded the corresponding isomeric mixture in 43%–58% yield (see Table 4, entries 2, 3, 5, and Scheme 5). **38e** was prepared starting from **38a** [43] and correspondingly less *t*BuOK (1.1 equiv) was used (Table 4, entry 4). Particularly notable is that, upon extension of the chain length of the alkylating agents from three to six atoms, the isolated yields of the regioisomeric mixtures decreased whereas the regioselectivity in favor of the 1,4-regioisomers improved (see Table 4, entries 1–4). The 1,4-isomers **38b**–**38f** that had been isolated in pure form from the mixture of regioisomers were finally hydrolyzed under alkaline conditions which yielded the free amino acids **9b**–**9f** in good yields (75%–94%) (Table 4, entries 1–5 and Scheme 5).

### 2.4. Synthesis of N-alkylated 3-(1H-imidazol-2-yl)propanoic acids

The synthesis of 3-(1*H*-imidazol-2-yl)propanoic acid derivatives with appropriate *N*-substituents, i.e. compounds **11b**–**11j**, **44**, and **45**, was again accomplished by a two step procedure, the *N*-alkylation of the imidazole ring of the carboxylic acid ester **39a** followed by the alkaline hydrolysis of the ester function (Scheme 6). The alkylation of **39a** with the alkyl bromide **20** was selected as a model reaction for the optimization of the reaction conditions.

The deprotonation of **39a** [29] with 1.1 equiv. NaH and subsequent treatment with 1.3 equiv. of the alkylating agent **20** yielded only 28% of **39b**. Raising the temperature to 40 °C increased the yield of **39b** to 42%. A further increase in yield was observed when the reaction was repeated using 1.1 equiv. of *t*BuOK, instead with NaH, whereupon **39b** was obtained in 52% yield. An increase in temperature from 40 °C to 60 °C provided **39b** finally in 83% yield (Table 5, entry 3). By contrast, a further increase in temperature had an adverse effect as *N*-alkylation of **52** at 80 °C gave only 60% of **39b** compared to 83% yield at 60 °C. Under these optimized reaction conditions, ethyl ester **39a** [29] was reacted with the alkylating agents **22**–**25**, **30**, **32**–**34**, **40** [19], and **41** [21] to afford the corresponding *N*-alkylated esters **39c**–**39j**, **42** and **43** (Table 5, entries 4–11, entry 1 and 2) in 46%–85% yield. The alkylating agents 4,4-diphenylbut-3-en-1-yl bromide (**40**) [19] and 4,4,4-tris(4-methoxyphenyl)but-2-enyl bromide (**41**) [21] (Table 5, entry 1 and 2) were included in this series as they are known from scaffolds such as nipecotic acid to facilitate subtype selectivities in favor of mGAT1 and mGAT4, respectively [19,21]. In case of synthesis of compound **39j**, it was found that reduction of the reaction time from 72 h to 18 h improved the yield from 46% to 57% (Table 5, entry 11). Since treatment of **39a** [29] with 4,4-diphenylbut-3-en-1-ylbromide (**40**) [19] under the conditions optimized for the preparation of **39b** afforded compound **42** only in very low yield (6%), it was repeated under modified conditions with *t*BuOK as base and, NaI as additive ($CH_3CN$), which improved the yield from 6% to 21% (Table 5, entry 1) [23,46]. Alkaline hydrolysis of the *N*-alkylated 3-(1*H*-imidazol-2-yl)propanoic acid ethyl esters **42**, **43**, and **39b**–**39j** afforded the desired final compounds **44, 45** and **11b**–**11j** in 73%–90% yield (Table 5, entries 1–11).

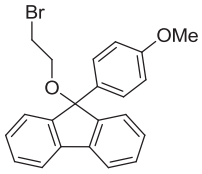
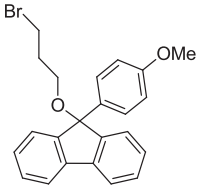
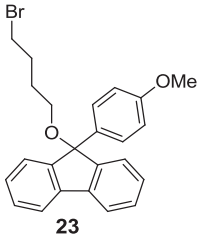
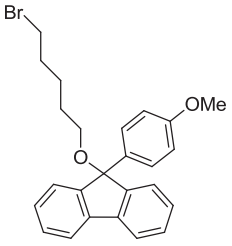
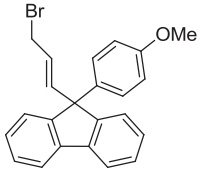
### 2.5. Synthesis of N-alkylated (2E)-3-(1H-imidazol-2-yl)prop-2-enoic acid *12e*

Additionally, compound **12e** comprising (2*E*)-3-(1*H*-imidazol-2-yl)prop-2-enoic acid as parent compound and the 9-(4-methoxyphenyl)-9*H*-fluoren moiety as lipophilic domain linked via a $C_5O$ spacer was prepared. The synthesis started from **46a** [29], which was treated at rt with *t*BuOK in DMF and subsequently with the alkylating agent **24** to provide **46e** in 97% yield. Subsequent alkaline hydrolysis of the ester group with 2 M NaOH afforded compound **12e** in 77% yield (Scheme 7).

## 3. Biological evaluation and discussion

The *N*-alkylated imidazolyl alkanoic acids **9b**–**9f**, **10b**–**10f**, **11b**–**11j**, **44**, **45**, and *N*-alkylated imidazolyl alkenoic acid **12e** were evaluated in [$^3$H]GABA uptake assays for their inhibitory potency at the four subtypes of GABA transporters, i.e. mGAT1, mGAT2, mGAT3, and mGAT4. These [$^3$H]GABA uptake assays were performed in a uniform manner using HEK cell lines, each stably

**Table 3**
Synthesis of *N*-alkylated 2-(1*H*-imidazol-5-yl)acetic acids **10b**–**10f**.

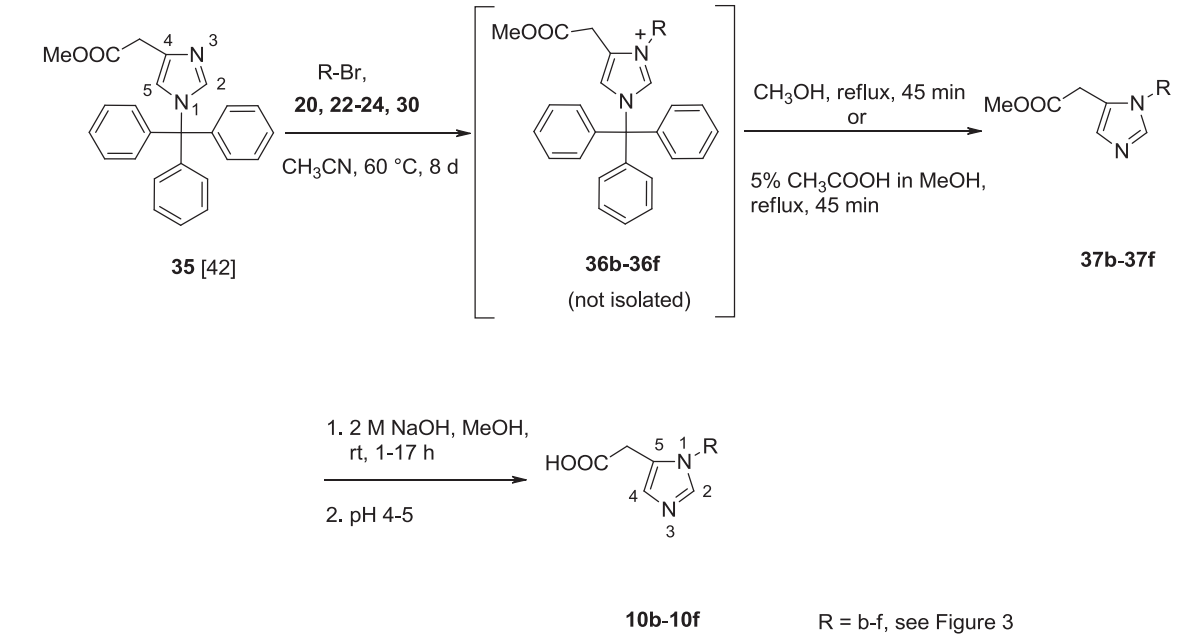
| Entry | R-Br | MeOOC | | HOOC | |
|---|---|---|---|---|---|
| | | Compound no. | Isolated yield [%] | Compound no. | Isolated yield [%] |
| 1 |  **20** [21] | **37b** | 58[a] | **10b** | 90 |
| 2 |  **22** | **37c** | 44[a] | **10c** | 65 |
| 3 |  **23** | **37d** | 55[b]<br>17[a] | **10d** | 74 |
| 4 |  **24** | **37e** | 42[b] | **10e** | 77 |
| 5 |  **30** | **37f** | 60[a] | **10f** | quant. |

[a] Deprotection with MeOH reflux [39].
[b] Deprotection with 5% HOAc in MeOH reflux [41].

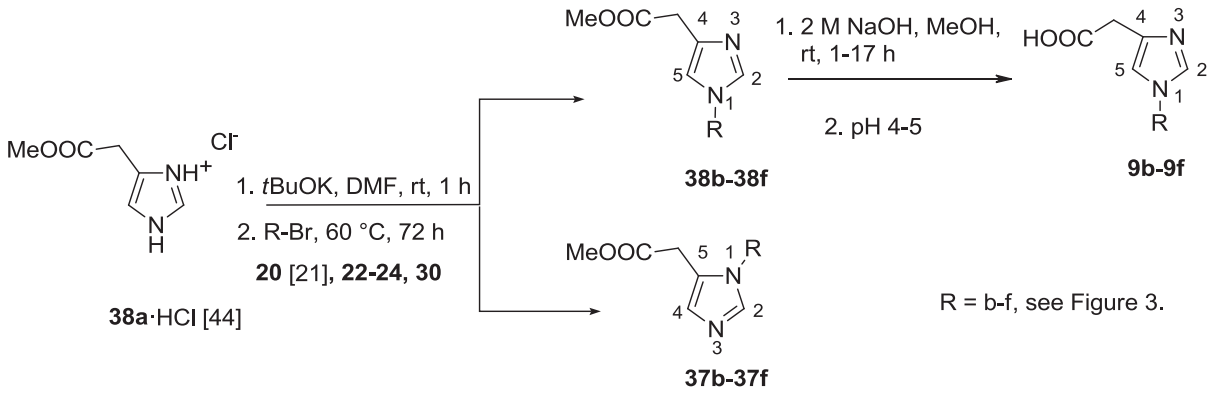
expressing one of the four GABA transporter subtypes as described in the literature [28,47]. The potency of the compounds is represented either as $pIC_{50} \pm SEM$ (for experiments done in triplicates, $n = 3$) or in exceptional cases just the $pIC_{50}$ value when one individual experiment was done. For compounds exhibiting lower potency, the percentage of the remaining [$^3$H]GABA uptake at the concentration of 100 μM is given. A $pIC_{50}$ value of $\leq 4$ was assumed for test compounds that do not reduce at 100 μM the [$^3$H]GABA uptake to $\leq$ 50% to collate the obtained results.

### 3.1. Biological evaluation of N-1-substituted 1H-imidazol-4-yl acetic acids *9b-f* and 1H-imidazol-5-yl acetic acids *10b-f*

The results of [$^3$H]GABA uptake assays at the four subtypes of GABA transporters mGAT1–mGAT4 for the N-1-substituted 1*H*-imidazol-4-ylacetic acids and 1*H*-imidazol-5-ylacetic acids, **9b**–**9f** and **10b**–**10f**, respectively, and the parent compound **9a** are summarized in Table 6. Previous studies have shown that 1*H*-imidazol-4-ylacetic acid (**9a**) exhibits good inhibitory activity especially related to mGAT3 in combination with an acceptable preference for mGAT3 compared to mGAT1 (mGAT3:mGAT1 = 35:1, Table 6, entry




**Scheme 4.** Synthesis of *N*-alkylated 2-(1*H*-imidazol-5-yl)acetic acids **10b**–**10f.**



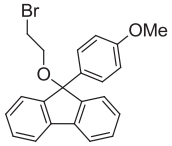
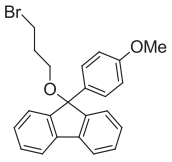
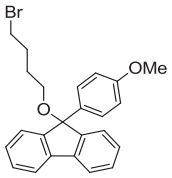
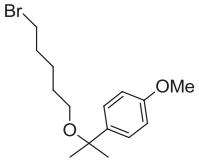
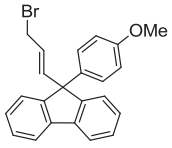

**Scheme 5.** Synthesis of *N*-alkylated 2-(1*H*-imidazol-4-yl)acetic acids **9b**–**9f**.

1) [29]. Worth mentioning here are compounds **10d** and **9d**. Both, the N-1-alkylated 1*H*-imidazol-5-ylacetic acid **10d** and the N-1-alkylated 1*H*-imidazol-4-ylacetic acid **9d** which are characterized by a spacer length of four C-atoms between nitrogen and oxygen exhibit an acceptable inhibitory potency at mGAT2 ($pIC_{50}$ value: 4.64 and 4.62, respectively, Table 6, entry 6 and 7). But both, **10d** and **9d**, show only marginal if any subtype selectivity against mGAT1, mGAT3, and mGAT4. The good inhibitory potencies of compounds **10d** and **9d** at mGAT2 is to be attributed to the $C_4O$ spacer. All other imidazole acetic acids derivatives, i.e. **9b**, **10b**, **9c**, **10c**, **9e, 10e**, **9f**, and **10f** show inhibitors potencies at mGAT1–mGAT4 in a range so low that they are almost neglectable (Table 6, entries 2–5 and entries 8–11).

### *3.2. Biological evaluation of N-1-substituted 3-(1H-imidazol-2-yl) propanoic acids **11a**–**j**, **44**, and **45***

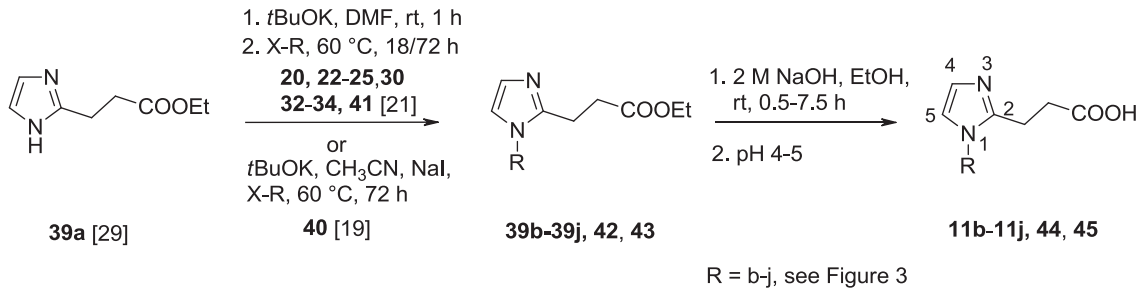
The results of the biological evaluation of 3-(1*H*-imidazol-2-yl) propanoic acid (**11a**) [29] and the *N*-alkylated derivatives **11b**–**11j**, and **44**, **45** are presented in Table 7. In this series, compounds **44** and **45** containing the 4,4-diphenylbut-3-en-1-yl and the 4,4,4-tris(4-methoxyphenyl)but-2-en-1-yl unit characteristic for GABA uptake inhibitors selective for mGAT1 and mGAT4, respectively, attached to the core structure **11a** have also been included to achieve a more comprehensive set of compounds for the establishment of structure-activity-relationship (Table 7, entries 2 and 3). As shown in previous studies, the starting compound **11a** displays slightly lower mGAT3 inhibitory potency than 2-(1*H*-imidazole-4-yl)acetic acid (**9a**), but exhibits an improved mGAT3 selectivity of 18-fold over mGAT2 and 7-fold over mGAT4 (Table 7, entry 1) [29]. Contrary to the expectations for an improved inhibitory potency at mGAT3, the introduction of the 2-[9-(4-methoxyphenyl)-9*H*-fluoren-9-yl]oxyethyl moiety (**b**) into **11a**, generally enhancing mGAT3 potency, does not give rise to a significant enhancement of potency at this or any other of the GABA transporter subtypes (Table 7, entry 4). For compound **44** in which the 3-(1*H*-imidazol-2-yl)propanoic acid (**11a**) is provided with a 4,4-diphenylbut-3-en-1-yl moiety also no significant improvement of inhibitory potency as compared to **11a** is observed, neither at mGAT1 or at any of the other GABA transporter subtypes (Table 7, entry 2). In contrast, with a $pIC_{50}$ value of 5.10 ± 0.04, **45** shows good mGAT4 inhibitory activity combined with certain preference

**Table 4**
*N*-Alkylated 2-(1*H*-imidazol-4-yl)acetic acids.

| Entry | R-Br | 1,4-Isomer | 1,5-Isomer | Isolated yield of 1,4-isomer [%] | Compound no. | Isolated yield [%] |
|---|---|---|---|---|---|---|
| | | [Ratio **1,4**-:**1,5**-isomer][a] Total isolated yield [%] | | | | |
| 1 |  **20** [21] | **38b** | **37b** [0.76:0.24] 64 | 42 | **9b** | 93 |
| 2 |  **22** | **38c** | **37c** [0.77:0.23] 50 | 27 | **9c** | 75 |
| 3 |  **23** | **38d** | **37d** [0.8:0.2] 43 | 29 | **9d** | 83 |
| 4 |  | **38e** | **37e** [0.9:0.1] 34 | 29[b] | **9e** | 88 |
| 5 |  **30** | **38f** | **37f** [0.6:0.4] 58 | 28 | **9f** | 94 |

[a] Ratio determined by $^1$H NMR-Spectrum.
[b] **38a** [43] was used as starting material. Correspondingly, less *t*BuOK (1.1 equiv.) was used.

for this subtype (subtype selectivity: mGAT4:mGAT1 ≥ 13:1, mGAT4:mGAT2 ≥ 13:1 and mGAT4:mGAT3 ~ 3:1, Table 7, entry 3). Worth mentioning are also compounds **11d**, **11h**, and **11i** with a $C_4O$ spacer. Similar to the 1,5-isomer **10d** (Table 6, entry 6) and the 1,4-isomer **9d** (Table 6, entry 7), the $C_4O$ spacer of compound **11d** also has positive effects on the mGAT2 inhibitory activity ($pIC_{50}$ value: 4.60 ± 0.08). With a subtype selectivity of mGAT2:mGAT1 = 6:1, mGAT2:mGAT3 = 4:1, and mGAT2:mGAT4 = 7:1 (Table 7, entry 6) **11d** displays an mGAT2 selectivity similar to that of the 1,5-isomer **10d**. As compared to **11d** possessing a $C_4O$ spacer, the (2*E*)-4-oxybut-2-ene-1-yl spacer of compound **11h** hardly influences the inhibitory potencies at mGAT1–mGAT4 (Table 7, entry 10). In contrast thereto, the change of the double bond configuration in **11h** from (*E*) to (*Z*) resulting in compound **11i** leads to an improvement in the potency at mGAT3 and mGAT4 from $pIC_{50}$ values of ~4 (**11h**, Table 7, entry 10) to $pIC_{50}$ values 4.80 and 4.88 ± 0.19, respectively (**11i**, Table 7, entry 11). The extension of the spacer to a $C_5O$ unit leads to compound **11e**, which exhibits with a $pIC_{50}$ value of 4.93 ± 0.03 an acceptable mGAT1 inhibition, but misses subtype selectivity (Table 7, entry 7). The additional ether oxygen within the spacer of compound **11j** ($C_2OC_2O$) deteriorates the inhibitory potencies relating to mGAT1, mGAT2, and mGAT4 as compared to compound **11e**, whereas the inhibitory potency at mGAT3 is hardly influenced (Table 7, entry 12). Compound **11f**, which consists of the 3-(1*H*-imidazol-2-yl)propanoic acid core structure (**11a**) and the (2*E*)-2-[9-(4-methoxyphenyl)-9*H*-fluoren-




**Scheme 6.** Synthesis of *N*-alkylated 3-(1*H*-imidazol-2-yl)propanoic acids **44**, **45**, and **11b**–**11j**.

9-yl]prop-2-en-1-yl moiety (**f**), exhibits low to mediocre potency at all four GABA transporter subtypes (Table 7, entry 8). Compound **11g**, derived from **11f** by a chain extension with a $C_2O$ unit shows similar inhibitory potencies ($pIC_{50} = 4.51–4.66$) at mGAT1–mGAT4 (Table 7, entry 9).

To summarize, among the N-1-substituted 3-(1*H*-imidazol-2-yl) propanoic acids **11b-j**, compound **11d** with a $C_4O$ spacer showed similar positive effects as compounds **9d** and **10d** on the mGAT2 inhibitory activity.

### 3.3. Biological evaluation of N-alkylated (2E)-3-(1H-imidazol-2-yl) prop-2-enoic acid *12e*

The results of the GABA uptake studies of SNAP-5294 (**6**) [21], (2*E*)-3-(1*H*-imidazol-2-yl)prop-2-enoic acid **12a** [29], and its *N*-alkyl derivative **12e** exhibiting the 2-[9-(4-methoxyphenyl)-9*H*-fluoren-9-yl]oxypentyl residue (**e**) are summarized in Table 8. According to results reported in literature [21], SNAP-5294 (**6**) exhibits moderate inhibitory potency at rGAT2 (≡ mGAT3) in combination with certain selectivity for this transporter (Table 8, entry 1). But according to the data obtained employing our test system based on HEK cell lines expressing mice transporters [28], SNAP-5294 (**6**) possesses its highest inhibitory but still mediocre potency at mGAT4 ($pIC_{50}$ 4.52 ± 0.08) in combination with low potency at mGAT3 ($pIC_{50}$ 4.03 ± 0.05, Table 8, entry 2). The reason for this reversal of the subtype selectivity of **6** at rGAT2 (≡ mGAT3) and hGAT3 (≡ mGAT4) versus mGAT3 and mGAT4 is unclear. Though not very likely this could be due to the different species, the transporters are derived from. Interestingly, core structure **12a** shows a lower inhibitory potency at mGAT3 as compared to the saturated analogue **11a** (**11a**: $pIC_{50}$ 4.54 ± 0.15; Table 7, entry 1; **12a**: $pIC_{50}$ 3.71 ± 0.05; Table 8, entry 3). The opposite is true for the *N*-substituted derivatives **12e** and **11e** both exhibiting the same residue (**e**). With a $pIC_{50}$ value of 5.13 ± 0.04 (Table 8, entry 4), imidazole derivative **12e** has gained about 1.5 log units in potency at mGAT3 as compared to the parent compound **12a** ($pIC_{50}$ 3.71 ± 0.05, Table 8, entry 3). This value surpasses the potency of its saturated analogue **11e** by about a half log unit (**11e**: $pIC_{50}$ 4.63, Table 7, entry 7) and exceeds the potency of SNAP-5294 (**6**), the prototypic inhibitor of mGAT3, at mGAT4 in the present test system by a factor of 13 (Table 8, entry 4). Clearly, the improved inhibitory potency at mGAT3 observed for imidazole derivative **12e** as compared to **11e** is to be attributed to the additional double bond present in the carboxylic acid side chain of this compound. Compared to the clinically marketed drug tiagabine (**5**: an mGAT1 selective inhibitor, Table 8, entry 5), **12e** shows a decrease in the inhibitory potency at mGAT1, but an increase in potency at mGAT2 to mGAT4 so that $pIC_{50}$ values at mGAT1-mGAT4 are all covering the same range - around $pIC_{50}$ of 5.0 – with the nominally highest potency being displayed at mGAT3.

## 4. Conclusion

In summary, new series of potential GABA uptake inhibitors derived from the core structures 2-(1*H*-imidazol-4-yl)acetic acid (**9a**) and 3-(1*H*-imidazol-2-yl)propanoic acid (**11a**) as conformational restricted analogs of GABA (**1**) by linkage with a 2-[9-(4-methoxyphenyl)-9*H*-fluoren-9-yl] moiety via spacers of different length attached to one of the ring nitrogens have been synthesized and characterized for their biological activity at mGAT1–mGAT4. Compounds, **9b**, **10b**, and **11b** comprising the core structure **9a** and **11a**, respectively, both of which exhibit good mGAT3 inhibition and preference for this transporter subtype, and the 2-[9-(4-methoxyphenyl)-9*H*-fluoren-9-yl]oxyethyl moiety with an $OC_2$ spacer which residue is characteristic for mGAT3 inhibitors [21], were found to be devoid of any significant inhibitory potency at all four GABA transporters. Upon elongation of the spacer-length between nitrogen, the fluorene moiety from $OC_2$ up to $OC_4$, a gain in inhibitory potency at mGAT2 occurred. Thus, **9d**, **10d**, and **11d** displaying a $C_4O$ spacer exhibit an acceptable mGAT2 inhibitory activity with $pIC_{50}$ values of, 4.62 4.64 and 4.60 ± 0.08, respectively. Of these, the imidazole acetic acid derivative **10d** and the propanoic acid derivative **11d** show also a slight preference for mGAT2. Within the series of imidazole-2-ylpropanoic acid and propenoic acids, the propenoic acid derivative **12e** was found to display a $pIC_{50}$ value of 5.13 ± 0.04 at mGAT3. With this $pIC_{50}$ value **12e** ranges among the most potent mGAT3 inhibitors. But it is devoid of any significant subtype selectivity. The $pIC_{50}$ value at mGAT3 though being nominally the highest is similar to those for the other GABA transporters as for example for mGAT4 ($pIC_{50}$ 4.99 ± 0.13). In contrast to SNAP-5294 (**6**) which in the present test system exhibits its best inhibitory potency at mGAT4 and not at mGAT3 as published [21], **12e** shows an inhibitory potency of approximately one log unit higher than that of **6** at mGAT3 (though this is similar to the value at mGAT4 for **12e**) (Table 8, entry 2 and 4).

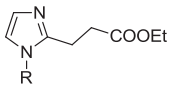
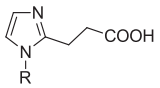
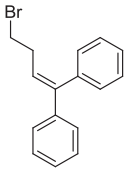
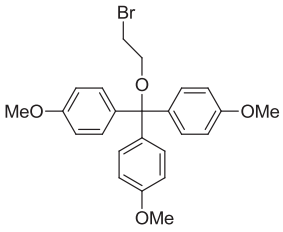
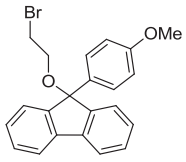
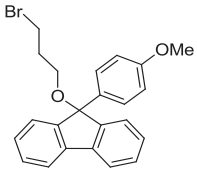
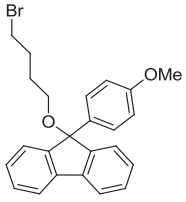
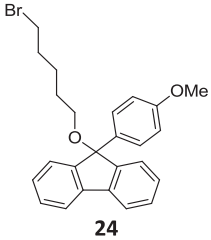
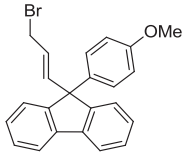
Up to date, only few selective inhibitors of mGAT3 have been published. In this study, the *N*-alkylated (2*E*)-3-(1*H*-imidazol-2-yl) prop-2-enoic acid **12e** has been identified as a reasonably potent inhibitor at mGAT3 that in the present test system surpasses SNAP-5294 (**6**), with regard to potency at and preference for mGAT3 over mGAT4. Thus, **12e** is to date the most potent mGAT3 inhibitor. This structure can be regarded as the best lead for the development of new uptake inhibitors of mGAT3 with high potency, their low selectivity to this transporter protein notwithstanding. Efforts to develop more potent and selective mGAT3 inhibitors are in progress.

## 5. Experimental protocols

### 5.1. Chemistry

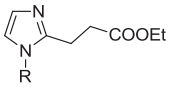
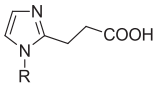
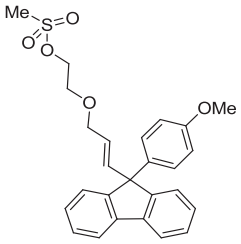
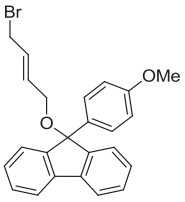
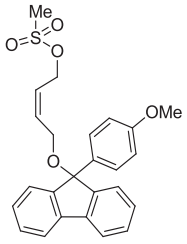
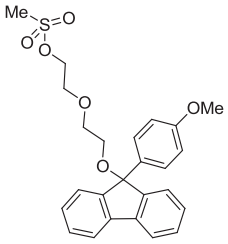
Solvents were p.a. quality and freshly distilled before use.

