Bioorganic & Medicinal Chemistry 21 (2013) 3363–3378

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and evaluation of N-substituted nipecotic acid derivatives with an unsymmetrical bis-aromatic residue attached to a vinyl ether spacer as potential GABA uptake inhibitors

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ARTICLE INFO

Article history:
Available online 2 April 2013

Keywords:
GABA uptake
Chelation-controlled Heck reaction
Fries rearrangment
Aromatic fluoro-compounds
SAR study

ABSTRACT

γ-Amino butyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system (CNS). A malfunction of the GABAergic neurotransmission is connected to several neuronal disorders like epilepsy, Alzheimer's disease, neuropathic pain, and depression. One possibility to enhance GABA levels in the synaptic cleft is to inhibit mGAT1, one of the four known plasma membrane bound GABA transporters, which is considered the most important GABA transporter subtype, being in charge of the removal of GABA from the synaptic cleft after a neuronal impulse. Lipophilic derivatives of nipecotic acid like Tiagabine (Gabitril®), an approved drug used in add-on therapy of epilepsy, are known to inhibit uptake of mGAT1 with high subtype selectivity and affinity. We synthesized new N-substituted nipecotic acid derivatives with a vinyl ether spacer and an unsymmetrical bis-aromatic residue, which carries fluorine substituents at various positions of the aromatic ring-system. The new compounds were characterized with respect to their potency and subtype selectivity as mGAT1 inhibitors.

1. Introduction

The regulation of neuronal signal transduction in the mammalian central nervous system (CNS) is mainly controlled by the interplay of the major excitatory neurotransmitter glutamate and the major inhibitory neurotransmitter γ-amino butyric acid (GABA, **1**). A malfunction of either one of these neurotransmitter systems can lead to severe neurological disorders. Low GABA levels are connected with epilepsy,[1] Alzheimer's disease,[2] neuropathic pain,[3] and depression.[4] Enhancing the amount of GABA in the synaptic cleft is believed to be beneficial in the treatment of these diseases. One approach for GABA upregulation is the inhibition of particular subtypes of the plasma membrane bound GABA transporters (GATs), which are in charge of the removal of GABA from the synaptic cleft after a neuronal impulse. Four subtypes of GABA transporters have been identified. They are described by different nomenclatures, depending on the origin of the cells they were cloned from. When cloned from rat or human cells, they are denoted as GAT-1, BGT-1, GAT-2, and GAT-3,[5,6] with a prefix indicating the individual species (e.g., rGAT-1 or hGAT-1) while the respective murine transporters are named mGAT1–4.[7] The Human Genome Organization (HUGO) suggested a nomenclature, which describes the transporters as GAT1 (slc6a1), BGT1 (slc6a12), GAT2 (slc6a13), and GAT3 (slc6a11)[8] which though—strictly speaking—refers to human might also be useful in the sense of a species independent nomenclature. However, as the biological test system employed in our group is based on GABA transporters originating from murine cells, we will refer to these transporters in this paper as mGAT1–4.

mGAT1 is the most abundant GABA transporter in the brain expressed throughout most regions of this organ whereas the expression of mGAT4 is lower and limited mostly to the retina, olfactory bulb, brainstem, and diencephalon.[8,9] For mGAT2 and mGAT3 main expressions were shown to refer to kidney and liver. In contrast to former assumptions these transporters do not play a significant role in GABA inactivation in the brain, displaying significant concentrations on the leptomeninges and some cerebral blood vessels only.[6,10–12] Being expressed closely along GABAergic pathways and in particular on presynaptic neurons, mGAT1 is considered as the most important transporter for neuronal GABA uptake and as an interesting drug target.[13]

Nipecotic acid (**2**), a cyclic amino acid which can be considered as a conformationally restricted β-alanine analog, shows high in vitro activity as inhibitor of [^{3}H]GABA uptake.[14] However, it cannot cross the blood brain barrier (BBB) due to its polar, zwitterionic structure.[15] Through N-alkylation, usually with a bis-aromatic moiety, provided with a C4 carbon unit as spacer, the lipophilicity of **2** is raised, allowing penetration of the BBB. Nipecotic acid derivatives with such a lipophilic side chain also show a significantly increased potency compared to their parent amino acid **2**, which is usually also combined with an improved subtype selectivity towards mGAT1. SKF 89976A (**3**) and Tiagabine (Gabitril®, **4**), a drug

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http://dx.doi.org/10.1016/j.bmc.2013.02.056

used in add-on therapy of epilepsy, are two examples for a successful realization of this concept (see Table 1).[16] Selectivity towards mGAT2–4 can also be achieved depending on the structure of the side chain, but as these compounds are not subject of this paper, they will not be described here (see Table 1).[17]

In a series of SAR studies, Andersen et al. developed several very potent new compounds inhibiting GABA uptake. Many of them are nipecotic acid derivatives with a lipophilic N-substituent consisting of an alkyl spacer and a bis-aromatic residue attached to the end of that spacer.[19–24] Several different structural elements were introduced to those compounds in order to improve selectivity and affinity. Among those structural elements, two were particularly interesting and seemed to be beneficial for uptake inhibition: a vinyl ether or an ether unit embedded in the spacer combined with either a symmetrical or an unsymmetrical substitution pattern in the bis-aromatic residue as exemplified by **5** and **6** (Fig. 1).[21,24] The oxygen atom of the vinyl ether in the spacer may be able to participate in hydrogen bonding and also increase the flexibility of the chain.[17] Thus, for example, compound **5** (Fig. 1, pIC_{50} (GAT1) = 7.85), shows an enhanced potency towards mGAT1 compared to compound **4** (pIC_{50} (GAT1) = 6.88), though it differs from the latter only by an additional oxygen atom in the spacer chain and an extended chain length resulting therefrom.[21] Another potent inhibitor is compound **6** (Fig. 1, pIC_{50} (GAT1) = 7.00), which exhibits the same spacer as compound **5**, however, in saturated form in this case. Also in contrast to inhibitors like **3**, **4**, and **5**, in which two identical aromatic rings are attached symmetrically to the terminal position of the spacer, compound **6** displays a 2-benzylphenyl moiety representing the terminal bis-aromatic residue exerting an unsymmetrical substitution pattern.[24]

We decided to create nipecotic acid derivatives similar to **6**, but with a vinyl ether unit being part of the spacer as in **5**, in which the two aromatic rings of the asymmetrically attached bis-aromatic residue (Fig. 1, **7** and **8**, ring 1 and ring 2) are connected either via a methanone (Fig. 1, **7**, Y = O) or a methylene bridge (Fig. 1, **8**, $Y = H_2$). Since fluorine, as the most electronegative atom, has a strong influence on several physicochemical properties of a compound and can have an indirect or a direct influence on protein–ligand interactions, our aim was also to insert fluorine substituents at various positions of the aromatic rings of the aforementioned target compounds. Introduction of fluorine substituents can for example result in a pK_A shift, depending on their position relative to the acidic or basic group in the molecule. Also, fluorine can polarize neighboring oxygen atoms, which leads to stronger hydrogen bonds and a decrease in lipophilicity. The electronegative fluorine atom can also directly participate in hydrogen bonding or interact with carbonyl groups of proteins.[25,26] Thus, the presence of fluorine could be expected to significantly effect the binding affinity and subtype selectivity of the target compounds **7** and **8** towards mGAT1 and potentially contribute to a better understanding of the protein–ligand interactions relevant for this system.

2. Results and discussion

2.1. Chemistry

Retrosynthetic analysis revealed a C–C-bond formation between the β-position of the vinyl ether moiety of the nipecotic acid scaffold **9** or its ester **20** and the respective aryl halides or triflates to represent an efficient and at the same time flexible approach to the target compounds (Fig. 2).

Being known to proceed with high β-regioselectivity, a chelation-controlled Heck reaction was expected to be well suited for this purpose. This method for controlling regioselectivity has been established by Hallberg and co-workers who performed chelation-controlled Heck arylations of (2-vinyloxyethyl)dimethylamine with various aryl triflates and aryl iodides.[27–30] The β-selectivities Hallberg et al. observed for these reactions are a result of the geometry of the reactive intermediate that forms upon coordination of palladium to the vinylic double bond and to the amino nitrogen of the substrate (see **21**, Scheme 5). As the same structural motif, a vinylether moiety and an amino group linked by an ethylene bridge, is present in **9** (or its ester **20**) as well, it was expected that this concept might be successful here, too.

2.1.1. Synthesis of the triflates

At first, a convenient method for the synthesis of the various fluorine substituted triflates as educts for the intended Heck reaction had to be established. The Fries rearrangement was considered to give a flexible access to the phenols and thus to the corresponding triflates required for the Heck reaction. The starting material for the Fries rearrangement was prepared by esterification of fluorophenols **12a–c** with fluorobenzoyl chlorides **13a–c** (Scheme 1, conditions a).[31] The reactions provided **14a–i** with high yields (83–99%, Table 2).

The obtained esters **14a–f** were subsequently transformed to the corresponding ketones **15a–f** (Table 2) by Fries rearrangement with $AlCl_3$ as catalyst. When heated to 200 °C for short reaction times (20 min to 1 h; Scheme 1, conditions b),[32,33] the 2-substituted rearrangement products **15a–f** were formed almost exclusively and with high yields (78–90%) (Scheme 2, Table 3).

To our regret, the rearrangement of the 2-fluorophenyl benzoates **14g–i** (R′ = F) did not lead to the desired 2-substituted products **15g–i**, but almost exclusively to the 4-substituted compounds **17a–c** (Scheme 3). This is, however, in line with the

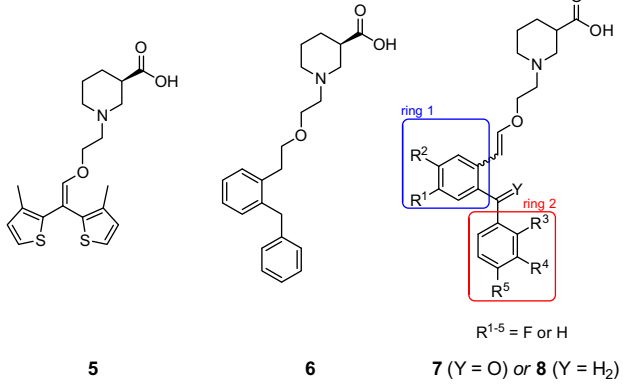


Figure 1. Template structures **5** and **6** and target structures **7** and **8**.

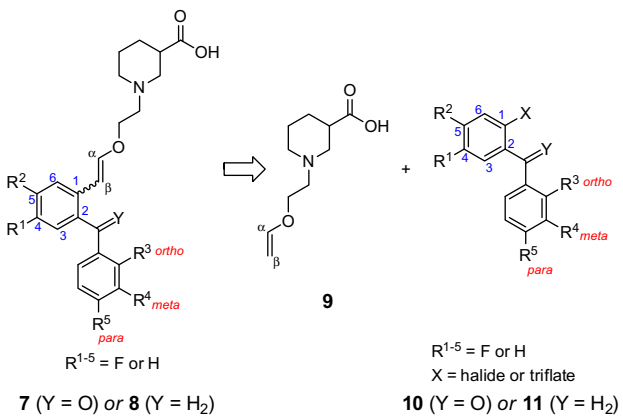
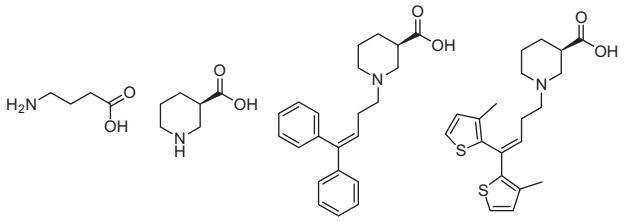


Figure 2. Retrosynthesis of **7** and **8**.

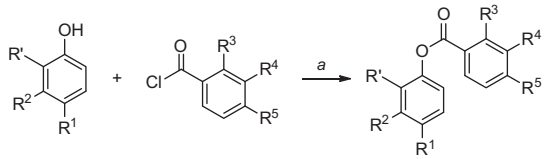
Table 1
pIC_{50} values of compounds **1–4**



1 **2** **3** **4**

Compound	GABA-uptake-inhibition (pIC_{50} ± SEM)[a]			
	mGAT1	mGAT2	mGAT3	mGAT4
1	5.14 ± 0.09	4.56 ± 0.06	4.94 ± 0.09	5.18 ± 0.13
2	5.07 ± 0.02	3.28 ± 0.05	4.71 ± 0.04	4.79 ± 0.05
3	6.16 ± 0.05	3.43 ± 0.07	3.71 ± 0.04	3.56 ± 0.06
4	6.88 ± 0.12	100 μM/ 50.3%[b]	100 μM/ 64.1%[b]	100 μM/ 73.4%[b]

[a] Shown values were measured with a standard assay run in our group.[18]
[b] Remaining [^{3}H]GABA uptake in presence of 100 μM test compound.



	R'	R^1	R^2
12a	H	F	H
12b	H	H	F
12c	F	H	H

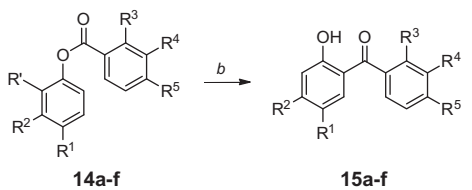
	R^3	R^4	R^5
13a	H	H	F
13b	H	F	H
13c	F	H	H

14a-i

Scheme 1. Reagents and conditions: (a) NEt_3/DMAP, CH_2Cl_2, reflux, 1 h, 83–99%.

Table 2
Esters **14a–i**

Compound	Ring 1			Ring 2			Yield (%)
	R^1	R^2	R'	R^3	R^4	R^5	
14a	F	H	H	H	H	F	99
14b	F	H	H	H	F	H	93
14c	F	H	H	F	H	H	96
14d	H	F	H	H	H	F	88
14e	H	F	H	H	F	H	83
14f	H	F	H	F	H	H	90
14g	H	H	F	H	H	F	94
14h	H	H	F	H	F	H	92
14i	H	H	F	F	H	H	94



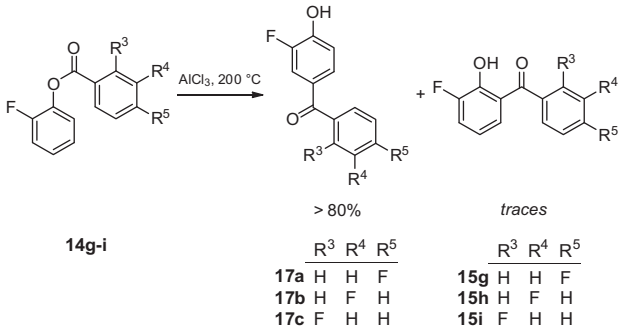
14a-f **15a-f**

Scheme 2. Reagents and conditions: (b) $AlCl_3$, 200 °C, 20 min to 1 h, 78–90%.

general observation according to which Fries rearrangements lead preferentially to the thermodynamically more stable 4-substituted product as soon as one of the 2-positions is occupied.[34] Being formed in trace amounts only, the available quantities of 2-substituted phenols **15g–i** were too low to be employed in the subsequent coupling reactions, whereas the 4-substituted products displaying the wrong substitution pattern were of no value for the present study.

Table 3
Methanones **15a–f**

Compound	Ring 1		Ring 2			Yield (%)
	R^1	R^2	R^3	R^4	R^5	
15a	F	H	H	H	F	80
15b	F	H	H	F	H	83
15c	F	H	F	H	H	90
15d	H	F	H	H	F	78
15e	H	F	H	F	H	78
15f	H	F	F	H	H	86



14g-i

	R^3	R^4	R^5
17a	H	H	F
17b	H	F	H
17c	F	H	H

> 80%

	R^3	R^4	R^5
15g	H	H	F
15h	H	F	H
15i	F	H	H

traces

Scheme 3. Fries rearrangement of **14g–i**.

In the next step, for the preparation of the 2-benzyl substituted phenols **16a–f** (Table 4), ketones **15a–f** were deoxygenated by treatment with sodium borohydride and trifluoroacetic acid (Scheme 4, conditions c).[35] The deoxygenation proceeded with moderate to high yields (54–94%). Reaction of **15a–f** and **16a–f** with triflic anhydride in the presence of 2,4,6-collidine led to the desired triflates **10a–f** and **11a–f**, respectively (Scheme 4), which were then introduced to the Heck reaction in the following step. In both cases, triflate syntheses had proceeded with high yields (88–99%, Table 5).

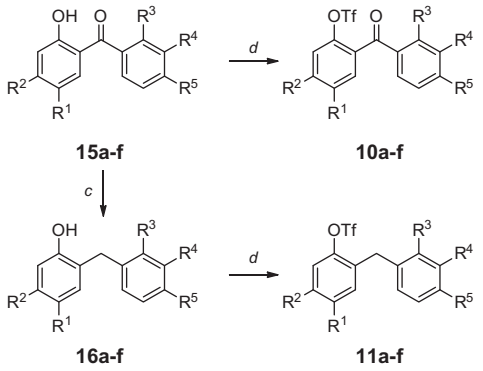
2.1.2. Synthesis of the carboxylic acids

The nipecotic acid derivative with a vinyl ether side chain **20** required for the Heck reaction was conveniently obtained by N-alkylation of the commercially available ethyl nipecotate (**18**) with 2-(vinyloxy)ethyl tosylate (**19**),[30] the yield amounting to 80% (Scheme 5).

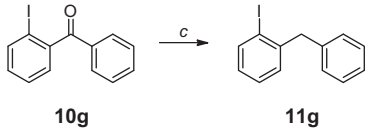
The chelation-controlled Heck-reaction with ethyl 1-(2-(vinyloxy)ethyl)nipecotate (**20**) and the fluorine substituted (2-benzoyl)phenyl triflates **10a–f** or (2-benzyl)phenyl triflates **11a–f**, respectively, was performed at 80 °C using $Pd(OAc)_2$ as a precatalyst, NEt_3 as a base, and DMF as solvent. Depending on the reactivity of the triflate, we either worked under ligand-free conditions or

Table 4
Phenols **16a–f**

Compound	Ring 1		Ring 2			Yield (%)
	R^1	R^2	R^3	R^4	R^5	
16a	F	H	H	H	F	96
16b	F	H	H	F	H	80
16c	F	H	F	H	H	94
16d	H	F	H	H	F	81
16e	H	F	H	F	H	53
16f	H	F	F	H	H	86



Scheme 4. Reagents and conditions: (c) $NaBH_4$/TFA, CH_2Cl_2, 0 °C to rt, 53–94%, (d) Tf_2O, 2,4,6-collidine, CH_2Cl_2, 0 °C to rt, 88–99%.



Scheme 5. Reagents and conditions: (c) $NaBH_4$/TFA, CH_2Cl_2, 0 °C to rt, 99%.

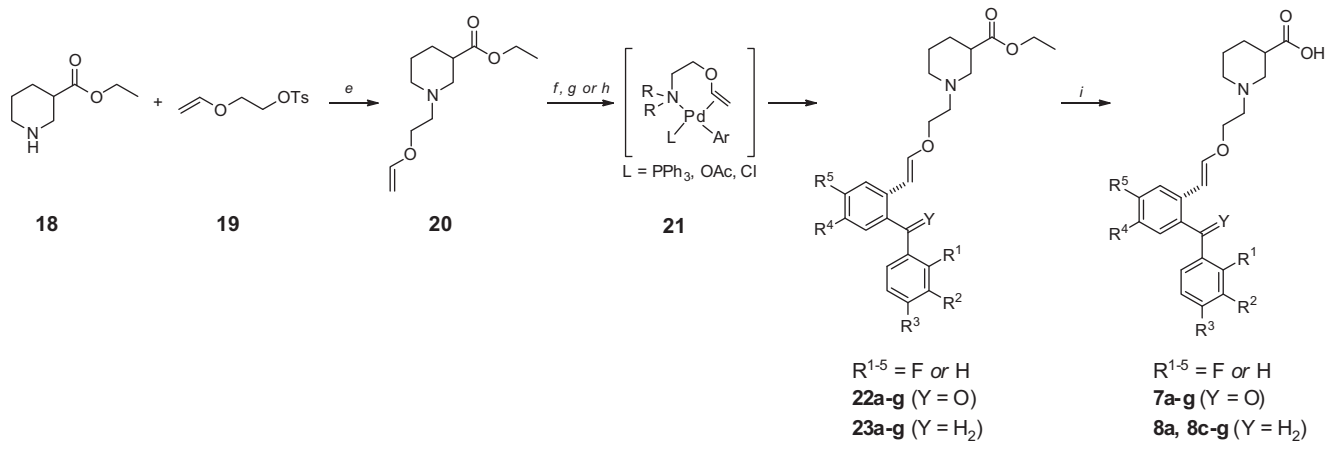
Table 5
Triflates **10a–f** and **11a–f**

Compound	Y	Ring 1		Ring 2			Yield (%)
		R^1	R^2	R^3	R^4	R^5	
10a	O	F	H	H	H	F	95
10b	O	F	H	H	F	H	88
10c	O	F	H	F	H	H	88
10d	O	H	F	H	H	F	94
10e	O	H	F	H	F	H	94
10f	O	H	F	F	H	H	90
11a	H_2	F	H	H	H	F	99
11b	H_2	F	H	H	F	H	91
11c	H_2	F	H	F	H	H	88
11d	H_2	H	F	H	H	F	96
11e	H_2	H	F	H	F	H	87
11f	H_2	H	F	F	H	H	89

in the presence of PPh_3 as a ligand. The phosphine ligand is known to accelerate the reduction of the Pd(II) precatalyst to the active Pd(0) species, but it can also promote the oxidative addition of the triflate to the Pd(0) complex and is therefore added when less reactive, electron-rich aryl triflates are used.[36]

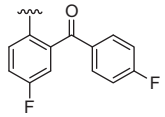
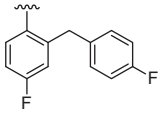
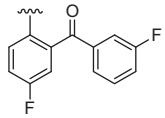
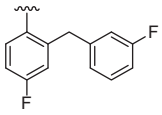
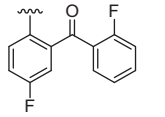
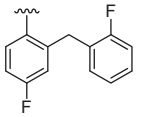
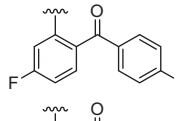
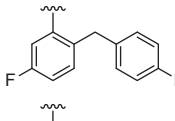
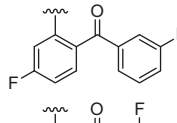
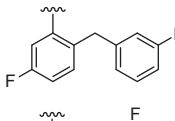
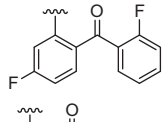
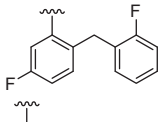
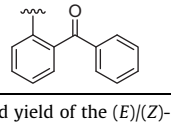
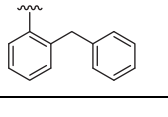
We added PPh_3 as a ligand when coupling the electron-richer and less reactive (2-benzyl)phenyl triflates **11a–f** to **20** (Scheme 6, conditions g, method B, **23a–f**). This resulted in increased yields and shorter reaction times. When working under so called ligand-free conditions, only traces of the products **23a–f** were obtained. The (2-benzoyl)phenyl triflates **10a–f** appeared to be more reactive probably due to the presence of the electron-withdrawing carbonyl function, and led to higher yields (Table 6). As these could not be enhanced through addition of phosphine ligand, the reactions were performed under ligand-free conditions (Scheme 6, conditions f, method A). In contrast to the Heck reactions with **11a–f** (Table 6, **23a–f**), all triflates **10a–f** could be successfully coupled with the scaffold **20** with reasonable to good yields (Table 6, **22a–f**). Compared to the yields for the syntheses of **22a–f**, those for **23a–f** were generally lower at similar reaction times, even though PPh_3 was added. Enhancing the reaction times or the temperature also did not lead to significantly higher yields. The lowest yields were obtained, when ring 1 carried a fluorine substituent in 4-position (**11a–c**, R^1 = F, Table 5 → **23a–c**, Table 6). Considering the higher energy of the 4-fluoro-substituted benzene anion as compared to its 3-substituted analog,[37] this is likely due to the fact that the electron density diminishing effect on the 1-position carrying the triflate moiety resulting from the fluorine substituent is less pronounced when the latter is located in the 4- instead in the 3-position. Besides, the position of the fluorine substituent in ring 2 has been found to have an influence on the reactivity of the (2-benzyl)phenyl triflate. Thus, in case of the reaction of **20** with **11b**, carrying a fluorine substituent in *meta*-position of ring 2, only trace amounts of the desired coupling product **23b** could be detected. As even modification of the reaction conditions, higher temperatures or longer reaction times did not improve yields, the product could not be isolated.

When synthesizing the parent compounds **22g** and **23g**, being devoid of fluorine substituents in the bis-aromatic moiety, only trace amounts of the product were obtained through the reaction with the unsubstituted triflates. This indicates that the presence of fluorine substituents has a significant influence on the electron density of the triflate and on their reactivity. Since the corresponding, unsubstituted iodides were easily available, we decided to test whether they would allow to perform the desired Heck reaction. Of the two starting materials required, 2-iodobenzophenone (**10g**) is commercially available and 2-benzyl-1-iodo benzene (**11g**) was found to be easily accessible from the former in an excellent yield



Scheme 6. Reagents and conditions: (e) 7 h, rt, 80%, (f) Method A: **10a–f**, $Pd(OAc)_2$/NEt_3, DMF, 80 °C, 20 h, 39–78%; (g) Method B: **11a–f**, $Pd(OAc)_2$/PPh_3/NEt_3, DMF, 80 °C, 20 h, 19–55%; (h) Method C: **10g** or **11g**, $Pd(OAc)_2$/LiCl/NaOAc/K_2CO_3, DMF/H_2O (v/v = 10:1), 80 °C, 20 h, 65–83%; (i) (1) 12 M NaOH or 2 M LiOH, EtOH, 0 °C to rt, 0.5–6.5 h; (2) phosphate buffer (50 mM, pH 6), CH_2Cl_2, 0 °C to rt, 78–99%.

Table 6
Conditions and yields for the coupling products **22a**–g **and 23a–g**

Compd	Ar	Method	(*E*)/(*Z*)	Isolated yield[a] (%)	Yield ((*E*)/(*Z*))[b] (%)	Compd	Ar	Method	(*E*)/(*Z*)	Isolated yield[a] (%)	Yield[b] ((*E*)/(*Z*)) (%)
22a		A	60:40	40	20/6	**23a**		B	74:26	19	8/4
22b		A	71:29	56	8/5	**23b**		B	n.d.	Traces	n.d.
22c		A	57:43	38	7/7	**23c**		B	71:29	30	19/6
22d		A	60:40	40	20/8	**23d**		B	71:29	46	28/6
22e		A	60:40	37	17/12	**23e**		B	71:29	42	23/2
22f		A	71:29	78	51/17	**23f**		B	75:25	55	32/13
22g		C	29:71	83	24/11	**23g**		C	40:60	65	21/22

[a] Isolated yield of the (*E*)/(*Z*)-mixture.
[b] Isolated yield of the isomers after FCC.

of 99% by deoxygenation with $NaBH_4$/TFA in analogy to the syntheses of **16a–f** (Scheme 5, conditions c).[35]

When coupling of the iodides **10g** and **11g** with the vinylether **20** was attempted by following the above described methods A and B, requiring anhydrous conditions, exclusively the undesired α-coupling products were formed.

But the reactions could be successfully performed under aqueous conditions comprising $Pd(OAc)_2$, K_2CO_3, LiCl, and NaOAc in DMF/H_2O (Scheme 6, conditions h, method C), conditions that had also been introduced by Hallberg and co-workers for β-selective coupling of aryl iodides with a vinyl ether scaffold.[30]

All coupling products were obtained as (*E*)/(*Z*)-mixtures in ratios ranging from 57:43 to 29:71 ((*E*)/(*Z*)), depending on the reaction conditions and reactants. But all isomers could be separated by flash-column chromatography (Et_2O + 1% NEt_3) and were obtained in reasonable amounts in pure form.

In the last step of the synthesis, the ethyl esters **22a–g** and **23a–g** were hydrolyzed with an excess of 12 M NaOH or 2 M LiOH, respectively, at 0 °C to room temperature. After complete conversion (after 30 min to 8.5 h) and workup (phosphate buffer pH 6, extraction with dichloromethane), the target compounds, the carboxylic acids **7a–g**, **8a**, and **8c–g** were obtained in yields of 78–99%.

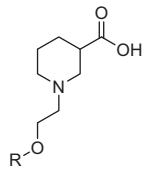
2.2. Biological evaluation

Uptake inhibition and subtype selectivity towards all four murine transporter subtypes mGAT1–4 were determined for all synthesized carboxylic acids using a standardized [^{3}H]GABA uptake assay based on HEK cell lines, each stably expressing one of the four GATs.[18] pIC_{50} values were determined as a measure of potency of the tested compounds. When the potency was low and the compounds were not able to reduce [^{3}H]GABA uptake to a value of below 50% at 100 μM (pIC_{50} <4.00), only the percentage is given, representing the remaining specific [^{3}H]GABA uptake at 100 μM.

In the following, the inhibitory potencies at as well as selectivities for mGAT1 as a function of the position of the fluorine substituents in ring 1 (Fig. 2, 4-position or 5-position) and ring 2 (Fig. 2, *ortho*, *meta,* or *para*) of the bis-aromatic residue attached to the vinyl ether spacer of the N-alkylated nipecotic acid derivatives **7a–g**, **8a** and **8c–g** are described. As compared to the potencies at mGAT1, all compounds tested were only weak to very weak inhibitors at mGAT2-4, the pIC_{50} values for these transporters ranging in most cases far below 5. Therefore, besides being mentioned with respect to the subtype selectivity in favor of mGAT1, these data did not appear to be sufficiently important to be included in the following discussion.

Regarding compounds **7a–f** (Table 7, entries 3–14), in which ring 1 and ring 2 are connected with a methanone bridge (Fig. 1, **7**, Y = O), the unsubstituted compounds (*E*)- and (*Z*)-**7g** (Table 7, entries 1 and 2) serve as references. (*E*)-**7g** (pIC_{50} 4.60, Table 7, entry 1) and (*Z*)-**7g** (pIC_{50} 5.15, Table 7, entry 2) both displayed moderate to poor inhibitiory potency and an acceptable selectivity towards mGAT1, the (*Z*)-isomer being slightly more potent at and selective for mGAT1. With regard to the (*E*)-isomers bearing a fluorine substituent at the 4-position of ring 1 (R^1 = F, Table 7, entry 3, 5 and 7), the inhibitory potency and subtype selectivity is significantly enhanced compared to (*E*)-**7g** when ring 2 is substituted with fluorine at the *para*-position (see (*E*)-**7a**, pIC_{50} 5.73, Table 7, entry 3). When ring 2 carries a fluorine substituent in the *meta*-position (see (*E*)-**7b**, $pIC_{50} \leqslant 4.00$, Table 7, entry 5), the inhibitory po-

Table 7
GABA-uptake inhibition of **7a–g**, **8a,** and **8c–g**



7a-g, **8a** *or* **8c-g**

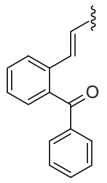
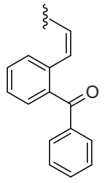
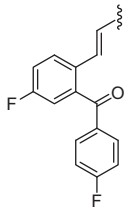
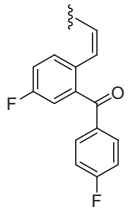
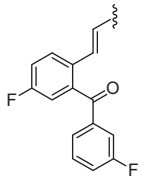
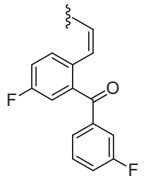
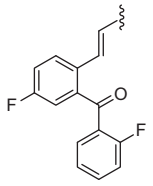
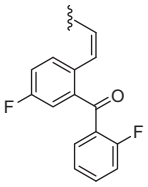
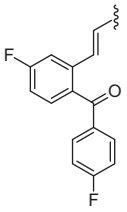
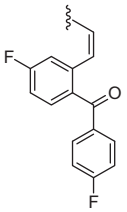
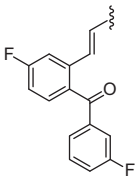
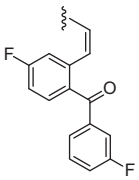
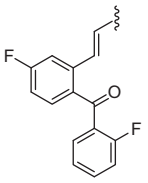
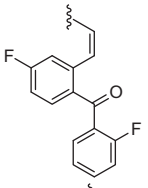
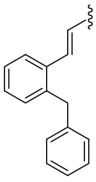
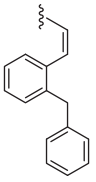
Entry	Compound	R	GABA-uptake inhibition (pIC_{50} ± SEM)			
			mGAT1	mGAT2	mGAT3	mGAT4
1	(*E*)-**7g**		4.60[b]	100 μM/67.5 %[a]	100 μM/55.9 %[a]	100 μM/79.8 %[a]
2	(*Z*)-**7g**		5.15 ± 0.07	100 μM/72.3 %[a]	100 μM/59.8 %[a]	100 μM/72.4 %[a]
3	(*E*)-**7a**		**5.73 ± 0.14**	100 μM/71.4 %[a]	100 μM/68.8 %[a]	100 μM/72.7 %[a]
4	(*Z*)-**7a**		**6.47 ± 0.08**	100 μM/73.0 %[a]	100 μM/59.8 %[a]	100 μM/44.8 %[a]
5	(*E*)-**7b**		100 μM/67.5 %[a]	100 μM/62.9 %[a]	100 μM/51.5 %[a]	100 μM/67.6 %[a]
6	(*Z*)-**7b**		**6.10 ± 0.04**	100 μM/56.9 %[a]	100 μM/52.7 %[a]	100 μM/45.2 %[a]
7	(*E*)-**7c**		4.97 ± 0.17	3.85[b]	3.43[b]	4.17 ± 0.02

Table 7 (*continued*)

Entry	Compound	R	GABA-uptake inhibition (pIC_{50} ± SEM)			
			mGAT1	mGAT2	mGAT3	mGAT4
8	(*Z*)-**7c**		**6.12 ± 0.13**	4.18[b]	100 μM/43.5 %[a]	100 μM/45.1 %[a]
9	(*E*)-**7d**		4.68 ± 0.02	100 μM/61.2 %[a]	100 μM/97.7 %[a]	100 μM/94.3 %[a]
10	(*Z*)-**7d**		5.12 ± 0.08	100 μM/70.2 %[a]	100 μM/79.5 %[a]	100 μMv82.2 %[a]
11	(*E*)-**7e**		4.53 ± 0.13	4.22[b]	3.47[b]	3.70[b]
12	(*Z*)-**7e**		5.58 ± 0.13	100 μMv96.1 %[a]	100 μMv83.6 %[a]	100 μM/52.1 %[a]
13	(*E*)-**7f**		5.09 ± 0.04	100 μM/68.6 %[a]	100 μM/57.6 %[a]	100 μM/52.1 %[a]
14	(*Z*)-**7f**		5.52 ± 0.08	100 μM/74.5 %[a]	100 μM/83.2 %[a]	100 μM/86.3 %[a]
15	(*E*)-**8g**		5.38 ± 0.10	100 μM/60.2 %[a]	4.43[b]	4.50[b]
16	(*Z*)-**8g**		**6.40 ± 0.09**	100 μM/68.6 %[a]	100 μM/56.0 %[a]	100 μM/66.0 %[a]

(*continued on next page*)

Table 7 (*continued*)

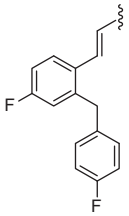
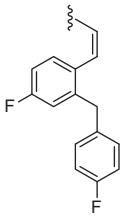
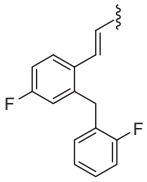
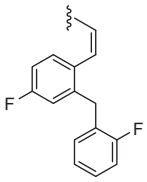
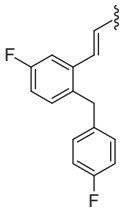
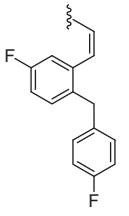
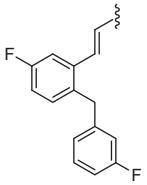
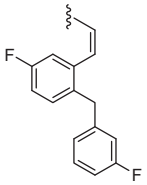
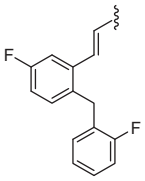
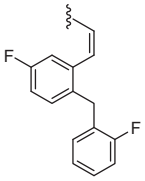
Entry	Compound	R	GABA-uptake inhibition (pIC_{50} ± SEM)			
			mGAT1	mGAT2	mGAT3	mGAT4
17	(*E*)-**8a**		5.34 ± 0.05	100 μM/71.6 %[a]	100 μM/49.3 %[a]	100 μM/63.7 %[a]
18	(*Z*)-**8a**		**5.93 ± 0.05**	100 μM/64.8 %[a]	4.46[b]	4.59[b]
19	(*E*)-**8c**		5.57 ± 0.12	100 μM/57.5 %[a]	100 μM/80.1 %[a]	4.23[b]
20	(*Z*)-**8c**		**6.20 ± 0.11**	100 μM/80.1 %[a]	4.71[b]	4.22[b]
21	(*E*)-**8d**		5.05 ± 0.12	100 μM/58.1 %[a]	100 μM/62.0 %[a]	4.03[b]
22	(*Z*)-**8d**		**5.96 ± 0.04**	4.04[b]	4.30[b]	100 μM/50.3 %[a]
23	(*E*)-**8e**		5.17 ± 0.07	100 μM/70.5 %[a]	100 μM/59.3 %[a]	100 μM/51.8 %[a]
24	(*Z*)-**8e**		**6.52 ± 0.09**	100 μM/60.3 %[a]	4.70[b]	100 μM/56.0 %[a]