**Table 5**
*N*-Alkylated 3-(1*H*-imidazol-2-yl)propanoic acids.

| Entry | X-R |  | |  | |
|---|---|---|---|---|---|
| | | Compound no. | Isolated yield [%] | Compound no. | Isolated yield [%] |
| 1 |  **40** [19] | **42** | 6[a]<br>21[b] | **44** | 85 |
| 2 |  **41** [21] | **43** | 70[a] | **45** | 85 |
| 3 |  **20** [21] | **39b** | 83[a] | **11b** | 90 |
| 4 |  **22** | **39c** | 78[a] | **11c** | 73 |
| 5 |  **23** | **39d** | 85[a] | **11d** | 80 |
| 6 |  **24** | **39e** | 74[a] | **11e** | 83 |
| 7 |  **30** | **39f** | 64[a] | **11f** | 90 |

(*continued on next page*)

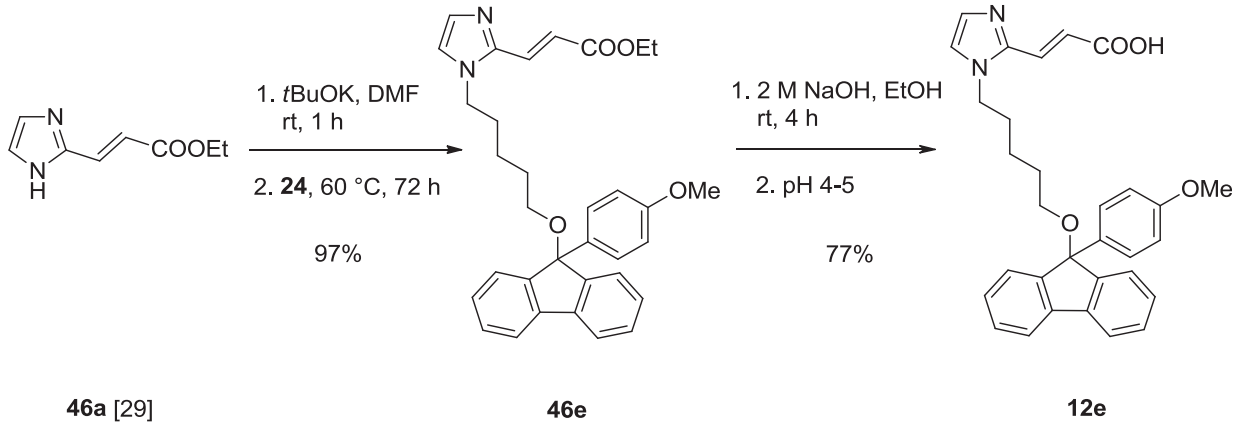
**Table 5** (*continued*)

| Entry | X-R |  | |  | |
|---|---|---|---|---|---|
| | | Compound no. | Isolated yield [%] | Compound no. | Isolated yield [%] |
| 8 |  **34** | **39g** | 69[a] | **11g** | 88 |
| 9 |  **25** | **39h** | 68[a] | **11h** | 82 |
| 10 |  **32** | **39i** | 54[a] | **11i** | 73 |
| 11 |  **33** | **39j** | 46[a]<br>57[c] | **11j** | 78 |

[a] *t*BuOK, DMF, r.t., 1 h 2. R-X, 60 °C, 72 h.
[b] R -X, C $H_3CN$, *t*BuOK, NaI, 60 °C, 72 h.
[c] *t*BuOK, DMF, r.t., 1 h 2. R-X, 60 °C, 18 h.

Purchased reagents were used without further purification. TLC plates were made from silica gel 60 $F_{254}$ on aluminium sheet (Merck). Column chromatography (CC) was carried out using Merck silica gel 60 (mesh 0.040–0.063 mm) as stationary phase. Melting points: m.p. (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) using TMS as internal standard and integrated with the NMR software MestReNova. IR spectroscopy: FT-IR Spectrometer 410 (Jasco); samples were measured as KBr-pellets. Mass spectrometry (MS): Mass Spectrometer 5989 A with 59980 B 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); analysis indicated by the symbols of the elements were within ±0.4% of the theoretical values.

9-(4-methoxyphenyl)-9*H*-fluoren-9-ol (**13**) [21], 4-bromobutanol (**16**) [33], 5-bromopentane-1-ol (**17**) [34], (2*E*)-4-bromobut-2-en-1-ol (**18**) [35], 9-(2-bromoethoxy)-9-methoxyphenyl-9*H*-fluorene (**20**) [21], (1-triphenylmethyl-1*H*-imidazol-4-yl)acetic acid methyl ester (**35**) [42], 1*H*-imidazol-4-ylacetic acid methyl ester HCl (**38a**·**HCl**) [43,44], 1*H*-imidazol-4-ylacetic acid methyl ester (**38a**) [43], 3-(1*H*-imidazol-2-yl)




**Scheme 7.** Synthesis of **12e.**

propanoic acid ethyl ester (**39a**) [29], and (2*E*)-3-(1*H*-Imidazol-2-yl)prop-2-enoic acid ethyl ester (**46a**) [29] were prepared according to standard procedures in the literature [21,29,33–35,43,44]. 2-iodoethanol (**14**), 3-bromopropanol (**15**), (2*Z*)-but-2-ene-1,4-diol (**19**), and allytributylstannane (**28**) were commercially available.

*5.1.1. General procedure for the synthesis of alkylating agents (**GP1**) [21].*

Conc. $H_2SO_4$ (0.3 equiv.) was added to 9-(4-methoxyphenyl) fluoren-9-ol (**13**) (1.0 equiv.) in toluene and warmed up to 60 °C for 15 min. After cooling the solution to rt the corresponding hydroxyl alkyl halide (1.5 equiv) or the alkyldiol (2.0 equiv.) was added. The reaction mixture was stirred at rt for the given time and then partitioned between water and toluene. The organic phase was dried over $MgSO_4$, filtered, and concentrated to dryness. The crude product was then purified by CC (*iso*-hexane/EtOAc = 9.5:0.5).

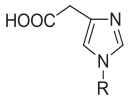
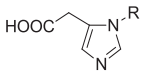
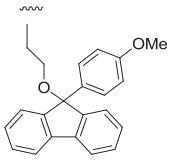
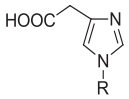
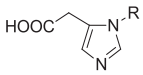
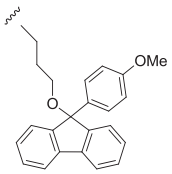
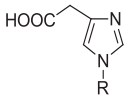
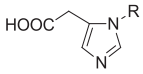
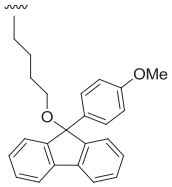
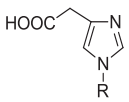
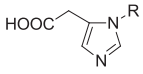
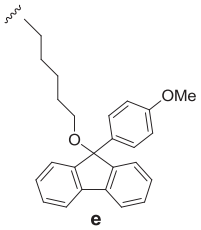
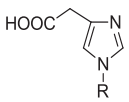
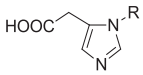
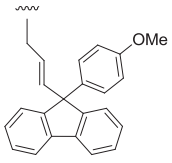
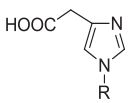
*5.1.1.1. 9-(2-Iodoethoxy)-9-(4-methoxyphenyl)-9H-fluorene (**21**).* According to **GP1:** 9-(4-methoxyphenyl)fluoren-9-ol (**13**) [21] (1.4 g, 4.8 mmol), toluene (12 mL), conc. $H_2SO_4$ (147 mg, 1.50 mmol, 80.0 μL), 2-iodoethanol (**14**) (1.26 g, 7.35 mmol, 0.573 mL), 20 h. Yield: 2.0 g (92%); colourless solid, m.p. 96–98 °C; TLC: $R_f$ = 0.24 (*iso*-hexane/EtOAc = 9.5/0.5); IR (KBr): 3035, 2931, 2903, 2841, 2044, 1951, 1918, 1605, 1580, 1508, 1447, 1302, 1252, 1184, 1169, 1107, 1031, 993 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 3.15–3.20 (m, 2 H, $CH_2O$), 3.20–3.24 (m, 2 H, $ICH_2$), 3.75 (s, 3 H, $CH_3$), 6.76–6.81 (m, 2 H, $H_{ar}$), 7.26 (td, $J$ = 7.4/1.2 Hz, 2 H, $H_{ar}$), 7.29–7.32 (m, 2 H, $H_{ar}$), 7.33 (d, $J$ = 7.4 Hz, 2 H, $H_{ar}$), 7.37 (td, $J$ = 7.4/1.2 Hz, 2 H, $H_{ar}$), 7.66 (d, $J$ = 7.4 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 4.43 (t, 1 C, $ICH_2$), 55.20 (q, 1 C, $CH_3$), 63.93 (t, 1 C, $CH_2O$), 88.42 (s, 1 C, $CH_2OC$), 113.55 (d, 2 C, $C_{ar}$), 120.00 (d, 2 C, $C_{ar}$), 125.43 (d, 2 C, $C_{ar}$), 126.84 (d, 2 C, $C_{ar}$), 128.23 (d, 2 C, $C_{ar}$), 129.15 (d, 2 C, $C_{ar}$), 135.29 (s, 1 C, $C_{ar}$), 140.51 (s, 2 C, $C_{ar}$), 146.87 (s, 2 C, $C_{ar}$), 158.83 (s, 1 C, $C_{ar}$); MS (EI, 70 eV) *m/z* (%): 442 (30, $M^+$), 271 (100); HRMS (EI, 70 eV): ($C_{22}H_{19}IO_2$) calc. 442.0430, found 442.0475; Anal. $C_{22}H_{19}IO_2$ (C, H, I, O).

*5.1.1.2. 9-(3-Bromopropoxy)-9-(4-methoxyphenyl)-9H-fluorene (**22**).* According to **GP1:** 9-(4-methoxyphenyl)fluoren-9-ol (**13**) [21] (1.4 g, 4.9 mmol), toluene (12 mL), conc. $H_2SO_4$ (147 mg, 1.50 mmol, 80.0 μL), 3-bromopropan-1-ol (**15**) (1.02 g, 7.35 mmol, 0.643 mL), 20 h. Yield: 1.8 g (90%); colourless solid, m.p. 102–105 °C; TLC: $R_f$ = 0.39 (*iso*-hexane/EtOAc = 9.5:0.5); IR (KBr): 3065, 3039, 3008, 2954, 2932, 2875, 2836, 2044, 1954, 1917, 1844, 1809, 1608, 1581, 1509, 1449, 1417, 1302, 1284, 1250, 1216, 1170, 1103, 1066, 1035 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 1.98–2.05 (m, 2 H, $BrCH_2CH_2$), 3.08 (t, $J$ = 5.7 Hz, 2 H, $CH_2O$), 3.54 (t, $J$ = 6.7 Hz, 2 H, $BrCH_2$), 3.74 (s, 3 H, $CH_3$), 6.73–6.80 (m, 2 H, $H_{ar}$), 7.19–7.31 (m, 6 H, $H_{ar}$), 7.36 (td, $J$ = 7.5/1.7 Hz, 2 H, $H_{ar}$), 7.67 (d, $J$ = 7.5 Hz, 2 H $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 30.73 (t, 1 C, $BrCH_2$), 33.32 (t, 1 C, $BrCH_2CH_2$), 55.17 (q, 1 C, $CH_3$), 60.68 (t, 1 C, $CH_2O$), 88.19 (s, 1 C, $CH_2OC$), 113.48 (d, 2 C, $C_{ar}$), 119.93 (d, 2 C, $C_{ar}$), 125.19 (d, 2 C, $C_{ar}$), 126.69 (d, 2 C, $C_{ar}$), 128.15 (d, 2 C, $C_{ar}$), 128.97 (d, 2 C, $C_{ar}$), 135.61 (s, 1 C, $C_{ar}$), 140.56 (s, 2 C, $C_{ar}$), 147.18 (s, 2 C, $C_{ar}$), 158.73 (s, 1 C, $C_{ar}$); MS (EI, 70 eV) *m/z* (%): 410 (10, $M^+$), 408 (10, $M^+$), 271 (100); HRMS (EI, 70 eV): ($C_{23}H_{21}O_2Br$) calc. 408.0725, found 408.0729.

*5.1.1.3. 9-(4-Bromobutoxy)-9-(4-methoxyphenyl)-9H-fluorene (**23**).* According to **GP1:** 9-(4-methoxyphenyl)fluoren-9-ol (**13**) [21] (2.6 g, 9.0 mmol), toluene (19 mL), conc. $H_2SO_4$ (275 mg, 2.81 mmol, 0.15 mL), 4-bromobutan-1-ol (**16**) [33] (2.10 g, 13.7 mmol), 20 h. Yield: 3.1 g (79%); colourless solid, m.p. 95–97 °C; TLC: $R_f$ = 0.3 (*iso*-hexane/EtOAc = 9.5:0.5); IR (KBr): 3037, 3003, 2935, 2867, 2837, 2042, 1968, 1933, 1899, 1830, 1646, 1605, 1508, 1450, 1441, 1297, 1247, 1178, 1165, 1101, 1071, 1029 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 1.57–1.70 (m, 2 H, $CH_2CH_2O$), 1.89–2.03 (m, 2 H, $BrCH_2CH_2$), 2.99 (t, $J$ = 6.0 Hz, 2 H, $CH_2O$), 3.37 (t, $J$ = 6.8 Hz, 2 H, $BrCH_2$), 3.74 (s, 3 H, $CH_3$), 6.72–6.80 (m, 2 H, $H_{ar}$), 7.21–7.29 (m, 6 H, $H_{ar}$), 7.31–7.42 (m, 2 H, $H_{ar}$), 7.67 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR (100 MHz, $CDCl_3$, 19.7 °C, $CDCl_3$): $\delta$ = 28.80 (t, 1 C, $CH_2CH_2O$), 29.94 (t, 1 C, $BrCH_2CH_2$), 34.05 (t, 1 C, $BrCH_2$), 55.39 (q, 1 C, $CH_3$), 62.23 (t, 1 C, $CH_2O$), 88.40 (s, 1 C, $CH_2OC$), 113.67 (d, 2 C, $C_{ar}$), 120.14 (d, 2 C, $C_{ar}$), 125.31 (d, 2 C, $C_{ar}$), 126.92 (d, 2 C, $C_{ar}$), 128.34 (d, 2 C, $C_{ar}$), 129.12 (d, 2 C, $C_{ar}$), 135.92 (s, 1 C, $C_{ar}$), 140.78 (s, 2 C, $C_{ar}$), 147.65 (s, 2 C, $C_{ar}$), 158.88 (s, 1 C, $C_{ar}$); MS (EI, 70 eV) *m/z* (%): 424 (6, $M^+$), 271 (100); HRMS (EI, 70 eV): ($C_{24}H_{23}BrO_2$) calc. 422.0881, found 422.0883; Anal. $C_{24}H_{23}BrO_2$ (C, H, Br, O).

*5.1.1.4. 9-(5-Bromopentoxy)-9-(4-methoxyphenyl)-9H-fluorene (**24**).* According to **GP1:** 9-(4-methoxyphenyl)fluoren-9-ol (**13**) [21] (5.0 g, 17 mmol), toluene (35 mL), conc. $H_2SO_4$ (514 mg, 5.24 mmol, 0.280 mL), 5-bromopentan-1-ol (**17**) [34] (3.34 g, 19.6 mmol), 20 h. Yield: 5.64 g (74%); light yellow crystals, m.p. 103–105 °C; TLC: $R_f$ = 0.24 (*iso*-hexane/EtOAc = 9.5:0.5); IR (KBr): 3062, 3004, 2930, 2911, 2866, 2834, 1604, 1578, 1508, 1448, 1301, 1251, 1167, 1083, 1033 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 1.43–1.55 (m, 4 H, $CH_2CH_2CH_2O$), 1.79 (tt, $J$ = 7.2/6.8 Hz, 2 H, $BrCH_2CH_2$), 2.97 (t, $J$ = 5.8 Hz, 2 H, $CH_2O$), 3.38 (t, $J$ = 6.8 Hz, 2 H, $BrCH_2$), 3.74 (s, 3 H, $CH_3$), 6.74–6.79 (m, 2 H, $H_{ar}$), 7.23–7.30 (m, 6 H, $H_{ar}$), 7.33–7.39 (m, 2 H, $H_{ar}$), 7.67 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 24.86 (t, 1 C, $CH_2CH_2CH_2O$), 29.14 (t, 1 C, $CH_2CH_2CH_2O$), 32.46 (t, 1 C, $BrCH_2CH_2$), 33.91 (t, 1 C, $BrCH_2$), 55.17 (q, 1 C, $CH_3$), 62.68 (t, 1 C, $CH_2O$), 88.15 (s, 1 C, $CH_2OC$), 113.44 (d, 2 C, $C_{ar}$), 119.88 (d, 2 C, $C_{ar}$),

**Table 6**
$pIC_{50}$ values of *N*-alkylated 2-(1*H*-imidazolyl)acetic acids **10b–10f** and **9a–9f** at mGAT1–mGAT4.

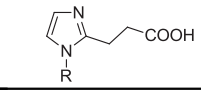
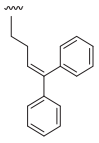
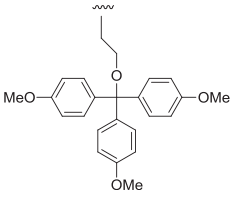
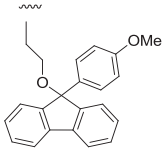
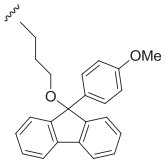
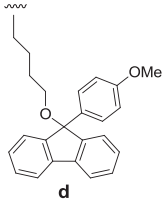
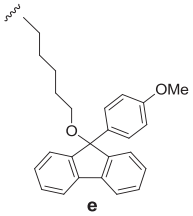
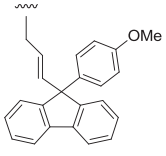
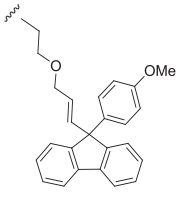
| Entry | Compound | | no. | mGAT1 | mGAT2 | mGAT3 | mGAT4 |
|---|---|---|---|---|---|---|---|
| | Core structure | R = | | | | | |
| 1 |  | H [29] **a** | **9a** | 3.21 ± 0.12 | 3.99 ± 0.05 | **4.76 ± 0.08** | 4.33 ± 0.01 |
| 2 |  |  **b** | **10b** | 67.2%[a] | 57.9%[a] | 50.8%[a] | 46.0%[a] |
| 3 |  | | **9b** | 56.6%[a] | 44.0%[a] | 46.7%[a] | 85.4%[a] |
| 4 |  |  **c** | **10c** | 50.1%[a] | 70.1%[a] | 4.09 ± 0.11 | 55.6%[a] |
| 5 |  | | **9c** | 84.2%[a] | 4.01 ± 0.15 | 51.4%[a] | 61.4%[a] |
| 6 |  |  **d** | **10d** | 70.8%[a] | **4.64**[b] | 41.7%[a] | 59.0%[a] |
| 7 |  | | **9d** | 64.9%[a] | **4.62**[b] | 4.40[b] | 4.31[b] |
| 8 |  |  **e** | **10e** | 4.10[b] | 38.5%[a] | 68.0%[a] | 77.4%[a] |
| 9 |  | | **9e** | 72.7%[a] | 4.21[b] | 4.01[b] | 3.98[b] |
| 10 |  |  **f** | **10f** | 3.90 ± 0.09 | 3.78 ± 0.05 | 4.10 ± 0.12 | 3.96 ± 0.09 |
| 11 |  | | **9f** | 62.4%[a] | 24.2%[a] | 4.32 ± 0.06 | 4.40 ± 0.07 |

[a] Percent inhibition at 100 μM.
[b] Value from a single experiment.

125.15 (d, 2 C, $C_{ar}$), 126.72 (d, 2 C, $C_{ar}$), 128.07 (d, 2 C, $C_{ar}$), 128.84 (d, 2 C, $C_{ar}$), 135.86 (s, 1 C, $C_{ar}$), 140.55 (s, 2 C, $C_{ar}$), 147.54 (s, 2 C, $C_{ar}$), 158.64 (s, 1 C, $C_{ar}$); MS (EI, 70 eV) *m/z* (%): 436 (4, $M^+$), 271 (100); HRMS (EI, 70 eV): ($C_{25}H_{25}BrO_2$) calc. 436.1038, found 436.1054; Anal. $C_{25}H_{25}BrO_2$ (C, H, Br, O).

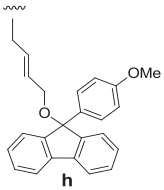
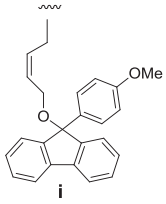
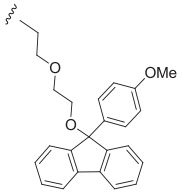
*5.1.1.5. 9-[(2E)-4-bromobut-2-en-1-yloxy]-9-(4-methoxyphenyl)-9H-fluorene (**25**).* According to **GP1:** 9-(4-methoxyphenyl)fluoren-9-ol (**13**) [21] (4.77 g, 16.5 mmol), toluene (30 mL), conc. $H_2SO_4$ (496 mg, 5.05 mmol, 0.270 mL), (2*E*)-4-bromobut-2-en-1-ol (**18**) [35] (3.74 g, 24.8 mmol), 18 h. Yield: 4.1 g (60%); light yellow solid, m.p. 95–97 °C; TLC: $R_f$ = 0.21 (*iso*-hexane/EtOAc = 9.5:0.5); IR (KBr): 3037, 2999, 2960, 2906, 2858, 2836, 2040, 1968, 1933, 1897, 1829, 1717, 1643, 1605, 1508, 1450, 1297, 1247, 1178, 1165, 1102, 1053, 1028, 1006 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 3.55 ($d_{br}$, $J$ = 5.1 Hz, 2 H, $CH_2O$), 3.74 (s, 3 H, $CH_3$), 3.91 (d, $J$ = 7.5 Hz, 2 H, $BrCH_2$), 5.74 (dt, $J$ = 5.1/15.2 Hz, 1 H, $CHCH_2O$), 5.90 (dtt, $J$ = 15.2/7.5/1.5 Hz, 1 H, $BrCH_2CH$), 6.73–6.82 (m, 2 H, $H_{ar}$), 7.21–7.32 (m, 6 H, $H_{ar}$), 7.37 (td, $J$ = 7.5/1.4 Hz, 2 H, $H_{ar}$), 7.67 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 32.47 (t, 1 C, $BrCH_2$), 55.17 (q, 1 C, $CH_3$), 63.06 (t, 1 C, $CH_2O$), 88.46 (s, 1 C, $CH_2OC$), 113.48 (d, 2 C, $C_{ar}$), 119.95 (d, 2 C, $C_{ar}$), 125.25 (d, 2 C, $C_{ar}$), 126.78 (d, 2 C, $C_{ar}$), 127.13 (d, 1 C, $BrCH_2CH$), 128.20 (d, 2 C, $C_{ar}$), 129.07 (d, 2 C, $C_{ar}$), 132.50 (d, 1 C, $CHCH_2O$), 135.28 (s, 1 C, $C_{ar}$), 140.56 (s, 2 C, $C_{ar}$), 147.04 (s, 2 C, $C_{ar}$), 159.74 (s, 1 C, $C_{ar}$); MS (FAB, NBA) *m/z* (%): 422.2 (21, $[M+H]^+$), 420.2 (21, $[M+H]^+$), 341.34 (10), 287.3 (23), 271.3 (100),; HRMS (EI, 70 eV): ($C_{24}H_{21}BrO_2$) calc. 420.0725, found 420.0735.

**Table 7**
$pIC_{50}$ values of *N*-alkylated 3-(1*H*-imidazol-2-yl)propanoic acids **44**, **45**, **11a**–**11j** at mGAT1–mGAT4.

| Entry |  | no. | mGAT1 | mGAT2 | mGAT3 | mGAT4 |
|---|---|---|---|---|---|---|
| 1 | H<br>**a** | **11a** [29] | 62.8%[a] | 3.28 ± 0.19 | **4.54 ± 0.15** | 3.51 ± 0.03 |
| 2 |  | **44** | 4.13[b] | 4.23[b] | 48.1%[a] | 53.7%[a] |
| 3 |  | **45** | 53.7%[a] | 65.4%[a] | 4.64[b] | 5.10 ± 0.04 |
| 4 |  <br>**b** | **11b** | 64.8%[a] | 53.0%[a] | 43.2%[a] | 58.3%[a] |
| 5 |  <br>**c** | **11c** | 4.00 ± 0.13 | 31.2%[a] | 48.6%[a] | 55.4%[a] |
| 6 |  <br>**d** | **11d** | 3.85 ± 0.04 | **4.60 ± 0.08** | 4.06 ± 0.22 | 3.76 ± 0.12 |
| 7 |  <br>**e** | **11e** | 4.93 ± 0.03 | 4.90[b] | 4.63[b] | 4.53 ± 0.04 |
| 8 |  <br>**f** | **11f** | 48.5%[a] | 4.60 ± 0.11 | 4.45 ± 0.05 | 4.36 ± 0.11 |
| 9 |  <br>**g** | **11g** | 4.58[b] | 4.51[b] | 4.61[b] | 4.66[b] |

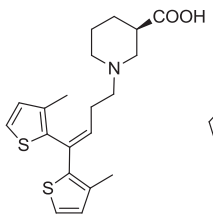
(*continued on next page*)

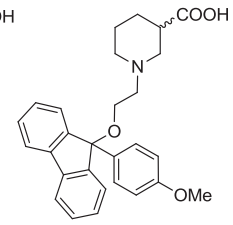
**Table 7** (*continued*)

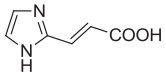
| Entry | | no. | mGAT1 | mGAT2 | mGAT3 | mGAT4 |
|---|---|---|---|---|---|---|
| 10 |  h | **11h** | 55.8%[a] | 4.49[b] | 43.9%[a] | 61.4%[a] |
| 11 |  i | **11i** | 4.15[b] | 4.43[b] | 4.80[b] | 4.88 ± 0.19 |
| 12 |  j | **11j** | 4.43[b] | 48.3%[a] | 4.55[b] | 50.7%[a] |

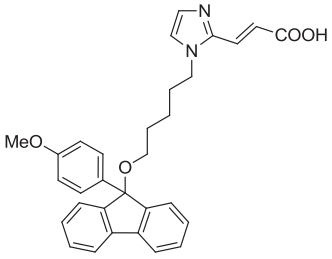
[a] Percent inhibition at 100 μM.
[b] Value from a single experiment.

**Table 8**
Affinities of SNAP-5294 (**6**) and compounds **12a** and **12e**.


Tiagabine (**5**)


SNAP-5294 (**6**) [21]


**12a** [29]


**12e**

| Entry | Compound no. | IC$_{50}$ (μM)[a] | | | |
|---|---|---|---|---|---|
| | | hGAT-1 | hBGT-1 | rGAT-2 | hGAT-3 |
| 1 | **6** | 133 ± 50 | 27 ± 10[c] | 51 ± 4 | 142 ± 21 |
| | | **pIC$_{50}$**[b] | | | |
| | | **mGAT1** | **mGAT2** | **mGAT3** | **mGAT4** |
| 2 | **6** | 73.1%[c] | 66.3%[c] | 4.03 ± 0.05 | 4.52 ± 0.08 |
| 3 | **12a** | 73.7%[c] | 77.3%[c] | **3.71 ± 0.05** | 47.2%[c] |
| 4 | **12e** | 4.90 ± 0.08 | 4.54[d] | **5.13 ± 0.04** | **4.99 ± 0.13** |
| 5 | **5** | **6.88 ± 0.12** | 52%[c] | 64%[c] | 73%[c] |

pIC$_{50}$ values in bold represent important inhibitory potencies.
[a] Values originate from literature [21].
[b] pIC$_{50}$ values were determined in our lab using the biological assay described in Ref. [47].
[c] Percent inhibition at 100 μM.
[d] Value from a single experiment.

*5.1.1.6. (2Z)-4-[9-(4-methoxyphenyl)-9H-fluoren-9-yloxy]but-2-enol (**26**).* According to **GP1:** 9-(4-methoxyphenyl)fluoren-9-ol (**13**) [21] (140 mg, 0.490 mmol), toluene (1.2 mL), conc. $H_2SO_4$ (15 mg, 0.15 mmol, 8.0 μL), (2*Z*)-but-2-en-1,4-diol (**19**) (8.6 mg, 1.0 mmol,

0.080 mL), 18 h. Yield: 53 mg (30%); colourless oil; TLC: $R_f = 0.38$ (*iso*-hexane/EtOAc = 1:1); IR (KBr): 3316, 3065, 3019, 2930, 2842, 1607, 1509, 1449, 1302, 1249, 1169, 1102, 1033 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$): $\delta = 1.40$ (t, $J = 5.9$ Hz, 1 H, OH), 3.58 (d, $J = 4.4$ Hz, 2 H, $CH_2O$), 3.73 (s, 3 H, $CH_3$), 3.90 (dd, $J = 5.9/5.0$ Hz, 2 H, $HOCH_2$), 5.59–5.67 (m, 2 H, CHCH), 6.73–6.79 (m, 2 H, $H_{ar}$), 7.20–7.25 (m, 2 H, $H_{ar}$), 7.25–7.31 (m, 4 H, $H_{ar}$), 7.36–7.43 (m, 2 H, $H_{ar}$), 7.71 (dt, $J = 7.6/0.9$ Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CD_2Cl_2$): $\delta = 55.71$ (q, 1 C, $CH_3$), 58.96 (t, 1 C, $HOCH_2$), 60.00 (t, 1 C, $CH_2O$), 89.15 (s, 1 C, $CH_2OC$), 113.98 (d, 2 C, $C_{ar}$), 120.61 (d, 2 C, $C_{ar}$), 125.75 (d, 2 C, $C_{ar}$), 127.25 (d, 2 C, $C_{ar}$), 128.69 (d, 2 C, $C_{ar}$), 129.17 (d, 1 C, $CHCHCH_2O$), 129.66 (d, 2 C, $C_{ar}$), 132.10 (d, 1 C, $CHCHCH_2O$), 135.92 (s, 1 C, $C_{ar}$), 141.18 (s, 2 C, $C_{ar}$), 147.69 (s, 2 C, $C_{ar}$), 159.48 (s, 1 C, $C_{ar}$); MS (EI, 70 eV) *m/z* (%): 358 (11, $M^+$), 287 (9), 271 (100); HRMS (EI, 70 eV): ($C_{24}H_{22}O_3$) calc. 358.1569, found 358.1563.

### 5.1.2. Synthesis of 9-allyl-9-(4-methoxyphenyl)-9H-fluorene (**29**)

To 9-(4-methoxyphenyl)fluoren-9-ol (**13**) [21] (288 mg, 1.00 mmol) and allyltributylstannane (**28**) (662 mg, 2.00 mmol, 0.620 mL) in $CH_2Cl_2$ (4 mL) was added slowly $BF_3 \cdot Et_2O$ (284 mg, 2.00 mmol, 0.254 mL). After stirring at rt for 72 h, saturated $NaHCO_3$ was added and the aqueous phase was washed three times with $CH_2Cl_2$. The combined organic layers were subsequently dried over $MgSO_4$, filtered, and concentrated to dryness. Purification was realized by CC (*iso*-hexane/EtOAc = 9.5:0.5). Yield: 320 mg (99%); colourless crystals, m.p. 64–67 °C; TLC: $R_f = 0.22$ (*iso*-hexane/EtOAc = 9.5:0.5); IR (KBr): 3003, 2905, 2857, 1607, 1509, 1446, 1248 1182, 1032 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): $\delta = 3.19$ (d, $J = 7.0$ Hz, 2 H, $CCH_2CH$), 3.71 (s, 3 H, $CH_3$), 4.61 (d, $J = 10.1$ Hz, 1 H, $CCH_2CHCH_2$), 4.75 (d, $J = 17.1$ Hz, 1 H, $CCH_2CHCH_2$), 5.08 (ddt, $J = 17.1/10.1/7.0$ Hz, 1 H, $CCH_2CH$), 6.74 (d, $J = 8.9$ Hz, 2 H, $H_{ar}$), 7.07 (d, $J = 8.9$ Hz, 2 H, $H_{ar}$), 7.23 (d, $J = 4.0$ Hz, 4 H, $H_{ar}$), 7.27–7.35 (m, 2 H, $H_{ar}$), 7.75 (d, $J = 7.5$ Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CD_3OD$): $\delta = 43.47$ (t, 1 C, $CCH_2CH$), 55.65 (q, 1 C, $CH_3$), 59.17 (s, 1 C, $C_{ar}$), 114.70 (d, 2 C, $C_{ar}$), 117.91 (t, 1 C, $CCH_2CHCH_2$), 120.82 (d, 2 C, $C_{ar}$), 125.72 (d, 2 C, $C_{ar}$), 128.28 (d, 2 C, $C_{ar}$), 128.44 (d, 2 C, $C_{ar}$), 128.82 (d, 2 C, $C_{ar}$), 135.01 (d, 1 C, $CCH_2CH$), 137.75 (s, 1 C, $C_{ar}$), 142.00 (s, 2 C, $C_{ar}$), 152.81 (s, 2 C, $C_{ar}$), 159.73 (s, 1 C, $C_{ar}$); MS (CI, $CH_5^+$) *m/z* (%): 313 (26, $[M+H]^+$), 271 (62), 205 (100); HRMS (EI, 70 eV): ($C_{23}H_{20}O$) calc. 312.1514, found 312.1486; Anal. $C_{23}H_{20}O$ (C, H, O).

### 5.1.3. Synthesis of 9-[(1E)-3-Bromopropenyl]-9-(4-methoxyphenyl)-9H-fluorene (**30**)

To 9-Allyl-9-(4-methoxyphenyl)-9*H*-fluorene (**29**) (200 mg, 0.640 mmol) in $CCl_4$ (2.5 mL) was added NBS (160 mg, 0.960 mmol) and AIBN (60 mg, 0.37 mmol). After refluxing for 16 h, the solid material was filtered off and the solvent was evaporated. The residue was purified by CC (*iso*-hexane/EtOAc = 9:1). Yield: 194 mg (78%); colourless crystals, m.p. 123–125 °C; TLC: $R_f = 0.10$ (*iso*-hexane/EtOAc = 9:1); IR (KBr): 3100, 2998, 2954, 2831, 1648, 1604, 1506, 1447, 1298, 1245, 1203, 1177, 1031 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta = 3.74$ (s, 3 H, $CH_3$), 3.94 (d, $J = 7.6$ Hz, 2 H, $BrCH_2$), 5.67 (dt, $J = 15.2/7.6$ Hz, 1 H, $CH_2CH$), 6.47 (d, $J = 15.2$ Hz, 1 H, $CH_2CHCH$), 6.74–6.80 (m, 2 H, $H_{ar}$), 7.04–7.10 (m, 2 H, $H_{ar}$), 7.23–7.33 (m, 4 H, $H_{ar}$), 7.34–7.42 (t, $J = 7.5$ Hz, 2 H, $H_{ar}$), 7.76 (d, $J = 7.5$ Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta = 32.77$ (t, 1 C, $CH_2$), 55.21 (q, 1 C, $CH_3$), 60.79 (s, 1 C, *C*CH), 113.89 (d, 2 C, $C_{ar}$), 120.37 (d, 2 C, $C_{ar}$), 125.29 (d, 1 C, $CH_2CH$), 125.48 (d, 2 C, $C_{ar}$), 127.61 (d, 2 C, $C_{ar}$), 127.65 (d, 2 C, $C_{ar}$), 128.20 (d, 2 C, $C_{ar}$), 135.62 (s, 1 C, $C_{ar}$), 138.34 (d, 1 C, *C*HC), 139.95 (s, 2 C, $C_{ar}$), 149.58 (s, 2 C, $C_{ar}$), 158.51 (s, 1 C, $C_{ar}$); MS (CI, $CH_5^+$) *m/z* (%): 393 (32, $[M+H]^+$), 313 (8), 311 (76), 285 (94), 283 (86), 203 (100); HRMS (EI, 70 eV): ($C_{23}H_{19}BrO$) calc. 390.0619, found 390.0631; Anal. $C_{23}H_{19}BrO$ (C, H, Br, O).

### 5.1.4. General procedure for Williamson ether synthesis (**GP2**)

Sodium (1.0 equiv) was added to dry ethane-1,2-diol (2.0 equiv.) and stirred overnight at rt. The unreacted ethane-1,2-diol was distilled at 80 °C under pressure (1.4. $10^{-2}$ Torr). Required amount of the Sodium monoethylene glycolate left as residue was suspended in the given amount of DMF and warmed up to 60 °C for 10 min before the alkyl bromide (1.0 equiv) was added. After stirring at 60 °C for 72 h, EtOAc (20 mL/mmol) was added and the reaction mixture was washed with $H_2O$ and brine three times. The organic layers were dried over $MgSO_4$, filtered, and concentrated to dryness. The crude product was then purified by CC (*iso*-hexane/EtOAc = 1:1).

#### 5.1.4.1. 2-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxyethoxy]ethanol (**27**).

According to **GP2:** Sodium monoethylene glycolate (85.5 mg, 1.01 mmol), DMF (2.0 mL), 9-(2-iodoethoxy)-9-(4-methoxyphenyl)-9*H*-fluoren (**21**) (150 mg, 0.339 mmol). Yield: 77 mg (60%); colourless oil; TLC: $R_f = 0.21$ (*iso*-hexane/EtOAc = 6:4); IR (KBr): 3451, 3061, 2926, 2869, 1608, 1509, 1449, 1301, 1249, 1170, 1081, 1033 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta = 3.16$ (t, $J = 4.9$ Hz, 2 H, $CH_2OC$), 3.54–3.60 (m, 4 H, $CH_2OCH_2$), 3.68–3.72 (m, 2 H, $HOCH_2$), 3.73 (s, 3 H, $CH_3$), 6.73–6.80 (m, 2 H, $H_{ar}$), 7.22–7.33 (m, 6 H, $H_{ar}$), 7.36 (td, $J = 7.5/1.3$ Hz, 2 H, $H_{ar}$), 7.67 (d, $J = 7.5$ Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta = 55.35$ (q, 1 C, $CH_3$), 62.02 (t, 1 C, $HOCH_2$), 63.17 (t, 1 C, $CH_2OC$), 70.77 (t, 1 C, $CH_2CH_2OC$), 72.30 (t, 1 C, $NCH_2CH_2$), 88.70 (s, 1 C, $CH_2OC$), 113.69 (d, 2 C, $C_{ar}$), 120.15 (d, 2 C, $C_{ar}$), 125.49 (d, 2 C, $C_{ar}$), 126.96 (d, 2 C, $C_{ar}$), 128.36 (d, 2 C, $C_{ar}$), 129.23 (d, 2 C, $C_{ar}$), 135.45 (s, 1 C, $C_{ar}$), 140.77 (s, 2 C, $C_{ar}$), 147.23 (s, 2 C, $C_{ar}$), 158.94 (s, 1 C, $C_{ar}$); MS (EI, 70 eV) *m/z* (%): 376 (4, $M^+$), 271 (100); HRMS (EI, 70 eV): ($C_{24}H_{24}O_4$) calc. 376.1675, found 376.1674.

#### 5.1.4.2. 3-[9-(4-Methoxyphenyl)-9H-fluoren-9-ylpropenyl]ethanol (**31**).

According to **GP2:** Sodium ethylene glycolate (36 mg, 0.43 mmol), DMF (1.5 mL), 9-[(1*E*)-3-Bromopropenyl]-9-(4-methoxyphenyl)-9*H*-fluorene (**30**) (150 mg, 0.339 mmol). Yield: 34 mg (35%); colourless oil; TLC: $R_f = 0.34$ (*iso*-hexane/EtOAc = 3:7). IR (KBr): 3418, 3062, 3035, 3007, 2932, 2860, 2045, 1951, 1915, 1809, 1606, 1582, 1508, 1447, 1354, 1297, 1248, 1178, 1117, 1032 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta = 3.50$ (t, $J = 4.6$ Hz, 2 H, $HOCH_2CH_2$), 3.69 (t, $J = 4.6$ Hz, 2 H, $HOCH_2$), 3.74 (s, 3 H, $CH_3$), 4.00 (d, $J = 5.9$ Hz, 2 H, $CH_2CH$), 5.52 (dt, $J = 15.5/5.9$ Hz, 1 H, $CH_2CH$), 6.43 (d, $J = 15.5$ Hz, 1 H, CHC), 6.73–6.80 (m, 2 H, $H_{ar}$), 7.05–7.11 (m, 2 H, $H_{ar}$), 7.24–7.30 (m, 4 H, $H_{ar}$), 7.32–7.40 (m, 2 H, $H_{ar}$), 7.76 (d, $J = 7.5$ Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta = 55.40$ (q, 1 C, $CH_3$), 61.29 (s, 1 C, CHC), 62.01 (t, 1 C, $HOCH_2$), 71.49 (t, 1 C, $HOCH_2CH_2$), 71.79 (t, 1 C, $CH_2CH$), 113.99 (d, 2 C, $C_{ar}$), 120.49 (d, 2 C, $C_{ar}$), 125.41 (d, 1 C, $CH_2CH$), 125.70 (d, 2 C, $C_{ar}$), 127.64 (d, 2 C, $C_{ar}$), 127.75 (d, 2 C, $C_{ar}$), 128.46 (d, 2 C, $C_{ar}$), 136.11 (s, 1 C, $C_{ar}$), 136.28 (d, 1 C, *C*HC), 140.13 (s, 2 C, $C_{ar}$), 150.31 (s, 2 C, $C_{ar}$), 158.59 (s, 1 C, $C_{ar}$); MS (EI, 70 eV) *m/z* (%): 372 (13, $M^+$), 310 (19), 297 (100); HRMS (EI, 70 eV): ($C_{25}H_{24}O_3$) calc. 372.1726, found 372.1829.

### 5.1.5. General procedure for mesylation (**GP3**) [38].

To a solution of the 9-methoxyphenyl-9*H*-fluorene derivative (1.0 equiv.) and methanesulfonyl chloride (2.0 equiv.) in $CH_2Cl_2$ (7 mL/mmol) was treated with $Et_3N$ (2.1 equiv.) at 0 °C. After 2 h at 0 °C, $H_2O$ was added and the solution was extracted three times with $CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by CC.

#### 5.1.5.1. 4-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxybutenyloxy] methane sulfonic acid (**32**).

According to **GP3:** (2*Z*)-4-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yloxy]but-2-enol (**26**) (598 mg, 1.67 mmol), $CH_2Cl_2$ (12 mL), methanesulfonyl chloride (382 mg,

3.34 mmol, 0.259 mL), $Et_3N$ (355 mg, 3.51 mmol, 0.489 mL), CC (*iso*-hexane/EtOAc = 7:3). Yield: 533 mg (73%); colourless oil; TLC: $R_f$ = 0.42 (*iso*-hexane/EtOAc = 6:4); IR (KBr): 3065, 3019, 2934, 2836, 1607, 1582, 1509, 1449, 1356, 1249, 1173, 1102, 1060, 1033 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$): $\delta$ = 2.87 (s, 3 H, $SO_2CH_3$), 3.63 (d, $J$ = 6.2 Hz, 2 H, $CH_2O$), 3.73 (s, 3 H, $OCH_3$), 4.59 (d, $J$ = 6.9 Hz, 2 H, $CH_2OSO_2$), 5.61 (dtt, $J$ = 11.2/6.9/1.6 Hz, 1 H, $SO_3CH_2CH$), 5.84 (dtt, $J$ = 11.2/6.2/1.3 Hz, 1 H, $CHCH_2O$), 6.74–6.79 (m, 2 H, $H_{ar}$), 7.22–7.25 (m, 2 H, $H_{ar}$), 7.27–7.31 (m, 4 H, $H_{ar}$), 7.37–7.44 (m, 2 H, $H_{ar}$), 7.72 (d, $J$ = 7.6 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CD_2Cl_2$): $\delta$ = 38.30 (q, 1 C, $SO_2CH_3$), 55.70 (q, 1 C, $OCH_3$), 60.02 (t, 1 C, $CH_2O$), 66.33 (t, 1 C, $CH_2OSO_2$), 89.26 (s, 1 C, $CH_2OC$), 113.99 (d, 2 C, $C_{ar}$), 120.71 (d, 2 C, $C_{ar}$), 124.47 (d, 1 C, $SO_3CH_2CH$), 125.72 (d, 2 C, $C_{ar}$), 127.25 (d, 2 C, $C_{ar}$), 128.79 (d, 2 C, $C_{ar}$), 129.78 (d, 2 C, $C_{ar}$), 133.76 (d, 1 C, $CHCH_2O$), 135.68 (s, 1 C, $C_{ar}$), 141.19 (s, 2 C, $C_{ar}$), 147.38 (s, 2 C, $C_{ar}$), 159.52 (s, 1 C, $C_{ar}$); MS (EI, 70 eV) *m/z* (%): 436 (9, $M^+$), 287 (8), 271 (100); HRMS (EI, 70 eV): ($C_{25}H_{24}O_5S$) calc. 436.1344, found 436.1353.

*5.1.5.2. 2-{4-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxyethoxy] ethoxy}methane sulfonic acid (**33**).* According to **GP3:** 2-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yloxyethoxy]ethanol (**27**) (691 mg, 1.84 mmol), $CH_2Cl_2$ (13 mL), menthanesulfonyl chloride (422 mg, 3.67 mmol, 0.286 mL), $Et_3N$ (391 mg, 3.86 mmol, 0.539 mL), CC (*iso*-hexane/EtOAc = 6:4). Yield: 641 mg (77%); colourless solid, m.p. 72–75 °C; TLC: $R_f$ = 0.29 (*iso*-hexane/EtOAc = 6:4). IR (KBr): 3055, 3019, 2933, 2870, 2836, 1608, 1580, 1509, 1449, 1352, 1301, 1249, 1174, 1139, 1084, 1031 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 3.01 (s, 3 H, $SO_2CH_3$), 3.15 (t, $J$ = 4.8 Hz, 2 H, $CH_2OC$), 3.58 (t, $J$ = 4.8 Hz, 2 H, $CH_2CH_2OC$), 3.72–3.74 (m, 2 H, $CH_2CH_2OSO_2$), 3.74 (s, 3 H, $OCH_3$), 4.35–4.38 (m, 2 H, $CH_2OSO_2$), 6.74–6.79 (m, 2 H, $H_{ar}$), 7.23–7.30 (m, 6 H, $H_{ar}$), 7.35–7.39 (m, 2 H, $H_{ar}$), 7.67 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 37.77 (q, 1 C, $SO_2CH_3$), 55.19 (q, 1 C, $OCH_3$), 62.89 (t, 1 C, $CH_2OC$), 68.92 (t, 1 C, $CH_2CH_2OSO_2$), 69.52 (t, 1 C, $CH_2OSO_2$), 70.80 (t, 1 C, $CH_2CH_2OC$), 88.49 (s, 1 C, $CH_2OC$), 113.50 (d, 2 C, $C_{ar}$), 119.99 (d, 2 C, $C_{ar}$), 125.27 (d, 2 C, $C_{ar}$), 126.78 (d, 2 C, $C_{ar}$), 128.20 (d, 2 C, $C_{ar}$), 129.07 (d, 2 C, $C_{ar}$), 135.24 (s, 1 C, $C_{ar}$), 140.59 (s, 2 C, $C_{ar}$), 147.00 (s, 2 C, $C_{ar}$), 158.79 (s, 1 C, $C_{ar}$); MS (EI, 70 eV) *m/z* (%): 454 (16, $M^+$), 271 (100); HRMS (EI, 70 eV): ($C_{25}H_{26}O_6S$) calc. 454.1450, found 454.1449.

*5.1.5.3. 3-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxypropenyl]ethanoxymethane sulfonic acid (**34**).* According to **GP3:** 3-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-ylpropenyl]ethanol (**31**) (1.13 g, 3.03 mmol), $CH_2Cl_2$ (20 mL), menthanesulfonyl chloride (695 mg, 6.07 mmol, 0.472 mL), $Et_3N$ (644 mg, 6.36 mmol, 0.887 mL), CC (*iso*-hexane/EtOAc = 6:4). Yield: 1.33 mg (97%); light yellow oil; TLC: $R_f$ = 0.23 (*iso*-hexane/EtOAc = 6:4). IR (KBr): 3061, 3031, 2936, 2906, 2863, 2838, 2945, 1921, 1607, 1580, 1508, 1448, 1353, 1249, 1176, 1120, 1031, 1014 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 2.93 (s, 3 H, $SO_2CH_3$), 3.60–3.65 (m, 2 H, $CH_2CH_2OSO_2$), 3.73 (s, 3 H, $OCH_3$), 4.00 (dd, $J$ = 5.9/1.2 Hz, 2 H, $CH_2CH$), 4.28–4.34 (m, 2 H, $CH_2OSO_2$), 5.48 (dt, $J$ = 15.5/5.9 Hz, 1 H, $CH_2CH$), 6.44 (d, $J$ = 15.5 Hz, 1 H, CHC), 6.73–6.80 (m, 2 H, $H_{ar}$), 7.04–7.10 (m, 2 H, $H_{ar}$), 7.22–7.30 (m, 4 H, $H_{ar}$), 7.32–7.38 (m, 2 H, $H_{ar}$), 7.75 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 37.79 (q, 1 C, $SO_2CH_3$), 55.37 (q, 1 C, $OCH_3$), 61.25 (s, 1 C, CHC), 67.94 (t, 1 C, $CH_2CH_2OSO_2$), 69.35 (t, 1 C, $CH_2OSO_2$), 71.66 (t, 1 C, $CH_2CH$), 113.98 (d, 2 C, $C_{ar}$), 120.50 (d, 2 C, $C_{ar}$), 124.72 (d, 1 C, $CH_2CH$), 125.61 (d, 2 C, $C_{ar}$), 127.67 (d, 2 C, $C_{ar}$), 127.76 (d, 2 C, $C_{ar}$), 128.38 (d, 2 C, $C_{ar}$), 135.88 (s, 1 C, $C_{ar}$), 136.89 (d, 1 C, CHC), 140.06 (s, 2 C, $C_{ar}$), 150.17 (s, 2 C, $C_{ar}$), 158.59 (s, 1 C, $C_{ar}$); MS (EI, 70 eV) *m/z* (%): 450 (7, $M^+$), 310 (8), 297 (100); HRMS (EI, 70 eV): ($C_{26}H_{26}O_5S$) calc. 450.1501, found 450.1484.

*5.1.6. General procedure for synthesis of N-alkylated 2-(1H-imidazol-5-yl)acetic acid methyl esters (**GP4**) [39,40].*

The corresponding alkyl bromide or alkyl mesylate (1.3 equiv.) was added to (1-triphenylmethyl-1*H*-imidazol-4-yl)acetic acid methyl ester (**35**) (1.0 equiv.) in $CH_3CN$. The reaction mixture was stirred for 8 d at 60 °C. After evaporating the solvent, the residue was dissolved in MeOH (2 mL) and refluxed for 45 min. The reaction solution was then concentrated to dryness and the crude product obtained was purified by CC.

*5.1.6.1. (1-{2-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]ethyl}-1H-imidazol-5-yl)acetic acid methyl ester (**37b**).* According to **GP4:** (1-Triphenylmethyl-1*H*-imidazol-4-yl)acetic acid methyl ester (**35**) [42] (315 mg, 0.824 mmol), $CH_3CN$ (2 mL), 9-(2-bromoethoxy)-9-(4-methoxyphenyl)-9*H*-fluorene (**20**) [21] (420 mg, 1.06 mmol), CC (acetone/*n*-pentane = 8:2). Yield: 217 mg (58%); yellow oil; TLC: $R_f$ = 0.15 (acetone/*n*-pentane = 7:3); IR (KBr): 3100, 2952, 1740, 1608, 1509, 1449, 1250, 1170, 1106, 1033 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 3.19 (t, $J$ = 5.2 Hz, 2 H, $CH_2O$), 3.51 (s, 2 H, $CH_2COO$), 3.60 (s, 3 H, $COOCH_3$), 3.75 (s, 3 H, $OCH_3$), 4.03 (t, $J$ = 5.2 Hz, 2 H, $NCH_2$), 6.72–6.78 (m, 2 H, $H_{ar}$), 6.98 (s, 1 H, $H_{[4H\text{-}Imid.]}$), 7.05 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$), 7.12–7.17 (m, 2 H, $H_{ar}$), 7.21 (td, $J$ = 7.5/1.0 Hz, 2 H, $H_{ar}$), 7.35 (td, $J$ = 7.5/1.0 Hz, 2 H, $H_{ar}$), 7.62–7.67 (m, 3 H, $H_{[2H\text{-}Imid.]}$, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 30.14 (t, 1 C, $CH_2COO$), 45.36 (t, 1 C, $NCH_2$), 52.42 (q, 1 C, $COOCH_3$), 55.41 (q, 1 C, $OCH_3$), 62.75 (t, 1 C, $CH_2O$), 88.95 (s, 1 C, $CH_2OC$), 113.80 (d, 2 C, $C_{ar}$), 120.19 (d, 2 C, $C_{ar}$), 124.25 (s, 1 C, $C_{[5C\text{-}Imid.]}$), 125.30 (d, 2 C, $C_{ar}$), 126.89 (d, 2 C, $C_{ar}$), 128.58 (d, 2 C, $C_{ar}$), 128.83 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 129.41 (d, 2 C, $C_{ar}$), 134.84 (s, 1 C, $C_{ar}$), 138.94 (d, 1 C, $C_{[2C\text{-}Imid.]}$), 140.69 (s, 2 C, $C_{ar}$), 146.60 (s, 2 C, $C_{ar}$), 159.09 (s, 1 C, $C_{ar}$), 172.37 (s, 1 C, COO); MS (CI, $CH_5^+$) *m/z* (%): 455 (34, $[M+H]^+$), 271 (100); HRMS (EI, 70 eV): ($C_{28}H_{26}N_2O_4$) calc. 454.1893, found 454.1878.

*5.1.6.2. (1-{3-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]propyl}-1H-imidazol-5-yl)acetic acid methyl ester (**37c**).* According to **GP4:** (1-Triphenylmethyl-1*H*-imidazol-4-yl)acetic acid methyl ester (**35**) [42] (315 mg, 0.824 mmol), $CH_3CN$ (4 mL), 9-(3-bromopropoxy)-9-(4-methoxyphenyl)-9*H*-fluorene (**22**) (436 mg, 1.07 mmol), CC ($CHCl_3$/MeOH = 100:1). Yield: 170 mg (44%); colourless oil; TLC: $R_f$ = 0.31 ($CHCl_3$/MeOH = 100:3).; IR (KBr): 3061, 3038, 3004, 2951, 2874, 2837, 2044, 1868, 1844, 1740, 1608, 1509, 1449, 1249, 1170, 1107, 1078, 1033 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 1.86 (tt, $J$ = 7.2/5.6 Hz, 2 H, $NCH_2CH_2$), 3.00 (t, $J$ = 5.6 Hz, 2 H, $CH_2O$), 3.62 (s, 2 H, $CH_2COO$), 3.68 (s, 3 H, $COOCH_3$), 3.76 (s, 3 H, $OCH_3$), 4.02 (t, $J$ = 7.2 Hz, 2 H, $NCH_2$), 6.79 (d, $J$ = 8.9 Hz, 2 H, $H_{ar}$), 6.91 (s, 1 H, $H_{[4H\text{-}Imid.]}$), 7.22–7.29 (m, 6 H, $H_{ar}$), 7.33–7.44 (m, 3 H, $H_{ar}$, $H_{[2H\text{-}Imid.]}$), 7.68 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 29.99 (t, 1 C, $CH_2COO$), 31.46 (t, 1 C, $NCH_2CH_2$), 42.17 (t, 1 C, $NCH_2$), 52.44 (q, 1 C, $COOCH_3$), 55.31 (q, 1 C, $OCH_3$), 59.74 (t, 1 C, $CH_2O$), 88.43 (s, 1 C, $CH_2OC$), 113.63 (d, 2 C, $C_{ar}$), 120.18 (d, 2 C, $C_{ar}$), 123.78 (s, 1 C, $C_{[5C\text{-}Imid.]}$), 125.17 (d, 2 C, $C_{ar}$), 126.77 (d, 2 C, $C_{ar}$), 128.38 (d, 2 C, $C_{ar}$), 128.86 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 129.27 (d, 2 C, $C_{ar}$), 135.35 (s, 1 C, $C_{ar}$), 137.90 (d, 1 C, $C_{[2C\text{-}Imid.]}$), 140.70 (s, 2 C, $C_{ar}$), 147.12 (s, 2 C, $C_{ar}$), 158.89 (s, 1 C, $C_{ar}$), 170.26 (s, 1 C, COO); MS (CI, $CH_5^+$) *m/z* (%): 469 (28, $[M+H]^+$), 447 (8), 271 (100); HRMS (EI, 70 eV): ($C_{29}H_{28}N_2O_4$) calc. 468.2049, found 468.2043.

*5.1.6.3. (1-{4-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]butyl}-1H-imidazol-5-yl)acetic acid methyl ester (**37d**).* **A**) According to **GP4:** (1-Triphenylmethyl-1*H*-imidazol-4-yl)acetic acid methyl ester (**35**) [42] (315 mg, 0.824 mmol), $CH_3CN$ (4 mL), 9-(4-bromobutoxy)-9-(4-methoxyphenyl)-9*H*-fluorene (**23**) (451 mg, 1.07 mmol), CC ($CHCl_3$/MeOH = 100:1). 69.5 mg (17%) **37d** was obtained.

**B**) According to **GP4:** (1-Triphenylmethyl-1*H*-imidazol-4-yl) acetic acid methyl ester (**35**)[42] (315 mg, 0.824 mmol), $CH_3CN$

(4 mL), 9-(4-bromobutoxy)-9-(4-methoxyphenyl)-9*H*-fluorene (**23**) (451 mg, 1.07 mmol), CC ($CHCl_3$/MeOH = 100:1). For deprotection, the residue was dissolved, differing to **GP4**, in 5% $CH_3COOH$ in MeOH (2 mL) [41]. Yield: 217 mg (55%); colourless oil; TLC: $R_f$ = 0.28 ($CH_2Cl_2$/MeOH = 100:3); IR (KBr): 3003, 2950, 1740, 1608, 1509, 1449, 1249, 1169, 1108, 1077, 1033 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 1.51 (tt, $J$ = 6.7/6.0, 2 H, $CH_2CH_2O$), 1.82 (tt, $J$ = 7.5/6.7 Hz, 2 H, $NCH_2CH_2$), 2.99 (t, $J$ = 6.0 Hz, 2 H, $CH_2O$), 3.58 (s, 2 H, $CH_2COO$), 3.66 (s, 3 H, $COOCH_3$), 3.75 (s, 3 H, $OCH_3$), 3.85 (t, $J$ = 7.5 Hz, 2 H, $NCH_2$), 6.74–6.79 (m, 2 H, $H_{ar}$), 6.93 (s, 1 H, $H_{[5H\text{-}Imid.]}$), 7.21–7.29 (m, 6 H, $H_{ar}$), 7.34–7.40 (m, 2 H, $H_{ar}$), 7.44 (s, 1 H, $H_{[2H\text{-}Imid.]}$), 7.67 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 27.11 (t, 1 C, $CH_2CH_2O$), 27.83 (t, 1 C, $NCH_2CH_2$), 30.16 (t, 1 C, $CH_2COO$), 44.93 (t, 1 C, $NCH_2$), 52.52 (q, 1 C, $COOCH_3$), 55.37 (q, 1 C, $OCH_3$), 62.40 (t, 1 C, $CH_2O$), 88.43 (s, 1 C, $CH_2OC$), 113.68 (d, 2 C, $C_{ar}$), 120.18 (d, 2 C, $C_{ar}$), 123.87 (s, 1 C, $C_{[5C\text{-}Imid.]}$), 125.26 (d, 2 C, $C_{ar}$), 126.87 (d, 2 C, $C_{ar}$), 128.34 (d, 2 C, $C_{ar}$) 129.02 (d, 1 C, $C_{[4C\text{-}Imid.]}$ or d, 2 C, $C_{ar}$), 129.18 (d, 1 C, $C_{[4C\text{-}Imid.]}$ or d, 2 C, $C_{ar}$), 135.68 (s, 1 C, $C_{ar}$), 137.84 (d, 1 C, $C_{[2C\text{-}Imid.]}$), 140.75 (s, 2 C, $C_{ar}$), 147.47 (s, 2 C, $C_{ar}$), 158.91 (s, 1 C, $C_{ar}$), 170.31 (s, 1 C, COO); MS (CI, $CH_5^+$) $m/z$ (%): 483 (28, $[M+H]^+$), 447 (12), 271 (100); HRMS (EI, 70 eV): ($C_{30}H_{30}N_2O_4$) calc. 482.2206, found 482.2207. Anal. $C_{30}H_{30}N_2O_4$ (C, H, N, O).