Table 7 (*continued*)

Entry	Compound	R	GABA-uptake inhibition (pIC_{50} ± SEM)			
			mGAT1	mGAT2	mGAT3	mGAT4
25	(*E*)-**8f**		4.99 ± 0.08	100 μM/47.8 %[a]	100 μM/83.7 %[a]	100 μM/53.8 %[a]
26	(*Z*)-**8f**		**6.52 ± 0.14**	100 μM/71.1 %[a]	4.55[b]	4.31[b]

[a] Remaining [^{3}H]GABA uptake in presence of 100 μM test compound.
[b] At low pIC_{50} values, only one measurement was performed in triplicate. Therefore, no SEM could be calculated.

tency and subtype-selectivity was lower than that of (*Z*)-**7g**. A fluorine substituent in the *ortho*-position (see (*E*)-**7c,** pIC_{50} 4.97, Table 7, entry 7), on the other hand did not enhance the selectivity or the potency significantly. The (*Z*)-isomers with a fluorine substituent in the 4-position of ring 1 (R^1 = F, Table 7, entry 4, 6, and 8) all showed significantly higher inhibitory potencies and also enhanced subtype selectivities towards mGAT1 than (*Z*)-**7g** (Table 7, entry 2). The most potent compound of this series and also of all the tested methanone bridged compounds was found to be (*Z*)-**7a** (pIC_{50} 6.47, Table 7, entry 4), which carries a fluorine substituent in the *para*-position of ring 2. It also exhibits an excellent selectivity towards mGAT1. When ring 2 carries the fluorine substituent in the *meta*-position (see (*Z*)-**7b,** pIC_{50} 6.10, Table 7, entry 6), or in the *ortho*-position (see (*Z*)-**7c**, pIC_{50} 6.12, Table 7, entry 8), lower, insignificantly different pIC_{50} values for mGAT1 together with similar mGAT1-selectivities are observed. Regarding the (*E*)-isomers (*E*)-**7d**–(*E*)-**7f** with a fluorine substituent at the 5-position of ring 1 (R^2 = F, Table 7 entries 9, 11 and 13), (*E*)-**7d** (pIC_{50} 4.68, Table 7, entry 9), which bears a fluorine substituent at the *para*-position of ring 2 and (*E*)-**7e** (pIC_{50} 4.53, Table 7, entry 11), with a fluorine substituent at the *meta*-position of ring 2, both do not show significant changes in inhibitory potency or mGAT1-selectivity compared to the unsubstituted (*E*)-**7g**. (*E*)-**7f** (pIC_{50} 5.09, Table 7, entry 13), in which the fluorine substituent in ring 2 is attached at the *ortho*-position, is slightly more potent and also slightly more mGAT1-selective than (*E*)-**7g**. When comparing the (*Z*)-isomers (*Z*)-**7d**–(*Z*)-**7f** with a fluorine substituent in 5-position of ring 1 (R^2 = F, Table 7, entries 10, 12 and 14), it is found that the potency of (*Z*)-**7d** (pIC_{50} 5.12, Table 7, entry 10), in which the fluorine substituent is attached to the *para*-position of ring 2, does not significantly differ from that of the unsubstituted compound (*Z*)-**7g** and that the subtype selectivities of the two compounds are very similar, too. (*Z*)-**7e** (pIC_{50} 5.58, Table 7, entry 12), with a fluorine substituent at the *meta*-position of ring 2, and (*Z*)-**7f** (pIC_{50} 5.52, Table 7, entry 14), with a fluorine substituent at the *ortho*-position of ring 2, both show only slightly enhanced inhibitory potencies and mGAT1-selectivities compared to (*Z*)-**7g**.

Compounds **8a** and **8c–f** (Table 7, entries 17–26), in which ring 1 and ring 2 are connected with a methylene bridge (Fig. 1, **8**, Y = H_2), were referenced to the unsubstituted compounds (*E*)- and (*Z*)-**8g** (Table 7, entries 15 and 16). Both of these compounds, (*E*)-**8g** and (*Z*)-**8g**, show enhanced potency compared to their methanone bridged counterparts (*E*)-**7g** and (*Z*)-**7g**. Whereas (*E*)-**8g** (pIC_{50} 5.38, Table 7, entry 15) shows still only poor mGAT1-potency and subtype selectivity, the potency at and the subtype selectivity for mGAT1 displayed by (*Z*)-**8g** (pIC_{50} 6.40, Table 7, entry 16) are quite pleasing. Actually, the potency of this compound (*Z*)-**8g** is the same, the differences of the pIC_{50} values being insignificant, as that of (*Z*)-**7a**, the most potent compound of all methanone bridged derivatives.

Of the methylene bridged derivatives, the two (*E*)-isomers with a fluorine substituent in 4-position of ring 1 (R^1 = F, Table 7, entries 17 and 19), (*E*)-**8a**, exhibiting a fluorine in *para*-position of ring 2 (pIC_{50} 5.34, Table 7, entry 17), and (*E*)-**8c** with fluorine in the *ortho*-position of ring 2 (pIC_{50} 5.57, Table 7, entry 19) display potencies at mGAT1 that are identical or somewhat higher than that of the unsubstituted (*E*)-**8g**, combined with a slightly improved subtype selectivity for this transporter. In case of the (*Z*)-isomers carrying a fluorine substituent in 4-position of ring 1 (R^1 = F, Table 7, entries 18 and 20), potency and mGAT1-selectivity were lower as those of the unsubstituted counterpart (*Z*)-**8g** when the fluorine substituent was present in *para*-position ((*Z*)-**8a**, pIC_{50} 5.93, Table 7, entry 18). The subtype selectivity was also lower for (*Z*)-**8c** with a fluorine in the *ortho*-position of ring 2 (pIC_{50} 6.20, Table 7, entry 20), but the potency displayed by this compound at mGAT1 was only numerically but not significantly lower that that of the reference compound (*Z*)-**8g**. Regarding the (*E*)-isomers carrying a fluorine substituent in 5-position of ring 1 (R^2 = F, Table 7, entries 21, 23 and 25), (*E*)-**8d** (pIC_{50} 5.05, Table 7, entry 21), with a fluorine substituent at the *para*-position, as well as (*E*)-**8e** (pIC_{50} 5.17, Table 7, entry 23), which is fluorine substituted at the *meta*-position of ring 2, and (*E*)-**8f** (pIC_{50} 4.99, Table 7, entry 25), which carries a fluorine substituent at the *ortho*-position of ring 2, all show similar or slightly decreased potencies at mGAT1 and similar mGAT1-selectivities as compared to their unsubstituted counterpart (*E*)-**8g**. The (*Z*)-isomers with a fluorine substituent at the 5-position of ring 1 (R^2 = F, Table 7, entries 22, 24 and 26), show to some extent strong differences with regard to their potencies and good to high subtype selectivities. Thus, (*Z*)-**8d** (pIC_{50} 5.96, Table 7, entry 22), in which ring 2 is substituted with fluorine at the *para*-position, is clearly the least potent inhibitor in this series, its pIC_{50} ranging almost a half log unit below that of the unsubstituted counterpart (*Z*)-**8g**. On the other hand, (*Z*)-**8e** (pIC_{50} 6.52, Table 7, entry 24), which bears a fluorine substituent at the *meta*-position, and (*Z*)-**8f** (pIC_{50} 6.52, Table 7, entry 26), with a fluorine substituent at the *ortho*-position of ring 2, show potencies towards mGAT1 that are identical and nominally even slightly higher than that of the unsubstituted counter part (*Z*)-**8g**. Furthermore, with pIC_{50} val-

ues amounting to 6.52, they also represent, along with (*Z*)-**7a** and (*Z*)-**8g,** the most potent uptake inhibitors at mGAT1 of all compounds studied, the subtype selectivities of these compounds in favor of mGAT1 being reasonable as well.

3. Conclusion

In conclusion, the β-selective, chelation-controlled Heck-reaction was found a convenient and versatile method to synthesize a series of new lipophilic N-alkylated nipecotic acid derivatives with a vinyl ether unit embedded in the spacer and an unsymmetrical bis-aromatic residue attached to the terminal position of that spacer. Most of the compounds display reasonable to good potencies at and selectivities for mGAT1. Differences in uptake-inhibition depending on whether the two aromatic rings were connected by a methanone (Fig. 1, **7**, Y = O) or a methylene bridge (Fig. 1, **8**, Y = H_2) were observed. Thus, the methylene bridged compounds bearing no fluorine substituents appeared to be more potent than their unsubstituted methanone bridged counterparts. Additionally, the influence of the presence and the position of fluorine substituents in the bis-aromatic residue concerning potency and selectivity of the new compounds could be defined by comparing the pharmacological profiles of those compounds without substituents in the bis-aromatic residue with those bearing fluorine substituents in both aromatic rings.

Generally, all (*Z*)-isomers of the synthesized compounds are more potent than their corresponding (*E*)-isomers. The influence of fluorine substituents on GAT1 uptake inhibition is generally more severe for those compounds, in which the two aromatic rings are linked by a methanone bridge (Y = O, (*E*)/(*Z*)-**7a**–**g**). Here, both, the (*E*)- and the (*Z*)-isomer of the unsubstituted compound ((*E*)/(*Z*)-**7g**) exhibit very poor potencies, but the potencies of most of the (*Z*)-isomers are significantly enhanced through the attachment of fluorine substituents to the two aromatic rings. A substitution with fluorine in 4-position of ring 1 (R^1 = F) and an additional fluorine substituent at the *para*-position of ring 2 is the most beneficial combination for uptake inhibition of this series leading to compound (*Z*)-**7a**, one of the most potent compounds of the whole series. When the two rings of the bis-aromatic residue are connected by a methylene bridge (Y = H_2, (*E*)/(*Z*)-**8a**, (*E*)/(*Z*)-**8c**–**g**), attachment of fluorine substituents does not have a big impact on uptake inhibition. (*Z*)-**8g**, the (*Z*)-isomer of the unsubstituted derivative, is already a good inhibitor and displays even higher potency than most of its fluorine-substituted counterparts. The best inhibitors of all tested compounds are the compounds (*Z*)-**8e** and (*Z*)-**8f**, which both show nominally a slightly enhanced, but almost identical potency towards mGAT1 compared to their parent compound (*Z*)-**8g**.

For economical reasons, only the racemic compounds have been synthesized, though Andersen et al. focused on the preparation and biological testing of the pure (*R*)-nipecotic acid derivatives, in line with former studies according to which for GAT1 inhibitors derived from nipecotic acid the higher potency resides in general in the (*R*)-configured isomer.[19–24] Thus, also for the GAT1 inhibitors developed in this study that had so far been prepared in racemic form only, it can be expected that their (*R*)-enantiomers display still higher potencies.

Future work will aim at the expansion of the library of compounds described in this study and at the synthesis and biological evaluation of similar compounds bearing only one fluorine substituent at either one of the rings. This can be expected to deepen the already achieved knowledge of the influence of the position of the fluorine substituents on mGAT1 binding, which can potentially lead to even more potent mGAT1-inhibitors and also to a better understanding of the binding mode of these inhibitors in the binding pocket of mGAT1.

4. Experimental

4.1. Chemistry

Unless otherwise noted, all reactions were performed in oven-dried glassware under moisture-free conditions and argon atmosphere. All commercial reagents were used without further purification. For the reactions, dried and freshly distilled solvents were used. NEt_3 was dried over sodium and distilled under nitrogen when needed. CH_2Cl_2 was distilled from CaH_2 under nitrogen and DMF was stored over molecular sieves (4 Å) prior to use. For chromatographic purposes, only distilled solvents were used. Flash column chromatography (FCC) was performed according to Still[38] using silica gel (0.040–0.063 mm, Acros and Merck). NMR spectra were measured with a Jeol Eclipse +400 (400 MHz) and a Jeol Eclipse +500 (500 MHz) spectrometer. The coupling constants were stated with an accuracy of 0.5 Hz. MestreNova was used for further analysis of the spectra. IR spectra were recorded with a FT-IR spectrometer Paragon 1000 (Perkin–Elmer) and Spectrum v2.00 software (Perkin–Elmer) was used for analysis. Mass spectra were measured with a Mass Spectrometer 59827A with 59980 Particle Beam LC/MS Interface (Hewlett Packard) or an Applied LC–MS/MS Mass Spectrometer API 2000. High resolution mass spectrometry (HRMS) was accomplished with an LTQ FT (ThermoFinnigan) or a JMS GCmate II (Jeol). Microanalytical data for carbon, hydrogen, nitrogen, and sulfur was determined using an Elementar Vario Micro Cube or an Elementar Vario EL analyzer.

For each general procedure (GP) the full characterization of at least one compound, which is not known in literature, is given in this paper. For the biologically tested compounds, those exhibiting the highest pIC_{50} values are characterized. All other compounds can be found in the Supplementary data.

4.1.1. General procedure for the synthesis of fluorophenyl-fluorobenzoates (GP1)

The respective fluorobenzoyl chloride **13a–c** (1.00 equiv) was added dropwise to a solution of the corresponding fluorophenol **12a–c** (1.00 equiv) and NEt_3 (1.20 equiv) in CH_2Cl_2. The solution was stirred under reflux for 1 h. After cooling to rt, the solution was diluted with CH_2Cl_2 and washed with sat $NaHCO_3$ solution and water. The organic layer was washed with brine, dried over $MgSO_4$ and the solvent was removed in vacuo to give the crude product.

4.1.1.1. 3-Fluorophenyl 3-fluorobenzoate (14e). According to **GP1**. 3-Fluorobenzoylchloride (**13b**) (7.90 g, 6.10 mL, 50.0 mmol), 3-fluorophenol (**12b**) (5.60 g, 4.00 mL, 50.0 mmol), and NEt_3 (6.10 g, 8.30 mL, 60.0 mmol) in CH_2Cl_2 (125 mL) were used. The crude product was purified via FCC (cyclohexane/EtOAc = 5:1) to yield **14e** (9.67 g, 83%) as colorless solid: mp 35.0 °C. IR (KBr): 3079, 1743, 1593, 1487, 1445, 1252, 1188, 1155, 1123, 1074, 953, 913, 893 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.98–7.04 (m, 3H, OCC*H*$_{ar}$CH$_{ar}$C*H*$_{ar}$CFC*H*$_{ar}$), 7.36 (td, *J* = 8.3/2.8 Hz, 1H, OOCCCH$_{ar}$CFC*H*$_{ar}$), 7.40 (td, *J* = 8.3/6.8 Hz, 1H, OCCH$_{ar}$C*H*$_{ar}$), 7.50 (td, *J* = 8.0/5.5 Hz, 1H, OOCCCH$_{ar}$C*H*$_{ar}$), 7.87 (ddd, *J* = 9.0/2.3/1.5 Hz, 1H, OOCCC*H*$_{ar}$CFCH$_{ar}$), 7.99 (ddd, *J* = 7.8/2.5/1.5 Hz, 1H, OOCCC*H*$_{ar}$CH$_{ar}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.8 (d, J_{CF} = 24.6 Hz, OC$_{ar}$C$_{ar}$HC$_{ar}$F), 113.2 (d, J_{CF} = 21.1 Hz, OC$_{ar}$C$_{ar}$HC$_{ar}$F-C$_{ar}$H), 117.1 (d, J_{CF} = 23.3 Hz, OOCC$_{ar}$C$_{ar}$HC$_{ar}$F), 117.4 (OC$_{ar}$C$_{ar}$H-C$_{ar}$H), 121.0 (d, J_{CF} = 21.4 Hz, OOCC$_{ar}$C$_{ar}$HC$_{ar}$FC$_{ar}$H), 126.0 (OOCC$_{ar}$C$_{ar}$HC$_{ar}$H), 130.3 (d, J_{CF} = 9.6 Hz, OOCC$_{ar}$C$_{ar}$HC$_{ar}$H), 130.4 (d, J_{CF} = 7.6 Hz, OC$_{ar}$C$_{ar}$HC$_{ar}$H), 131.3 (d, J_{CF} = 7.6 Hz, OOCC$_{ar}$), 151.5 (d, J_{CF} = 10.9 Hz, OC$_{ar}$), 162.6 (d, J_{CF} = 249 Hz, OOCC$_{ar}$C$_{ar}$H-C$_{ar}$F), 163.0 (d, J_{CF} = 249 Hz, OC$_{ar}$C$_{ar}$HC$_{ar}$F), 163.7 (COO) ppm. M ($C_{13}H_8F_2O_2$) = 234.20. MS (CI, CH_5^+) *m*/*z* (%): 235 (100, $[M+H]^+$),

123 (24), 141 (7). HRMS (EI+): M^+ calcd for $C_{13}H_8F_2O_2$ 234.0492; found: 234.0497.

4.1.2. General procedure for the Fries rearrangement (GP2)

The fluorophenyl benzoate **14a–f** (1.0 equiv) was liquefied through heating and $AlCl_3$ (1.2 equiv) was added. The mixture was stirred at 200 °C for 20 min to 1 h. After cooling to rt, the glass-like material was grinded to a powder and added slowly to a mixture of 12 M HCl (25 equiv), crushed ice and water. The resulting suspension was extracted several times with Et_2O. The combined organic layers were washed with water and dried over $MgSO_4$. The solvent was removed in vacuo to give the crude product.

4.1.2.1. (4-Fluoro-2-hydroxyphenyl)(3-fluorophenyl)-methanone (15e). According to **GP2** with **14e** (8.00 g, 34.2 mmol) and $AlCl_3$ (5.47 g, 41.4 mmol). The reaction time was 20 min. The crude product was purified via FCC (cyclohexane/EtOAc = 9:1) to yield **15e** (6.25 g, 78%) as yellow solid: mp 74.7 °C. IR (KBr): 3447, 3075, 1699, 1634, 1616, 1683, 1506, 1479, 1439, 1263, 965, 851, 834, 803, 778, 706 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.62 (ddd, J = 9.2/8.2/2.5 Hz, 1H, $HOCCH_{ar}CFCH_{ar}$), 6.77 (dd, J = 10.4/2.4 Hz, 1H, $HOCCH_{ar}$), 7.30 (tdd, J = 8.4/2.7/1.1 Hz, 1H, $CH_{ar}CH_{ar}CH_{ar}CF$), 7.36 (ddd, J = 8.8/2.4/1.6 Hz, 1H, $CH_{ar}CH_{ar}CH_{ar}CF$-CH_{ar}), 7.43 (dt, J = 7.6/1.2 Hz, 1H, $CH_{ar}CH_{ar}CH_{ar}CF$), 7.50 (td, J = 7.9/5.5 Hz, 1H, $CH_{ar}CH_{ar}CH_{ar}CF$), 7.60 (dd, J = 8.8/6.4 Hz, 1H, $HOCC$-CH_{ar}), 12.3 (s, 1H, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 105.3 (d, J_{CF} = 23.9 Hz, $HOC_{ar}C_{ar}H$), 107.3 (d, J_{CF} = 22.8 Hz, $HOC_{ar}C_{ar}HC_{ar}F$-$C_{ar}H$), 116.0 (d, J_{CF} = 22.9 Hz, $C_{ar}HC_{ar}HC_{ar}HC_{ar}FC_{ar}H$), 115.9 ($HOC_{ar}$-$C_{ar}CO$), 119.1 (d, J_{CF} = 21.3 Hz, $C_{ar}HC_{ar}HC_{ar}HC_{ar}FC_{ar}H$), 124.7 (d, J_{CF} = 3.00 Hz, $C_{ar}HC_{ar}HC_{ar}HC_{ar}FC_{ar}H$), 130.26 (d, J_{CF} = 7.80 Hz, $C_{ar}H$-$C_{ar}HC_{ar}HC_{ar}FC_{ar}H$), 135.8 (d, J_{CF} = 11.8 Hz, $HOC_{ar}C_{ar}C_{ar}H$), 139.7 (d, J_{CF} = 6.70 Hz, $HOC_{ar}C_{ar}COC_{ar}$), 162.5 (d, J_{CF} = 250 Hz, $C_{ar}HC_{ar}HC_{ar}H$-$C_{ar}FC_{ar}H$), 165.9 (d, J_{CF} = 14.5 Hz, HOC_{ar}), 167.7 (d, J_{CF} = 259 Hz, HO-$C_{ar}C_{ar}HC_{ar}F$), 199.0 (ArCOAr) ppm. M ($C_{13}H_8F_2O_2$) = 234.20. MS (CI, CH_5^+) m/z (%): 315 (18), 235 (100, $[M+H]^+$), 215 (9), 139 (8). HRMS (EI+): M^+ calcd for $C_{13}H_8F_2O_2$, 234.0492; found: 234.0470. $C_{13}H_8F_2O_2$ (234.20): calcd C 66.67, H 3.44; found: C 66.37, H 3.30.

4.1.3. General procedure for the deoxygenation (GP3)

$NaBH_4$ pellets (6–7 equiv) were added to cooled (0 °C) TFA and stirred at this temperature until it was almost completely dissolved. A solution of the methanone **15a–f** in CH_2Cl_2 was added within 30 min and the mixture was stirred at rt until TLC control revealed completion of the reaction. If necessary, more $NaBH_4$ was added after 15 h. The reaction was quenched with an excess of water and NaOH pellets were added under ice bath cooling until the solution showed a basic pH. The mixture was then extracted several times with Et_2O and the combined organic layers were washed with water and brine and dried over $MgSO_4$. Evaporation of the solvent gave the crude product.

4.1.3.1. 15-Fluoro-2-(3-fluorobenzyl) phenol (16e). According to **GP3** with $NaBH_4$ (1.02 g, 27.0 mmol, 1.00 pellet) in TFA (20.3 mL) and **15e** (949 mg, 4.05 mmol) in CH_2Cl_2 (12.2 mL). After 15 h, another $NaBH_4$ pellet (1.04 g, 27.4 mmol) was added. The total reaction time was 40 h. The crude product was purified via FCC (cyclohexane/EtOAc = 9:1) to yield **16e** (458 mg, 51%) as colorless solid: mp 44.3 °C. IR (KBr): 3332, 3070, 2956, 2934, 2858, 1614, 1594, 1485, 1443, 1427, 1272, 1250, 1234, 1149, 1139, 1091, 973, 848, 753 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.93 (s, 2H, CH_2), 4.86 (s, 1H, OH), 6.53 (dd, J = 10.0/2.5 Hz, 1H, $HOCCH_{ar}$), 6.61 (td, J = 8.5/2.5 Hz, 1H, $HOCCH_{ar}CFCH_{ar}$), 6.90 (m, 2H, $CH_{ar}CH$-$_{ar}CH_{ar}CFCH_{ar}$), 6.98 (d, J = 7.5 Hz, 1H, $CH_{ar}CH_{ar}CH_{ar}CFCH_{ar}$), 7.04 (dd, J = 8.5/6.5 Hz, 1H, $HOCCH_{ar}CFCH_{ar}CH_{ar}$), 7.24 (q, J = 7.8 Hz, 1H, $CH_{ar}CH_{ar}CH_{ar}CFCH_{ar}$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 35.35 (CH_2), 103.4 (d, J_{CF} = 24.4 Hz, $HOC_{ar}C_{ar}H$), 107.7 (d, J_{CF} = 21.0 Hz, $HOC_{ar}C_{ar}HC_{ar}FC_{ar}H$), 113.3 (d, J_{CF} = 21.0 Hz, $C_{ar}HC_{ar}HC_{ar}H$-$C_{ar}F$), 115.5 (d, J_{CF} = 21.5 Hz, $C_{ar}HC_{ar}HC_{ar}HC_{ar}FC_{ar}H$), 122.2 (d, J_{CF} = 3.30 Hz, $HOC_{ar}C_{ar}CH_2$), 124.2 (d, J_{CF} = 2.80 Hz, $C_{ar}HC_{ar}HC_{ar}H$-$C_{ar}FC_{ar}H$), 130.0 (d, J_{CF} = 8.40 Hz, $C_{ar}HC_{ar}HC_{ar}HC_{ar}F$), 131.7 (d, J_{CF} = 9.70 Hz, $HOC_{ar}C_{ar}HC_{ar}FC_{ar}HC_{ar}H$), 142.5 (d, J_{CF} = 7.20 Hz, HO-$C_{ar}C_{ar}CH_2C_{ar}$), 154.4 (d, J_{CF} = 10.7 Hz, HOC_{ar}), 162.3 (d, J_{CF} = 245 Hz, $HOC_{ar}C_{ar}HC_{ar}F$), 163.1 (d, J_{CF} = 246 Hz, $H_2CC_{ar}CH_{ar}C_{ar}F$) ppm. M ($C_{13}H_{10}F_2O$) = 220.22. MS (CI, CH_5^+) m/z (%): 109 (41), 125 (74), 221 (100, $[M+H]^+$). HRMS (EI+): M^+ calcd for $C_{13}H_{10}F_2O$, 220.06998; found: 220.06948. $C_{13}H_{10}F_2O$ (220.22): calcd C 70.90, H 4.58; found: C 70.62, H 4.61.

4.1.4. General procedure for the synthesis of triflates (GP4)

The phenol (**15a–f** or **16a–f**, 1.0 equiv) and 2,4,6-collidin (4.0 equiv) were dissolved in CH_2Cl_2 and cooled to 0 °C. At this temperature, triflic anhydride was added dropwise. The solution was stirred at rt until TLC control revealed completion of the reaction. After dilution with Et_2O, the mixture was washed twice with water, the organic layer was separated and the aqueous layer extracted with Et_2O. The combined organic layers were washed several times with satd $CuSO_4$ solution and dried over $MgSO_4$. Evaporation of the solvent gave the crude product.

4.1.4.1. 5-Fluoro-2-(3-fluorobenzoyl)phenyl triflate (10e). According to **GP4** with **15e** (2.00 g, 8.50 mmol), 2,4,6-collidin (4.16 g, 4.60 mL, 34.3 mmol) and triflic anhydride (2.88 g, 1.70 mL, 10.2 mmol) in CH_2Cl_2 (42.5 mL). After 19 h, more triflic anhydride (1.19 g, 0.70 mL, 4.25 mmol) was added. The total reaction time was 20.5 h. The crude product was purified via FCC (cyclohexane/EtOAc = 9:1) to yield **10e** (2.94 g, 94%) as colorless oil: IR (KBr): 3103, 3080, 1676, 1611, 1589, 1430, 1409, 1300, 1271, 1215, 1139, 1073, 987, 964, 833, 762 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.19 (dd, J = 8.3/2.3 Hz, 1H, $TfOCCH_{ar}$), 7.24 (ddd, J = 8.8/7.5/2.3 Hz, 1H, $TfOCCH_{ar}CFCH_{ar}$), 7.34 (tdd, J = 8.3/2.5/1.0 Hz, 1H, $CH_{ar}CH_{ar}CH_{ar}CF$), 7.46–7.49 (td, J = 7.9/5.3 Hz, 1H, $CH_{ar}CH_{ar}CH_{ar}CF$), 7.51 (ddd, J = 8.8/2.5/1.5 Hz, 1H, $CH_{ar}CH_{ar}CH_{ar}CF$-CH_{ar}), 7.54 (ddd, J = 8.0/1.5/1.0 Hz, 1H, $CH_{ar}CH_{ar}CH_{ar}CF$), 7.62 (dd, J = 8.8/6.3 Hz, 1H, $TfOCCH_{ar}CFCH_{ar}CH_{ar}$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 111.2 (d, J_{CF} = 25.8 Hz, $TfOC_{ar}C_{ar}H$), 115.6 (d, J_{CF} = 21.3 Hz, $TfOC_{ar}C_{ar}HC_{ar}FC_{ar}H$), 116.6 (d, J_{CF} = 22.7 Hz, $C_{ar}HC_{ar}HC_{ar}HC_{ar}FC_{ar}H$), 118.4 (q, J_{CF} = 321 Hz, CF_3), 121.0 (d, J_{CF} = 21.5 Hz, $C_{ar}HC_{ar}HC_{ar}H$-$C_{ar}F$), 126.0 (d, J_{CF} = 3.00 Hz, $C_{ar}HC_{ar}HC_{ar}HC_{ar}F$), 128.3 (d, J_{CF} = 4.20 Hz, $TfOC_{ar}C_{ar}CO$), 130.4 (d, J_{CF} = 7.80 Hz, $C_{ar}HC_{ar}HC_{ar}H$-$C_{ar}F$), 132.9 (d, J_{CF} = 9.60 Hz, $TfOC_{ar}C_{ar}HC_{ar}FC_{ar}HC_{ar}H$), 138.5 (d, J_{CF} = 6.40 Hz, $TfOC_{ar}C_{ar}COC_{ar}$), 147.6 (d, J_{CF} = 11.0 Hz, $TfOC_{ar}$), 162.7 (d, J_{CF} = 250 Hz, $C_{ar}HC_{ar}HC_{ar}HC_{ar}F$), 164.2 (d, J_{CF} = 258 Hz, $TfOC_{ar}C_{ar}HC_{ar}F$), 190.4 (CO) ppm. M ($C_{14}H_7F_5O_4S$) = 366.27. MS (CI, CH_5^+) m/z (%): 123 (9), 367 (100, $[M+H]^+$). HRMS (EI+): M^+ calcd for $C_{14}H_7F_5O_4S$, 365.99853; found: 365.99924. $C_{14}H_7F_5O_4S$ (366.27): calcd C 45.91, H 1.93; found: C 45.98, H 1.99.

4.1.5. Synthesis of ethyl 1-(2-(vinyloxy)ethyl)nipecotate (20)

Compound **18** (4.74 g, 4.65 mL, 30.2 mmol) was added dropwise and under stirring to **19** (1.00 g, 4.13 mmol). The solution was stirred at rt for 4.5 h, until the completion of the reaction (TLC). The reaction was quenched with water (2.50 mL) and the mixture extracted several times with pentane. The combined organic layers were dried over K_2CO_3 and the solvent was evaporated. The crude product was purified via FCC (cyclohexane/EtOAc = 3:1 + 1% NEt_3) to yield **20** (761 mg, 80%) as colorless oil: IR (KBr): 3117, 2942, 2870, 2790, 1731, 1635, 1616, 1467, 1453, 1370, 1319, 1274, 1201, 1155, 1030, 1000, 964 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.25 (t, J = 7.3 Hz, 3H, CH_3), 1.44 (ddd, J = 16.8/11.8/4.2 Hz, 1H, $NCH_2CH_2CH_{2,ax}$), 1.56–1.65 (m, 1H, $NCH_2CH_{2,ax}CH_2$), 1.69–1.76 (m, 1H, $NCH_2CH_{2,eq}CH_2$), 1.91–1.98 (m, 1H, $NCCH_2CH_2CH_{2,eq}$),

2.07 (td, J = 11.2/2.9 Hz, 1H, NC$H_{2,ax}$CH$_2$CH$_2$), 2.23 (t, J = 10.8 Hz, 1H, NC$H_{2,ax}$CH), 2.59 (tt, J = 10.9/3.9 Hz, 1H, NCH$_2$CH), 2.64–2.74 (m, 2H, NCH_2CH$_2$O), 2.83 (d, J = 11.2 Hz, 1H, NC$H_{2,eq}$CH$_2$CH$_2$), 3.04 (d, J = 11.2 Hz, 1H, NC$H_{2,eq}$CH), 3.81 (t, J = 5.8 Hz, 2H, NCH$_2$CH_2O), 4.00 (dd, J = 6.8/2.1 Hz, 1H, OCHC$H_{2,cis}$), 4.13 (q, J = 7.1 Hz, 2H, CH_2CH$_3$), 4.18 (dd, J = 14.4/2.1 Hz, 1H, OCHC$H_{2,trans}$), 6.50 (dd, J = 14.4/6.8 Hz, 1H, OCHCH$_2$) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ 12.71 (CH$_3$), 23.04 (NCH$_2$CH_2CH$_2$), 25.37 (NCH$_2$CH$_2$CH_2), 40.31 (NCH$_2$CH), 52.55 (NCH_2CH$_2$CH$_2$), 54.27 (NCH_2CH), 55.84 (NCH_2CH$_2$O), 58.80 (CH_2CH$_3$), 63.74 (NCH$_2$CH_2O), 84.91 (OCHCH_2), 150.25 (OCHCH$_2$), 172.65 (COOEt) ppm. MS (CI, CH_5^+) m/z (%): 228 (87, [M+H]$^+$), 184 (90), 170 (100). HRMS (EI+): M$^+$ calcd for $C_{12}H_{21}NO_3$, 227.1521; found: 227.1478. $C_{12}H_{21}NO_3$ (227.31): calcd C 63.41, H 9.31, N 6.16; found: C 63.22, H 9.32, N 6.55.

4.1.6. General procedures for the Heck reaction (GP5)

Method A (Scheme 5, conditions f): The aryl triflate **10a–f** (1.0 equiv) was dissolved in DMF and the reactants were added in the following order: (1) Pd(OAc)$_2$ (3–10 mol %), (2) NEt$_3$ (1.5 equiv), and (3) **20** (1.5 equiv). The reaction mixture was stirred for 20 h at 80 °C. After cooling to rt, the black solution was diluted with CH_2Cl_2 and washed with water and brine. The organic layer was dried over K_2CO_3, filtered, and the solvent was removed in vacuo.

Method B (Scheme 5, conditions g): Pd(OAc)$_2$ (10 mol %) and PPh$_3$ (20 mol %) were dissolved in DMF and the reactants were added in the following order: (1) aryl triflate **11a–f** (1.0 equiv), (2) NEt$_3$ (1.5 equiv), and **20** (1.5 equiv). The reaction mixture was stirred at 80 °C for 20 h and work up was performed according to method A.

Method C (Scheme 5, conditions h): The aryl iodide (1.0 equiv) was dissolved in DMF and the reactants were added in the following order: (1) **20** (2.0 equiv), (2) Pd(OAc)$_2$ (10 mol%), (3) NaOAc (1.2 equiv), (4) LiCl (2.0 equiv), (5) K_2CO_3 (1.2 equiv), and water (DMF/H$_2$O (v/v) = 10:1). The reaction mixture was stirred at 80 °C for 20 h and work up was performed according to method A.

4.1.6.1. Ethyl 1-(2-{2-[4-fluoro-2-(4-fluorobenzoyl)phenyl]-vinyloxy}ethyl)nipecotate (22a). According to **GP5** (method A) using **10a** (549 mg, 150 μmol) in DMF (6.00 mL), Pd(OAc)$_2$ (10.2 mg, 45.0 μmol), NEt$_3$ (228 mg, 310 μL, 225 μmol), and **20** (511 mg, 225 μmol). The crude product was purified by FCC (cyclohexane/EtOAc = 5:1 + 1% NEt$_3$) to yield **22a** (268 mg, 40%) as (*E*)/(*Z*)-mixture. The isomers were separated by FCC (Et$_2$O + 1% NEt$_3$).