*5.1.6.4. (1-{5-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]pentyl}-1H-imidazol-5-yl)acetic acid methyl ester (**37e**).* According to **GP4:** (1-Triphenylmethyl-1*H*-imidazol-4-yl)acetic acid methyl ester (**35**) [42] (308 mg, 0.805 mmol), $CH_3CN$ (4 mL), 9-(5-bromopentoxy)-9-(4-methoxyphenyl)-9*H*-fluorene (**24**) (458 mg, 1.05 mmol), CC ($CHCl_3$/MeOH = 100:1). For deprotection, the residue was dissolved, differing to **GP4**, in 5% $CH_3COOH$ in MeOH (2 mL). Yield: 180 mg (42%); colourless oil; TLC: $R_f$ = 0.28 ($CH_2Cl_2$/MeOH = 100:2); IR (KBr): 3059, 2936, 2865, 1740, 1608, 1509, 1449, 1249, 1169, 1109, 1078, 1032 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 1.31–1.43 (m, 2 H, $NCH_2CH_2CH_2$), 1.52 (tt, $J$ = 7.3/6.1 Hz, 2 H, $CH_2CH_2O$), 1.66 (tt, $J$ = 7.6/7.4 Hz, 2 H, $NCH_2CH_2$), 2.96 (t, $J$ = 6.1 Hz, 2 H, $CH_2O$), 3.59 (s, 2 H, $CH_2COO$), 3.68 (s, 3 H, $COOCH_3$), 3.75 (s, 3 H, $OCH_3$), 3.83 (t, $J$ = 7.4 Hz, 2 H, $NCH_2$), 6.73–6.80 (m, 2 H, $H_{ar}$), 6.93 (s, 1H, $H_{[4H\text{-}Imid.]}$), 7.21–7.28 (m, 6 H, $H_{ar}$), 7.33–7.40 (m, 2 H, $H_{ar}$), 7.43 (s, 1 H, $H_{[2H\text{-}Imid.]}$), 7.67 (d, $J$ = 7.5 Hz, 2 H,, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 23.25 (t, 1 C, $NCH_2CH_2CH_2$), 29.45 (t, 1 C, $CH_2CH_2O$), 29.99 (t, 1 C, $CH_2COO$), 30.51 (t, 1 C, $NCH_2CH_2$), 44.93 (t, 1 C, $NCH_2$), 52.35 (q, 1 C, $COOCH_3$), 55.19 (q, 1 C, $OCH_3$), 62.59 (t, 1 C, $CH_2O$), 88.18 (s, 1 C, $CH_2OC$), 113.47 (d, 2 C, $C_{ar}$), 119.94 (d, 2 C, $C_{ar}$), 123.67 (s, 1 C, $C_{[5C\text{-}Imid.]}$), 125.09 (d, 2 C, $C_{ar}$), 126.71 (d, 2 C, $C_{ar}$), 128.09(d, 2 C, $C_{ar}$),128.73(s, 1 C, $C_{[4C\text{-}Imid.]}$), 129.91 (d, 2 C, $C_{ar}$), 135.70 (s, 1 C $C_{ar}$), 137.62 (d, 1 C, $C_{[2C\text{-}Imid.]}$), 140.56 (s, 2 C, $C_{ar}$), 147.44 (s, 2 C, $C_{ar}$), 158.70 (s, 1 C, $C_{ar}$), 170.13 (s, 1 C, COO); MS (ESI+) $m/z$ (%): 993.6 (6), 497.1 (86, $[M+H]^+$), 271.0 (100),; HRMS (EI, 70 eV): ($C_{31}H_{32}N_2O_4$) calc. 496.2362, found 496.2371.

*5.1.6.5. (1-{(1E)-3-[9-(4-Methoxyphenyl)-9H-fluoren-9-yl]prop-2-en-1-yl}-1H-imidazol-5-yl)acetic acid methyl ester (**37f**).* According to **GP4:** (1-Triphenylmethyl-1*H*-imidazol-4-yl)acetic acid methyl ester (**35**) [42] (283 mg, 0.740 mmol), $CH_3CN$ (4 mL), 9-((1*E*)-3-bromopropenyl)-9-(4-methoxyphenyl)-9*H*-fluorene (**30**) (376 mg, 0.961 mmol), CC (acetone/*n*-pentane = 8:2). Yield: 200 mg (60%); yellow oil; TLC: $R_f$ = 0.37 ($CH_2Cl_2$/MeOH = 100:2); IR (KBr): 3034, 3003, 2950, 2835, 1739, 1606, 1508, 1447, 1340, 1249, 1177, 1109, 1031 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 3.46 (s, 2 H, $CH_2COO$), 3.62 (s, 3 H, $COOCH_3$), 3.74 (s, 3 H, $OCH_3$), 4.50 (d, $J$ = 5.8 Hz, 2 H, $NCH_2$), 5.46 (dt, $J$ = 15.5/5.8 Hz, 1 H, $NCH_2CH$), 6.28 (d, $J$ = 15.5 Hz, 1 H, CHC), 6.73–6.78 (m, 2 H, $H_{ar}$), 6.93 (s, 1 H, $H_{[4H\text{-}Imid.]}$), 6.98–7.04 (m, 2 H, $H_{ar}$), 7.20 (d, $J$ = 7.6 Hz, 2 H, $H_{ar}$), 7.27 (td, $J$ = 7.6/1.1 Hz, 2 H, $H_{ar}$), 7.36 (td, $J$ = 7.6/1.1 Hz, 2 H, $H_{ar}$), 7.42 (s, 1 H, $H_{[2H\text{-}Imid.]}$), 7.76 (d, $J$ = 7.6 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 29.82 (t, 1 C, $CH_2COO$), 46.83 (t, 1 C, $NCH_2$), 52.28 (q, 1 C, $COOCH_3$), 55.21 (q, 1 C, $OCH_3$), 60.98 (s, 1 C, CHC), 113.93 (d, 2 C, $C_{ar}$), 120.45 (d, 2 C, $C_{ar}$), 122.86 (d, 1 C, $NCH_2CH$), 124.00 (s, 1 C, $C_{[5C\text{-}Imid.]}$), 125.28 (d, 2 C, $C_{ar}$), 127.69 (d, 2 C, $C_{ar}$), 127.72 (d, 2 C, $C_{ar}$), 128.05 (d, 2 C, $C_{ar}$), 128.99 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 135.26 (s, 1 C, $C_{ar}$), 137.79 (d, 1 C, $C_{[2C\text{-}Imid.]}$), 137.82 (d, 1 C, CHC), 139.84 (s, 2 C, $C_{ar}$), 149.57 (s, 2 C, $C_{ar}$), 158.52 (s, 1 C, $C_{ar}$), 170.01 (s, 1 C, COO); MS (CI, $CH_5^+$) $m/z$ (%): 451 (100, $[M+H]^+$); HRMS (EI, 70 eV): ($C_{29}H_{26}N_2O_3$) calc. 450.1944, found 450.1920. Anal. $C_{29}H_{26}N_2O_3$ (C, H, N, O).

*5.1.7. General procedure for N-alkylation of 2-(1H-imidazol-4-yl) acetic acid methyl esters, 3-(1H-imidazol-2-yl)propanoic acid ethyl esters and (2E)-3-(1H-imidazol-2-yl)prop-2-enoic acid ethyl esters (**GP5**) [45]*

A suspension of *t*BuOK (1.1 equiv. or 2.2 equiv.) and the imidazole derivative (1.0 equiv.) in DMF (6 mL/mmol) was stirred at rt for 1 h. The reaction mixture was treated with the corresponding alkyl bromide or alkyl mesylate (1.3 equiv. or 2.0 equiv.) and the temperature was raised up to 60 °C and stirred at this temperature for 72 h. The solution was then diluted with EtOAc (20 mL/mmol) and washed three times with brine and $H_2O$. The organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by CC.

*5.1.7.1. (1-{2-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]ethyl}-1H-imidazol-4-yl)acetic acid methyl ester (**38b**).* According to **GP5:** 1*H*-Imidazol-4-ylacetic acid methyl ester·HCl (**38a·HCl**) [43,44] (150 mg, 0.850 mmol), DMF (5 mL), *t*BuOK (210 mg, 1.87 mmol), 9-(2-bromoethoxy)-9-methoxyphenyl-9*H*-fluorene (**20**) [21] (700 mg, 1.77 mmol), CC (acetone/*n*-pentane = 8: 2). 64% (65.0 mg, 0.143 mmol) of a mixture of 1,4- and 1,5-disubtitued (1-{2-[9-(4-methoxyphenyl)-9*H*-fluoren-9-yloxy]ethyl}-1*H*-imidazolyl)acetic acid methyl esters (**38b**, **37b**) was obtained as a yellow oil which could be separated by CC (acetone/*n*-pentane = 7:3) to yield **38b** as yellow oil. Yield: 480 mg (42%); yellow oil; TLC: $R_f$ = 0.22 (acetone/*n*-pentane = 7:3); IR (KBr): 3003, 2950, 2837, 1739, 1608, 1509, 1448, 1250, 1169 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 3.13 (t, $J$ = 5.1 Hz, 2 H, $CH_2O$), 3.60 (s, 2 H, $CH_2COO$), 3.64 (s, 3 H, $COOCH_3$), 3.67 (s, 3 H, $OCH_3$), 3.89 (t, $J$ = 5.1 Hz, 2 H, $NCH_2$), 6.66–6.71 (m, 2 H, $H_{ar}$), 6.76 (s, 1 H, $H_{[5H\text{-}Imid.]}$), 7.02 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$), 7.07–7.12 (m, 2 H, $H_{ar}$), 7.14 (t, $J$ = 7.5 Hz, 2 H, $H_{ar}$), 7.28 (t, $J$ = 7.5 Hz, 2 H, $H_{ar}$), 7.39 (s, 1 H, $H_{[2H\text{-}Imid.]}$), 7.58 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 34.43 (t, 1 C, $CH_2COO$), 47.42 (t, 1 C, $NCH_2$), 52.00 (q, 1 C, $COOCH_3$), 55.20 (q, 1 C, $OCH_3$), 62.62 (t, 1 C, $NCH_2CH_2$), 88.64 (s, 1 C, $CH_2OC$), 113.58 (d, 2 C, $C_{ar}$), 117.51 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 119.99 (d, 2 C, $C_{ar}$), 125.16 (d, 2 C, $C_{ar}$), 126.70 (d, 2 C, $C_{ar}$), 128.33 (d, 2 C, $C_{ar}$), 129.19 (d, 2 C, $C_{ar}$), 134.72 (s, 1 C, $C_{ar}$ or s, 1 C, $C_{[4C\text{-}Imid.]}$), 134.81 (s, 1 C, $C_{ar}$ or s, 1 C, $C_{[4C\text{-}Imid.]}$), 137.18 (d, 1 C, $C_{[2C\text{-}Imid.]}$), 140.49 (s, 2 C, $C_{ar}$), 146.43 (s, 2 C, $C_{ar}$), 158.84 (s, 1 C, $C_{ar}$), 171.83 (s, 1 C, COO); MS (EI, 70 eV) $m/z$ (%): 454 (28, $M^+$), 271 (100); HRMS (EI, 70 eV): ($C_{28}H_{26}N_2O_4$) calc. 454.1893, found 454.1888.

*5.1.7.2. (1-{3-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]propyl}-1H-imidazol-4-yl)acetic acid methyl ester (**38c**).* According to **GP5:** 1*H*-imidazol-4-ylacetic acid methyl ester·HCl (**38a·HCl**) [43,44] (145 mg, 0.820 mmol), DMF (4 mL), *t*BuOK (202 mg, 1.80 mmol), 9-(3-bromopropoxy)-9-(4-methoxyphenyl)-9*H*-fluorene (**22**) (671 mg, 1.64 mmol), CC (acetone/*iso*-hexane = 7:3). Yield: 103 mg (27%); yellow oil; TLC: $R_f$ = 0.32 ($CHCl_3$/MeOH = 100:3); IR (KBr): 30033063, 3005, 2951, 2875, 2837, 2044, 1739, 1608, 1509, 1449, 1249, 1169, 1081, 1033 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 1.84–1.94 (m, 2 H, $NCH_2CH_2$), 2.98 (t, $J$ = 5.7 Hz, 2 H, $CH_2O$), 3.60 (s, 2 H, $CH_2COO$), 3.70 (s, 3 H, $COOCH_3$), 3.76 (s, 3 H, $OCH_3$), 4.02 (t, $J$ = 7.0 Hz, 2 H, $NCH_2$), 6.76–6.82 (m, 3 H, $H_{[5H\text{-}Imid.]}$, $H_{ar}$), 7.23–7.27 (m, 6 H, $H_{ar}$), 7.29 (s, 1 H, $H_{[2H\text{-}Imid.]}$), 7.35–7.40 (m, 2 H, $H_{ar}$), 7.67 (d, $J$ = 7.6 Hz,

2 H, $H_{ar}$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 31.67 (t, 1 C, $NCH_2CH_2$), 34.37 (t, 1 C, $CH_2COO$), 44.31 (t, 1 C, $NCH_2$), 52.06 (q, 1 C, $COOCH_3$), 55.27 (q, 1 C, $OCH_3$), 59.68 (t, 1 C, $CH_2O$), 88.39 (s, 1 C, $CH_2OC$), 113.64 (d, 2 C, $C_{ar}$), 117.10 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 120.16 (d, 2 C, $C_{ar}$), 125.21 (d, 2 C, $C_{ar}$), 126.78 (d, 2 C, $C_{ar}$), 128.33 (d, 2 C, $C_{ar}$), 129.26 (d, 2 C, $C_{ar}$), 134.85 (s, 1 C, $C_{[4C\text{-}Imid.]}$), 135.41 (s, 1 C, $C_{ar}$), 136.61 (d, 1 C, $C_{[2C\text{-}Imid.]}$), 140.72 (s, 2 C, $C_{ar}$), 147.15 (s, 2 C, $C_{ar}$), 158.91 (s, 1 C, $C_{ar}$), 171.86 (s, 1 C, COO); MS (EI, 70 eV) *m/z* (%): 468 (8, $M^+$), 271 (100); HRMS (ESI+): ($C_{29}H_{29}N_2O_4$) calc. 469.2127, found 469.2125.

*5.1.7.3. (1-{4-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]butyl}-1H-imidazol-4-yl) acetic acid methyl ester (**38d**).* According to **GP5:** 1*H*-imidazol-4-ylacetic acid methyl ester (**38a**) [44] (317 mg, 2.26 mmol), DMF (8 mL), *t*BuOK (278 mg, 2.48 mmol), 9-(4-bromobutoxy)-9-(4-methoxyphenyl)-9*H*-fluorene (**23**) (1.63 g, 3.84 mmol), CC (acetone/*iso*-hexane = 7:3 und $CHCl_3$/MeOH = 100:1). Yield: 316 mg (29%); colourless solid, m.p. 83–85 °C; TLC: $R_f$ = 0.40 ($CH_2Cl_2$/MeOH = 100:2); IR (KBr): 3582, 3451, 3038, 2940, 2869, 2839, 2048, 1976, 1905, 1741, 1605, 1508, 1448, 1299, 1250, 1167, 1080, 1031 $cm^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ = 1.49 (tt, *J* = 7.5/6.0 Hz, 2 H, $CH_2CH_2O$), 1.85 (tt, *J* = 7.5/7.2 Hz, 2 H, $NCH_2CH_2$), 2.98 (t, *J* = 6.0 Hz, 2 H, $CH_2O$), 3.64 (s, 2 H, $CH_2COO$), 3.71 (s, 3 H, $COOCH_3$), 3.75 (s, 3 H, $OCH_3$), 3.84 (t, *J* = 7.2 Hz, 2 H, $NCH_2$), 6.75–6.80 (m, 2 H, $H_{ar}$), 6.83 (s, 1 H, $H_{[5H\text{-}Imid.]}$), 7.22–7.27 (m, 6 H, $H_{ar}$), 7.34 (s, 1 H, $H_{[2H\text{-}Imid.]}$), 7.35–7.40 (m, 2 H, $H_{ar}$), 7.67 (d, *J* = 7.6 Hz, 2 H, $H_{ar}$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 26.85 (t, 1 C, $CH_2CH_2O$), 27.87 (t, 1 C, $NCH_2CH_2$), 34.32 (t, 1 C, $CH_2COO$), 46.87 (t, 1 C, $NCH_2$), 52.00 (q, 1 C, $COOCH_3$), 55.20 (q, 1 C, $OCH_3$), 62.19 (t, 1 C, $CH_2O$), 88.26 (s, 1 C, $CH_2OC$), 113.52 (d, 2 C, $C_{ar}$), 116.87 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 119.99 (d, 2 C, $C_{ar}$), 125.09 (d, 2 C, $C_{ar}$), 126.71 (d, 2 C, $C_{ar}$), 128.15 (d, 2 C, $C_{ar}$), 129.00 (d, 2 C, $C_{ar}$), 134.86 (s, 1C, $C_{[4C\text{-}Imid.]}$), 135.54 (s, 1 C, $C_{ar}$), 136.47 (d, 1 C, $C_{[2C\text{-}Imid.]}$), 140.60 (s, 2 C, $C_{ar}$), 147.33 (s, 2 C, $C_{ar}$), 158.76 (s, 1 C, $C_{ar}$), 171.82 (s, 1 C, COO); MS (EI, 70 eV) *m/z* (%): 482 (8, $M^+$), 271 (100); HRMS (EI, 70 eV): ($C_{30}H_{30}N_2O_4$) calc. 482.2206, found 482.2229.

*5.1.7.4. (1-{5-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]pentyl}-1H-imidazol-4-yl)acetic acid methyl ester (**38e**).* According to **GP5:** 1*H*-imidazol-4-ylacetic acid methyl ester (**38a**) [44] (280 mg, 2.00 mmol), DMF (8 mL), *t*BuOK (246 mg, 2.20 mmol), 9-(5-bromopentoxy)-9-(4-methoxyphenyl)-9*H*-fluorene (**24**) (1.75 g, 4.00 mmol), CC (acetone/*iso*-hexane = 7:3 and $CHCl_3$/MeOH = 100:1). Yield: 336 mg (29%); light yellow oil; TLC: $R_f$ = 0.34 ($CH_2Cl_2$/MeOH = 100:2); IR (KBr): 3063, 3038, 3004, 2938, 2866, 2044, 1960, 1901, 1740, 1676, 1608, 1581, 1509, 1449, 1249, 1169, 1102, 1079, 1033 $cm^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ = 1.28–1.42 (m, 2 H, $NCH_2CH_2CH_2$), 1.52 (tt, *J* = 7.4/6.2 Hz, 2 H, $CH_2CH_2O$), 1.68 (tt, *J* = 7.5/7.2 Hz, 2 H, $NCH_2CH_2$), 2.95 (t, *J* = 6.2 Hz, 2 H, $CH_2O$), 3.63 (s, 2 H, $CH_2COO$), 3.70 (s, 3 H, $COOCH_3$), 3.74 (s, 3 H, $OCH_3$), 3.83 (t, *J* = 7.2 Hz, 2 H, $NCH_2$), 6.73–6.80 (m, 2 H, $H_{ar}$), 6.83 (s, 1 H, $H_{[5H\text{-}Imid.]}$), 7.21–7.28 (m, 6 H, $H_{ar}$), 7.32–7.40 (m, 3 H, $H_{ar}$, $H_{[2H\text{-}Imid.]}$), 7.67 (d, *J* = 7.5 Hz, 2 H, $H_{ar}$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 23.22 (t, 1 C, $NCH_2CH_2CH_2$), 29.37 (t, 1 C, $CH_2CH_2O$), 30.66 (t, 1 C, $NCH_2CH_2$), 34.32 (t, 1 C, $CH_2COO$), 47.04 (t, 1 C, $NCH_2$), 51.99 (q, 1 C, $COOCH_3$), 55.18 (q, 1 C, $OCH_3$), 62.58 (t, 1 C, $CH_2O$), 88.17 (s, 1 C, $CH_2OC$), 113.47 (d, 2 C, $C_{ar}$), 116.90 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 119.93 (d, 2 C, $C_{ar}$), 125.10 (d, 2 C, $C_{ar}$), 126.70 (d, 2 C, $C_{ar}$), 128.08 (d, 2 C, $C_{ar}$), 128.90 (d, 2 C, $C_{ar}$), 134.84 (s, 1 C, $C_{[4C\text{-}Imid.]}$), 135.72 (s, 1 C, $C_{ar}$), 136.46 (d, 1 C, $C_{[2C\text{-}Imid.]}$), 140.55 (s, 2 C, $C_{ar}$), 147.46 (s, 2 C, $C_{ar}$), 158.68 (s, 1 C, $C_{ar}$), 171.86 (s, 1 C, COO); MS (EI, 70 eV) *m/z* (%): 496 (30, $M^+$), 271 (100); HRMS (EI, 70 eV): ($C_{31}H_{32}N_2O_4$) calc. 496.2362, found 496.2375.

*5.1.7.5. (1-{1-(1E)-3-[9-(4-Methoxyphenyl)-9H-fluoren-9-yl]propenyl}-1H-imidazol-4-yl) acetic acid methyl ester (**38f**).* According to **GP5:** 1*H*-imidazol-4-ylacetic acid methyl ester·HCl (**38a·HCl**) [43,44] (70 mg, 0.40 mmol), DMF (3 mL), *t*BuOK (100 mg, 0.891 mmol), 9-((1*E*)-3-bromopropenyl)-9-(4-methoxyphenyl)-9*H*-fluorene (**30**) (200 mg, 0.511 mmol), CC: (acetone/*iso*-hexane = 7:3). Yield: 50 mg (28%); yellow oil; TLC: $R_f$ = 0.40 ($CH_2Cl_2$/MeOH = 100:2); IR (KBr): 3034, 3002, 2950, 2835, 1736, 1606, 1508, 1447, 1341, 1247, 1249, 1178, 1031 $cm^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ = 3.64 (s, 2 H, $CH_2COO$), 3.70 (s, 3 H, $COOCH_3$), 3.74 (s, 3 H, $OCH_3$), 4.45 (d, *J* = 6.3 Hz, 2 H, $NCH_2$), 5.53 (dt, *J* = 15.4/6.3 Hz, 1 H, $NCH_2CH$), 6.39 (d, *J* = 15.4 Hz, 1 H, CHC), 6.74–6.79 (m, 2 H, $H_{ar}$), 6.81 (s, 1 H, $H_{[5H\text{-}Imid.]}$), 7.00–7.06 (m, 2 H, $H_{ar}$), 7.22 (d, *J* = 7.5 Hz, 2H, $H_{ar}$), 7.26–7.30 (m, 2H, $H_{ar}$), 7.34–7.39 (m, 3 H, $H_{ar}$, $H_{[2H\text{-}Imid.]}$), 7.76 (d, *J* = 7.5 Hz, 2 H, $H_{ar}$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 34.21 (t, 1 C, $CH_2COO$), 48.82 (t, 1 C, $NCH_2$), 52.03 (q, 1 C, $COOCH_3$), 55.21 (q, 1 C, $OCH_3$), 60.98 (s, 1 C, CHC), 113.94 (d, 2 C, $C_{ar}$), 117.13 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 120.44 (d, 2 C, $C_{ar}$), 123.00 (d, 1 C, $NCH_2CH$), 125.35 (d, 2 C, $C_{ar}$), 127.69 (d, 2 C, $C_{ar}$), 127.72 (d, 2 C, $C_{ar}$), 128.09 (d, 2 C, $C_{ar}$), 134.87 (s, 1 C, $C_{[4C\text{-}Imid.]}$), 135.29 (s, 1 C, $C_{ar}$), 136.22 (d, 1 C, $C_{[2C\text{-}Imid.]}$), 138.34 (d, 1 C, CHC), 139.88 (s, 2 C, $C_{ar}$), 149.53 (s, 2 C, $C_{ar}$), 158.52 (s, 1 C, $C_{ar}$), 171.67 (s, 1 C, COO); MS (CI, $CH_5^+$) *m/z* (%): 451 (100, $[M+H]^+$); HRMS (EI, 70 eV): ($C_{29}H_{26}N_2O_3$) calc. 450.1944, found 450.1946.

*5.1.7.6. 3-[1-(4,4-Diphenylbut-3-en-1-yl)-1H-imidazol-2-yl]propanoic acid ethyl ester (**42**).* A) To 3-(1*H*-Imidazol-2-yl)propanoic acid ethyl ester (**52**) [29] (100 mg, 0.595 mmol) dissolved in $CH_3CN$ (4 mL), *t*BuOK (74 mg, 0.66 mmol), NaI (234 mg, 1.56 mmol) and 4,4-diphenylbut-3-en-1-ylbromide (**40**) [19] (224 mg, 0.780 mmol) solved in $CH_3CN$ (3 mL) was added. The reaction mixture was warmed up to 60 °C and stirred for 72 h. Having filtered the solvent was evaporated and the crude product was purified by CC (acetone/*iso*-hexane = 6:4 and $CHCl_3$/MeOH = 100:1) [45].

B) According to **GP5:** 3-(1*H*-Imidazol-2-yl)propanoic acid ethyl ester (**39a**) (200 mg, 1.19 mmol), DMF (8 mL), *t*BuOK (147 mg, 1.31 mmol), 4,4-diphenylbut-3-en-1-ylbromide (**40**) (444 mg, 1.55 mmol), CC (acetone/*iso*-hexane = 6:4 and $CHCl_3$/MeOH = 100:1). 28 mg (6%) **42** was obtained. Yield: 46 mg (21%); colourless oil; TLC: $R_f$ = 0.24 ($CH_2Cl_2$/MeOH = 100:2); IR (KBr): 3103, 3079, 3055, 3023, 2979, 2931, 1954, 1891, 1732, 1597, 1493, 1444, 1374, 1277, 1175, 1120, 1074, 1021 $cm^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ = 1.24 (t, *J* = 7.1 Hz, 3 H, $CH_3$), 2.52 (dt, *J* = 7.6/7.2 Hz, 2 H, $CH_2CH$), 2.74–2.90 (m, 4 H, $CH_2CH_2COO$), 3.98 (t, *J* = 7.2 Hz, 2 H, $NCH_2$), 4.12 (q, *J* = 7.1 Hz, 2 H, $CH_2CH_3$), 6.02 (t, *J* = 7.6 Hz, 1 H, CH), 6.75 (d, *J* = 1.1 Hz, 1 H, $H_{[5H\text{-}Imid.]}$), 6.94 (d, *J* = 1.1 Hz, 1 H, $H_{[4H\text{-}Imid.]}$), 6.96–7.01 (m, 2 H, $H_{ar}$), 7.15–7.20 (m, 2 H, $H_{ar}$), 7.23–7.28 (m, 2 H, $H_{ar}$), 7.28–7.39 (m, 4 H, $H_{ar}$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 14.37 (q, 1 C $CH_3$), 21.77 (t, 1 C, $CH_2CH_2COO$), 31.37 (t, 1 C, $CH_2CH$), 31.93 t, 1 C, $CH_2CH_2COO$), 45.67 (t, 1 C, $NCH_2$), 60.73 (t, 1 C $CH_2CH_3$), 119.60 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 123.81 (d, 1 C, CH), 127.28 (d, 2 C, $C_{ar}$), 127.42 59 (d, 1 C, $C_{[4C\text{-}Imid.]}$ or d, 1 C, $C_{ar}$ or d, 1 C, $C_{ar}$), 127.50 (d, 1 C, $C_{[4C\text{-}Imid.]}$ or d, 1 C, $C_{ar}$ or d, 1 C, $C_{ar}$), 127.59 (d, 1 C, $C_{[4C\text{-}Imid.]}$ or d, 1 C, $C_{ar}$ or d, 1 C, $C_{ar}$), 128.38 (d, 2 C, $C_{ar}$), 128.59 (d, 2 C, $C_{ar}$), 129.65 (d, 2 C, $C_{ar}$), 139.46 (s, 1 C, $C_{ar}$), 141.85 (s, 1 C, $C_{ar}$), 145.32 (s, 1 C, CHC), 146.36 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 173.05 (s, 1 C, COO); MS (APCI+) *m/z* (%): 523.2 (44), 509.4 (12), 375.0 (100, $[M+H]^+$); HRMS (EI, 70 eV): ($C_{24}H_{26}N_2O_2$) calc. 374.1994, found 374.1991.

*5.1.7.7. 3-(1-{2-[1-(Tris-4-methoxyphenyl)methoxy]ethyl}-1H-imidazol-2-yl)propanoic acid ethyl ester (**43**).* According to **GP5:** 3-(1*H*-Imidazol-2-yl)propanoic acid ethyl ester (**39a**) [29] (95 mg, 0.56 mmol), DMF (3 mL), *t*BuOK (70 mg, 0.62 mmol), 4,4-tris(4-methoxyphenyl)methoxyethylbromide (**41**) [21] (333 mg, 0.728 mmol), CC ($CHCl_3$/MeOH = 100:1). Yield: 215.5 mg (70%); colourless oil; TLC: $R_f$ = 0.32 ($CH_2Cl_2$/MeOH = 100:3); IR (KBr): 3104, 3036, 2999, 1952, 1836, 1038, 1903, 1732, 1607, 1582, 1508, 1463, 1442, 1374, 1302, 1250, 1175, 1095, 1034 $cm^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ = 1.24 (t, *J* = 7.1 Hz, 3 H, $CH_2CH_3$), 2.84–2.91 (m, 2 H,

$CH_2CH_2COO$), 2.92–2.99 (m, 2 H, $CH_2CH_2COO$), 3.32 (t, $J$ = 5.2 Hz, 2 H, $CH_2O$), 3.77 (s, 9 H, $OCH_3$), 4.05 (t, $J$ = 5.2 Hz, 2 H, $NCH_2$), 4.13 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 6.75–6.81 (m, 6 H, $H_{ar}$), 6.93 (d, $J$ = 1.3 Hz, 1 H, $H_{[5H\text{-}Imid.]}$), 7.00 (d, $J$ = 1.3 Hz, 1 H, $H_{[4H\text{-}Imid.]}$), 7.10–7.17 (m, 6 H, $H_{ar}$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 14.18 (q, 1 C $CH_2CH_3$), 21.70 (t, 1 C, $CH_2CH_2COO$), 31.86 (t, 1 C, $CH_2CH_2COO$), 46.05 (t, 1 C, $NCH_2$), 55.21 (q, 3 C, $OCH_3$), 60.56 (t, 1 C $CH_2CH_3$), 62.97 (t, 1 C, $CH_2O$), 86.25 (s, 1 C, OC), 113.14 (d, 6 C, $C_{ar}$), 120.29 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 127.04 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 129.60 (d, 6 C, $C_{ar}$), 136.03 (s, 3 C, $C_{ar}$), 146.56 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 158.40 (s, 3 C, $C_{ar}$), 172.92 (s, 1 C, COO); MS (ESI+) $m/z$ (%): 545.2 (100, $[M+H]^+$); HRMS (ESI+): ($C_{32}H_{37}N_2O_6$) calc. 545.2652, found 545.2646.

*5.1.7.8. 3-(1-{2-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]ethyl}-1H-imidazol-2-yl)propanoic acid ethyl ester (**39b**).* According to **GP5**: 3-(1*H*-Imidazol-2-yl)propanoic acid ethyl ester (**39a**) [29] (200 mg, 1.19 mmol), DMF (7 mL), *t*BuOK (146 mg, 1.31 mmol), 9-(2-bromoethoxy)-9-methoxyphenyl-9*H*-fluorene (**20**) [21] (610 mg, 1.54 mmol), CC (acetone/*iso*-hexane = 8:2). Yield: 480 mg (83%); colourless crystals, m.p. 72–75 °C; TLC: $R_f$ = 0.45 (acetone/*n*-pentane = 8:2); IR (KBr): 3063, 2934, 2872, 2836, 1731, 1608, 1509, 1449, 1249, 1171, 1105, 1034 $cm^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ = 1.16 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 2.66–2.76 (m, 4 H, $CH_2CH_2COO$), 3.12 (t, $J$ = 5.3 Hz, 2 H, $CH_2O$), 3.66 (s, 3 H, $OCH_3$), 3.92 (t, $J$ = 5.3 Hz, 2 H, $NCH_2$), 4.03 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 6.64–6.70 (m, 2 H, $H_{ar}$), 6.76 (s, 1 H, $H_{[5H\text{-}Imid.]}$), 6.88 (s, 1 H, $H_{[4H\text{-}Imid.]}$), 6.96 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$), 7.06–7.11 (m, 2 H, $H_{ar}$), 7.13 (t, $J$ = 7.5 Hz, 2 H, $H_{ar}$), 7.28 (t, $J$ = 7.5 Hz, 2 H, $H_{ar}$), 7.57 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 14.19 (q, 1 C, $CH_2CH_3$), 21.61 (t, 1 C, $CH_2CH_2COO$), 31.90 (t, 1 C, $CH_2CH_2COO$), 46.02 (t, 1 C, $NCH_2$), 55.19 (q, 1 C, $OCH_3$), 60.51 (t, 1 C, $CH_2CH_3$), 62.60 (t, 1 C, $CH_2O$), 88.73 (s, 1 C, $CH_2OC$), 113.57 (d, 2 C, $C_{ar}$), 119.99 (d, 2 C, $C_{ar}$), 120.12 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 125.12 (d, 2 C, $C_{ar}$), 126.70 (d, 2 C, $C_{ar}$), 126.83 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 128.37 (d, 2 C, $C_{ar}$), 129.18 (d, 2 C, $C_{ar}$), 134.77 (s, 1 C, $C_{ar}$), 140.53 (s, 2 C, $C_{ar}$), 146.52 (s, 2 C, $C_{ar}$), 146.63 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 158.86 (s, 1 C, $C_{ar}$), 172.87 (s, 1 C, COO); MS (EI, 70 eV) $m/z$ (%): 482 (12, $M^+$), 437 (14), 409 (18), 271 (100); HRMS (EI, 70 eV): ($C_{30}H_{30}N_2O_4$) calc. 482.2206, found 482.2208; Anal. $C_{30}H_{30}N_2O_4$ (C, H, N, O).

*5.1.7.9. 3-(1-{3-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]propyl}-1H-imidazol-2-yl)propan-oic acid ethyl ester (**39c**).* According to **GP5:** 3-(1*H*-Imidazol-2-yl)propanoic acid ethyl ester (**39a**) [29] (101 mg, 0.600 mmol), DMF (4 mL), *t*BuOK (74 mg, 0.66 mmol), 9-(3-bromopropoxy)-9-(4-methoxyphenyl)-9*H*-fluorene (**22**) (319 mg, 0.780 mmol), CC ($CHCl_3$/MeOH = 100:1). Yield: 231 mg (78%); colourless oil; TLC: $R_f$ = 0.30 ($CHCl_3$/MeOH = 100:3); IR (KBr): 3063, 3038, 2981, 2950, 2933, 2874, 2836, 2044, 1731, 1608, 1581, 1509, 1449, 1375, 1302, 1249, 1170, 1103, 1073, 1034 $cm^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ = 1.23 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 1.87 (tt, $J$ = 7.2/5.7 Hz, 2 H, $NCH_2CH_2$), 2.81–2.89 (m, 2 H, $CH_2CH_2COO$), 2.90–2.96 (m, 2 H, $CH_2CH_2COO$), 3.00 (t, $J$ = 5.7 Hz, 2 H, $CH_2OC$), 3.76 (s, 3 H, $OCH_3$), 4.01 (t, $J$ = 7.2 Hz, 2 H, $NCH_2$), 4.12 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 6.74 (s, 1 H, $H_{[5H\text{-}Imid.]}$), 6.76–6.82 (m, 2 H, $H_{ar}$), 6.89 (s, 1 H, $H_{[4H\text{-}Imid.]}$), 7.22–7.29 (m, 6 H, $H_{ar}$), 7.33–7.42 (m, 2 H, $H_{ar}$), 7.67 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 14.18 (q, 1 C, $CH_2CH_3$), 21.65 (t, 1 C, $CH_2CH_2COO$), 31.40 (t, 1 C, $NCH_2CH_2$), 31.72 (t, 1 C, $CH_2CH_2COO$), 42.93 (t, 1 C, $NCH_2$), 55.20 (q, 1 C, $OCH_3$), 59.77 (t, 1 C, $CH_2O$), 60.56 (t, 1 C, $CH_2CH_3$), 88.34 (s, 1 C, $CH_2OC$), 113.55 (d, 2 C, $C_{ar}$), 119.37 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 120.04 (d, 2 C, $C_{ar}$), 125.12 (d, 2 C, $C_{ar}$), 126.69 (d, 2 C, $C_{ar}$), 126.97 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 128.24 (d, 2 C, $C_{ar}$), 129.12 (d, 2 C, $C_{ar}$), 135.31 (s, 1 C, $C_{ar}$), 140.61 (s, 2 C, $C_{ar}$), 146.14 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 147.10 (s, 2 C, $C_{ar}$), 158.79 (s, 1 C, $C_{ar}$), 172.85 (s, 1 C, COO); MS (EI, 70 eV) $m/z$ (%): 496 (6, $M^+$), 451 (18), 423 (10), 271 (76), 225 (100); HRMS (ESI+): ($C_{31}H_{33}N_2O_4$) calc. 497.2439, found 497.2443.

*5.1.7.10. 3-(1-{4-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]butyl}-1H-imidazol-2-yl)propan-oic acid ethyl ester (**39d**).* According to **GP5:** 3-(1*H*-Imidazol-2-yl)propanoic acid ethyl ester (**39a**) [29] (50 mg, 0.30 mmol), DMF (2 mL), *t*BuOK (39 mg, 0.35 mmol), 9-(4-bromobutoxy)-9-(4-methoxyphenyl)-9*H*-fluorene (**23**) (173 mg, 0.409 mmol), CC ($CHCl_3$/MeOH = 100:1). Yield: 130 mg (85%); colourless oil; TLC: $R_f$ = 0.33 ($CH_2Cl_2$/MeOH = 100:2); IR (KBr): 3065, 3006, 2871, 2837, 2045, 1955, 1898, 1732, 1609, 1509, 1449, 1249, 1170, 1079, 1035 $cm^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ = 1.23 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 1.50 (tt, $J$ = 7.4/6.0 Hz, 2 H, $CH_2CH_2OC$), 1.81 (quin, $J$ = 7.4 Hz, 2 H, $NCH_2CH_2$), 2.85–2.90 (m, 4 H, $CH_2CH_2COO$), 2.98 (t, $J$ = 6.0 Hz, 2 H, $CH_2OC$), 3.74 (s, 3 H, $OCH_3$), 3.84 (t, $J$ = 7.4 Hz, 2 H, $NCH_2$), 4.12 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 6.73–6.80 (m, 3 H, $H_{ar}$, $H_{[5H\text{-}Imid.]}$), 6.92 (s, 1 H, $H_{[4H\text{-}Imid.]}$), 7.20–7.28 (m, 6 H, $H_{ar}$), 7.32–7.40 (m, 2 H, $H_{ar}$), 7.67 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 14.19 (q, 1 C, $CH_2CH_3$), 21.66 (t, 1 C, $CH_2CH_2COO$), 26.99 (t, 1 C, $CH_2CH_2OC$), 27.70 (t, 1 C, $NCH_2CH_2$), 31.71 (t, 1 C, $CH_2CH_2COO$), 45.54 (t, 1 C, $NCH_2$), 55.18 (q, 1 C, $OCH_3$), 60.58 (t, 1 C, $CH_2CH_3$), 62.27 (t, 1 C, $CH_2O$), 88.23 (s, 1 C, $CH_2OC$), 113.48 (d, 2 C, $C_{ar}$), 119.18 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 119.98 (d, 2 C, $C_{ar}$), 125.09 (d, 2 C, $C_{ar}$), 126.69 (d, 2 C, $C_{ar}$), 127.00 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 128.15 (d, 2 C, $C_{ar}$), 128.97 (d, 2 C, $C_{ar}$), 135.55 (s, 1 C, $C_{ar}$), 140.57 (s, 2 C, $C_{ar}$), 146.16 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 147.32 (s, 2 C, $C_{ar}$), 158.72 (s, 1 C, $C_{ar}$), 172.89 (s, 1 C, COO); MS (CI, $CH_5^+$) $m/z$ (%): 511 (46, $[M+H]^+$), 271 (100); HRMS (EI, 70 eV): ($C_{32}H_{34}N_2O_4$) calc. 510.2519, found 510.2566.

*5.1.7.11. 3-(1-{5-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]pentyl}-1H-imidazol-2-yl)prop-anoic acid ethyl ester (**39e**).* According to **GP5:** 3-(1*H*-Imidazol-2-yl)propanoic acid ethyl ester (**39a**) [29] (101 mg, 0.600 mmol), DMF (4 mL), *t*BuOK (74 mg, 0.66 mmol), 9-(5-bromopentoxy)-9-(4-methoxyphenyl)-9*H*-fluorene (**24**) (342 mg, 0.780 mmol), CC ($CHCl_3$/MeOH = 100:1). Yield: 233 mg (74%); colourless solid, m.p. 102–105 °C; TLC: $R_f$ = 0.24 ($CH_2Cl_2$/MeOH = 100:2); IR (KBr): 3109, 3057, 3037, 2996, 2931, 2902, 2869, 2839, 2046, 1961, 1927, 1831, 1732, 1604, 1508, 1447, 1374, 1298, 1250, 1168, 1078, 1034 $cm^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ = 1.23 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 1.33–1.41 (m, 2 H), 1.52 (tt, $J$ = 7.6/6.1 Hz, 2 H, $CH_2CH_2O$), 1.66 (tt, $J$ = 7.5/7.4 Hz, 2 H), 2.84–2.93 (m, 4 H, $CH_2CH_2COO$), 2.96 (t, $J$ = 6.1 Hz, 2 H, $CH_2O$), 3.74 (s, 3 H, $OCH_3$), 3.82 (t, $J$ = 7.4 Hz, 2 H), 4.13 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 6.74–6.79 (m, 3 H, $H_{ar}$, $H_{[5H\text{-}Imid.]}$), 6.92 (d, $J$ = 1.3 Hz, 1 H, $H_{[4H\text{-}Imid.]}$), 7.22–7.27 (m, 6 H, $H_{ar}$), 7.32–7.39 (m, 2 H, $H_{ar}$), 7.66 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 14.19 (q, 1 C, $CH_2CH_3$), 21.74 (t, 1 C, $CH_2CH_2COO$), 23.38 (t, 1 C, $NCH_2CH_2CH_2$), 29.54 (t, 1 C, $CH_2CH_2O$), 30.61 (t, 1 C, $NCH_2CH_2$), 31.79 (t, 1 C, $CH_2CH_2COO$), 45.65 (d, 1 C, $NCH_2$), 55.18 (q, 1 C, $OCH_3$), 60.55 (t, 1 C, $CH_2CH_3$), 62.66 (t, 1 C, $CH_2O$), 88.21 (s, 1 C, $CH_2OC$), 113.50 (d, 2 C, $C_{ar}$), 119.19 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 119.92 (d, 2 C, $C_{ar}$), 125.13 (d, 2 C, $C_{ar}$), 126.73 (d, 2 C, $C_{ar}$), 127.16 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 128.07 (d, 2 C, $C_{ar}$), 128.89 (d, 2 C, $C_{ar}$), 135.77 (s, 1 C, $C_{ar}$), 140.59 (s, 2 C, $C_{ar}$), 146.13 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 147.53 (s, 2 C, $C_{ar}$), 158.73 (s, 1 C, $C_{ar}$), 172.89 (s, 1 C, COO); MS (CI, $CH_5^+$) $m/z$ (%): 525 (18, $[M+H]^+$), 271 (100); HRMS (EI, 70 eV): ($C_{33}H_{33}N_2O_4$) calc. 524.2675, found 524.2702. Anal. $C_{33}H_{36}N_2O_4$ (C, H, N, O).

*5.1.7.12. 3-(1-{(1E)-3-[9-(4-Methoxyphenyl)-9H-fluoren-9-yl]propenyl}-1H-imidazol-2-yl)propanoic acid ethyl ester (**39f**).* According to **GP5:** 3-(1*H*-Imidazol-2-yl)propanoic acid ethyl ester (**39a**) [29] (106 mg, 0.630 mmol), DMF (4 mL), *t*BuOK (78 mg, 0.70 mmol), 9-((1*E*)-3-bromopropenyl)-9-(4-methoxyphenyl)-9*H*-fluorene (**30**) (320 mg, 0.818 mmol), CC (acetone/*iso*-hexane = 8:2). Yield: 193 mg (64%); colourless oil; TLC: $R_f$ = 0.4 (acetone/*iso*-hexane = 8:2). IR (KBr): 3035, 2930, 2834, 1730, 1606, 1508, 1447, 1374, 1248, 1177, 1931 $cm^{-1}$; $^1$H NMR ($CD_3OD$): $\delta$ = 1.17 (t, $J$ = 7.1 Hz, 3 H, $CH_3$), 2.62 (t, $J$ = 7.5 Hz, 2 H, $CH_2COO$), 2.78 (t, $J$ = 7.5 Hz, 2 H, $CH_2CH_2COO$), 3.67 (s, 3 H, $OCH_3$), 4.05 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$),

4.48 (d, $J$ = 5.5 Hz, 2 H, $NCH_2$), 5.41 (dt, $J$ = 15.5/5.5 Hz, 1 H, $NCH_2CH$), 6.18 (d, $J$ = 15.5 Hz, 1 H, CHC), 6.71–6.75 (m, 2 H, $H_{ar}$), 6.81 (d, $J$ = 1.4 Hz, 1 H, $H_{[4H\text{-}Imid.]}$), 6.85 (d, $J$ = 1.4 Hz, 1 H, $H_{[5H\text{-}Imid.]}$), 6.91–7.04 (m, 2 H, $H_{ar}$), 7.16 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$), 7.22 (t, $J$ = 7.5 Hz, 2 H, $H_{ar}$), 7.32 (t, $J$ = 7.5 Hz, 2 H, $H_{ar}$), 7.77 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$); $^{13}$C NMR ($CD_3OD$): $\delta$ = 14.65 (q, 1 C, $CH_3CH_2$), 22.62 (t, 1 C, $CH_2CH_2COO$), 32.95 (t, 1 C, $CH_2COO$), 48.40 (t, 1 C, $CH_2CH$), 55.80 (q, 1 C, $OCH_3$), 61.79 (t, 1 C, $CH_2CH_3$), 62.38 (s, 1 C, CHC), 115.03 (d, 2 C, $C_{ar}$), 121.29 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 121.53 (d, 2 C, $C_{ar}$), 125.15 (d, 1 C, $NCH_2CH$), 126.66 (d, 2 C, $C_{ar}$), 127.38 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 128.79 (d, 2 C, $C_{ar}$), 128.85 (d, 2 C, $C_{ar}$), 129.34 (d, 2 C, $C_{ar}$), 137.00 (s, 1 C, $C_{ar}$), 138.06 (d, 1 C, CHC), 141.40 (s, 2 C, $C_{ar}$), 148.22 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 151.40 (s, 2 C, $C_{ar}$), 160.18 (s, 1 C, $C_{ar}$), 173.99 (s, 1 C, COO); MS (EI, 70 eV) $m/z$ (%): 478 (2, $M^+$), 455 (2), 433 (2), 297 (46), 203 (42), 107 (100); HRMS (EI, 70 eV): ($C_{31}H_{30}N_2O_3$) calc. 478.2257, found 478.2240.

*5.1.7.13. 3-[1-(2-{(1E)-3-[9-(4-Methoxyphenyl)-9H-fluoren-9-yl] propenyloxy}ethyl)-1H-imidazol-2-yl]-propanoic acid ethyl ester (**39g**).* According to **GP5:** 3-(1*H*-Imidazol-2-yl)propanoic acid ethyl ester (**39a**) [29] (100 mg, 0.595 mmol), DMF (4 mL), *t*BuOK (74 mg, 0.66 mmol), 9-{(1*E*)-3-[2-(2-methyl-sulfonyl)ethoxy]propenyl}-9-(4-methoxyphenyl)-9*H*-fluorene (**34**) (349 mg, 0.774 mmol), CC (acetone/*iso*-hexane = 8:2 and $CH_2Cl_2$/MeOH = 100:0.75). Yield: 215 mg (68%); colourless oil; TLC: $R_f$ = 0.35 ($CH_2Cl_2$/MeOH = 100:3); IR (KBr): 3036, 2932, 2858, 2728, 1606, 1507, 1447, 1374, 1353, 1296, 1279, 1246, 1177, 1117, 1030 cm$^{-1}$; $^1$H NMR ($CD_2Cl_2$): $\delta$ = 1.21 (t, $J$ = 7.1 Hz, 3 H,$CH_2CH_3$), 2.78 (t, $J$ = 6.9 Hz, 2 H, $CH_2CH_2COO$), 2.89 (t, $J$ = 6.9 Hz, 2 H, $CH_2CH_2COO$), 3.61 ($t_{br}$, $J$ = 5.4 Hz, 2 H, $NCH_2CH_2$), 3.73 (s, 3 H, $OCH_3$), 3.92 (dd, $J$ = 5.6/1.3 Hz, 2 H, $CH_2CH$), 4.01 (t, $J$ = 5.4 Hz, 2 H, $NCH_2$), 4.08 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 5.42 (dt, $J$ = 15.5/5.6 Hz, 1 H, $CH_2CH$), 6.38 (d, $J$ = 15.5 Hz, 1 H, CHC), 6.73–6.79 (m, 2 H, $H_{ar}$), 6.83 (s, 1 H, $H_{[4H\text{-}Imid.]}$), 6.84 (s, 1 H, $H_{[5H\text{-}Imid.]}$), 6.99–7.05 (m, 2 H, $H_{ar}$), 7.23 (d, $J$ = 7.4 Hz, 2 H, $H_{ar}$), 7.29 (td, $J$ = 7.4/1.0 Hz, 2 H, $H_{ar}$), 7.37 (td, $J$ = 7.4/1.0 Hz, 2 H, $H_{ar}$), 7.78 (d, $J$ = 7.4 Hz, 2 H, $H_{ar}$); $^{13}$C NMR ($CD_2Cl_2$): $\delta$ = 14.41 (q, 1 C $CH_2CH_3$), 22.13 (t, 1 C, $CH_2CH_2COO$), 32.09 (t, 1 C, $CH_2CH_2COO$), 46.05 (t, 1 C, $NCH_2$), 55.58 (q, 1 C, $OCH_3$), 60.79 (t, 1 C, $CH_2CH_3$), 61.46 (s, 1 C, CHC), 69.75 (t, 1 C, $NCH_2CH_2$), 71.62 (t, 1 C, $CH_2CH$), 114.15 (d, 2 C, $C_{ar}$), 120.03 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 120.72 (d, 2 C, $C_{ar}$), 125.42 (d, 1 C, $CH_2CH$), 125.86 (d, 2 C, $C_{ar}$), 127.36 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 127.88 (d, 2 C, $C_{ar}$), 127.96 (d, 2 C, $C_{ar}$), 128.51 (d, 2 C, $C_{ar}$), 136.09 (d, 1 C, CHC), 136.28 (s, 1 C, $C_{ar}$), 140.28 (s, 2 C, $C_{ar}$), 147.13 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 150.56 (s, 2 C, $C_{ar}$), 158.97 (s, 1 C, $C_{ar}$), 173.15 (s, 1 C, COO); MS (CI, $CH_5^+$) $m/z$ (%): 523 (100, $[M+H]^+$); HRMS (ESI+): ($C_{33}H_{35}N_2O_4$) calc. 523.2597, found 523.2588.

*5.1.7.14. 3-(1-{(2E)-4-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy] but-2-en-1-yl}-1H-imidazol-2-yl)propanoic acid ethyl ester (**39h**).* According to **GP5:** 3-(1*H*-Imidazol-2-yl)propanoic acid ethyl ester (**39a**) [29] (101 mg, 0.600 mmol), DMF (4 mL), *t*BuOK (74 mg, 0.66 mmol), 9-[(2*E*)-4-bromobut-2-en-1-yloxy]-9-(4-methoxyphenyl)-9*H*-fluorene (**25**) (329 mg, 0.780 mmol), CC ($CHCl_3$/MeOH = 100:1). Yield: 208 mg (68%); colourless oil; TLC: $R_f$ = 0.39 ($CH_2Cl_2$/MeOH = 100:3); IR (KBr): 3062, 3039, 2979, 2933, 2859, 2045, 1963, 1732, 1608, 1509, 1449, 1249, 1170, 1107, 1034 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ = 1.23 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 2.79–2.92 (m, 4 H, $CH_2CH_2COO$), 3.52 (dd, $J$ = 5.0/1.3 Hz, 2 H, $CH_2O$), 3.74 (s, 3 H, $OCH_3$), 4.12 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 4.45 (dd, $J$ = 5.5/1.3 Hz, 2 H, $NCH_2$), 5.46 ($dt_{br}$, $J$ = 15.5/5.0 Hz, 1 H, $CHCH_2O$), 5.77 ($dt_{br}$, $J$ = 15.5/5.5 Hz, 1 H, $NCH_2CH$), 6.72–6.80 (m, 3 H, $H_{ar}$, $H_{[5H\text{-}Imid.]}$), 6.93 (d, $J$ = 1.2 Hz, 1 H, $H_{[4H\text{-}Imid.]}$), 7.20–7.20 (m, 6 H, $H_{ar}$), 7.36 (td, $J$ = 7.5/1.6 Hz, 2 H, $H_{ar}$), 7.66 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 14.18 (q, 1 C, $CH_2CH_3$), 21.66 (t, 1 C, $CH_2CH_2COO$), 31.75 (t, 1 C, $CH_2CH_2COO$), 47.14 (t, 1 C, $NCH_2$), 55.17 (q, 1 C, $OCH_3$), 60.56 (t, 1 C, $CH_2CH_3$), 63.09 (t, 1 C, $CH_2O$), 88.44 (s, 1 C, $CH_2OC$), 113.49 (d, 2 C, $C_{ar}$), 119.49 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 119.96 (d, 2 C, $C_{ar}$), 125.21 (d, 2 C, $C_{ar}$), 125.68 (d, 1 C, $NCH_2CH$), 126.75 (d, 2 C, $C_{ar}$), 127.19 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 128.19 (d, 2 C, $C_{ar}$), 129.08 (d, 2 C, $C_{ar}$), 130.69 (d, 1 C, $CHCH_2O$), 135.26 (s, 1 C, $C_{ar}$), 140.54 (s, 2 C, $C_{ar}$), 146.34 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 147.01 (s, 2 C, $C_{ar}$), 158.75 (s, 1 C, $C_{ar}$), 172.85 (s, 1 C, COO); MS (EI, 70 eV) $m/z$ (%): 508 (10, $M^+$), 463 (7), 373 (11), 271 (100); HRMS (EI, 70 eV): ($C_{32}H_{32}N_2O_4$) calc. 508.2362, found 508.2352.

*5.1.7.15. 3-(1-{(2Z)-4-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy] but-2-en-1-yl}-1H-imidazol-2-yl)propanoic acid ethyl ester (**39i**).* According to **GP5:** 3-(1*H*-Imidazol-2-yl)propanoic acid ethyl ester (**39a**) [29] (111 mg, 0.660 mmol), DMF (4 mL), *t*BuOK (82 mg, 0.73 mmol), 9-[(2*Z*)-4-(2-methylsulfonyloxy)but-2-en-1-yloxy]-9-(4-methoxyphenyl)-9*H*-fluorene (**32**) (375 mg, 0.858 mmol), CC ($CHCl_3$/MeOH = 100:1). Yield: 182 mg (54%); colourless solid, m.p. 85–87 °C; TLC: $R_f$ = 0.32 ($CH_2Cl_2$/MeOH = 100:2); IR (KBr): 3135, 3105, 3055, 2971, 2925, 2840, 2041, 1967, 1900, 1730, 1605, 1508, 1449, 1246. 1170, 1076, 1031 cm$^{-1}$; $^1$H NMR ($CD_2Cl_2$): $\delta$ = 1.21 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 2.74–2.77 (m, 4 H, $CH_2CH_2COO$), 3.65 ($d_{br}$, $J$ = 6.4 Hz, 2 H, $CH_2O$), 3.73 (s, 3 H, $OCH_3$), 4.08 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 4.31 ($d_{br}$, $J$ = 6.7 Hz, 2 H, $NCH_2$), 5.50 (dtt, $J$ = 11.2/6.7/1.6 Hz, 1 H, $NCH_2CH$), 5.76 (dtt, $J$ = 11.2/6.4/1.6 Hz, 1 H, $CHCH_2O$), 6.70 (d, $J$ = 1.3 Hz, 1 H, $H_{[5H\text{-}Imid.]}$), 6.74–6.79 (m, 2 H, $H_{ar}$), 6.79 (d, $J$ = 1.3 Hz, 1 H, $H_{[4H\text{-}Imid.]}$), 7.23–7.26 (m, 2 H, $H_{ar}$), 7.26–7.32 (m, 4 H, $H_{ar}$), 7.38–7.42 (m, 2 H, $H_{ar}$), 7.73 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$); $^{13}$C NMR ($CD_2Cl_2$): $\delta$ = 14.41 (q, 1 C, $CH_2CH_3$), 22.03 (t, 1 C, $CH_2CH_2COO$), 31.92 (t, 1 C, $CH_2CH_2COO$), 43.22 (t, 1 C, $NCH_2$), 55.56 (q, 1 C, $OCH_3$), 59.71 (t, 1 C, $CH_2O$), 60.80 (t, 1 C, $CH_2CH_3$), 89.07 (s, 1 C, $CH_2OC$), 113.85 (d, 2 C, $C_{ar}$), 119.35 (d, 1C, $C_{[5C\text{-}Imid.]}$), 120.57 (d, 2 C, $C_{ar}$), 125.55 (d, 2 C, $C_{ar}$), 127.11 (d, 2 C, $C_{ar}$ or $NCH_2CH$), 127.38 (d, 2 C, $C_{ar}$ or $NCH_2CH$), 127.38 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 128.64 (d, 2 C, $C_{ar}$), 129.61 (d, 2 C, $C_{ar}$), 130.63 (d, 1 C, $CHCH_2O$), 135.63 (s, 1 C, $C_{ar}$), 141.07 (s, 2 C, $C_{ar}$), 146.66 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 147.40 (s, 2 C, $C_{ar}$), 159.37 (s, 1 C, $C_{ar}$), 172.98 (s, 1 C, COO); MS (CI, $CH_5^+$) $m/z$ (%): 509 (2, $[M+H]^+$), 271 (100); MS (ESI+) $m/z$ (%): 509.4 (100, $[M+H]^+$); HRMS (ESI+): ($C_{32}H_{33}N_2O_4$) calc. 509.2440, found 509.2435.