Compound **(*E*)-22a**: 134 mg (20%). Pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ 1.24 (t, J = 7.0 Hz, 3H, CH$_3$), 1.41 (ddd, J = 24.5/11.9/4.1 Hz, 1H, NCH$_2$CH$_2$C$H_{2,ax}$), 1.57 (m, 1H, NCH$_2$C$H_{2,ax}$CH$_2$), 1.70 (dt, J = 13.5/3.5 Hz, 1H, NCH$_2$C$H_{2,eq}$CH$_2$), 1.94 (dd, J = 12.9/3.8 Hz, 1H, NCH$_2$CH$_2$C$H_{2,eq}$), 2.00 (td, J = 11.2/2.9 Hz, 1H, NC$H_{2,eq}$CH$_2$CH$_2$), 2.17 (t, J = 10.8 Hz, 1H, NC$H_{2,ax}$CH), 2.55 (m, 1H, NCH$_2$CH), 2.60 (m, 2H, NCH_2CH$_2$O), 2.75 (d, J = 11.2 Hz, 1H, NC$H_{2,eq}$CH$_2$CH$_2$), 2.97 (d, J = 11.0 Hz, 1H, NC$H_{2,eq}$CH), 3.75 (t, J = 5.7 Hz, 2H,NCH$_2$CH_2O), 4.12 (q, J = 7.1 Hz, 2H, CH_2CH$_3$), 5.77 (d, J = 12.9 Hz, 1H, OCHCH), 6.84 (d, J = 12.9 Hz, 1H, OCHCH), 7.01 (dd, J = 8.5/2.5 Hz, 1H, COCCH$_{ar}$CF), 7.12 (td, J = 8.3/3.0 Hz, 1H, COCCH$_{ar}$CFCH_{ar}), 7.13 (t, J = 8.8 Hz, 2H, COCCH$_{ar}$CH_{ar}CFCH_{ar}), 7.39 (dd, J = 8.8/5.3 Hz, 1H, OCHCHCCH_{ar}), 7.81 (dd, J = 8.5/5.5 Hz, 2H, COCCH_{ar}CH$_{ar}$CFCH$_{ar}$CH_{ar}) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ 14.21 (CH$_3$), 24.51 (NCH$_2$CH_2CH$_2$), 26.83 (NCH$_2$CH$_2$CH_2), 41.79 (NCH$_2$CH), 53.98 (NCH_2CH$_2$CH$_2$), 55.73 (NCH_2CH), 57.30 (NCH_2CH$_2$O), 60.34 (CH_2CH$_3$), 66.98 (NCH$_2$CH_2O), 102.34 (OCHCH), 115.34 (d, J_{CF} = 22.7 Hz, COC$_{ar}$C$_{ar}$H), 115.81 (d, J_{CF} = 21.9 Hz, 2 C, COC$_{ar}$C$_{ar}$HC$_{ar}$HC$_{ar}$FC$_{ar}$H), 117.72 (d, J_{CF} = 21.4 Hz, COC$_{ar}$C$_{ar}$HC$_{ar}$FC$_{ar}$H), 127.28 (d, J_{CF} = 7.4 Hz, OCHCHC$_{ar}$C$_{ar}$H), 131.31 (OCHCHC$_{ar}$), 132.91 (d, J_{CF} = 9.6 Hz, 2 C, COC$_{ar}$C$_{ar}$HC$_{ar}$HC$_{ar}$F-C$_{ar}$HC$_{ar}$H), 133.47 (COC$_{ar}$C$_{ar}$HC$_{ar}$HC$_{ar}$F), 137.88 (d, J_{CF} = 5.8 Hz, CO-C$_{ar}$C$_{ar}$HC$_{ar}$F), 149.61 (OCHCH), 160.41 (d, J_{CF} = 247.6 Hz, COC$_{ar}$C$_{ar}$HC$_{ar}$F), 166.00 (d, J_{CF} = 256.7 Hz, COC$_{ar}$C$_{ar}$HC$_{ar}$HC$_{ar}$F), 174.08 (COOEt), 195.55 (ArCOAr) ppm. M ($C_{25}H_{27}F_2NO_4$) 443.50. MS (CI, CH_5^+) m/z (%): 444 (53, [M+H]$^+$) , 243 (5), 170 (100), 185 (94). HRMS (EI+): M$^+$ calcd for $C_{25}H_{27}F_2NO_4$ 443.1908; found: 443.1939.

Compound **(*Z*)-22a**: Pale yellow oil. 40.2 mg (6%). ^{1}H NMR (500 MHz, CDCl$_3$): δ 1.24 (t, J = 7.0 Hz, 3H, CH$_3$), 1.45 (qd, J = 11.5/3.8 Hz, 1H, NCH$_2$CH$_2$C$H_{2,ax}$), 1.50–1.61 (m, 1H, NCH$_2$C$H_{2,ax}$CH$_2$), 1.68–1.75 (m, 1H, NCH$_2$CH$_2$C$H_{2,eq}$CH$_2$), 1.89–1.97 (m, 1H, NCH$_2$CH$_2$CH$_2$C$H_{2,eq}$), 2.12 (td, J = 10.8/2.8 Hz, 1H, NC$H_{2,ax}$CH$_2$CH$_2$), 2.30 (t, J = 10.8 Hz, 1H, NC$H_{2,ax}$CH), 2.54 (tt, J = 10.3/3.9 Hz, 1H, NCH$_2$CH), 2.64 (t, J = 6.0 Hz, 2H, NCH_2CH$_2$O), 2.75 (d$_{br}$, J = 11.0 Hz, 1H, NC$H_{2,eq}$CH$_2$CH$_2$), 2.98 (d$_{br}$, J = 10.5 Hz, 1H, NC$H_{2,eq}$CH), 3.95 (t, J = 6.0 Hz, 2H, NCH$_2$CH_2O), 4.12 (qd, J = 7.2/1.5 Hz, 2H, CH_2CH$_3$), 5.14 (d, J = 7.5 Hz, 1H, OCHCH), 6.10 (d, J = 7.5 Hz, 1H, OCHCH), 6.97 (dd, J = 8.5/2.5 Hz, 1H, COCCH$_{ar}$CF), 7.13 (t, J = 8.8 Hz, 2H, COCCH$_{ar}$CH$_{ar}$CFCH_{ar}), 7.15 (dd, J = 8.5/3.0 Hz, 1H, COCCH$_{ar}$CFCH_{ar}), 7.84 (dd, J = 9.0/5.5 Hz, 2H, COCCH_{ar}CH$_{ar}$CFCH$_{ar}$CH_{ar}), 8.09 (dd, J = 9.0/5.5 Hz, 1H, OCHCHCCH_{ar}) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ 14.20 (CH$_3$), 24.61 (NCH$_2$CH_2CH$_2$), 26.69 (NCH$_2$CH$_2$CH_2), 41.86 (NCH$_2$CH), 54.11 (NCH$_2$CH$_2$CH$_2$), 55.80 (NCH$_2$CH), 57.74 (NCH$_2$CH$_2$O), 60.37 (CH_2CH$_3$), 71.38 (NCH$_2$CH_2O), 101.3 (OCHCH), 114.6 (d, J_{CF} = 22.8 Hz, COC$_{ar}$C$_{ar}$HC$_{ar}$F), 115.7 (d, J_{CF} = 21.9, 2C, CO-C$_{ar}$C$_{ar}$HC$_{ar}$HC$_{ar}$FC$_{ar}$H), 117.0 (d, J_{CF} = 20.8 Hz, COC$_{ar}$C$_{ar}$HC$_{ar}$FC$_{ar}$H), 130.1 (d, J_{CF} = 3.5 Hz, OCHCHC$_{ar}$), 131.6 (d, J_{CF} = 7.4 Hz, OCH-CHC$_{ar}$C$_{ar}$H), 133.0 (d, J_{CF} = 9.5 Hz, 2 C, COC$_{ar}$C$_{ar}$HC$_{ar}$HC$_{ar}$FC$_{ar}$HC$_{ar}$H), 133.4 (d, J_{CF} = 2.9 Hz, COC$_{ar}$C$_{ar}$HC$_{ar}$HC$_{ar}$F), 138.5 (d, J_{CF} = 5.8 Hz, CO-C$_{ar}$C$_{ar}$HC$_{ar}$F), 147.4 (OCHCH), 159.9 (d, J_{CF} = 246.3 Hz, COC$_{ar}$C$_{ar}$H-C$_{ar}$F), 166.0 (d, J_{CF} = 254.4 Hz, COC$_{ar}$C$_{ar}$HC$_{ar}$HC$_{ar}$F), 174.0 (COOEt), 195.6 (ArCOAr) ppm. ^{19}F NMR (470 MHz, CDCl$_3$): δ −104.2, −115.7 ppm. M ($C_{25}H_{27}F_2NO_4$) 443.50. MS (CI, CH_5^+) m/z (%): 444 (100, [M+H]$^+$), 184 (31), 170 (45). HRMS (EI+): M$^+$ calcd for $C_{25}H_{27}F_2NO_4$ 443.1908; found: 443.1920.

4.1.6.2. Ethyl 1-(2-{2-[4-fluoro-2-(4-fluorobenzyl)phenyl]-vinyloxy}ethyl)nipecotate (23a). According to **GP5** (method B) using **11a** (1.06 g, 3.00 mmol), **20** (1.02 g, 4.50 mmol), NEt$_3$ (455 mg, 0.620 mL, 4.50 mmol), Pd(OAc)$_2$ (67.4 mg, 0.300 mmol), and PPh$_3$ (157 mg, 0.600 mmol) in DMF (12.0 mL). The crude product was purified by FCC (cyclohexane/MTBE = 2.5:1 + 1% NEt$_3$) to yield **23a** (250 mg, 19%) as (*E*)/(*Z*)-mixture. The isomers were separated via FCC (Et$_2$O + 1% NEt$_3$).

Compound **(*E*)-23a**: 101 mg (8%) Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ 1.25 (t, J = 7.3 Hz, 3H, CH$_3$), 1.44 (qd, J = 12.0/4.1 Hz, 1H, NCH$_2$CH$_2$C$H_{2,ax}$), 1.56–1.66 (m, 1H, NCH$_2$C$H_{2,ax}$CH$_2$), 1.73 (dt, J = 13.5/3.6 Hz, 1H, NCH$_2$C$H_{2,eq}$CH$_2$), 1.93–2.00 (m, 1H, NCH$_2$CH$_2$C$H_{2,eq}$), 2.06 (td, J = 11.1/3.0 Hz, 1H, NC$H_{2,ax}$CH$_2$CH$_2$), 2.23 (t, J = 10.8 Hz, 1H, NC$H_{2,ax}$CH), 2.59 (tt, J = 10.8/3.8 Hz, 1H, NCH$_2$CH), 2.69 (td, J = 5.6/1.8 Hz, 2H, NCH_2CH$_2$O), 2.82 (d$_{br}$, J = 11.0 Hz, 1H, NC$H_{2,eq}$CH$_2$CH$_2$), 3.04 (d$_{br}$, J = 10.0 Hz, 1H, NC$H_{2,eq}$CH), 3.87 (t, J = 5.8 Hz, 2H, NCH$_2$CH_2O), 3.94 (s, 2H, ArCH$_2$-Ar), 4.13 (q, J = 7.0 Hz, 2H, CH_2CH$_3$), 5.83 (d, J = 12.5 Hz, 1H, OCHCH), 6.75 (d, J = 13.0 Hz, 1H, OCHCH), 6.76 (dd, J = 9.8/2.8 Hz, 1H, CH$_2$CCH_{ar}CF), 6.87 (td, J = 8.4/2.8 Hz, 1H, CH$_2$CCH$_{ar}$CFCH_{ar}), 6.97 (t, J = 8.8 Hz, 2H, CH$_{ar}$CH_{ar}CFCH_{ar}CH$_{ar}$), 7.07 (dd, J = 8.5/5.5 Hz, 2H, CH_{ar}CH$_{ar}$CFCH$_{ar}$CH_{ar}), 7.23 (dd, J = 8.8/5.8 Hz, 1H, CH$_2$CCH$_{ar}$CFCH$_{ar}$CH_{ar}) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ 14.21 (CH$_3$), 24.52 (NCH$_2$CH_2CH$_2$), 26.84 (NCH$_2$CH$_2$CH_2), 38.52 (ArCH$_2$-Ar), 41.75 (NCH$_2$CH), 54.08 (NCH$_2$CH$_2$CH$_2$), 55.76 (NCH$_2$CH), 57.47 (NCH$_2$CH$_2$O), 60.37 (CH_2CH$_3$), 67.16 (NCH$_2$CH_2O), 102.8 (OCHCH), 113.5 (d, J_{CF} = 20.9 Hz, CH$_2$C$_{ar}$C$_{ar}$HC$_{ar}$FC$_{ar}$H), 115.3 (d, J_{CF} = 21.0 Hz, 2 C, C$_{ar}$HC$_{ar}$HC$_{ar}$FC$_{ar}$HC$_{ar}$H), 116.7 (d, J_{CF} = 21.4 Hz, CH$_2$C$_{ar}$C$_{ar}$HC$_{ar}$F), 127.1 (d, J_{CF} = 7.8 Hz, CH$_2$C$_{ar}$C$_{ar}$HC$_{ar}$FC$_{ar}$HC$_{ar}$H), 130.1 (d, J_{CF} = 7.9 Hz, 2 C, C$_{ar}$HC$_{ar}$HC$_{ar}$FC$_{ar}$HC$_{ar}$H), 131.2 (d, J_{CF} = 3.1 Hz, OCHCHC$_{ar}$), 135.4 (d, J_{CF} = 3.1 Hz, CH$_2$C$_{ar}$C$_{ar}$HC$_{ar}$HC$_{ar}$F-

$C_{ar}HC_{ar}H$), 139.2 (d, J_{CF} = 6.9 Hz, OCHCHC$_{ar}$C$_{ar}$CH$_2$), 148.7 (OCHCH), 161.4 (d, J_{CF} = 242.9 Hz, $C_{ar}HC_{ar}HC_{ar}FC_{ar}HC_{ar}H$), 161.5 (d, J_{CF} = 243.3 Hz, $CH_2C_{ar}C_{ar}HC_{ar}F$), 174.1 (COOEt) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ −116.7, −116.9 ppm. M ($C_{25}H_{29}F_2NO_3$) 429.51. MS (CI, CH_5^+) *m*/*z* (%): 430 (64, $[M+H]^+$), 184 (100), 170 (67). HRMS (EI+): M^+ calcd for $C_{25}H_{29}F_2NO_3$ 429.2116; found: 429.2151.

Compound **(*Z*)-23a:** 49.1 mg (4%). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.0 Hz, 3H, CH_3), 1.45 (dq, *J* = 11.7/3.6 Hz, 1H, NCH$_2$CH$_2$C*H*$_{2,ax}$), 1.51–1.62 (m, 1H, NCH$_2$C*H*$_{2,ax}$CH$_2$), 1.71 (dt, *J* = 13.0/3.6 Hz, 1H, NCH$_2$C*H*$_{2,eq}$CH$_2$), 1.91–1.94 (m, 1H, NCH$_2$CH$_2$C*H*$_{2,eq}$), 2.13 (td, *J* = 10.9/2.8 Hz, 1H, NC*H*$_{2,ax}$CH$_2$CH$_2$), 2.31 (t, *J* = 10.8 Hz, 1H, NC*H*$_{2,ax}$CH), 2.55 (tt, *J* = 10.5/3.9 Hz, 1H, NCH$_2$C*H*), 2.69 (t, *J* = 5.8 Hz, 2H, NC*H*$_2$CH$_2$O), 2.78 (d$_{br}$, *J* = 11.0 Hz, 1H, NC*H*$_{2,eq}$CH$_2$CH$_2$), 3.01 (d$_{br}$, *J* = 10.0 Hz, 1H, NC*H*$_{2,eq}$CH), 3.95 (s, 2H, ArCH$_2$Ar), 3.99 (t, *J* = 6.0 Hz, 2H, NCH$_2$C*H*$_2$O), 4.11 (qd, *J* = 7.1/1.3 Hz, 2H, C*H*$_2$CH$_3$), 5.21 (d, *J* = 7.0 Hz, 1H, OCHC*H*), 6.18 (d, *J* = 7.5 Hz, 1H, OC*H*CH), 6.74 (dd, *J* = 9.8/2.8 Hz, 1H, OCHCHCCH$_{ar}$CH$_{ar}$CFC*H*$_{ar}$), 6.90 (td, *J* = 8.5/2.5 Hz, 1H, OCHCHCCH$_{ar}$C*H*$_{ar}$), 6.96 (t, *J* = 8.8 Hz, 2H, CH$_{ar}$C*H*$_{ar}$CFC*H*$_{ar}$CH$_{ar}$), 7.06 (dd, *J* = 8.3/5.8 Hz, 2H, C*H*$_{ar}$CH$_{ar}$CFCH$_{ar}$C*H*$_{ar}$), 7.94 (dd, *J* = 8.8/6.3 Hz, 1H, OCHCHCC*H*$_{ar}$) ppm. [v] (125 MHz, $CDCl_3$): δ 14.20 (CH_3), 24.62 (NCH$_2$*C*H$_2$CH$_2$), 26.71 (NCH$_2$CH$_2$*C*H$_2$), 38.49 (ArCH$_2$Ar), 41.88 (NCH$_2$*C*H), 54.13 (N*C*H$_2$CH$_2$CH$_2$), 55.82 (N*C*H$_2$CH), 57.82 (N*C*H$_2$CH$_2$O), 60.36 (*C*H$_2$CH$_3$), 71.27 (NCH$_2$*C*H$_2$O), 101.5 (OCH*C*H), 113.1 (d, J_{CF} = 20.7 Hz, OCHCHC$_{ar}$C$_{ar}$H*C*$_{ar}$H), 115.3 (d, J_{CF} = 21.3 Hz, 2 C, $C_{ar}HC_{ar}HC_{ar}FC_{ar}HC_{ar}H$), 116.5 (d, J_{CF} = 21.5 Hz, OCHCHC$_{ar}$C$_{ar}$HC$_{ar}$HC$_{ar}$F*C*$_{ar}$H), 130.1 (d, J_{CF} = 7.88 Hz, 2 C, *C*$_{ar}$HC$_{ar}$HC$_{ar}$FC$_{ar}$HC$_{ar}$H), 130.2 (d, J_{CF} = 3.33 Hz, OCHCH*C*$_{ar}$), 131.1 (d, J_{CF} = 7.78 Hz, OCHCHC$_{ar}$C$_{ar}$H), 135.5 (d, J_{CF} = 3.13 Hz, OCHCHC$_{ar}$C$_{ar}$CH$_2$*C*$_{ar}$), 139.2 (d, J_{CF} = 6.87 Hz, OCHCHC$_{ar}$*C*$_{ar}$CH$_2$), 146.6 (O*C*HCH), 160.9 (d, J_{CF} = 246 Hz, OCHCHC$_{ar}$C$_{ar}$HC$_{ar}$H*C*$_{ar}$F), 161.4 (d, J_{CF} = 245 Hz, $C_{ar}HC_{ar}HC_{ar}FC_{ar}HC_{ar}H$), 174.1 (COOEt) ppm. ^{19}F NMR (470 MHz): δ −116.1, −117.1 ppm. M ($C_{25}H_{29}F_2NO_3$) 429.51. MS (CI, CH_5^+) *m*/*z* (%): 430 (100, $[M+H]^+$), 184 (36), 170 (44). HRMS (EI+): M^+ calcd for $C_{25}H_{29}F_2NO_3$ 429.2116; found: 429.2108. $C_{25}H_{29}F_2NO_3$ (429.51): calcd C 69.91, H 6.81, N 3.26; found: C 68.67, H 6.40, N 2.96.

4.1.6.3. Ethyl 1-(2-{2-[2-benzoylphenyl]vinyloxy}ethyl) nipecotate (22g). According to **GP5** (method C) using **10g** (924 mg, 0.57 mL, 3.00 mmol) in DMF (12.0 mL), **20** (1.36 g, 6.00 mmol) Pd(OAc)$_2$ (67.3 mg, 0.300 mmol), NaOAc (295 mg, 3.60 mmol), K_2CO_3 (498 mg, 3.60 mmol), LiCl (254 mg, 6.00 mmol), and H_2O (1.32 mL). The crude product was purified via FCC (cyclohexane/MTBE = 2.5:1 + 1% NEt_3) to yield **22g** (1.02 g, 83%) as (*E*)/(*Z*)-mixture. The isomers were separated by FCC (Et_2O + 1% NEt_3).

Compound **(*E*)-22g**: 291 mg (24%). Colorless oil. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 1.21 (t, *J* = 7.3 Hz, 3H, CH_3), 1.40 (qd, *J* = 11.8/3.8 Hz, 1H, NCH$_2$CH$_2$C*H*$_{2,ax}$), 1.46–1.57 (m, 1H, NCH$_2$C*H*$_{2,ax}$CH$_2$), 1.63–1.70 (m, 1H, NCH$_2$C*H*$_{2,eq}$CH$_2$), 1.84–1.91 (m, 1H, NCH$_2$CH$_2$C*H*$_{2,eq}$), 2.01 (td, *J* = 11.0/2.5 Hz, 1H, NC*H*$_{2,ax}$CH$_2$CH$_2$), 2.17 (t, *J* = 10.5 Hz, 1H, NC*H*$_{2,ax}$CH), 2.49 (tt, *J* = 10.3/3.8 Hz, 1H, NCH$_2$C*H*), 2.52–2.60 (m, 2H, NC*H*$_2$CH$_2$O), 2.69 (d$_{br}$, *J* = 11.0 Hz, 1H, NC*H*$_{2,eq}$CH$_2$CH$_2$), 2.90 (d$_{br}$, *J* = 8.0 Hz, 1H, NC*H*$_{2,eq}$CH), 3.73 (t, *J* = 5.5 Hz, 2H, NCH$_2$C*H*$_2$O), 4.08 (q, *J* = 7.0 Hz, 2H, C*H*$_2$CH$_3$), 5.85 (d, *J* = 13.0 Hz, 1H, OCHC*H*), 6.92 (d, *J* = 12.5 Hz, 1H, OC*H*CH), 7.22 (td, *J* = 7.4/1.3 Hz, 1H, OCHCHCCH$_{ar}$CH$_{ar}$C*H*$_{ar}$CH$_{ar}$), 7.30 (dd, *J* = 8.0/1.5 Hz, 1H, OCHCHCCH$_{ar}$CH$_{ar}$CH$_{ar}$C*H*$_{ar}$), 7.41 (td, *J* = 7.6/1.3 Hz, 1H, OCHCHCCH$_{ar}$C*H*$_{ar}$CH$_{ar}$CH$_{ar}$), 7.44–7.48 (m, 3H, OCHCHCC*H*$_{ar}$ and CH$_{ar}$C*H*$_{ar}$CH$_{ar}$C*H*$_{ar}$CH$_{ar}$), 7.58 (tt, *J* = 7.5/1.5 Hz, 1H, CH$_{ar}$CH$_{ar}$C*H*$_{ar}$CH$_{ar}$CH$_{ar}$), 7.74–7.77 (m, 2H, C*H*$_{ar}$CH$_{ar}$CH$_{ar}$CH$_{ar}$C*H*$_{ar}$) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2): δ 14.42 (CH_3), 24.99 (NCH$_2$*C*H$_2$CH$_2$), 21.18 (NCH$_2$CH$_2$*C*H$_2$), 42.23 (NCH$_2$*C*H), 54.35 (N*C*H$_2$CH$_2$CH$_2$), 56.17 (N*C*H$_2$CH), 57.72 (N*C*H$_2$CH$_2$O), 60.58 (*C*H$_2$CH$_3$), 67.84 (NCH$_2$*C*H$_2$O), 103.8 (OCH*C*H), 125.4 (OCHCHC$_{ar}$*C*$_{ar}$H), 125.5 (OCHCHC$_{ar}$C$_{ar}$HC$_{ar}$H*C*$_{ar}$H), 128.8 (2 C, $C_{ar}HC_{ar}HC_{ar}HC_{ar}HC_{ar}H$), 129.3 (OCHCHC$_{ar}C_{ar}HC_{ar}HC_{ar}$H*C*$_{ar}$H), 130.5 (2 C, *C*$_{ar}HC_{ar}HC_{ar}HC_{ar}HC_{ar}$H), 130.8 (OCHCHC$_{ar}C_{ar}$H*C*$_{ar}$H), 133.5 (C$_{ar}HC_{ar}$H*C*$_{ar}HC_{ar}HC_{ar}$H), 135.7 (OCHCH*C*$_{ar}$), 137.2 (OCHCHC$_{ar}$*C*$_{ar}$CO), 138.2 (OCHCHC$_{ar}C_{ar}$CO*C*$_{ar}$), 150.1 (O*C*HCH), 174.3 (COOEt), 198.7 (ArCOAr) ppm. M ($C_{25}H_{29}NO_4$) 407.51. MS (CI, CH_5^+) *m*/*z* (%): 408 (100, $[M+H]^+$), 184 (34), 170 (11), 83 (29), 79 (21). HRMS (EI+): M^+ calcd for $C_{25}H_{29}NO_4$ 407.2097; found: 407.2088.

Compound **(*Z*)-22g**: 135 mg (11%). Colorless oil. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 1.20 (t, *J* = 7.3 Hz, 3H, CH_3), 1.42, (qd, *J* = 11.8/3.7 Hz, 1H, NCH$_2$CH$_2$C*H*$_{2,ax}$), 1.48–1.58 (m, 1H, NCH$_2$C*H*$_{2,ax}$CH$_2$), 1.64–1.73 (m, 1H, NCH$_2$C*H*$_{2,eq}$CH$_2$), 1.84–1.91 (m, 1H, NCH$_2$CH$_2$C*H*$_{2,eq}$), 2.10 (td, *J* = 10.9/2.7 Hz, 1H, NC*H*$_{2,ax}$CH$_2$CH$_2$), 2.27 (t, *J* = 10.5 Hz, 1H, NC*H*$_{2,ax}$CH), 2.51 (tt, *J* = 10.3/4.0 Hz, 1H, NCH$_2$C*H*), 2.56–2.66 (m, 2H, NC*H*$_2$CH$_2$O), 2.73 (d$_{br}$, *J* = 11.0 Hz, 1H, NC*H*$_{2,eq}$CH$_2$CH$_2$), 2.96 (d$_{br}$, *J* = 9.0 Hz, 1H, NC*H*$_{2,eq}$CH), 3.93 (t, *J* = 5,8 Hz, 2H, NCH$_2$C*H*$_2$O), 4.02–4.13 (m, 2H, C*H*$_2$CH$_3$), 5.21 (d, *J* = 7.0 Hz, 1H, OCHC*H*), 6.15 (d, *J* = 7.5 Hz, 1H, OC*H*CH), 7.20 (td, *J* = 7.5/1.0 Hz, 1H, OCHCHCCH$_{ar}$CH$_{ar}$C*H*$_{ar}$), 7.25 (dd, *J* = 7.5/1.5 Hz, 1H, OCHCHCCH$_{ar}$CH$_{ar}$CH$_{ar}$C*H*$_{ar}$), 7.41–7.47 (m, 3H, OCHCHCCH$_{ar}$C*H*$_{ar}$ und CH$_{ar}$C*H*$_{ar}$CH$_{ar}$C*H*$_{ar}$CH$_{ar}$), 7.58 (tt, *J* = 7.5/1.5 Hz, 1H, CH$_{ar}$CH$_{ar}$C*H*$_{ar}$CH$_{ar}$CH$_{ar}$), 7.76–7.80 (m, 2H, C*H*$_{ar}$CH$_{ar}$CH$_{ar}$CH$_{ar}$C*H*$_{ar}$), 8.11 (d, *J* = 8.0 Hz, 1H, OCHCHCC*H*$_{ar}$) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2): δ 14.54 (CH_3), 25.17 (NCH$_2$*C*H$_2$CH$_2$), 27.26 (NCH$_2$CH$_2$*C*H$_2$), 42.41 (NCH$_2$*C*H), 54.58 (N*C*H$_2$CH$_2$CH$_2$), 56.39 (N*C*H$_2$CH), 58.32 (N*C*H$_2$CH$_2$O), 60.72 (*C*H$_2$CH$_3$), 71.92 (NCH$_2$*C*H$_2$O), 102.4 (OCH*C*H), 125.5 (OCHCHC$_{ar}$C$_{ar}$HC$_{ar}$H*C*$_{ar}$H), 128.5 (OCHCHC$_{ar}$C$_{ar}$HC$_{ar}$HC$_{ar}$H*C*$_{ar}$H), 128.9 (2 C, C$_{ar}$H*C*$_{ar}$HC$_{ar}$H*C*$_{ar}$HC$_{ar}$H), 130.1 (OCHCHC$_{ar}$*C*$_{ar}$H), 130.4 (OCHCHC$_{ar}$C$_{ar}$H*C*$_{ar}$H), 130.7 (2 C, *C*$_{ar}$HC$_{ar}$HC$_{ar}$HC$_{ar}$HC$_{ar}$H), 133.6 (C$_{ar}$HC$_{ar}$H*C*$_{ar}$HC$_{ar}$HC$_{ar}$H), 134.6 (OCHCH*C*$_{ar}$), 137.8 (OCHCHC$_{ar}$*C*$_{ar}$CO), 138.3 (OCHCHC$_{ar}$C$_{ar}$CO*C*$_{ar}$), 148.5 (O*C*HCH), 174.4 (COOEt), 198.8 (ArCOAr) ppm. M ($C_{25}H_{29}NO_4$) 407.51. MS (CI, CH_5^+) *m*/*z* (%): 408 (100, $[M+H]^+$), 184 (32), 170 (16). HRMS (EI+): M^+ calcd for $C_{25}H_{29}NO_4$ 407.2097; found: 407.2105.

4.1.7. General procedure for the ester hydrolysis (GP6)

The ethyl ester (**22a–g**, **23a**, **23c–g**, 1.0 equiv) was dissolved in EtOH and cooled to 0 °C. An excess of 12 M NaOH or 2.0 M LiOH (6.0–10 equiv) was added dropwise at this temperature. After the reaction was complete (TLC), the solution was diluted with CH_2Cl_2 and phosphate buffer (0.4 M, pH 6.0) was added until a clear solution with a pH of 6.0 was obtained. The aqueous layer was extracted with CH_2Cl_2 several times, the combined organic layers were dried with $MgSO_4$ and the solvent was removed in vacuo to give the pure neutral form of the desired carboxylic acid.

4.1.7.1. 1-(2-{(*E*)-2-[4-Fluoro-2-(4-fluorobenzoyl)phenyl]vinyloxy}ethyl)nipecotic acid ((*E*)-7a). According to **GP6** with (*E*)-**22a** (40.0 mg, 0.090 mmol) and 12 M NaOH (0.080 mL, 0.900 mmol) in EtOH (0.500 mL). The reaction time was 1 h.

Compound **(*E*)-7a**: 35.7 mg (96%). Colorless oil. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 1.58–1.69 (m, 2H, NCH$_2$C*H*$_{2,ax}$C*H*$_{2,ax}$), 1.70–1.82 (m, 1H, NCH$_2$C*H*$_{2,eq}$CH$_2$), 1.83–1.93 (m, 1H, NCH$_2$CH$_2$C*H*$_{2,eq}$), 2.30–2.41 (m, 1H, NC*H*$_{2,ax}$CH$_2$CH$_2$), 2.42–2.54 (m, 1H, NC*H*$_{2,ax}$CH), 2.59–2.65 (m, 1H, NCH$_2$C*H*), 2.74 (t, *J* = 5.3 Hz, 2H, NC*H*$_2$CH$_2$O), 2.82–2.92 (m, 1H, NC*H*$_{2,eq}$CH$_2$CH$_2$), 2.93–3.03 (m, 1H, NC*H*$_{2,eq}$CH), 3.80 (t, *J* = 5.3 Hz, 2H, NCH$_2$C*H*$_2$O), 5.79 (d, *J* = 12.5 Hz, 1H, OCHC*H*), 6.84 (d, *J* = 13.0 Hz, 1H, OC*H*CH), 7.03 (dd, *J* = 8.8/2.8 Hz, 1H, COCCH$_{ar}$CF), 7.15 (t, *J* = 8.8 Hz, 2H, CH$_{ar}$C*H*$_{ar}$CFC*H*$_{ar}$CH$_{ar}$), 7.13–7.18 (m, 1H, OCHCHCCH$_{ar}$C*H*$_{ar}$), 7.44 (dd, *J* = 8.8/5.3 Hz, 1H, OCHCHCC*H*$_{ar}$CH$_{ar}$), 7.80 (dd, *J* = 9.0/5.5 Hz, 2H, C*H*$_{ar}$CH$_{ar}$CFCH$_{ar}$C*H*$_{ar}$) ppm. ^{13}C NMR (125 MHz, CD_2Cl_2): δ 22.72 (NCH$_2$*C*H$_2$CH$_2$), 26.78 (NCH$_2$CH$_2$*C*H$_2$), 40.85 (NCH$_2$*C*H), 53.75 (N*C*H$_2$CH$_2$CH$_2$), 55.49 (N*C*H$_2$CH), 56.58 (N*C*H$_2$CH$_2$O), 66.26 (NCH$_2$*C*H$_2$O), 103.7 (OCH*C*H),

115.9 (d, J_{CF} = 22.8 Hz, $COC_{ar}C_{ar}HC_{ar}F$), 116.2 (d, J_{CF} = 22.0 Hz, 2 C, $C_{ar}HC_{ar}HC_{ar}FC_{ar}HC_{ar}H$), 118.2 (d, J_{CF} = 21.4 Hz, $OCHCHC_{ar}C_{ar}HC_{ar}H$), 128.0 (d, J_{CF} = 7.38 Hz, $OCHCHC_{ar}C_{ar}HC_{ar}H$), 131.6 (d, J_{CF} = 3.38 Hz, $OCHCHC_{ar}$), 133.4 (d, J_{CF} = 9.50 Hz, 2 C, $C_{ar}HC_{ar}HC_{ar}FC_{ar}HC_{ar}H$), 134.1 (d, J_{CF} = 2.88 Hz, $COC_{ar}C_{ar}HC_{ar}HC_{ar}F$),138.5 (d, J_{CF} = 5.75 Hz, $OCHCHC_{ar}C_{ar}CO$), 149.5 (OCHCH), 161.0 (d, J_{CF} = 245 Hz, $CHC_{ar}C_{ar}HC_{ar}F$), 166.5 (d, J_{CF} = 254 Hz, $C_{ar}HC_{ar}HC_{ar}FC_{ar}HC_{ar}H$), 176.5 (COOH), 195.7 (ArCOAr) ppm. ^{19}F NMR (470 MHz, CD_2Cl_2): δ −105.0, −116.9 ppm. M ($C_{23}H_{23}F_2NO_4$) 415.44. MS (CI, CH_5^+) *m*/*z* (%): 416 (21, $[M+H]^+$), 156 (20), 142 (100). HRMS (EI+): M^+ calcd for $C_{23}H_{23}F_2NO_4$ 415.1595; found: 415.1591.

4.1.7.2. 1-(2-{(*Z*)-2-[4-Fluoro-2-(4-fluorobenzoyl)phenyl]vinyloxy}ethyl)nipecotic acid ((*Z*)-7a). According to **GP6** with (*Z*)-**22a** (31.3 mg, 0.070 mmol) and 12 M NaOH (0.060 mL, 0.700 mmol) in EtOH (0.500 mL). The reaction time was 30 min.

Compound **(*Z*)-7a**: 27.2 mg (94%). Colorless oil. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 1.58–1.71 (m, 2H, $NCH_2CH_{2,ax}CH_{2,ax}$), 1.75–1.86 (m, 1H, $NCH_2CH_{2,eq}CH_2$), 1.89–1.97 (m, 1H, $NCH_2CH_2CH_{2,eq}$), 2.33 (t, *J* = 10.5 Hz, 1H, $NCH_{2,ax}CH_2CH_2$), 2.47 (d, *J* = 11.5 Hz, 1H, $NCH_{2,ax}CH$), 2.63–2.69 (m, 1H, NCH_2CH), 2.71–2.83 (m, 2H, NCH_2CH_2O), 2.94–3.03 (m, 1H, $NCH_{2,eq}CH_2CH_2$), 3.05–3.13 (m, 1H, $NCH_{2,eq}CH$), 3.96–4.06 (m, 2H, NCH_2CH_2O), 5.18 (d, *J* = 7.0 Hz, 1H, OCHCH), 6.11 (d, *J* = 7.0 Hz, 1H, OCHCH), 6.98 (dd, *J* = 8.8/2.8 Hz, 1H, $COCCH_{ar}CF$), 7.15 (t, *J* = 8.8 Hz, 2H, $CH_{ar}CH_{ar}CFCH_{ar}CH_{ar}$), 7.19 (td, *J* = 8.9/3.0 Hz, 1H, $COCCH_{ar}CFCH_{ar}$), 7.83 (dd, *J* = 9.0/5.5 Hz, 2H, $CH_{ar}CH_{ar}CFCH_{ar}CH_{ar}$), 8.07 (dd, *J* = 8.8/5.8 Hz, 1H, $OCHCHCCH_{ar}$) ppm. ^{13}C NMR (125 MHz, CD_2Cl_2): δ 22.72 ($NCH_2CH_2CH_2$), 26.79 ($NCH_2CH_2CH_2$), 40.88 (NCH_2CH), 53.82 ($NCH_2CH_2CH_2$), 55.79 (NCH_2CH), 57.26 (NCH_2CH_2O), 70.40 (NCH_2CH_2O), 102.5 (OCHCH), 115.2 (d, J_{CF} = 22.8 Hz, $COC_{ar}C_{ar}HC_{ar}F$), 116.2 (d, J_{CF} = 22.0 Hz, 2 C, $C_{ar}HC_{ar}HC_{ar}FC_{ar}HC_{ar}H$), 117.5 (d, J_{CF} = 20.8 Hz, $COC_{ar}C_{ar}HC_{ar}FC_{ar}H$), 130.3 (d, J_{CF} = 3.38 Hz, $OCHCHC_{ar}$), 132.3 (d, J_{CF} = 7.50 Hz, $OCHCHC_{ar}C_{ar}H$), 133.5 (d, J_{CF} = 9.50 Hz, 2 C, $C_{ar}HC_{ar}HC_{ar}FC_{ar}HC_{ar}H$), 134.1 (d, J_{CF} = 2.75 Hz, $OCHCHC_{ar}C_{ar}COC_{ar}$), 139.3 (d, J_{CF} = 5.75 Hz, $OCHCHC_{ar}C_{ar}CO$), 147.3 (OCHCH), 160.6 (d, J_{CF} = 246 Hz, $COC_{ar}C_{ar}HC_{ar}F$), 166.5 (d, J_{CF} = 254 Hz, $C_{ar}HC_{ar}HC_{ar}FC_{ar}HC_{ar}H$), 175.4 (COOH), 195.8 (ArCOAr) ppm. ^{19}F NMR (470 MHz, CD_2Cl_2): δ −105.1, −116.0 ppm. M ($C_{23}H_{23}F_2NO_4$) 415.44. MS (CI, CH_5^+) *m*/*z* (%): 416 (23, $[M+H]^+$), 201 (16), 156 (33), 142 (100), 123 (24). HRMS (EI+): M^+ calcd for $C_{23}H_{23}F_2NO_4$ 415.1595; found: 415.1595.