*5.1.7.16. 3-[1-(2-{2-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy] ethoxy}ethyl)-1H-imidazol-2-yl]propanoic acid ethyl ester (**39j**).* According to **GP5:** 3-(1*H*-Imidazol-2-yl)propanoic acid ethyl ester (**39a**) [29] (100 mg, 0.595 mmol), DMF (4 mL), *t*BuOK (74 mg, 0.66 mmol), 9-{2-[2-(2-methylsulfonyloxy)ethoxy]-ethoxy}-9-(4-methoxyphenyl)-9*H*-fluorene (**33**) (352 mg, 0.774 mmol), CC (acetone/*iso*-hexane = 8:2 and $CH_2Cl_2$/MeOH = 100:1). Yield: 177 mg (57%); colourless oil; TLC: $R_f$ = 0.32 ($CH_2Cl_2$/MeOH = 100:2); IR (KBr): 3106, 3064, 3038, 2933, 2871, 1837, 2045, 1957, 1914, 1732, 1698, 1581, 1509, 1449, 1375, 1301, 1282, 1249, 1171, 1132, 1102, 1082, 1034 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ = 1.23 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 2.85–2.92 (m, 2 H, $CH_2CH_2COO$), 2.92–3.00 (m, 2 H, $CH_2CH_2COO$), 3.11 (t, $J$ = 4.9 Hz, 2 H, $CH_2OC$), 3.49 (t, $J$ = 4.9 Hz, 2 H, $CH_2CH_2OC$), 3.70 (t, $J$ = 5.3 Hz, 2 H, $NCH_2CH_2$), 3.75 (s, 3 H, $OCH_3$), 4.07 (t, $J$ = 5.3 Hz, 2 H, $NCH_2$), 4.12 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 6.74–6.80 (m, 2 H, $H_{ar}$), 6.94 (d, $J$ = 1.2 Hz, 1 H, $H_{[4H\text{-}Imid.]}$), 6.96 (d, $J$ = 1.2 Hz, 1 H, $H_{[5H\text{-}Imid.]}$), 7.21–7.29 (m, 6H, $H_{ar}$), 7.32–7.40 (m, 2 H, $H_{ar}$), 7.67 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 14.19 (q, 1 C, $CH_2CH_3$), 21.62 (t, 1 C, $CH_2CH_2COO$), 31.87 (t, 1 C, $CH_2CH_2COO$), 45.89 (t, 1 C, $NCH_2$), 55.21 (q, 1 C, $OCH_3$), 60.60 (t, 1 C, $CH_2CH_3$), 62.86 (t, 1 C, $CH_2OC$), 70.24 (t, 1 C, $NCH_2CH_2$), 70.83 (t, 1 C, $CH_2CH_2OC$), 88.43 (s, 1 C, $CH_2OC$), 113.49 (d, 2 C, $C_{ar}$), 119.98 (d, 2 C, $C_{ar}$ or d, 1 C, $C_{[5C\text{-}Imid.]}$), 120.01 (d, 2 C, $C_{ar}$ or d, 1 C, $C_{[5C\text{-}Imid.]}$), 125.26 (d, 2 C, $C_{ar}$), 126.55 (d, 2 C, $C_{ar}$, or d, 1 C, $C_{[4C\text{-}Imid.]}$), 126.78 (d, 2 C, $C_{ar}$, or d, 1 C, $C_{[4C\text{-}Imid.]}$), 128.19 (d, 2 C, $C_{ar}$), 129.04 (d, 2 C, $C_{ar}$), 135.32 (s, 1 C, $C_{ar}$), 140.58 (s, 2 C, $C_{ar}$), 146.58 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 147.05 (s, 2 C, $C_{ar}$), 158.76 (s, 1 C, $C_{ar}$), 172.95 (s, 1 C, COO); MS (CI, $CH_5^+$) $m/z$ (%): 527

(59, $[M+H]^+$), 513 (5), 448 (6), 279 (6), 257 (100); HRMS (EI, 70 eV): ($C_{32}H_{34}N_2O_5$) calc. 526.2468, found 526.2457.

*5.1.7.17. 3-(1-{5-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]pentyl}-1H-imidazol-2-yl)prop-2-enoic acid ethyl ester (**46e**).* According to **GP5:** (*E*)-3-(1*H*-Imidazol-2-yl)prop-2-enoic acid ethyl ester (**46a**) [29] (72 mg, 0.43 mmol), DMF (3 mL), *t*BuOK (53 mg, 0.48 mmol), 9-(5-bromopentoxy)-9-(4-methoxyphenyl)-9*H*-fluorene (**24**) (246 mg, 0.563 mmol), CC ($CHCl_3$/MeOH = 100:1). Yield: 220 mg (97%); light red solid, m.p. 131–133 °C; TLC: $R_f$ = 0.42 ($CH_2Cl_2$/MeOH = 100:2); IR (KBr): 3037, 2995, 2933, 2902, 2871, 1709, 1634, 1508, 1474, 1448, 1296, 1250, 1167, 1079, 1033 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 1.31 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 1.33–1.41 (m, 2 H, $NCH_2CH_2CH_2$), 1.52 (tt, $J$ = 7.5/6.0 Hz, 2 H, $CH_2CH_2O$), 1.70 (tt, $J$ = 7.7/7.3 Hz, 2 H, $NCH_2CH_2$), 2.95 (t, $J$ = 6.0 Hz, 2 H, $CH_2O$), 3.75 (s, 3 H, $OCH_3$), 3.99 (t, $J$ = 7.3 Hz, 2 H, $NCH_2$), 4.25 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 6.74–6.80 (m, 2 H, $H_{ar}$), 6.85 (d, $J$ = 15.4 Hz, 1 H, CHCOO), 6.96 (d, $J$ = 1.0 Hz, 1 H, $H_{[5H\text{-}Imid.]}$), 7.15 (d, $J$ = 1.0 Hz, 1 H, $H_{[4H\text{-}Imid.]}$), 7.20–7.25 (m, 6 H, $H_{ar}$), 7.33–7.39 (m, 2 H, $H_{ar}$), 7.48 (d, $J$ = 15.4 Hz, 1 H, CHCHCOO), 7.66 (d, $J$ = 7.6 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 14.28 (q, 1 C $CH_2CH_3$), 23.32 (t, 1 C, $NCH_2CH_2CH_2$), 29.40 (t, 1 C, $CH_2CH_2O$), 31.11 (t, 1 C, $NCH_2CH_2$), 46.15 (t, 1 C, $NCH_2$), 55.19 (q, 1 C, $OCH_3$), 60.67 (t, 1 C, $CH_2CH_3$), 62.51 (t, 1 C, $CH_2O$), 88.18 (s, 1 C, $CH_2OC$), 113.48 (d, 2 C, $C_{ar}$), 119.92 (d, 2 C, $C_{ar}$), 120.73 (d, 1 C, CHCOO), 122.25 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 125.10 (d, 2 C, $C_{ar}$), 126.71 (d, 2 C, $C_{ar}$), 128.09 (d, 2 C, $C_{ar}$),128.22 (d, 1 C, CHCHCOO), 128.90 (d, 2 C, $C_{ar}$), 130.24 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 135.70 (s, 1 C, $C_{ar}$), 140.56 (s, 2 C, $C_{ar}$), 142.49 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 147.44 (s, 2 C, $C_{ar}$), 158.70 (s, 1 C, $C_{ar}$), 167.03 (s, 1 C, COO); MS (ESI+) *m/z* (%): 1045.4 (8), 545.2 (16, $[M+Na]^+$), 523.4 (100, $[M+H]^+$); HRMS (EI, 70 eV): ($C_{33}H_{34}N_2O_4$) calc. 522.2519, found 522.2552.

*5.1.8. General procedure for hydrolysis (**GP6**)*

The carboxylic acid ester (1.0 equiv.) dissolved in excess of MeOH or EtOH was treated with NaOH (2 M). The mixture was stirred for 1 h and then the pH value was adjusted to 4–5 with HCl (1 M). After extraction with $CH_2Cl_2$, the combined organic layers were dried over $MgSO_4$, filtered, and concentrated.

*5.1.8.1. (1-{2-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]ethyl}-1H-imidazol-5-yl)acetic acid (**10b**).* According to **GP6:** (1-{2-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yloxy]ethyl}-1*H*-imidazol-5-yl)acetic acid methyl ester (**37b**) (21 mg, 0.046 mmol), $CH_3OH$ (1 mL), 2 M NaOH (80.0 mg, 2.00 mmol, 1.00 mL). Yield: 18.3 mg (90%); colourless solid; m.p. 90–95 °C; IR (KBr): 2928, 1719, 1607, 1509, 1449, 1249, 1169, 1105, 1074, 1031 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): $\delta$ = 3.24 (t, $J$ = 4.9 Hz, 2 H, $CH_2O$), 3.64 (s, 2 H, $CH_2COO$), 3.73 (s, 3 H, $CH_3$), 4.28 (t, $J$ = 4.9 Hz, 2 H, $NCH_2$), 6.75–6.80 (m, 2 H, $H_{ar}$), 6.95 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$), 7.10–7.16 (m, 2 H, $H_{ar}$), 7.21 (td, $J$ = 7.5/1.0 Hz, 2 H, $H_{ar}$), 7.32 (s, 1 H, $H_{[4H\text{-}Imid.]}$), 7.39 (td, $J$ = 7.5/1.0 Hz, 2 H, $H_{ar}$), 7.75 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$), 8.56 (s, 1 H, $H_{[2H\text{-}Imid.]}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 31.36 (t, 1 C, $CH_2COO$), 46.99 (t, 1 C, $NCH_2$), 55.42 (q, 1 C, $CH_3$), 61.89 (t, 1 C, $CH_2O$), 89.01 (s, 1 C, $CH_2OC$), 113.92 (d, 2 C, $C_{ar}$), 120.38 (d, 2 C, $C_{ar}$), 120.76 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 125.01 (d, 2 C, $C_{ar}$), 126.81 (d, 2 C, $C_{ar}$), 128.72 (d, 2 C, $C_{ar}$), 129.67 (d, 2 C, $C_{ar}$), 134.38 (s, 1 C, $C_{ar}$), 135.61 (s, 2 C, $C_{[2C\text{-}Imid.]}$, $C_{[5C\text{-}Imid.]}$), 140.69 (s, 2 C, $C_{ar}$), 146.21 (s, 2 C, $C_{ar}$), 158.15 (s, 1 C, $C_{ar}$), 172.20 (s, 1 C, COO); MS (ESI+) *m/z* (%): 441.2 (100, $[M+H]^+$); HRMS (FAB, NBA): ($C_{27}H_{24}N_2O_4$) calc. 441.1814, found 441.1845. Anal. $C_{27}H_{24}N_2O_4$ x $H_2O$ (C, H, N, O).

*5.1.8.2. (1-{3-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]propyl}-1H-imidazol-5-yl)acetic acid (**10c**).* According to **GP6:** (1-{3-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yloxy]propyl}-1*H*-imidazol-5-yl) acetic acid methyl ester (**37c**) (28.0 mg, 0.060 mmol), $CH_3OH$ (1 mL), 2 M NaOH (80.0 mg, 2.00 mmol, 1.00 mL). Yield: 17.7 mg (65%); colourless solid, m.p. 115–120 °C; IR (KBr): 3449, 2926, 2860, 1717, 1607, 1508, 1448, 1249, 1168, 1105, 1073, 1031 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): $\delta$ = 1.89 (m, 2 H, $NCH_2CH_2$), 3.00 (t, $J$ = 5.5 Hz, 2 H, $CH_2O$), 3.65 (s, 2 H, $CH_2COO$), 3.72 (s, 3 H, $CH_3$), 4.23 (t, $J$ = 7.3 Hz, 2 H, $NCH_2$), 6.78 (d, $J$ = 8.9 Hz, 2 H, $H_{ar}$), 7.16–7.20 (m, 3 H, $H_{[4H\text{-}Imid.]}$, $H_{ar}$), 7.22 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$), 7.27 (t, $J$ = 7.5 Hz, 2 H, $H_{ar}$), 7.38 (t, $J$ = 7.5 Hz, 2 H, $H_{ar}$), 7.74 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$), 8.38 (s, 1 H, $H_{[2H\text{-}Imid.]}$); $^{13}C$ NMR ($CD_3OD$): $\delta$ = 31.37 (t, 1 C, $NCH_2CH_2$), 32.49 (t, 1 C, $CH_2COO$), 45.23 (t, 1 C, $NCH_2$), 55.67 (q, 1 C, $CH_3$), 60.96 (t, 1 C, $CH_2O$), 89.80 (s, 1 C, $CH_2OC$), 114.54 (d, 2 C, $C_{ar}$), 121.21 (d, 2 C, $C_{ar}$), 121.71 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 126.26 (d, 2 C, $C_{ar}$), 127.85 (d, 2 C, $C_{ar}$), 129.33 (d, 2 C, $C_{ar}$), 130.40 (d, 2 C, $C_{ar}$), 131.30 (s, 1 C, $C_{[5C\text{-}Imid.]}$), 136.49 (s, 1 C, $C_{ar}$), 136.68 (d, 1 C, $C_{[2C\text{-}Imid.]}$), 142.10 (s, 2 C, $C_{ar}$), 148.39 (s, 2 C, $C_{ar}$), 160.43 (s, 1 C, $C_{ar}$), 174.40 (s, 1 C, COO); MS (ESI+) *m/z* (%): 455.2 (30, $[M+H]^+$), 271.2 (28), 154.1 (100); HRMS (ESI+): ($C_{28}H_{27}N_2O_4$) calc. 455.1971, found 455.1950. Anal. $C_{28}H_{26}N_2O_4$ x 0.45 $H_2O$ (C, H, N, O).

*5.1.8.3. (1-{4-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]butyl}-1H-imidazol-5-yl)acetic acid (**10d**).* According to **GP6:** (1-{4-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yloxy]butyl}-1*H*-imidazol-5-yl) acetic acid methyl ester (**37d**) (24.0 mg, 0.050 mmol), $CH_3OH$ (1 mL), 2 M NaOH (80.0 mg, 2.00 mmol, 1.00 mL). Yield: 17.2 mg (74%); colourless solid, m.p. 103–107 °C; IR (KBr): 3424, 2930, 2868, 1924, 1718, 1608, 1508, 1449, 1248, 1169, 1103, 1076, 1032 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 1.45 (tt, $J$ = 5.8/7.3 Hz, 2 H, $CH_2CH_2O$), 1.81 (tt, $J$ = 7.3/7.4 Hz, 2 H, $NCH_2CH_2$), 2.94 (t, $J$ = 5.8 Hz, 2 H, $CH_2O$), 3.52 (s, 2 H, $CH_2COO$), 3.70 (s, 3 H, $CH_3$), 3.94 (t, $J$ = 7.4 Hz, 2 H, $NCH_2$), 6.71–6.77 (m, 2 H, $H_{ar}$), 7.02 (s, 1 H, $H_{[4H\text{-}Imid.]}$), 7.16–7.24 (m, 6 H, $H_{ar}$), 7.29–7.37 (m, 2 H, $H_{ar}$), 7.64 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$), 7.90 (s, 1 H, $H_{[2H\text{-}Imid.]}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 26.84 (t, 1 C, $CH_2CH_2O$), 27.11 (t, 1 C, $NCH_2CH_2$), 31.58 (t, 1 C, $CH_2COO$), 45.99 (t, 1 C, $NCH_2$), 55.18 (q, 1 C, $CH_3$), 62.12 (t, 1 C, $CH_2O$), 88.28 (s, 1 C, $CH_2OC$), 113.54 (d, 2 C, $C_{ar}$), 120.01 (d, 2 C, $C_{ar}$), 122.25 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 125.08 (d, 2 C, $C_{ar}$), 126.71 (d, 2 C, $C_{ar}$), 128.21 (d, 2 C, $C_{ar}$, s, 1 C, $C_{[5C\text{-}Imid.]}$), 129.04 (d, 2 C, $C_{ar}$), 134.93 (d, 1 C, $C_{[2C\text{-}Imid.]}$), 135.41 (s, 1 C, $C_{ar}$), 140.54 (s, 2 C, $C_{ar}$), 147.20 (s, 2 C, $C_{ar}$), 158.74 (s, 1 C, $C_{ar}$), 172.72 (s, 1 C, COO); MS (FAB, NBA) *m/z* (%): 469.4 (59, $[M+H]^+$), 271.3 (100); HRMS (EI, 70 eV): ($C_{29}H_{28}N_2O_4$) calc. 468.2049, found 468.2055.

*5.1.8.4. (1-{5-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]pentyl}-1H-imidazol-5-yl)acetic acid (**10e**).* According to **GP6:** (1-{5-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yloxy]pentyl}-1*H*-imidazol-5-yl) acetic acid methyl ester (**37e**) (24.0 mg, 0.048 mmol), $CH_3OH$ (1 mL), 2 M NaOH (80.0 mg, 2.00 mmol, 1.00 mL). Yield: 18 mg (77%); colourless solid, m.p. 103–108 °C; IR (KBr): 3386, 2919, 2850, 1722, 1607,1509, 1449, 1366, 1248, 1169, 1015 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 1.27–1.36 (m, 2 H, $NCH_2CH_2CH_2$), 1.47 (tt, $J$ = 7.2/6.0 Hz, 2 H, $CH_2CH_2O$), 1.65 (tt, $J$ = 7.8/7.5 Hz, 2 H, $NCH_2CH_2$), 2.92 (t, $J$ = 6.0 Hz, 2 H, $CH_2O$), 3.55 (s, 2 H, $CH_2COO$), 3.71 (s, 3 H, $CH_3$), 3.95 (t, $J$ = 7.5 Hz, 2 H, $NCH_2$), 6.72–6.78 (m, 2 H, $H_{ar}$), 7.10 (s, 1 H, $H_{[4H\text{-}Imid.]}$), 7.19–7.25 (m, 6 H, $H_{ar}$), 7.30–7.36 (m, 2 H, $H_{ar}$), 7.64 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$), 8.16 (s, 1 H, $H_{[2H\text{-}Imid.]}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 23.24 (t, 1 C, $NCH_2CH_2CH_2$), 29.45 (t, 1 C, $CH_2CH_2O$), 29.89 (t, 1 C, $NCH_2CH_2$), 31.48 (t, 1 C, $CH_2COO$), 46.55 (t, 1 C, $NCH_2$), 55.29 (q, 1 C, $CH_3$), 62.59 (t, 1 C, $CH_2O$), 88.28 (s, 1 C, $CH_2OC$), 113.60 (d, 2 C, $C_{ar}$), 120.09 (d, 2 C, $C_{ar}$), 120.85 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 125.18 (d, 2 C, $C_{ar}$), 126.83 (d, 2 C, $C_{ar}$), 128.22 (d, 2 C, $C_{ar}$), 128.71 (s, 1 C, $C_{[5C\text{-}Imid.]}$), 129.07 (d, 2 C, $C_{ar}$), 134.56 (d, 1 C, $C_{[2C\text{-}Imid.]}$), 135.72 (s, 1 C, $C_{ar}$), 140.62 (s, 2 C, $C_{ar}$), 147.44 (s, 2 C, $C_{ar}$), 158.80 (s, 1 C, $C_{ar}$), 172.32 (s, 1 C, COO); MS (FAB, NBA) *m/z* (%): 483.4 (22, $[M+H]^+$), 271.3 (100); HRMS (ESI+): ($C_{30}H_{30}N_2O_4$) calc. 483.2284, found 483.2277. Anal. $C_{30}H_{30}N_2O_4$ x 2.5 $H_2O$ (C, H, N, O).

*5.1.8.5. (1-{(1E)-3-[9-(4-Methoxyphenyl)-9H-fluoren-9-yl]prop-2-en-1-yl}-1H-imidazol-5-yl)acetic acid (**10f**).* According to **GP6:** (1-{(1*E*)-3-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yl]prop-2-en-1-yl}-1*H*-imidazol-5-yl)acetic acid methyl ester (**37f**) (38.0 mg, 0.084 mmol), $CH_3OH$ (1 mL), 2 M NaOH (80.0 mg, 2.00 mmol, 1.00 mL). Yield: 37 mg (quant.); colourless solid, m.p. 135–145 °C; IR (KBr): 3432, 2929, 1717, 1607, 1508, 1447, 1298, 1249, 1179, 1106, 1031 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): $\delta = 3.56$ (s, 2 H, $CH_2COO$), 3.69 (s, 3 H, $CH_3$), 4.72 (d, $J = 5.9$ Hz, 2 H, $NCH_2$), 5.48 (dt, $J = 5.9/15.5$ Hz, 1 H, $NCH_2CH$), 6.50 (d, $J = 15.5$ Hz, 1 H, CHC), 6.76 (d, $J = 8.8$ Hz, 2 H, $H_{ar}$), 7.00 (d, $J = 8.8$ Hz, 2H, $H_{ar}$), 7.18 (s, 1H, $H_{[4H\text{-}Imid.]}$), 7.20–7.29 (m, 4 H, $H_{ar}$), 7.30–7.40 (m, 2 H, $H_{ar}$), 7.79 (d, $J = 7.5$ Hz, 2 H, $H_{ar}$), 8.26 (s, 1 H, $H_{[2H\text{-}Imid.]}$); $^{13}C$ NMR ($CD_3OD$): $\delta = 31.91$ (t, 1 C, $CH_2COO$), 49.03 (t, 1 C, $NCH_2$), 55.67 (q, 1 C, $CH_3$), 62.36 (s, 1 C, CHC), 114.95 (d, 2 C, $C_{ar}$), 121.46 (d, 2 C, $C_{ar}$), 122.38 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 123.16 (d, 1 C, $NCH_2CH$), 126.62 (d, 2 C, $C_{ar}$), 128.81 (d, 2 C, $C_{ar}$), 128.86 (d, 2 C, $C_{ar}$), 129.24 (d, 2 C, $C_{ar}$), 130.74 (s, 1 C, $C_{[5C\text{-}Imid.]}$), 136.66 (s, 1 C, $C_{ar}$), 136.79 (d, 1 C, $C_{[2C\text{-}Imid.]}$), 140.61 (d, 1 C, CHC), 141.30 (s, 2 C, $C_{ar}$), 151.01 (s, 2 C, $C_{ar}$), 160.12 (s, 1 C, $C_{ar}$), 173.75 (s, 1 C, COO); MS (FAB, NBA) *m/z* (%): 437.3 (100, $[M+H]^+$); HRMS (ESI+): ($C_{28}H_{25}N_2O_3$) calc. 437.1866, found 437.1873.

*5.1.8.6. (1-{2-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]ethyl}-1H-imidazol-4-yl)acetic acid (**9b**).* According to **GP6:** (1-{2-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yloxy]ethyl}-1*H*-imidazol-4-yl)acetic acid methyl ester (**38b**) (14.4 mg, 0.032 mmol), $CH_3OH$ (1 mL), 2 M NaOH (80.0 mg, 2.00 mmol, 1.00 mL). Yield: 130 mg (93%); colourless solid, m.p. 100–105 °C; IR (KBr): 3423, 3127, 2930, 1718, 1607, 1509, 1448, 1249, 1170, 1106, 1077, 1032 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): $\delta = 3.21$ (t, $J = 4.8$ Hz, 2 H, $CH_2O$), 3.65 (s, 2 H, $CH_2COO$), 3.72 (s, 3 H, $CH_3$), 4.19 (t, $J = 4.8$ Hz, 2 H, $NCH_2$), 6.73–6.81 (m, 2 H, $H_{ar}$), 7.00 (d, $J = 7.5$ Hz, 2 H, $H_{ar}$), 7.11–7.15 (m, 2 H, $H_{ar}$), 7.17 (s, 1 H, $H_{[5H\text{-}Imid.]}$), 7.22 (td, $J = 7.5/1.0$ Hz, 2 H, $H_{ar}$), 7.37 (td, $J = 7.5/1.0$ Hz, 2 H, $H_{ar}$), 7.74 (d, $J = 7.5$ Hz, 2 H, $H_{ar}$) 8.30 (s, 1 H, $H_{[2H\text{-}Imid.]}$); $^{13}C$ NMR ($CD_3OD$): $\delta = 34.30$ (t, 1 C, $CH_2COO$), 49.17 (t, 1 C, $NCH_2$) 55.84 (t, 1 C, $CH_2O$), 63.73 (q, 1 C, $CH_3$), 90.13 (s, 1 C, $CH_2OC$), 114.72 (d, 2 C, $C_{ar}$), 120.37 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 121.32 (d, 2 C, $C_{ar}$), 126.35 (d, 2 C, $C_{ar}$), 127.95 (d, 2 C, $C_{ar}$), 129.57 (d, 2 C, $C_{ar}$), 130.61 (d, 2 C, $C_{ar}$), 133.91 (s, 1 C, $C_{[4C\text{-}Imid.]}$), 136.32 (s, 1 C, $C_{ar}$), 137.42 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 142.19 (s, 2 C, $C_{ar}$), 147.95 (s, 2 C, $C_{ar}$), 160.63 (s, 1 C, $C_{ar}$), 174.65 (s, 1 C, COO); MS (CI, $CH_5^+$) *m/z* (%): 441 (12, $[M+H]^+$), 411 (24), 362 (14), 271 (60), 236 (54), 200 (64), 171 (56), 128 (100); HRMS (EI, 70 eV): ($C_{27}H_{24}N_2O_4$) calc. 440.1736, found 440.1734; Anal. $C_{27}H_{24}N_2O_4$ x 2.25 $H_2O$ (C, H, N, O).

*5.1.8.7. (1-{3-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]propyl}-1H-imidazol-4-yl)acetic acid (**9c**).* According to **GP6:** (1-{3-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]propyl}-1*H*-imidazol-4-yl) acetic acid methyl ester (**38c**) (25.7 mg, 0.055 mmol), $CH_3OH$ (1 mL), 2 M NaOH (80.0 mg, 2.00 mmol, 1.00 mL). Yield: 18.7 mg (75%); colourless solid, m.p. 115–120 °C; IR (KBr): 3422, 3134, 3005, 2931, 2872, 2835, 1868, 1844, 1829, 1792, 1717, 1608, 1508, 1449, 1301, 1248, 1169, 1104, 1081, 1032 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): $\delta = 1.98$ (tt, $J = 6.5/5.8$ Hz, 2 H, $NCH_2CH_2$), 2.96 (t, $J = 5.8$ Hz, 2 H, $CH_2O$), 3.53 (s, 2 H, $CH_2COO$), 3.72 (s, 3 H, $CH_3$), 4.18 (t, $J = 6.5$ Hz, 2 H, $NCH_2$), 6.75–6.80 (m, 2 H, $H_{ar}$), 7.12 (s, 1 H, $H_{[5H\text{-}Imid.]}$), 7.16–7.20 (m, 2 H, $H_{ar}$), 7.21 (d, $J = 7.4$ Hz, 2 H, $H_{ar}$), 7.26 (td, $J = 7.4/1.0$ Hz, 2 H, $H_{ar}$), 7.37 (td, $J = 7.4/1.0$ Hz, 2 H, $H_{ar}$), 7.73 (d, $J = 7.4$ Hz, 2 H, $H_{ar}$), 8.14 (s, 1 H, $H_{[2H\text{-}Imid.]}$); $^{13}C$ NMR ($CD_3OD$): $\delta = 31.09$ (t, 1 C, $NCH_2CH_2$), 34.09 (t, 1 C, $CH_2COO$), 47.01 (t, 1 C, $NCH_2$), 55.82 (q, 1 C, $CH_3$), 60.86 (t, 1 C, $CH_2O$), 89.87 (s, 1 C, $CH_2OC$), 114.64 (d, 2 C, $C_{ar}$), 120.05 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 121.33 (d, 2 C, $C_{ar}$), 126.39 (d, 2 C, $C_{ar}$), 127.96 (d, 2 C, $C_{ar}$), 129.42 (d, 2 C, $C_{ar}$), 130.52 (d, 2 C, $C_{ar}$), 133.63 (s, 1 C, $C_{[4C\text{-}Imid.]}$), 136.55 (d, 1 C, $C_{[2C\text{-}Imid.]}$), 136.70 (s, 1 C, $C_{ar}$), 142.21 (s, 2 C, $C_{ar}$), 148.51 (s, 2 C, $C_{ar}$), 160.57 (s, 1 C, $C_{ar}$), 174.66 (s, 1 C, COO); MS (ESI+) *m/z* (%): 455.4 (100, $[M+H]^+$); HRMS (ESI+): ($C_{28}H_{27}N_2O_4$) calc. 455.1970, found 455.1975.