4.1.7.3. 1-(2-{(*Z*)-2-[4-Fluoro-2-(3-fluorobenzoyl)phenyl]vinyloxy}ethyl)nipecotic acid ((*Z*)-7b). According to **GP6** with (*Z*)-**22b** (33.3 mg, 0.075 mmol) and 12 M NaOH (0.060 mL, 0.750 mmol) in abs EtOH (0.500 mL). The reaction time was 1.5 h.

Compound **(*Z*)-7b**: 27.8 mg (89%). Colorless oil. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 1.59–1.70 (m, 2H, $NCH_2CH_{2,ax}CH_{2,ax}$), 1.72–1.84 (m, 1H, $NCH_2CH_{2,eq}CH_2$), 1.84–1.93 (m, 1H, $NCH_2CH_2CH_{2,eq}$), 2.31–2.43 (m, 1H, $NCH_{2,ax}CH_2CH_2$), 2.48–2.58 (m, 1H, $NCH_{2,ax}CH$), 2.60–2.67 (m, 1H, NCH_2CH), 2.70–2.83 (m, 2H, NCH_2CH_2O), 2.84–2.96 (m, 1H, $NCH_{2,eq}CH_2CH_2$), 2.96–3.08 (m, 1H, $NCH_{2,eq}CH$), 4.00 (t, *J* = 5.3 Hz, 2H, NCH_2CH_2O), 5,20 (d, *J* = 7.0 Hz, 1H, OCHCH), 6.13 (d, *J* = 7.0 Hz, 1H, OCHCH), 6.99 (dd, *J* = 8.8/2.8 Hz, 1H, $OCHCHCCH_{ar}CH_{ar}CFCH_{ar}$), 7.20 (td, *J* = 8.5/3.0 Hz, 1H, $OCHCHCCH_{ar}CH_{ar}$), 7.31 (tdd, *J* = 8.3/2.8/1.1 Hz, 1H, $CH_{ar}CFCH_{ar}CH_{ar}CH_{ar}$), 7.45 (td, *J* = 8.0/5.5 Hz, 1H, $CH_{ar}CFCH_{ar}CH_{ar}CH_{ar}$), 7.51 (ddd, *J* = 9.5/2.5/1.5 Hz, 1H, $CH_{ar}CFCH_{ar}CH_{ar}CH_{ar}$), 7.55 (dt, *J* = 8.0/1.4 Hz, 1H, $CH_{ar}CFCH_{ar}CH_{ar}CH_{ar}$), 8.05 (dd, *J* = 8.8/5.8 Hz, 1H, $OCHCHCCH_{ar}$) ppm. ^{13}C NMR (125 MHz, CD_2Cl_2): δ 22.74 ($NCH_2CH_2CH_2$), 26.68 ($NCH_2CH_2CH_2$), 40.93 (NCH_2CH), 53.74 ($NCH_2CH_2CH_2$), 55.76 (NCH_2CH), 57.15 (NCH_2CH_2O), 70.32 (NCH_2CH_2O), 102.3 (OCHCH), 115.2 (d, J_{CF} = 22.9 Hz, $OCHCHC_{ar}C_{ar}HC_{ar}HC_{ar}FC_{ar}H$), 116.8 (d, J_{CF} = 22.3 Hz, $C_{ar}HC_{ar}FC_{ar}HC_{ar}HC_{ar}H$), 117.7 (d, J_{CF} = 20.9 Hz, $OCHCHC_{ar}C_{ar}HC_{ar}H$), 120.8 (d, J_{CF} = 21.5 Hz, $C_{ar}HC_{ar}FC_{ar}HC_{ar}HC_{ar}H$), 126.7 (d, J_{CF} = 2.88 Hz, $C_{ar}HC_{ar}FC_{ar}HC_{ar}HC_{ar}H$), 130.4 (d, J_{CF} = 3.50 Hz, $OCHCHC_{ar}$), 130.7 (d, J_{CF} = 7.63 Hz, $C_{ar}HC_{ar}FC_{ar}HC_{ar}HC_{ar}H$), 132.2 (d, J_{CF} = 7.38 Hz, $OCHCHC_{ar}C_{ar}H$), 138.7 (d, J_{CF} = 5.88 Hz, $OCHCHC_{ar}C_{ar}CO$), 139.6 (d, J_{CF} = 6.25 Hz, $OCHCHC_{ar}C_{ar}COC_{ar}$), 147.3 (OCHCH), 160.4 (d, J_{CF} = 246 Hz, $OCHCHC_{ar}C_{ar}HC_{ar}HC_{ar}F$), 163.1 (d, J_{CF} = 246 Hz, $C_{ar}HC_{ar}FC_{ar}HC_{ar}HC_{ar}H$), 176.6 (COOH), 195.8 (ArCOAr) ppm. ^{19}F NMR (470 MHz, CD_2Cl_2): δ −112.6, −116.0 ppm. M ($C_{23}H_{23}F_2NO_4$) 415.44. MS (CI, CH_5^+) *m*/*z* (%): 416 (100, $[M+H]^+$), 261 (22), 247 (23), 174 (69), 156 (85), 142 (61), 130 (29). HRMS (EI+): M^+ calcd for $C_{23}H_{23}F_2NO_4$ 415.1595; found: 415.1583.

4.1.7.4. 1-(2-{(*Z*)-2-[4-Fluoro-2-(2-fluorobenzoyl)phenyl]vinyloxy}ethyl)nipecotic acid ((*Z*)-7c). According to **GP6** with (*Z*)-**22c** (29.3 mg, 0.066 mmol) and 12 M NaOH (0.060 mL, 0.660 mmol) in EtOH (0.500 mL). The reaction time was 1 h.

Compound **(*Z*)-7c**: 23.4 mg (85%). Colorless oil. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 1.58–1.71 (m, 2H, $NCH_2CH_{2,ax}CH_{2,ax}$), 1.74–1.85 (m, 1H, $NCH_2CH_{2,eq}CH_2$), 1.85–1.95 (m, 1H, $NCH_2CH_2CH_{2,eq}$), 2.32–2.45 (m, 1H, $NCH_{2,ax}CH_2CH_2$), 2.47–2.59 (m, 1H, $NCH_{2,ax}CH$), 2.62–2.68 (m, 1H, NCH_2CH), 2.74–2.88 (m, 2H, NCH_2CH_2O), 2.89–3.00 (m, 1H, $NCH_{2,eq}CH_2CH_2$), 3.01–3.13 (m, 1H, $NCH_{2,eq}CH$), 4.04 (t, *J* = 5.3 Hz, 2H, NCH_2CH_2O), 5.48 (d, *J* = 7.5 Hz, 1H, OCHCH), 6.14 (d, *J* = 7.5 Hz, 1H, OCHCH), 7.04 (dd, *J* = 9.0/3.0 Hz, 1H, $COCCH_{ar}CF$), 7.13 (ddd, *J* = 10.6/8.4/1.1 Hz, 1H, $CH_{ar}CH_{ar}CH_{ar}CH_{ar}CF$), 7.19 (td, *J* = 8.5/2.8 Hz, 1H, $OCHCHCCH_{ar}CH_{ar}$), 7.26 (td, *J* = 7.8/1.2 Hz, 1H, $CH_{ar}CH_{ar}CH_{ar}CH_{ar}CF$), 7.57 (dddd, *J* = 8.4/7.3/5.3/1.9 Hz, 1H, $CH_{ar}CH_{ar}CH_{ar}CH_{ar}CF$), 7.63 (td, *J* = 7.5/1.5 Hz, 1H, $CH_{ar}CH_{ar}CH_{ar}CH_{ar}CF$), 8.02 (dd, *J* = 8.8/5.8 Hz, 1H, $OCHCHCCH_{ar}$) ppm. ^{13}C NMR (125 MHz, CD_2Cl_2): δ 22.62 ($NCH_2CH_2CH_2$), 26.60 ($NCH_2CH_2CH_2$), 40.77 (NCH_2CH), 53.71 ($NCH_2CH_2CH_2$), 55.68 (NCH_2CH), 57.12 (NCH_2CH_2O), 70.27 (NCH_2CH_2O), 102.4 (OCHCH), 115.8 (d, J_{CF} = 22.8 Hz, $COC_{ar}C_{ar}HC_{ar}F$), 117.0 (d, J_{CF} = 21.9 Hz, $C_{ar}HC_{ar}HC_{ar}HC_{ar}HC_{ar}F$), 118.2 (d, J_{CF} = 21.0 Hz, $OCHCHC_{ar}C_{ar}HC_{ar}H$), 124.8 (d, J_{CF} = 3.63 Hz, $C_{ar}HC_{ar}HC_{ar}HC_{ar}HC_{ar}F$), 127.2 (d, J_{CF} = 11.1 Hz, $COC_{ar}C_{ar}F$), 130.6 (d, J_{CF} = 3.38 Hz, $OCHCHC_{ar}$), 132.1 (d, J_{CF} = 1.75 Hz, $C_{ar}HC_{ar}HC_{ar}HC_{ar}HC_{ar}F$), 132.4 (d, J_{CF} = 7.25 Hz, $OCHCHC_{ar}C_{ar}H$), 135.1 (d, J_{CF} = 8.75 Hz, $C_{ar}HC_{ar}HC_{ar}HC_{ar}HC_{ar}F$), 139.6 (d, J_{CF} = 6.13 Hz, $OCHCHC_{ar}C_{ar}CO$), 147.2 (OCHCH), 160.5 (d, J_{CF} = 245 Hz, $COC_{ar}C_{ar}HC_{ar}F$), 161.6 (d, J_{CF} = 255 Hz, $C_{ar}HC_{ar}HC_{ar}HC_{ar}HC_{ar}F$), 176.3 (COOH), 194.0 (ArCOAr) ppm. ^{19}F NMR (470 MHz, CD_2Cl_2): δ −111.0, −116.2 ppm. M ($C_{23}H_{23}F_2NO_4$) 415.44. MS (CI, CH_5^+) *m*/*z* (%): 416 (100, $[M+H]^+$), 261 (16), 247 (14), 174 (27), 156 (75), 142 (31), 130 (12). HRMS (EI+): M^+ calcd for $C_{23}H_{23}F_2NO_4$ 415.1595; found: 415.1582.

4.1.7.5. 1-(2-{(*Z*)-2-[4-Fluoro-2-(4-fluorobenzyl)phenyl]vinyloxy}ethyl)nipecotic acid ((*Z*)-8a). According to **GP6** with (*Z*)-**23a** (32.2 mg, 0.075 mmol) and 12 M NaOH (0.060 mL, 0.700 mmol) in abs EtOH (0.500 mL). The reaction time was 4 h.

Compound **(*Z*)-8a**: 33.4 mg (99%). Colorless oil. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 1.49–1.62 (m, 2H, $NCH_2CH_{2,ax}CH_{2,ax}$), 1.64–1.76 (m, 1H, $NCH_2CH_{2,eq}CH_2$), 1.77–1.86 (m, 1H, $NCH_2CH_2CH_{2,eq}$), 2.23–2.36 (m, 1H, $NCH_{2,ax}CH_2CH_2$), 2.38–2.48 (m, 1H, $NCH_{2,ax}CH$), 2.54–2.59 (m, 1H, NCH_2CH), 2.68–2.79 (m, 2H, NCH_2CH_2O), 2.81–2.93 (m, 1H, $NCH_{2,eq}CH_2CH_2$), 2.94–3.05 (m, 1H, $NCH_{2,eq}CH$), 3.88 (s, 2H, $ArCH_2Ar$), 3.96 (t, *J* = 5.3 Hz, 2H, NCH_2CH_2O), 5.22 (d, *J* = 7.5 Hz, 1H, OCHCH), 6.10 (d, *J* = 7.5 Hz, 1H, OCHCH), 6.70 (dd, *J* = 10.0/3.0 Hz, 1H, $CH_2CCH_{ar}CF$), 6.84 (td, *J* = 8.6/2.8 Hz, 1H, $OCHCHCCH_{ar}CH_{ar}$), 6.89 (t, *J* = 8.8 Hz, 2H, $CH_{ar}CH_{ar}CFCH_{ar}CH_{ar}$), 7.01 (dd, *J* = 8.5/5.5 Hz, 2H, $CH_{ar}CH_{ar}CFCH_{ar}CH_{ar}$), 7.81 (dd, *J* = 8.5/6.0 Hz, 1H, $OCHCHCCH_{ar}$) ppm. ^{13}C NMR (125 MHz, CD_2Cl_2): δ 22.74 ($NCH_2CH_2CH_2$), 26.73 ($NCH_2CH_2CH_2$), 38.91 ($ArCH_2Ar$), 40.91 (NCH_2CH), 53.90 ($NCH_2CH_2CH_2$), 55.82 (NCH_2CH), 57.33 (NCH_2CH_2O), 70.29 (NCH_2CH_2O), 102.7 (OCHCH), 113.6 (d, J_{CF} = 20.6 Hz, $OCHCHC_{ar}C_{ar}HC_{ar}H$), 115.7 (d, J_{CF} = 21.1 Hz, 2 C, $C_{ar}HC_{ar}HC_{ar}FC_{ar}HC_{ar}H$), 116.9 (d, J_{CF} = 21.4 Hz, $CH_2C_{ar}C_{ar}HC_{ar}F$), 130.5 (d,

J_{CF} = 3.00 Hz, OCHCHC$_{ar}$), 130.7 (d, J_{CF} = 7.88 Hz, 2 C, C$_{ar}$HC$_{ar}$HC$_{ar}$F-C$_{ar}$HC$_{ar}$H), 131.9 (d, J_{CF} = 7.75 Hz, OCHCHC$_{ar}$C$_{ar}$H), 136.4 (d, J_{CF} = 3.13 Hz, CH$_2$C$_{ar}$C$_{ar}$HC$_{ar}$HC$_{ar}$F), 140.3 (d, J_{CF} = 7.00 Hz, OCHCHC$_{ar}$C$_{ar}$CH$_2$), 146.5 (OCHCH), 161.5 (d, J_{CF} = 243 Hz, CH$_2$C$_{ar}$C$_{ar}$H-C$_{ar}$F), 161.9 (d, J_{CF} = 242 Hz, C$_{ar}$HC$_{ar}$HC$_{ar}$FC$_{ar}$HC$_{ar}$H), 176.5 (COOH) ppm. ^{19}F NMR (470 MHz, CD_2Cl_2): δ −112.2, −113.5 ppm. M ($C_{23}H_{25}F_2NO_3$) 401.46. MS (CI, CH_5^+) m/z (%): 402 (100, $[M+H]^+$), 156 (58), 142 (53). HRMS (EI+): M^+ calcd for $C_{23}H_{25}F_2NO_3$ 401.1803; found: 401.1806.

4.1.7.6. 1-(2-{(*Z*)-2-[4-Fluoro-2-(2-fluorobenzyl)phenyl]vinyloxy}ethyl)nipecotic acid ((*Z*)-8c). According to **GP6** with (*Z*)-**23c** (29.0 mg, 0.070 mmol) and 12 M NaOH (0.060 mL, 0.720 mmol) in EtOH (0.500 mL). The reaction time was 2 h.