*5.1.8.8. (1-{4-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]butyl}-1H-imidazol-4-yl)acetic acid (**9d**).* According to **GP6:** (1-{4-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yloxy]butyl}-1*H*-imidazol-4-yl) acetic acid methyl ester (**38d**) (23.3 mg, 0.048 mmol), $CH_3OH$ (1 mL), 2 M NaOH (80.0 mg, 2.00 mmol, 1.00 mL). Yield: 18.7 mg (83%); colourless solid, m.p. 105–110 °C; IR (KBr): 3424, 2928, 2867, 1924, 1718, 1608, 1508, 1448, 1301, 1248, 1168, 1076, 1031 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta = 1.40$ (tt, $J = 7.4/5.9$ Hz, 2 H, $CH_2CH_2O$), 1.77 (tt, $J = 7.4/7.2$ Hz, 2 H, $NCH_2CH_2$), 2.90 (t, $J = 5.9$ Hz, 2 H, $CH_2O$), 3.58 (s, 2 H, $CH_2COO$), 3.67 (s, 3 H, $CH_3$), 3.79 (t, $J = 7.2$ Hz, 2 H, $NCH_2$), 6.70 (m, 3H, $H_{ar}$, $H_{[5H\text{-}Imid.]}$), 7.13–7.21 (m, 6 H, $H_{ar}$), 7.25–7.33 (m, 2 H, $H_{ar}$), 7.54 (s, 1 H, $H_{[2H\text{-}Imid.]}$), 7.60 (d, $J = 7.5$ Hz, 2 H, $H_{ar}$), 7.77 (s, 1 H, $NH^+$); $^{13}C$ NMR ($CDCl_3$): $\delta = 26.94$ (t, 1 C, $CH_2CH_2O$), 27.88 (t, 1 C, $NCH_2CH_2$), 33.50 (t, 1 C, $CH_2COO$), 47.64 (t, 1 C, $NCH_2$), 55.40 (q, 1 C, $CH_3$), 62.31 (t, 1 C, $CH_2O$), 88.47 (s, 1 C, $CH_2OC$), 113.72 (d, 2 C, $C_{ar}$), 116.92 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 120.22 (d, 2 C, $C_{ar}$), 125.26 (d, 2 C, $C_{ar}$), 126.89 (d, 2 C, $C_{ar}$), 128.38 (d, 2 C, $C_{ar}$), 129.24 (d, 2 C, $C_{ar}$), 134.42 (s, 1 C, $C_{[4C\text{-}Imid.]}$), 135.62 (d, 1 C, $C_{[2C\text{-}Imid.]}$, s, 1 C, $C_{ar}$), 140.77 (s, 2 C, $C_{ar}$), 147.42 (s, 2 C, $C_{ar}$), 158.95 (s, 1 C, $C_{ar}$), 172.88 (s, 1 C, COO); MS (FAB, NBA) *m/z* (%): 469.4 (76, $[M+H]^+$), 424.4 (13), 271.3 (100); HRMS (FAB, NBA): ($C_{29}H_{29}N_2O_4$) calc. 469.2127, found 469.2111.

*5.1.8.9. (1-{5-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]pentyl}-1H-imidazol-4-yl)acetic acid (**9e**).* According to **GP6:** (1-{5-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yloxy]pentyl}-1*H*-imidazol-4-yl) acetic acid methyl ester (**38e**) (24.5 mg, 0.049 mmol), $CH_3OH$ (1 mL), 2 M NaOH (80.0 mg, 2.00 mmol, 1.00 mL). Yield: 20.7 mg (88%); colourless solid, m.p. 95–100 °C; IR (KBr): 3433, 3126, 3005, 2934, 2864, 2550, 1956, 1718, 1608, 1508, 1448, 1301, 1248, 1169, 1101, 1078, 1032 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta = 1.29–1.39$ (m, 2 H, $NCH_2CH_2CH_2$), 1.51 (tt, $J = 7.0/6.1$ Hz, 2 H, $CH_2CH_2O$), 1.69 (tt, $J = 7.4/7.1$ Hz, 2 H, $NCH_2CH_2$), 2.95 (t, $J = 6.1$ Hz, 2 H, $CH_2O$), 3.65 (s, 2 H, $CH_2COO$), 3.75 (s, 3 H, $CH_3$), 3.86 (t, $J = 7.1$ Hz, 2 H, $NCH_2$), 6.74–6.80 (m, 3 H, $H_{ar}$, $H_{[5H\text{-}Imid.]}$), 7.19–7.29 (m, 6 H, $H_{ar}$), 7.32–7.41 (m, 2 H, $H_{ar}$), 7.58 (s, 1 H, $H_{[2H\text{-}Imid.]}$), 7.67 (d, $J = 7.5$ Hz, 2 H, $H_{ar}$), 7.74 (s, 1 H, $NH^+$); $^{13}C$ NMR ($CDCl_3$): $\delta = 23.14$ (t, 1 C, $NCH_2CH_2CH_2$), 29.27 (t, 1 C, $CH_2CH_2O$), 30.44 (t, 1 C, $NCH_2CH_2$), 33.09 (t, 1 C, $CH_2COO$), 47.57 (t, 1 C, $NCH_2$), 55.20 (q, 1 C, $CH_3$), 62.52 (t, 1 C, $CH_2O$), 88.18 (s, 1 C, $CH_2OC$), 113.48 (d, 2 C, $C_{ar}$), 116.57 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 119.96 (d, 2 C, $C_{ar}$), 125.08 (d, 2 C, $C_{ar}$), 126.69 (d, 2 C, $C_{ar}$), 128.08 (d, 2 C, $C_{ar}$), 128.93 (d, 2 C, $C_{ar}$), 134.25 (s, 1 C, $C_{[4C\text{-}Imid.]}$), 135.31 (d, 1 C, $C_{[2C\text{-}Imid.]}$), 135.63 (s, 1 C, $C_{ar}$), 140.55 (s, 2 C, $C_{ar}$), 147.40 (s, 2 C, $C_{ar}$), 158.72 (s, 1 C, $C_{ar}$), 172.31 (s, 1 C, COO); MS (FAB, NBA) *m/z* (%): 483.4 (21, $[M+H]^+$), 438.4 (6), 271.3 (100); HRMS (EI, 70 eV): ($C_{30}H_{30}N_2O_4$) calc. 482.2206, found 482.2214.

*5.1.8.10. (1-{(1E)-3-[9-(4-Methoxyphenyl)-9H-fluoren-9-yl]propenyl}-1H-imidazol-4-yl) acetic acid (**9f**).* According to **GP6:** (1-{1-(1*E*)-3-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yl]-propenyl}-1*H*-imidazol4-yl)acetic acid methyl ester (**38f**) (22.8 mg, 0.051 mmol), $CH_3OH$ (1 mL), 2 M NaOH (80.0 mg, 2.00 mmol, 1.00 mL). Yield: 20.8 mg (94%); colourless solid, m.p. 115–120 °C. IR (KBr): 3431, 3036, 2937, 2853, 1718, 1606, 1508, 1447, 1382, 1297, 1249, 1179, 1031 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): $\delta = 3.54$ (s, 2 H, $CH_2COO$), 3.71 (s, 3 H, $CH_3$), 4.64 (d, $J = 6.3$ Hz, 2 H, $NCH_2$), 5.53 (dt, $J = 15.3/6.3$ Hz, 1 H, $NCH_2CH$), 6.55 (d, $J = 15.3$ Hz, 1 H, CHC), 6.73–6.80 (m, 2 H, $H_{ar}$), 6.97–7.03 (m, 2 H, $H_{ar}$), 7.06 (s, 1 H, $H_{[5H\text{-}Imid.]}$), 7.19–7.29 (m, 4 H, $H_{ar}$), 7.35 (td, $J = 7.5/1.5$ Hz, 2 H, $H_{ar}$), 7.80 (d, $J = 7.5$ Hz, 2 H, $H_{ar}$), 8.01 (s, 1 H, $H_{[2H\text{-}Imid.]}$); $^{13}C$ NMR ($CD_3OD$): $\delta = 32.85$ (t, 1 C, $CH_2COO$), 49.10 (t, 1 C, $NCH_2$), 54.32 (q, 1 C, $CH_3$), 60.96 (s, 1 C, CHC), 113.57 (d, 2 C, $C_{ar}$), 118.14 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 120.07 (d, 2 C, $C_{ar}$), 122.67 (d, 1 C, $NCH_2CH$), 125.30 (d, 2 C, $C_{ar}$), 127.38 (d, 2 C, $C_{ar}$),

127.45 (d, 2 C, $C_{ar}$), 127.89 (d, 2 C, $C_{ar}$), 133.09 (s, 1 C, $C_{[4C\text{-}Imid.]}$), 135.23 (d, 1 C, $C_{[2C\text{-}Imid.]}$), 135.45 (s, 1 C, $C_{ar}$), 138.91 (d, 1 C, *C*HC), 139.99 (s, 2 C, $C_{ar}$), 149.75 (s, 2 C, $C_{ar}$), 158.77 (s, 1 C, $C_{ar}$), 173.47 (s, 1 C, COO); MS (ESI+) *m/z* (%): 437.2 (84, $[M+H]^+$), 311.2 (17), 203.3 (100); HRMS (ESI+): ($C_{28}H_{25}N_2O_3$) calc. 437.1866, found 437.1872. Anal. $C_{28}H_{24}N_2O_3$ x 1.5$H_2O$ (C, H, N, O).

*5.1.8.11. 3-[1-(4,4-Diphenylbut-3-en-1-yl)-1H-imidazol-2-yl]propanoic acid (**44**).* According to **GP6:** 3-[1-(4,4-Diphenylbut-3-en-1-yl)-1*H*-imidazol-2-yl]propanoic acid ethyl ester (**42**) (22.8 mg, 0.061 mmol), EtOH (1 mL), 2 M NaOH (80.0 mg, 2.00 mmol, 1.00 mL). Yield: 17.8 mg (85%); colourless solid, m.p. 105–110 °C; IR (KBr): 3431, 3048, 2924, 2500, 1716, 1597, 1493, 1443, 1213 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 2.54 (dt, *J* = 7.7/7.2 Hz, 2 H, C*H*$_2$CH), 2.79 (s, 4 H, $CH_2CH_2COO$), 4.08 (t, *J* = 7.2 Hz, 2 H, $NCH_2$), 6.02 (t, *J* = 7.7 Hz, 1 H, CH), 6.81 (d, *J* = 1.6 Hz, 1 H, $H_{[5H\text{-}Imid.]}$), 6.91–6.96 (m, 2 H, $H_{ar}$), 7.04 (d, *J* = 1.6 Hz, 1 H, $H_{[4H\text{-}Imid.]}$), 7.13–7.18 (m, 2 H, $H_{ar}$), 7.21–7.28 (m, 3 H, $H_{ar}$), 7.30–7.39 (m, 3 H, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 21.01 (t, 1 C, *C*H$_2$CH$_2$COO), 30.65 (t, 1 C, *C*H$_2$CH), 33.07 (t, 1 C, *C*H$_2$CH$_2$COO), 46.87 (t, 1 C, $NCH_2$), 120.49 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 121.95 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 122.43 (d, 1 C, CH), 127.23 (d, 2 C, $C_{ar}$), 127.82 (d, 1 C, $C_{ar}$), 127.87 (d, 1 C, $C_{ar}$), 128.50 (d, 2 C, $C_{ar}$), 128.81 (d, 2 C, $C_{ar}$), 129.43 (d, 2 C, $C_{ar}$), 139.10 (s, 1 C, $C_{ar}$), 141.36 (s, 1 C, $C_{ar}$), 146.29 (s, 1 C, CH*C*), 147.06 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 174.82 (s, 1 C, COO); MS (FAB, NBA) *m/z* (%): 347.3 (60, $[M+H]^+$), 206.3 (8); HRMS (EI, 70 eV): ($C_{22}H_{22}N_2O_2$) calc. 346.1681, found 346.1690.

*5.1.8.12. 3-(1-{2-[1-(Tris-4-methoxyphenyl)methoxy]ethyl}-1H-imidazol-2-yl)propanoic acid (**45**).* According to **GP6:** 3-(1-{2-[1-(Tris-4-methoxyphenyl)methoxy]ethyl}-1*H*-imidazol-2-yl)propanoic acid ethyl ester (**43**) (27.1 mg, 0.050 mmol), EtOH (1 mL), 2 M NaOH (80.0 mg, 2.00 mmol, 1.00 mL). Yield: 22 mg (86%); colourless solid, m.p. 90–92 °C; IR (KBr): 3433, 2932, 2836, 2547, 2035, 1717, 1607, 1508, 1463, 1302, 1250, 1175, 1032 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$): $\delta$ = 2.71–2.79 (m, 2 H, C*H*$_2$C*H*$_2$COO), 2.90–2.98 (m, 2 H, C*H*$_2$C*H*$_2$COO), 3.32 (t, *J* = 5.0 Hz, 2 H, $CH_2O$), 3.77 (s, 9 H, $CH_3$), 4.03 (t, *J* = 5.0 Hz, 2 H, $NCH_2$), 6.76–6.82 (m, 6 H, $H_{ar}$), 6.97 (s, 1 H, $H_{[5H\text{-}Imid.]}$), 6.99 (s, 1H, $H_{[4H\text{-}Imid.]}$), 7.07–7.13 (m, 6 H, $H_{ar}$); $^{13}C$ NMR ($CD_2Cl_2$): $\delta$ = 19.84 (t, 1 C, *C*H$_2$CH$_2$COO), 31.68 (t, 1 C, *C*H$_2$CH$_2$COO), 44.80 (t, 1 C, $NCH_2$), 53.49 (q, 3 C, $CH_3$), 60.74 (t, 1 C, $CH_2O$), 84.66 (s, 1 C, OC), 111.41 (d, 6 C, $C_{ar}$), 119.04 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 122.80 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 127.78 (d, 6 C, $C_{ar}$), 134.19 (s, 3 C, $C_{ar}$), 146.25 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 156.91 (s, 3 C, $C_{ar}$), 171.96 (s, 1 C, COO); MS (FAB, NBA) *m/z* (%): 517.5 (24, $[M+H]^+$), 333.4 (44), 307.3 (23); HRMS (FAB, NBA): ($C_{30}H_{32}N_2O_6$) calc. 517.2339, found 517.2342.

*5.1.8.13. 3-(1-{2-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]ethyl}-1H-imidazol-2-yl)propan-oic acid (**11b**).* According to **GP6:** 3-(1-{2-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yloxy]ethyl}-1*H*-imidazol-2-yl)propanoic acid ethyl ester (**39b**) (24.0 mg, 0.050 mmol), $CH_3OH$ (1 mL), 2 M NaOH (80.0 mg, 2.00 mmol, 1.00 mL). Yield: 20 mg (90%); colourless solid, m.p. 105–110 °C; IR (KBr): 2925, 1717, 1608, 1509, 1449, 1249, 1169, 1105, 1083, 1031 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 2.73–2.79 (m, 2 H, C*H*$_2$C*H*$_2$COO), 2.79–2.86 (m, 2 H, C*H*$_2$C*H*$_2$COO), 3.19 (t, *J* = 4.8 Hz, 2 H, $CH_2O$), 3.74 (s, 3 H, $CH_3$), 4.08 (t, *J* = 4.8 Hz, 2 H, $NCH_2$), 6.75 (d, *J* = 8.8 Hz, 2 H, $H_{ar}$), 6.89 (s, 1 H, $H_{[4H\text{-}Imid.]}$ or $H_{[5H\text{-}Imid.]}$), 6.96 (d, *J* = 7.5 Hz, 2 H, $H_{ar}$), 7.05 (s, 1 H, $H_{[4H\text{-}Imid.]}$ or $H_{[5H\text{-}Imid.]}$), 7.12 (d, *J* = 8.8 Hz, 2 H, $H_{ar}$), 7.21 (t, *J* = 7.5 Hz, 2 H, $H_{ar}$), 7.36 (t, *J* = 7.5 Hz, 2 H, $H_{ar}$), 7.65 (d, *J* = 7.5 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 21.07 (t, 1 C, *C*H$_2$CH$_2$COO), 33.17 (t, 1 C, *C*H$_2$CH$_2$COO), 47.03 (t, 1 C, $NCH_2$), 55.23 (q, 1 C, $CH_3$), 61.92 (t, 1 C, $CH_2O$), 88.79 (s, 1 C, $CH_2OC$), 113.66 (d, 2 C, $C_{ar}$), 120.15 (d, 2 C, $C_{ar}$), 120.87 (d, 1 C, $C_{[4C\text{-}Imid.]}$ or $C_{[5C\text{-}Imid.]}$), 122.52 (d, 1 C, $C_{[4C\text{-}Imid.]}$ or $C_{[5C\text{-}Imid.]}$), 124.84 (d, 2 C, $C_{ar}$), 126.56 (d, 2 C, $C_{ar}$), 128.50 (d, 2 C, $C_{ar}$), 129.46 (d, 2 C, $C_{ar}$), 134.23 (s, 1 C, $C_{ar}$), 140.51 (s, 2 C, $C_{ar}$), 146.07 (s, 2 C, $C_{ar}$), 147.58 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 158.98 (s, 1 C, $C_{ar}$), 174.39 (s, 1 C, COO); MS (ESI+) *m/z* (%): 455.3 (58, $[M+H]^+$), 271.1 (100); HRMS (FAB, NBA): ($C_{28}H_{26}N_2O_4$) calc. 455.1971, found 455.1928; Anal. $C_{28}H_{26}N_2O_4$ x $H_2O$ (C, H, N, O).

*5.1.8.14. 3-(1-{3-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]propyl}-1H-imidazol-2-yl prop-anoic acid (**11c**).* According to **GP6:** 3-(1-{3-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yloxy]propyl}-1*H*-imidazol-2-yl) propanoic acid ethyl ester (**39c**) (29.0 mg, 0.058 mmol), EtOH (1 mL), 2 M NaOH (80.0 mg, 2.00 mmol, 1.00 mL). Yield: 20 mg (73%); colourless solid, m.p. 125–127 °C; IR (KBr): 2933, 1716, 1683, 1608, 1508, 1302, 1249, 1169, 1103, 1074, 1033 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): $\delta$ = 1.94 (m, 2 H, $NCH_2CH_2$), 2.61 (t, *J* = 7.0 Hz, 2 H, C*H*$_2$CH$_2$COO), 2.96–3.05 (m, 4 H, $CH_2O$, C*H*$_2$CH$_2$COO), 3.72 (s, 3 H, $CH_3$), 4.16 (t, *J* = 7.1 Hz, 2 H, $NCH_2$), 6.75–6.81 (m, 2 H, $H_{ar}$), 7.04 (s, 1 H, $H_{[4H\text{-}Imid.]}$), 7.10 (s, 1 H, $H_{[5H\text{-}Imid.]}$), 7.17–7.21 (m, 2 H, $H_{ar}$), 7.22 (d, *J* = 7.5 Hz, 2 H, $H_{ar}$), 7.26 (td, *J* = 7.5/1.0 Hz, 2 H, $H_{ar}$), 7.38 (td, *J* = 7.5/1.0 Hz, 2 H, $H_{ar}$), 7.74 (d, *J* = 7.5 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CD_3OD$): $\delta$ = 22.96 (t, 1 C, *C*H$_2$CH$_2$COO), 32.10 (t, 1 C, $NCH_2CH_2$), 34.98 (t, 1 C, *C*H$_2$CH$_2$COO), 45.26 (t, 1 C, $NCH_2$), 55.82 (q, 1 C, $CH_3$), 61.13 (t, 1 C, $CH_2O$), 89.92 (s, 1 C, $CH_2OC$), 114.69 (d, 2 C, $C_{ar}$), 121.34 (d, 2 C, $C_{ar}$), 121.92 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 123.66 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 126.41 (d, 2 C, $C_{ar}$), 127.98 (d, 2 C, $C_{ar}$), 129.42 (d, 2 C, $C_{ar}$), 130.52 (d, 2 C, $C_{ar}$), 136.67 (s, 1 C, $C_{ar}$), 142.22 (s, 2 C, $C_{ar}$), 148.56 (s, 2 C, $C_{ar}$), 149.04 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 160.57 (s, 1 C, $C_{ar}$), 178.82 (s, 1 C, COO); MS (ESI+) *m/z* (%): 469.3 (100, $[M+H]^+$); HRMS (ESI+): ($C_{29}H_{29}N_2O_4$) calc. 469.2127, found 469.2125.

*5.1.8.15. 3-(1-{4-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]butyl}-1H-imidazol-2-yl)prop-anoic acid (**11d**).* According to **GP6:** 3-(1-{4-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yloxy]butyl}-1*H*-imidazol-2-yl) propanoic acid ethyl ester (**39d**) (49.0 mg, 0.097 mmol), EtOH (1 mL), 2 M NaOH (80.0 mg, 2.00 mmol, 1.00 mL). Yield: 36 mg (80%); colourless solid, m.p. 95–98 °C; IR (KBr): 3433, 3038, 2932, 2869, 1925, 1719, 1608, 1509, 1449, 1301, 1283, 1248, 1169, 1103, 1078, 1032 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 1.49 (tt, *J* = 7.4/6.2 Hz, 2 H, C*H*$_2$CH$_2$O), 1.84 (tt, *J* = 7.4/7.3 Hz, 2 H, $NCH_2CH_2$), 2.86 (t, *J* = 6.2 Hz, 2 H, C*H*$_2$C*H*$_2$COO), 2.94–3.07 (m, 4 H, $CH_2O$, C*H*$_2$C*H*$_2$COO), 3.73 (s, 3 H, $CH_3$), 3.99 (t, *J* = 7.3 Hz, 2 H, $NCH_2$), 6.74–6.79 (m, 2 H, $H_{ar}$), 6.88 (s, 1 H, $H_{[5H\text{-}Imid.]}$), 7.10 (s, 1 H, $H_{[4H\text{-}Imid.]}$), 7.19–7.29 (m, 6 H, $H_{ar}$), 7.33–7.40 (m, 2 H, $H_{ar}$), 7.67 (d, *J* = 7.5 Hz, 2 H, $H_{ar}$), 12.65 (s, 1 H, OH); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 21.06 (t, 1 C, *C*H$_2$CH$_2$COO), 26.65 (t, 1 C, *C*H$_2$CH$_2$O), 27.28 (t, 1 C, $NCH_2CH_2$), 32.88 (t, 1 C, *C*H$_2$CH$_2$COO), 46.70 (t, 1 C, $NCH_2$), 55.20 (q, 1 C, $CH_3$), 62.10 (t, 1 C, $CH_2O$), 88.28 (s, 1 C, $CH_2OC$), 113.53 (d, 2 C, $C_{ar}$), 119.76 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 120.05 (d, 2 C, $C_{ar}$), 121.81 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 125.05 (d, 2 C, $C_{ar}$), 126.69 (d, 2 C, $C_{ar}$), 128.20 (d, 2 C, $C_{ar}$), 129.07 (d, 2 C, $C_{ar}$), 135.32 (s, 1 C, $C_{ar}$), 140.55 (s, 2 C, $C_{ar}$), 146.80 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 147.12 (s, 2 C, $C_{ar}$), 158.77 (s, 1 C, $C_{ar}$), 174.72 (s, 1 C, COO); MS (FAB, NBA) *m/z* (%): 483.2 (100, $[M+H]^+$); HRMS (ESI+): ($C_{30}H_{31}N_2O_4$) calc. 483.2284, found 483.2261.

*5.1.8.16. 3-(1-{5-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]pentyl}-1H-imidazol-2-yl)prop-anoic acid (**11e**).* According to **GP6:** 3-(1-{5-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yloxy]pentyl}-1*H*-imidazol-2-yl)propanoic acid ethyl ester (**39e**) (25.0 mg, 0.048 mmol), EtOH (1 mL), 2 M NaOH (80.0 mg, 2.00 mmol, 1.00 mL). Yield: 20 mg (83%); colourless solid, m.p. 87–90 °C; IR (KBr): 3005, 2932, 2865, 2501, 1953, 1718, 1608, 1509, 1449, 1249, 1169, 1079, 1033 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 1.32–1.44 (m, 2 H, $NCH_2CH_2CH_2$), 1.52 (tt, *J* = 7.2/6.3 Hz, 2 H, C*H*$_2$CH$_2$O), 1.67 (tt, *J* = 7.5/7.4 Hz, 2 H, $NCH_2CH_2$), 2.84 (m, 2 H, C*H*$_2$C*H*$_2$COO), 2.97 (m, 4 H, C*H*$_2$C*H*$_2$COO, $CH_2O$), 3.74 (s, 3 H, $CH_3$), 3.87 (t, *J* = 7.4 Hz, 2 H, $NCH_2$), 6.78 (m, 2 H, $H_{ar}$), 6.79 (s, 1 H, $H_{[5H\text{-}Imid.]}$), 6.99 (s, 1 H, $H_{[4H\text{-}Imid.]}$), 7.20–7.29 (m, 6 H, $H_{ar}$), 7.33–7.40 (m, 2 H, $H_{ar}$), 7.67 (d, *J* = 7.5 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR

($CDCl_3$): $\delta$ = 21.45 (t, 1 C, $CH_2CH_2COO$), 23.25 (t, 1 C, $NCH_2CH_2CH_2$), 29.35 (t, 1 C, $CH_2CH_2O$), 30.25 (t, 1 C, $NCH_2CH_2$), 33.07 (t, 1 C, $CH_2CH_2COO$), 46.34 (t, 1 C, $NCH_2$), 55.20 (q, 1 C, $CH_3$), 62.50 (t, 1 C, $CH_2O$), 88.19 (s, 1 C, $CH_2OC$), 113.48 (d, 2 C, $C_{ar}$), 119.52 (d, 1C, $C_{[5C\text{-}Imid.]}$), 119.98 (d, 2C, $C_{ar}$), 123.80 (d, 1C, $C_{[4C\text{-}Imid.]}$), 125.07 (d, 2 C, $C_{ar}$), 126.70 (d, 2 C, $C_{ar}$), 128.10 (d, 2 C, $C_{ar}$), 128.95 (d, 2 C, $C_{ar}$), 135.63 (s, 1 C, $C_{ar}$), 140.56 (s, 2 C, $C_{ar}$), 146.86 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 147.39 (s, 2 C, $C_{ar}$), 158.72 (s, 1 C, $C_{ar}$), 174.71 (s, 1 C, COO); MS (ESI+) *m/z* (%): 993.6 (9), 519.3 (6, $[M+Na]^+$), 497.1 (76, $[M+H]^+$), 271.0 (100); HRMS (ESI+): ($C_{31}H_{33}N_2O_4$) calc. 497.2440, found 497.2438.

*5.1.8.17. 3-(1-{(1E)-3-[9-(4-Methoxyphenyl)-9H-fluoren-9-yl]propenyl}-1H-imidazol-2-yl)propanoic acid (**11f**).* According to **GP6:** 3-(1-{(1*E*)-3-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yl]propenyl}-1*H*-imidazol-2-yl) propanoic acid ethyl ester (**39f**) (29.0 mg, 0.061 mmol), EtOH (1 mL), 2 M NaOH (80.0 mg, 2.00 mmol, 1.00 mL). Yield: 24.5 mg (90%); colourless solid, m.p. 115–120 °C; IR (KBr): 3035, 3003,2930, 2835, 2484,1920, 1717, 1606, 1508, 1447, 1249, 1178, 1118, 1031 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 2.69–2.77 (m, 2 H, $CH_2CH_2COO$), 2.80–2.87 (m, 2 H, $CH_2CH_2COO$), 3.74 (s, 3 H, $CH_3$), 4.49 (d, $J$ = 5.7 Hz, 2 H, $NCH_2$), 5.42 (dt, $J$ = 15.4/5.7 Hz, 1 H, $NCH_2CH$), 6.26 (d, $J$ = 15.4 Hz, 1 H, CHC), 6.73–6.80 (m, 3 H, $H_{ar}$, $H_{[5H\text{-}Imid.]}$), 6.96 (s, 1 H, $H_{[4H\text{-}Imid.]}$), 6.97–7.03 (m, 2 H, $H_{ar}$), 7.20 (d, $J$ = 7.4 Hz, 2 H, $H_{ar}$), 7.28 (td, $J$ = 7.4/1.1 Hz, 2 H, $H_{ar}$), 7.37 (td, $J$ = 7.4/1.1 Hz, 2 H, $H_{ar}$), 7.76 (d, $J$ = 7.4 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 21.40 (t, 1 C, $CH_2CH_2COO$), 32.94 (t, 1 C, $CH_2CH_2COO$), 48.04 (t, 1 C, $NCH_2$), 55.24 (q, 1 C, $CH_3$), 61.00 (s, 1 C, CHC), 114.01 (d, 2 C, $C_{ar}$), 119.74 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 120.53 (d, 2 C, $C_{ar}$), 121.88 (d, 1 C, $NCH_2CH$), 124.21 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 125.23 (d, 2 C, $C_{ar}$), 127.80 (d, 2 C, $C_{ar}$), 127.82 (d, 2 C, $C_{ar}$), 128.01 (d, 2 C, $C_{ar}$), 135.00 (s, 1 C, $C_{ar}$), 138.51 (d, 1 C, CHC), 139.84 (s, 2 C, $C_{ar}$), 147.22 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 149.36 (s, 2 C, $C_{ar}$), 158.60 (s, 1 C, $C_{ar}$), 174.37 (s, 1 C, COO); MS (ESI+) *m/z* (%): 451.3 (100, $[M+H]^+$); HRMS (EI, 70 eV): ($C_{29}H_{26}N_2O_3$) calc. 450.1944, found 450.1929; Anal. $C_{29}H_{26}N_2O_3$ x $1.5H_2O$ (C, H, N, O).

*5.1.8.18. 3-[1-(2-{(1E)-3-[9-(4-Methoxyphenyl)-9H-fluoren-9-yl]propenyloxy}ethyl)-1H-imidazol-2-yl]propanoic acid (**11g**).* According to **GP6:** 3-[1-(2-{(1*E*)-3-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yl]propenyloxy}ethyl)-1*H*-imidazol-2-yl]-propanoic acid ethyl ester (**39g**) (22.2 mg, 0.046 mmol), EtOH (1 mL), 2 M NaOH (16 mg, 0.40 mmol, 0.20 mL). Yield: 18.4 mg (88%); colourless solid, m.p. 110–113 °C; IR (KBr): 3036, 2931, 2858, 2485, 1917, 1711, 1606, 1507, 1447, 1354, 1246, 1177, 1117, 1029 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$): $\delta$ = 2.67–2.74 (m, 2 H, $CH_2CH_2COO$), 2.90–2.95 (m, 2 H, $CH_2CH_2COO$), 3.59 ($t_{br}$, $J$ = 5.1 Hz, 2 H, $NCH_2CH_2$), 3.73 (s, 3 H, $CH_3$), 3.91 (dd, $J$ = 5.7/1.3 Hz, 2 H, $CH_2CH$), 4.00 (t, $J$ = 5.1 Hz, 2 H, $NCH_2$), 5.38 (dt, $J$ = 15.5/5.7 Hz, 1 H, $CH_2CH$), 6.36 (d, $J$ = 15.5 Hz, 1 H, CHC), 6.74–6.79 (m, 2 H, $H_{ar}$), 6.86 (s, 1 H, $H_{[5H\text{-}Imid.]}$), 6.89 (s, 1 H, $H_{[4H\text{-}Imid.]}$), 6.99–7.04 (m, 2 H, $H_{ar}$), 7.22 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$), 7.29 (td, $J$ = 7.5/1.1 Hz, 2 H, $H_{ar}$), 7.37 (td, $J$ = 7.5/1.1 Hz, 2 H, $H_{ar}$), 7.79 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CD_2Cl_2$): $\delta$ = 21.90 (t, 1 C, $CH_2CH_2COO$), 33.68 (t, 1 C, $CH_2CH_2COO$), 46.70 (t, 1 C, $NCH_2$), 55.60 (q, 1 C, $CH_3$), 61.44 (s, 1 C, CHC), 69.28 (t, 1 C, $NCH_2CH_2$), 71.67 (t, 1 C, $CH_2CH$), 114.16 (d, 2 C, $C_{ar}$), 120.44 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 120.78 (d, 2 C, $C_{ar}$), 124.72 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 125.11 (d, 1 C, $CH_2CH$), 125.79 (d, 2 C, $C_{ar}$), 127.95 (d, 2 C, $C_{ar}$), 128.00 (d, 2 C, $C_{ar}$), 128.48 (d, 2 C, $C_{ar}$), 136.12 (s, 1 C, $C_{ar}$), 136.49 (d, 1 C, CHC), 140.26 (s, 2 C, $C_{ar}$), 148.52 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 150.43 (s, 2 C, $C_{ar}$), 158.99 (s, 1 C, $C_{ar}$), 174.25 (s, 1 C, COO); MS (FAB, NBA) *m/z* (%): 495.4 (9, $[M+H]^+$); HRMS (ESI+): ($C_{31}H_{31}N_2O_4$) calc. 495.2284, found 495.2276.

*5.1.8.19. 3-(1-{(2E)-4-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]but-2-en-1-yl}-1H-imidazol-2-yl)propanoic acid (**11h**).* According to **GP6:** 3-(1-{(2*E*)-4-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yloxy]but-2-en-1-yl}-1*H*-imidazol-2-yl)propanoic acid ethyl ester (**39h**) (23.0 mg, 0.045 mmol), EtOH (1 mL), 2 M NaOH (80.0 mg, 2.00 mmol, 1.00 mL). Yield: 17.7 mg (82%); colourless solid, m.p. 92–95 °C; IR (KBr): 3448, 3005, 2927, 2854, 2486, 1924, 1718, 1608, 1509, 1449, 1249, 1169, 1104, 1032 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 2.79–2.85 (m, 2 H, $CH_2CH_2COO$), 2.91–2.98 (m, 2 H, $CH_2CH_2COO$), 3.54 (d, $J$ = 5.0 Hz, 2 H, $CH_2O$), 3.74 (s, 3 H, $CH_3$), 4.48 (d, $J$ = 5.7 Hz, 2 H, $NCH_2$), 5.51 (dt, $J$ = 15.5/5.0 Hz, 1 H, $CHCH_2O$), 5.77 (dt, $J$ = 15.5/5.7 Hz, 1 H, $NCH_2CH$), 6.74–6.79 (m, 2 H, $H_{ar}$), 6.79 (s, 1 H, $H_{[5H\text{-}Imid.]}$), 6.98 (s, 1 H, $H_{[4H\text{-}Imid.]}$), 7.21–7.31 (m, 6 H, $H_{ar}$), 7.34–7.40 (m, 2 H, $H_{ar}$), 7.67 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ = 21.46 (t, 1 C, $CH_2CH_2COO$), 32.99 (t, 1 C, $CH_2CH_2COO$), 47.77 (t, 1 C, $NCH_2$), 55.20 (q, 1 C, $CH_3$), 62.90 (t, 1 C, $CH_2O$), 88.50 (s, 1 C, $CH_2OC$), 113.55 (d, 2 C, $C_{ar}$), 119.78 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 120.02 (d, 2 C, $C_{ar}$), 124.12 (d, 1 C, $C_{[4C\text{-}Imid.]}$ or $NCH_2CH$), 124.22 (d, 1 C, $C_{[4C\text{-}Imid.]}$ or $NCH_2CH$), 125.20 (d, 2 C, $C_{ar}$), 126.74 (d, 2 C, $C_{ar}$), 128.24 (d, 2 C, $C_{ar}$), 129.17 (d, 2 C, $C_{ar}$), 131.99 (d, 1 C, $CHCH_2O$), 135.11 (s, 1 C, $C_{ar}$), 140.56 (s, 2 C, $C_{ar}$), 146.87 (s, 2 C, $C_{ar}$), 147.09 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 158.81 (s, 1 C, $C_{ar}$), 174.54 (s, 1 C, COO); MS (ESI+) *m/z* (%): 961.5 (7), 495.2 (22, $[M+Na]^+$), 481.1 (100, $[M+H]^+$), 271.0 (100); HRMS (EI, 70 eV): ($C_{30}H_{28}N_2O_4$) calc. 480.2049, found 480.2042.

*5.1.8.20. 3-(1-{(2Z)-4-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]but-2-en-1-yl}-1H-imidazol-2-yl)propanoic acid (**11i**).* According to **GP6:** 3-(1-{(2*Z*)-4-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yloxy]but-2-en-1-yl}-1*H*-imidazol-2-yl)propanoic acid ethyl ester (**39i**) (22.3 mg, 0.044 mmol), EtOH (1 mL), 2 M NaOH (80.0 mg, 2.00 mmol, 1.00 mL). Yield: 15.4 mg (73%); colourless solid, m.p. 75–77 °C; IR (KBr): 3143, 3006, 2918, 2849, 1955, 1720, 1606, 1509, 1249, 1169, 1058, 1032 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$): $\delta$ = 2.78–2.83 (m, 2 H, $CH_2CH_2COO$), 2.86–2.93 (m, 2 H, $CH_2CH_2COO$), 3.65 (dd, $J$ = 6.2/1.5 Hz, 2 H, $CH_2O$), 3.73 (s, 3 H, $CH_3$), 4.46 (dd, $J$ = 6.8/1.5 Hz, 2 H, $NCH_2$), 5.50 (dtt, $J$ = 11.0/6.8/1.5 Hz, 1 H, $NCH_2CH$), 5.84 (dtt, $J$ = 11.0/6.2/1.5 Hz, 1 H, $CHCH_2O$), 6.73–6.79 (m, 2 H, $H_{ar}$), 6.82 (d, $J$ = 1.4 Hz, 1 H, $H_{[5H\text{-}Imid.]}$), 7.01 (d, $J$ = 1.4 Hz, 1 H, $H_{[4H\text{-}Imid.]}$), 7.21–7.25 (m, 2 H, $H_{ar}$), 7.26–7.31 (m, 4 H, $H_{ar}$), 7.37–7.44 (m, 2 H, $H_{ar}$), 7.73 (dt, $J$ = 7.6/0.8 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CD_2Cl_2$): $\delta$ = 19.28 (t, 1 C, $CH_2CH_2COO$), 30.86 (t, 1 C, $CH_2CH_2COO$), 42.22 (t, 1 C, $NCH_2$), 53.46 (q, 1 C, $CH_3$), 57.72 (t, 1 C, $CH_2O$), 87.05 (s, 1 C, $CH_2OC$), 111.78 (d, 2 C, $C_{ar}$), 118.04 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 118.52 (d, 2 C, $C_{ar}$), 120.52 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 122.78 (d, 1 C, $NCH_2CH$), 123.38 (d, 2 C, $C_{ar}$), 124.95 (d, 2 C, $C_{ar}$), 126.56 (d, 2 C, $C_{ar}$), 127.61 (d, 2 C, $C_{ar}$), 130.45 (d, 1 C, $CHCH_2O$), 133.19 (s, 1 C, $C_{ar}$), 138.94 (s, 2 C, $C_{ar}$), 144.99 (s, 2 C, $C_{ar}$), 145.26 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 157.31 (s, 1 C, $C_{ar}$), 171.76 (s, 1 C, COO); MS (ESI+) *m/z* (%): 961.6 (6), 481.3 (100, $[M+H]^+$); HRMS (ESI+): ($C_{30}H_{29}N_2O_4$) calc. 481.2127, found 481.2117.

*5.1.8.21. 3-[1-(2-{2-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]ethoxy}ethyl)-1H-imidazol-2-yl]propanoic acid (**11j**).* According to **GP6:** 3-[1-(2-{2-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yloxy]ethoxy}-ethyl)-1*H*-imidazol-2-yl] propanoic acid ethyl ester (**39j**) (20.0 mg, 0.038 mmol), EtOH (1 mL), 2 M NaOH (16 mg, 0.40 mmol, 0.20 mL). Yield: 14.8 mg (78%); colourless solid, m.p. 93–97 °C; IR (KBr): 3349, 3061, 2927, 2869, 2501, 1953, 1710, 1607, 1508, 1448, 1247, 1168, 1099, 1078, 1030 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$): $\delta$ = 2.71–2.76 (m, 2 H, $CH_2CH_2COO$), 2.94–2.99 (m, 2 H, $CH_2CH_2COO$), 3.08 (t, $J$ = 4.8 Hz, 2 H, $CH_2OC$), 3.49 (t, $J$ = 4.8 Hz, 2 H, $CH_2CH_2OC$), 3.69 (t, $J$ = 5.0 Hz, 2 H, $NCH_2CH_2$), 3.74 (s, 3 H, $CH_3$), 4.04 (t, $J$ = 5.0 Hz, 2 H, $NCH_2$), 6.75–6.79 (m, 2 H, $H_{ar}$), 6.93 (s, 1 H, $H_{[4H\text{-}Imid.]}$), 6.99 (s, 1H, $H_{[5H\text{-}Imid.]}$), 7.18–7.23 (m, 4 H, $H_{ar}$), 7.27 (td, $J$ = 7.5/1.1 Hz, 2 H, $H_{ar}$), 7.39 (td, $J$ = 7.5/1.1 Hz, 2 H, $H_{ar}$), 7.70 (d, $J$ = 7.5 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CD_2Cl_2$): $\delta$ = 21.97 (t, 1 C, $CH_2CH_2COO$), 33.77 (t, 1 C, $CH_2CH_2COO$), 46.78 (t, 1 C, $NCH_2$), 55.59 (q, 1 C, $CH_3$), 63.27 (t, 1 C, $CH_2OC$), 70.40 (t, 1 C, $NCH_2CH_2$), 71.23 (t, 1 C, $CH_2CH_2OC$), 88.82 (s, 1 C, $CH_2OC$), 113.83 (d, 2 C, $C_{ar}$), 120.50 (d, 2 C, $C_{ar}$), 120.69 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 124.74 (d, 1 C, $C_{[4C\text{-}Imid.]}$), 125.51 (d, 2 C, $C_{ar}$), 127.10 (d, 2 C,

$C_{ar}$), 128.54 (d, 2 C, $C_{ar}$), 129.53 (d, 2 C, $C_{ar}$), 135.72 (s, 1 C, $C_{ar}$), 141.02 (s, 2 C, $C_{ar}$), 147.43 (s, 2 C, $C_{ar}$), 148.54 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 159.37 (s, 1 C, $C_{ar}$), 174.22 (s, 1 C, COO); MS (FAB, NBA) *m/z* (%): 499.3 (36, $[M+H]^+$), 271.2 (55); HRMS (ESI+): ($C_{30}H_{31}N_2O_5$) calc. 499.2233, found 499.2225. Anal. $C_{30}H_{30}N_2O_5$ x 1.75$H_2O$ (C, H, N, O).

*5.1.8.22. 3-(1-{5-[9-(4-Methoxyphenyl)-9H-fluoren-9-yloxy]pentyl}-1H-imidazol-2-yl)prop-2-enoic acid (**12e**).* According to **GP6:** 3-(1-{5-[9-(4-Methoxyphenyl)-9*H*-fluoren-9-yloxy]pentyl}-1*H*-imidazol-2-yl)prop-2-enoic acid ethyl ester (**46e**) (27.0 mg, 0.052 mmol), EtOH (2 mL), 2 M NaOH (160 mg, 4.00 mmol, 2.00 mL). Yield: 19.6 mg (77%); colourless solid, m.p. 143–145 °C; IR (KBr): 3434, 2936, 2857, 2427, 1895, 1701, 1636, 1608, 1509, 1449, 1301, 1289, 1247, 1170, 1132, 1100, 1079, 1035 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 1.32–1.42 (m, 2 H, $NCH_2CH_2CH_2$), 1.52 (tt, *J* = 7.5/6.1 Hz, 2 H, $CH_2CH_2O$), 1.70 (tt, *J* = 7.6/7.4 Hz, 2 H, $NCH_2CH_2$), 2.95 (t, *J* = 6.1 Hz, 2 H, $CH_2O$), 3.74 (s, 3 H, $CH_3$), 4.01 (t, *J* = 7.4 Hz, 2 H, $NCH_2$), 6.74–6.80 (m, 2 H, $H_{ar}$), 6.95 (s, 1 H, $H_{[5H\text{-}Imid.]}$), 7.00 (d, *J* = 15.5 Hz, 1 H, CHCOO), 7.21–7.28 (m, 6 H, $H_{ar}$), 7.35 (m, 3 H, $H_{ar}$, $H_{[4H\text{-}Imid.]}$), 7.51 (d, *J* = 15.5 Hz, 1 H, *CH*CHCOO), 7.66 (d, *J* = 7.5 Hz, 2 H, $H_{ar}$); $^{13}C$ NMR ($CDCl_3$):$\delta$ = 23.29 (t, 1 C, $NCH_2CH_2CH_2$), 29.37 (t, 1 C, $CH_2CH_2O$), 30.98 (t, 1 C, $NCH_2CH_2$), 46.47 (t, 1 C, $NCH_2$), 55.20 (q, 1 C, $CH_3$), 62.52 (t, 1 C, $CH_2O$), 88.20 (s, 1 C, $CH_2OC$), 113.50 (d, 2 C, $C_{ar}$), 119.93 (d, 2 C, $C_{ar}$), 121.96 (d, 1 C, $C_{[5C\text{-}Imid.]}$), 123.58 (d, 1 C, *CH*COO), 125.13 (d, 2 C, $C_{ar}$), 126.73 (d, 2 C, $C_{ar}$), 127.09 (d, 1 C, *CH*CHCOO), 128.12 (d, 2 C, $C_{ar}$), 128.92 (d, 1 C, $C_{[4C\text{-}Imid.]}$, d, 2 C, $C_{ar}$), 135.69 (s, 1 C, $C_{ar}$), 140.56 (s, 2 C, $C_{ar}$), 142.23 (s, 1 C, $C_{[2C\text{-}Imid.]}$), 147.43 (s, 2 C, $C_{ar}$), 158.71 (s, 1 C, $C_{ar}$), 169.43 (s, 1 C, COO); MS (ESI+) *m/z* (%): 989.5 (11), 517.2 (96, $[M+Na]^+$), 495.2 (100, $[M+H]^+$); HRMS (ESI+): ($C_{31}H_{31}N_2O_4$) calc. 495.2284, found 495.2274.

### 5.2. Pharmacological methods

#### 5.2.1. GABA uptake assays

[$^3$H]GABA uptake assays with mGAT1, mGAT2, mGAT3, and mGAT4 expressing HEK293 cells were performed as described earlier [47].

## Acknowledgements

We would like to thank Dr. Jörg Pabel for discussion and suggestions. Our acknowledgements go to Katharina Heimberger for proof reading and editorial assistance.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2016.09.012.

## References

[1] D.M. Treiman, GABAergic mechanisms in epilepsy, Epilepsia 42 (2001) 8–12.
[2] J. Liu, D. Huang, J. Xu, J. Tong, Z. Wang, L. Huang, Y. Yang, X. Bai, P. Wang, H. Suo, Y. Ma, M. Yu, J. Fei, F. Huang, Tiagabine protects dopaminergic neurons against neurotoxins by inhibiting microglial activation, Sci. Rep. 5 (2015) 15720.
[3] Z. Du, M. Chazalon, E. Bestaven, T. Leste-Lasserre, J. Baufreton, J.-R. Cazalets, Y.H. Cho, M. Garret, Early GABAergic transmission defects in the external globus pallidus and rest/activity rhythm alteration in a mouse model of Huntington's disease, Neuroscience 329 (2016) 363–379.
[4] P.N. Plummer, N.J. Colson, J.M. Lewohl, R.K. MacKay, F. Fernandez, L.M. Haupt, L.R. Griffiths, Significant differences in gene expression of GABA receptors in peripheral blood leukocytes of migraineurs, Gene 490 (2011) 32–36.
[5] S.J. Jeon, H.J. Park, Q. Gao, H.E. Lee, S.J. Park, E. Hong, D.S. Jang, C.Y. Shin, J.H. Cheong, J.H. Ryu, Positive effects of β-amyrin on pentobarbital-induced sleep in mice via GABAergic neurotransmitter system, Behav. Brain Res. 291 (2015) 232–236.
[6] D. Richter, H.J. Luhmann, W. Kilb, Intrinsic activation of $GABA_A$ receptors suppresses epileptiform activity in the cerebral cortex of immature mice, Epilepsia 51 (2010) 1483–1492.
[7] D.A. Richards, N.G. Bowery, Comaprative effects of the GABA uptake inhibitors, tiagabine and NNC-711, on extracellular GABA levels in the rat ventrolateral thalamus, Neurochem. Res. 21 (1996) 135–140.
[8] A. Scimemi, Structure, function, and plasticity of GABA transporters, Front. Cell Neurosci. 8 (2014) 161/1–161/14.
[9] P. Kowalczyk, K. Kulig, GABA system as a target for new drugs, Curr. Med. Chem. 21 (2014) 3294–3309.
[10] Q.-R. Liu, B. López-Corcuera, S. Mandiyan, H. Nelson, N. Nelson, Molecular characterization of four pharmacologically distinct α-aminobutyric acid transporters in mouse brain, J. Biol. Chem. 268 (1993) 2106–2112.
[11] B. Christiansen, A.-K. Meinilid, A.A. Jensen, H. Bräuner-Osborne, Cloning and characterization of a functional human γ-Aminobutyric acid (GABA) transporter, Human GAT-2, J. Biol. Chem. 282 (2007) 19331–19341.
[12] K.K. Madsen, H.S. White, A. Schousboe, Neuronal and non-neuronal GABA transporters as targets for antiepileptic drugs, Pharmacol. Ther. 125 (2010) 394–401.
[13] N.O. Dalby, Inhibition of γ-aminobutyric acid uptake: anatomy, physiology and effects against epileptic seizures, Eur. J. Pharmacol. 479 (2003) 127–137.
[14] A. Minelli, S. DeBiasi, N.C. Brecha, L.V. Zuccarello, F. Conti, GAT-3, a high-affinity GABA plasma membrane transporter, is localized to astrocytic processes, and it is not confined to the vicinity of GABAergic synapses in the cerebral cortex, J. Neurosci. 16 (1996) 6255–6264.
[15] Y. Zhou, S. Holmseth, R. Hua, A.C. Lehre, A.M. Olofsson, I. Poblete-Naredo, S.A. Kempson, N.C. Danbolt, The Betaine-GABA transporter (BGT1, slc6a12) is predominantly expressed in the liver and at the lower levels in the kidneys and at the brain surface, Am. J. Physiol. Ren. Physiol. 302 (2012) F316–F328.
[16] Y. Zhou, S. Holmseth, C. Guo, B. Hassel, G. Höfner, H.S. Huitfeldt, K.T. Wanner, N.C. Danbolt, Deletion of the γ-aminobutyric acid transporter 2 (GAT2 and SLC6A 13) gene in mice leads to changes in liver and brain taurine contents, J. Biol. Chem. 287 (2012) 35733–35746.
[17] S. Hog, J.R. Greenwood, K.B. Madsen, O.M. Larsson, B. Frolund, A. Schousboe, P. Krogsgaard-Larsen, R.P. Clausen, Structure-activity relationships of selective GABA uptake inhibitors, Curr. Top. Med. Chem. 6 (2006) 1861–1882.
[18] C. Braestrup, E.B. Nielsen, U. Sonnewald, L.J.S. Knutsen, K.E. Andersen, J.A. Jansen, K. Frederiksen, P.H. Andersen, A. Mortensen, P.D. Suzdak, (*R*)-N-[4,4-Bis( 3-Methyl-2-Thienyl)but-3-en-1-yl]Nipecotic acid binds with high affinity to the brain y-Aminobutyric acid uptake carrier, J. Neurochem. 54 (1990) 639–647.
[19] F.E. Ali, W.E. Bondinell, P.A. Dandridge, J.S. Frazee, E. Garvey, G.R. Girard, C. Kaiser, T.W. Ku, J.J. Lafferty, G.I. Moonsammy, H.-J. Oh, J.A. Rush, P.E. Setler, O.D. Stringer, J.W. Venslavsky, B.W. Volpe, L.M. Yunger, C.L. Zirkle, Orally active and potent inhibitors of y-aminobutyric acid uptake, J. Med. Chem. 28 (1985) 653–660.
[20] K.E. Andersen, C. Braestrup, F.C. Groenwald, A.S. Joergensen, E.B. Nielsen, U. Sonnewald, P.O. Soerensen, P.D. Suzdak, L.J.S. Knutsen, The synthesis of novel GABA uptake inhibitors. 1.Elucidation of the structure-activity studies leading to the choice of (*R*)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic acid (tiagabine) as an anticonvulsant drug candidate, J. Med. Chem. 36 (1993) 1716–1725.
[21] T.G.M. Dhar, L.A. Borden, S. Tyagarajan, K.E. Smith, T.A. Branchek, R.L. Weinshank, C. Gluchowski, Design, synthesis and evaluation of substituted triarylnipecotic acid derivatives as GABA uptake inhibitors: identification of a ligand with moderate affinity and selectivity for the cloned human GABA transporter GAT-3, J. Med. Chem. 37 (1994) 2334–2342.
[22] E.B. Nielsen, P.D. Suzdak, K.E. Andersen, L.J.S. Knutsen, U. Sonnewald, C. Braestrup, Characterization of tiagabine (NO-328), a new and potent and selective GABA inhibitor, Eur. J. Pharmacol. 196 (1991) 257–266.
[23] T. Steffan, T. Renukappa-Gutke, G. Höfner, K.T. Wanner, Design, synthesis and SAR studies of GABA uptake inhibitors derived from 2-substituted pyrrolidine-2-yl-acetic acidsBioorg, Med. Chem. 23 (2015) 1284–1306.
[24] T. Kobayashi, A. Suemasa, A. Igawa, S. Ide, H. Fukuda, H. Abe, M. Arisawa, M. Minami, S. Shuto, Conformationally restricted GABA with Bicyclo[3.1.0] hexane backbone as the first highly selective BGT-1 inhibitor, ACS Med. Chem. Lett. 5 (2014) 889–893.
[25] D.A. Pizzi, C.P. Leslie, R.D. Fabio, C. Seri, G. Bernasconi, M. Squaglia, G. Carnevale, A. Falchi, E. Greco, L. Mangiarini, M. Negri, Stereospecific synthesis and structure–activity relationships of unsymmetrical 4,4-diphenylbut-3-enyl derivatives of nipecotic acid as GAT-1 inhibitors, Bioorg. Med. Chem. Lett. 21 (2011) 602–605.
[26] G. Quandt, G. Höfner, J. Pabel, J. Dine, M. Eder, K.T. Wanner, First photoswitchable neurotransmitter transporter inhibitor: light-induced control of γ-aminobutyric acid transporter 1 (GAT1) activity in mouse brain, J. Med. Chem. 57 (2014) 6809–6821.
[27] S.B. Vogensen, L. Jørgensen, K.K. Madsen, A. Jurik, N. Borkar, E. Rosatelli, B. Nielsen, G.F. Ecker, A. Schousboe, Structure activity relationship of selective GABA uptake inhibitors, Bioorg. Med. Chem. 23 (2015) 2480–2488.
[28] A. Kragler, G. Höfner, K.T. Wanner, Novel parent structures for inhibitors of the murine GABA transporters mGAT3 and mGAT4, Eur. J. Pharmacol. 519 (2005) 43–47.
[29] S. Hack, B. Wörlein, G. Höfner, J. Pabel, K.T. Wanner, Development of imidazole alkanoic acids as mGAT3 selective GABA uptake inhibitors, Eur. J. Med. Chem. 46 (2011) 1483–1498.
[30] J. Pabel, M. Faust, C. Prehn, B. Wörlein, L. Allmendinger, G. Höfner, K.T. Wanner, Development of an (*S*)-1-{2-[Tris(4-methoxyphenyl)-methoxy]

ethyl}piperidine-3-carboxylic acid [(S)-SNAP-5114]Carba analogue inhibitor for murine γ-aminobutyric acid transporter type 4, ChemMedChem 7 (2012) 1245–1255.
[31] M. Kurzepa, J. Cz Dobrowolski, A.P. Mazurek, Theoretical studies on tautomerism and IR spectra of C-5 substituted imidazoles, J. Mol. Struct. 565–566 (2001) 107–113.
[32] K.E. Andersen, J. Lau, B.F. Lundt, H. Petersen, P.O. Huusfeldt, P.D. Suzdak, M.D.B. Swedberg, Synthesis of novel GABA uptake inhibitors. Part 6y: preparation and evaluation of *N*-Ω asymmetrically substituted nipecotic acid derivatives, Bioorg. Med. Chem. 9 (2001) 2773–2785.
[33] E. Vedejs, M.J. Arnost, J.P. Hagen, Conformational effects on the 2,3-Sigmatropic shift of sulfur-stabilized Ylides and Enolates involving bicyclic transition states, J. Org. Chem. 44 (1979) 3230–3238.
[34] A. Huefner, A. Presser, Part 1, stereoselective synthesis of isomersof the naturally Occurring 13-Hydroxy-2,4,9-tetradecatrienic acid I, Monatsh. Chem. 129 (1998) 931–936.
[35] B. DeBoef, W.R. Counts, S.R. Gilbertson, Rhodium-catalyzed synthesis of Eight-membered rings, J. Org. Chem. 72 (2007) 799–804.
[36] M. Rubin, V. Gevorgyan, B(C6F5)3-Catalyzed allylation of secondary benzyl acetates with allylsilanes, Org. Lett. 3 (2001) 2705–2707.
[37] H. Meislich, J. Costanza, J. Strelitz, Steric requirements for free-radical substitutions. I. Phenyl migration during bromination, J. Org. Chem. 33 (1968) 3221–3225.
[38] P. Tavecchia, P. Gentili, M. Kurz, C. Sottani, R. Bonfichi, E. Selva, S. Lociuro, E. Restelli, R. Ciabatti, Degradation studies of antibiotic MDL 62,879 (GE2270A) and revision of the structure, Tetrahedron 51 (1995) 4867–4890.
[39] N.J. Anthony, R.P. Gomez, M.D. Schaber, S.D. Mosser, K.A. Hamilton, T.J. O'Neil, K.S. Koblan, S.L. Graham, G.D. Hartman, D. Shah, E. Rands, N.E. Kohl, J.B. Gibbs, A.I. Oliff, Design and in vivo analysis of potent non-thiol inhibitors of farnesyl protein transferase, J. Med. Chem. 42 (1999) 3356–3368.
[40] A.R. Fletcher, J.H. Jones, W.I. Ramage, A.V. Stachulski, The use of the *N*(π)-Phenacyl group for the protection of the histidine side chain in peptide synthesis, J. Chem. Soc. Perkin Trans. 1 (1979) 2261–2267.
[41] J.H. Jones, D.L. Rathbone, P.B. Wyatt, The regiospecific alkylation of histidine side chains, Synthesis 1987 (1987) 1110–1113.
[42] K.J. Lee, K.C. Joo, E.-J. Kim, M. Lee, D.H. Kim, A new type of carboxypeptidase a inhibitors designed using an imidazole as a zinc coordinating ligand, Bioorg. Med. Chem. 5 (1997) 1989–1998.
[43] K.L. Seley, S. Salim, L. Zhang, "Molecular chameleons". Design and synthesis of C-4-Substituted imidazole fleximers, Org. Lett. 7 (2005) 63–66.
[44] M.J. Bouchet, A. Rendon, C.G. Wermuth, M. Goeldner, C. Hirth, Aryl diazo compounds and diazonium salts as potential irreversible probes of the y-aminobutyric acid receptor, J. Med. Chem. 30 (1987) 2222–2227.
[45] K.H. Baggaley, M. Heald, R.M. Hindley, B. Morgan, J.L. Tee, J. Green, Hypolipidemic imidazoles, J. Med. Chem. 18 (1975) 833–836.
[46] I. Sitka, L. Allmendinger, G. Fülep, G. Höfner, K.T. Wanner, Synthesis of N-substituted acyclic β-amino acids and their investigation as GABA uptake inhibitors, Eur. J. Med. Chem. 65 (2013) 487–499.
[47] A. Kragler, G. Höfner, K.T. Wanner, Synthesis and biological evaluation of aminomethylphenol derivatives as inhibitors of the murine GABA transporters mGAT1-mGAT4, Eur. J. Med. Chem. 43 (2008) 2404–2411.