Compound **(*Z*)-8c**: 24.8 mg (88%). Colorless oil. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 1.49–1.63 (m, 2H, NCH$_2$CH$_{2,ax}$CH$_{2,ax}$), 1.66–1.78 (m, 1H, NCH$_2$CH$_{2,eq}$CH$_2$), 1.79–1.88 (m, 1H, NCH$_2$CH$_2$CH$_{2,eq}$), 2.24–2.34 (m, 1H, NCH$_{2,ax}$CH$_2$CH$_2$), 2.36–2.48 (m, 1H, NCH$_{2,ax}$CH), 2.54–2.60 (m, 1H, NCH$_2$CH), 2.68–2.81 (m, 2H, NCH$_2$CH$_2$O), 2.84–2.96 (m, 1H, NCH$_{2,eq}$CH$_2$CH$_2$), 2.98–3.09 (m, 1H, NCH$_{2,eq}$CH), 3.92 (s, 2H, ArCH$_2$Ar), 3.97 (t, J = 5.3 Hz, 2H, NCH$_2$CH$_2$O), 5.26 (d, J = 7.0 Hz, 1H, OCHCH), 6.13 (d, J = 7.5 Hz, 1H, OCHCH), 6.68 (dd, J = 9.8/2.8 Hz, 1H, CH$_2$CCH$_{ar}$CF), 6.85 (td, J = 8.5/3.0 Hz, 1H, OCHCHCCH$_{ar}$CH$_{ar}$), 6.91 (td, J = 7.8/2.0 Hz, 1H, CH$_{ar}$CH$_{ar}$CH$_{ar}$CH$_{ar}$CF), 6.97 (td, J = 7.4/1.2 Hz, 1H, CH$_{ar}$CH$_{ar}$CH$_{ar}$CH$_{ar}$CF), 6.98 (ddd, J = 9.9/8.4/1.4 Hz, 1H, CH$_{ar}$CH$_{ar}$CH$_{ar}$CH$_{ar}$CF), 7.11–7.17 (m, 1H, CH$_{ar}$CH$_{ar}$CH$_{ar}$CH$_{ar}$CF), 7.80 (dd, J = 8.8/6.3 Hz, 1H, OCHCHCCH$_{ar}$) ppm. ^{13}C NMR (125 MHz, CD_2Cl_2): δ 22.67 (NCH$_2$CH$_2$CH$_2$), 26.73 (NCH$_2$CH$_2$CH$_2$), 32.48 (dd, J_{CF} = 3.5/1.5 Hz, ArCH$_2$Ar), 40.86 (NCH$_2$CH), 53.89 (NCH$_2$CH$_2$CH$_2$), 55.80 (NCH$_2$CH), 57.19 (NCH$_2$CH$_2$O), 70.29 (NCH$_2$CH$_2$O), 102.7 (OCHCH), 113.6 (d, J_{CF} = 20.6 Hz, OCHCHC$_{ar}$C$_{ar}$HC$_{ar}$H), 115.6 (d, J_{CF} = 21.9 Hz, C$_{ar}$HC$_{ar}$H-C$_{ar}$HC$_{ar}$HC$_{ar}$F), 116.7 (d, J_{CF} = 21.6 Hz, CH$_2$C$_{ar}$C$_{ar}$HC$_{ar}$F), 124.7 (d, J_{CF} = 3.63 Hz, C$_{ar}$HC$_{ar}$HC$_{ar}$HC$_{ar}$HC$_{ar}$F), 127.3 (d, J_{CF} = 15.6 Hz, CH$_2$C$_{ar}$-C$_{ar}$F), 128.6 (d, J_{CF} = 7.88 Hz, C$_{ar}$HC$_{ar}$HC$_{ar}$HC$_{ar}$HC$_{ar}$F), 130.6 (d, J_{CF} = 3.13 Hz, OCHCHC$_{ar}$), 131.3 (d, J_{CF} = 4.38 Hz, C$_{ar}$HC$_{ar}$HC$_{ar}$HC$_{ar}$H-C$_{ar}$F), 131.8 (d, J_{CF} = 7.75 Hz, OCHCHC$_{ar}$C$_{ar}$H), 139.1 (d, J_{CF} = 6.63 Hz, OCHCHC$_{ar}$C$_{ar}$CH$_2$), 146.5 (d, J_{CF} = 1.75 Hz, OCHCH), 161.4 (d, J_{CF} = 243 Hz, CH$_2$C$_{ar}$C$_{ar}$HC$_{ar}$F), 161.6 (d, J_{CF} = 243 Hz, C$_{ar}$HC$_{ar}$HC$_{ar}$H-C$_{ar}$HC$_{ar}$F), 176.5 (COOH) ppm. ^{19}F NMR (470 MHz, CD_2Cl_2): δ −116.5, −118.1 ppm. M ($C_{23}H_{25}F_2NO_3$) 401.46. MS (CI, CH_5^+) m/z (%): 402 (41, $[M+H]^+$), 249 (15), 170 (15), 156 (100), 142 (62). HRMS (EI+): M^+ calcd for $C_{23}H_{25}F_2NO_3$ 401.1803; found: 401.1799.

4.1.7.7. 1-(2-{(*Z*)-2-[5-Fluoro-2-(4-fluorobenzyl)phenyl]vinyloxy}ethyl)nipecotic acid ((*Z*)-8d). According to **GP6** with (*Z*)-**23d** (70.9 mg, 0.165 mmol) and 12 M NaOH (0.140 mL, 1.65 mmol) in EtOH (1.00 mL). The reaction time was 6.5 h.

Compound **(*Z*)-8d**: 60.7 mg (92%). Colorless oil. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.58–1.73 (m, 2H, NCH$_2$CH$_{2,ax}$CH$_{2,ax}$), 1.74–1.87 (m, 1H, NCH$_2$CH$_{2,eq}$CH$_2$), 1.87–1.97 (m, 1H, NCH$_2$CH$_2$CH$_{2,eq}$), 2.34–2.47 (m, 1H, NCH$_{2,ax}$CH$_2$CH$_2$), 2.48–2.59 (m, 1H, NCH$_{2,ax}$CH), 2.62–2.71 (m, 1H, NCH$_2$CH), 2.86 (t, J = 5.6 Hz, 2H, NCH$_2$CH$_2$O), 2.95–3.06 (m, 1H, NCH$_{2,eq}$CH$_2$CH$_2$), 3.06–3.17 (m, 1H, NCH$_{2,eq}$CH), 3.96 (s, 2H, ArCH$_2$Ar), 4.08 (t, J = 5.2 Hz, 2H, NCH$_2$CH$_2$O), 5.31 (dd, J = 7.6/1.6 Hz, 1H, OCHCH), 6.23 (d, J = 7.6 Hz, 1H, OCHCH), 6.84 (td, J = 8.2/2.9 Hz, 1H, OCHCHCCH$_{ar}$CFCH$_{ar}$), 6.96 (t, J = 8.6 Hz, 2H, CH$_{ar}$CH$_{ar}$CFCH$_{ar}$CH$_{ar}$), 7.06 (dd, J = 8.6/5.8 Hz, 2H, CH$_{ar}$CH$_{ar}$CF-CH$_{ar}$CH$_{ar}$), 7.07 (dd, J = 8.6/6.2 Hz, 1H, OCHCHCCH$_{ar}$CFCH$_{ar}$CH$_{ar}$), 7.69 (dd, J = 11.2/2.8 Hz, 1H, OCHCHCCH$_{ar}$) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2): δ 22.53 (NCH$_2$CH$_2$CH$_2$), 26.54 (NCH$_2$CH$_2$CH$_2$), 38.19 (ArCH$_2$Ar), 40.69 (NCH$_2$CH), 53.88 (NCH$_2$CH$_2$CH$_2$), 55.60 (NCH$_2$CH), 57.16 (NCH$_2$CH$_2$O), 70.53 (NCH$_2$CH$_2$O), 102.6 (d, J_{CF} = 2.30 Hz, OCHCH), 113.2 (d, J_{CF} = 21.3 Hz, OCHCHC$_{ar}$C$_{ar}$HC$_{ar}$FC$_{ar}$H), 115.4 (d, J_{CF} = 21.1 Hz, 2 C, C$_{ar}$HC$_{ar}$HC$_{ar}$FC$_{ar}$H-C$_{ar}$H), 22.7 (d, J_{CF} = 116.3 Hz, OCHCHC$_{ar}$C$_{ar}$H), 130.3 (d, J_{CF} = 7.80 Hz, 2 C, C$_{ar}$HC$_{ar}$HC$_{ar}$FC$_{ar}$HC$_{ar}$H), 131.8 (d, J_{CF} = 8.30 Hz, OCHCHC$_{ar}$C$_{ar}$HC$_{ar}$FC$_{ar}$HC$_{ar}$H), 133.3 (d, J_{CF} = 2.90 Hz, OCHCHC$_{ar}$C$_{ar}$CH$_2$), 136.1 (d, J_{CF} = 8.70 Hz, OCHCHC$_{ar}$), 136.9 (d, J_{CF} = 2.90 Hz, OCHCHC$_{ar}$C$_{ar}$CH$_2$C$_{ar}$), 147.6 (OCHCH), 161.7 (d, J_{CF} = 242 Hz, C$_{ar}$HC$_{ar}$HC$_{ar}$FC$_{ar}$HC$_{ar}$H), 161.8 (d, J_{CF} = 241 Hz, OCHCHC$_{ar}$C$_{ar}$HC$_{ar}$F), 176.3 (COOH) ppm. ^{19}F NMR (470 MHz, CD_2Cl_2): δ 117.2, −118.1 ppm. M ($C_{23}H_{25}F_2NO_3$) 401.46. MS (CI, CH_5^+) m/z (%): 402 (100, $[M+H]^+$), 174 (53), 156 (42), 142 (47). HRMS (EI+): M^+ calcd for $C_{23}H_{25}F_2NO_3$ 401.1803; found: 401.1803.

4.1.7.8. 1-(2-{(*Z*)-2-[5-Fluoro-2-(3-fluorobenzyl)phenyl]vinyloxy}ethyl)nipecotic acid ((*Z*)-8e). According to **GP6** with (*Z*)-**23e** (13.0 mg, 0.030 mmol) and 12 M NaOH (0.030 mL, 0.300 mmol) in EtOH (0.500 mL). The reaction time was 1.5 h.

Compound **(*Z*)-8e**: 10.5 mg (87%). Colorless oil. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 1.56–1.71 (m, 2H, NCH$_2$CH$_{2,ax}$CH$_{2,ax}$), 1.75–1.86 (m, 1H, NCH$_2$CH$_{2,eq}$CH$_2$), 1.89–1.97 (m, 1H, NCH$_2$CH$_2$CH$_{2,eq}$), 2.32–2.41 (m, 1H, NCH$_{2,ax}$CH$_2$CH$_2$), 2.45–2.52 (m, 1H, NCH$_{2,ax}$CH), 2.62–2.68 (m, 1H, NCH$_2$CH), 2.81–2.86 (m, 2H, NCH$_2$CH$_2$O), 2.97–3.06 (m, 1H, NCH$_{2,eq}$CH$_2$CH$_2$), 3.07–3.16 (m, 1H, NCH$_{2,eq}$CH), 3.99 (s, 2H, ArCH$_2$Ar), 4.02–4.12 (m, 2H, NCH$_2$CH$_2$O), 5.30 (dd, J = 7.3/1.3 Hz, 1H, OCHCH), 6.23 (d, J = 7.0 Hz, 1H, OCHCH), 6.76–6.80 (m, 1H, CH$_{ar}$CFCH$_{ar}$CH$_{ar}$CH$_{ar}$), 6.85 (td, J = 8.3/2.8 Hz, 1H, OCHCHCCH$_{ar}$CFCH$_{ar}$), 6.88 (td, J = 8.3/3.0 Hz, 1H, CH$_{ar}$CFCH$_{ar}$CH$_{ar}$CH$_{ar}$), 6.90–6.93 (m, 1H, CH$_{ar}$CFCH$_{ar}$CH$_{ar}$CH$_{ar}$), 7.09 (dd, J = 8.3/6.3 Hz, 1H, OCHCHCCH$_{ar}$CFCH$_{ar}$CH$_{ar}$), 7.24 (td, J = 8.0/6.0 Hz, 1H, CH$_{ar}$CF-CH$_{ar}$CH$_{ar}$CH$_{ar}$), 7.69 (dd, J = 11.0/3.0 Hz, 1H, OCHCHCCH$_{ar}$) ppm. ^{13}C NMR (125 MHz, CD_2Cl_2): δ 22.53 (NCH$_2$CH$_2$CH$_2$), 26.61 (NCH$_2$CH$_2$CH$_2$), 38.74 (ArCH$_2$Ar), 40.72 (NCH$_2$CH), 53.91 (NCH$_2$CH$_2$CH$_2$), 55.61 (NCH$_2$CH), 57.17 (NCH$_2$CH$_2$O), 70.66 (NCH$_2$CH$_2$O), 102.6 (d, J_{CF} = 2.13 Hz, OCHCH), 113.2 (d, J_{CF} = 21.2 Hz, 2 C, OCHCHC$_{ar}$C$_{ar}$HC$_{ar}$FC$_{ar}$H and C$_{ar}$HC$_{ar}$FC$_{ar}$HC$_{ar}$H-C$_{ar}$H), 115.6 (d, J_{CF} = 21.3 Hz, C$_{ar}$HC$_{ar}$FC$_{ar}$HC$_{ar}$HC$_{ar}$H), 116.4 (d, J_{CF} = 22.8 Hz, OCHCHC$_{ar}$C$_{ar}$H), 124.7 (d, J_{CF} = 2.63 Hz, C$_{ar}$HC$_{ar}$FC$_{ar}$H-C$_{ar}$HC$_{ar}$H), 130.2 (d, J_{CF} = 8.25 Hz, C$_{ar}$HC$_{ar}$FC$_{ar}$HC$_{ar}$HC$_{ar}$H), 131.9 (d, J_{CF} = 8.50 Hz, OCHCHC$_{ar}$C$_{ar}$HC$_{ar}$FC$_{ar}$HC$_{ar}$H), 132.7 (d, J_{CF} = 3.00 Hz, OCHCHC$_{ar}$C$_{ar}$CH$_2$), 136.2 (d, J_{CF} = 8.75 Hz, OCHCHC$_{ar}$), 143.9 (d, J_{CF} = 7.75 Hz, OCHCHC$_{ar}$C$_{ar}$CH$_2$C$_{ar}$), 147.7 (OCHCH), 161.9 (d, J_{CF} = 241 Hz, OCHCHC$_{ar}$C$_{ar}$HC$_{ar}$F), 163.4 (d, J_{CF} = 243 Hz, C$_{ar}$HC$_{ar}$F-C$_{ar}$HC$_{ar}$HC$_{ar}$H), 176.2 (COOH) ppm. ^{19}F NMR (470 MHz, CD_2Cl_2): δ −114.2, −117.0 ppm. M ($C_{23}H_{25}F_2NO_3$) 401.46. MS (CI, CH_5^+) m/z (%): 402 (8, $[M+H]^+$), 145 (13), 127 (12), 109 (11), 85 (81), 83 (100), 79 (25). HRMS (EI+): M^+ calcd for $C_{23}H_{25}F_2NO_3$ 401.1803; found: 401.1802.

4.1.7.9. 1-(2-{(*Z*)-2-[5-Fluoro-2-(2-fluorobenzyl)phenyl]vinyloxy}ethyl)nipecotic acid ((*Z*)-8f). According to **GP6** with (*Z*)-**23f** (36.0 mg, 0.084 mmol) and 12 M NaOH (0.100 mL, 1.20 mmol) in EtOH (0.500 mL). The reaction time was 6.5 h.

Compound **(*Z*)-8f**: 30.0 mg (89%). Colorless oil. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 1.57–1.73 (m, 2H, NCH$_2$CH$_{2,ax}$CH$_{2,ax}$), 1.75–1.86 (m, 1H, NCH$_2$CH$_{2,eq}$CH$_2$), 1.87–1.96 (m, 1H, NCH$_2$CH$_2$CH$_{2,eq}$), 2.37–2.47 (m, 1H, NCH$_{2,ax}$CH$_2$CH$_2$), 2.48–2.58 (m, 1H, NCH$_{2,ax}$CH), 2.64–2.70 (m, 1H, NCH$_2$CH), 2.86 (t, J = 5.3 Hz, 2H, NCH$_2$CH$_2$O), 2.97–3.06 (m, 1H, NCH$_{2,eq}$CH$_2$CH$_2$), 3.07–3.16 (m, 1H, NCH$_{2,eq}$CH), 3.99 (s, 2H, ArCH$_2$Ar), 4.09 (t, J = 5.3 Hz, 2H, NCH$_2$CH$_2$O), 5.35 (dd, J = 7.0/1.0 Hz, 1H, OCHCH), 6.25 (d, J = 7.0 Hz, 1H, OCHCH), 6.83 (td, J = 8.4/2.8 Hz, 1H, CH$_2$CCH$_{ar}$CH$_{ar}$CF), 6.93 (td, J = 7.7/1.8 Hz, 1H, CH$_{ar}$CH$_{ar}$CH$_{ar}$CH$_{ar}$CF), 7.01–7.08 (m, 3H, CH$_2$CCH$_{ar}$CH$_{ar}$CF and CH$_{ar}$CH$_{ar}$CH$_{ar}$CH$_{ar}$CF), 7.17–7.23 (m, 1H, CH$_{ar}$CH$_{ar}$CH$_{ar}$CH$_{ar}$CF), 7.68 (dd, J = 11.3/2.8 Hz, 1H, OCHCHCCH$_{ar}$) ppm. ^{13}C NMR (125 MHz, CD_2Cl_2): δ 22.54 (NCH$_2$CH$_2$CH$_2$), 26.57 (NCH$_2$CH$_2$CH$_2$), 31.67 (d, J_{CF} = 3.38 Hz, ArCH$_2$Ar), 40.71 (NCH$_2$CH), 53.91 (NCH$_2$CH$_2$CH$_2$), 55.60 (NCH$_2$CH), 57.15 (NCH$_2$CH$_2$O), 70.48 (NCH$_2$CH$_2$O), 102.6 (OCHCH), 113.2 (d, J_{CF} = 21.1 Hz, CH$_2$C$_{ar}$C$_{ar}$H-C$_{ar}$HC$_{ar}$F), 115.4 (d, J_{CF} = 21.9 Hz, C$_{ar}$HC$_{ar}$HC$_{ar}$HC$_{ar}$HC$_{ar}$F), 116.3 (d,

J_{CF} = 22.9 Hz, OCHCHC$_{ar}$C$_{ar}$H), 124.5 (d, J_{CF} = 3.50 Hz, C$_{ar}$HC$_{ar}$HC$_{ar}$H-C$_{ar}$HC$_{ar}$F), 127.9 (d, J_{CF} = 15.6 Hz, CH$_2$C$_{ar}$C$_{ar}$F), 128.3 (d, J_{CF} = 8.00 Hz, C$_{ar}$HC$_{ar}$HC$_{ar}$HC$_{ar}$HC$_{ar}$F), 131.0 (d, J_{CF} = 4.38 Hz, C$_{ar}$HC$_{ar}$HC$_{ar}$HC$_{ar}$H-C$_{ar}$F), 131.6 (d, J_{CF} = 8.50 Hz, CH$_2$C$_{ar}$C$_{ar}$HC$_{ar}$HC$_{ar}$F), 132.2 (d, J_{CF} = 3.00 Hz, OCHCHC$_{ar}$C$_{ar}$CH$_2$), 136.2 (d, J_{CF} = 8.63 Hz, OCHCHC$_{ar}$), 147.6 (OCHCH), 161.2 (d, J_{CF} = 243 Hz, CH$_2$C$_{ar}$C$_{ar}$F), 161.8 (d, J_{CF} = 240 Hz, CH$_2$C$_{ar}$C$_{ar}$HC$_{ar}$HC$_{ar}$F), 176.1 (COOH) ppm. ^{19}F NMR (470 MHz, CD_2Cl_2): δ −117.2, −118.2 ppm. M ($C_{23}H_{25}F_2NO_3$) 401.46. MS (ESI+) m/z (%): 402 ([M+H]$^+$), 424 ([M+Na]$^+$). HRMS (EI+): M$^+$ calcd for $C_{23}H_{25}F_2NO_3$ 401.1803; found: 401.1805.

4.1.7.10. 1-(2-{(*Z*)-2-[2-Benzylphenyl]vinyloxy}ethyl) nipecotic acid ((*Z*)-8g). According to **GP6** with (*Z*)-**23g** (32.8 mg, 0.083 mmol) and 12 M NaOH (0.070 mL, 0.830 mmol) in EtOH (0.500 mL). The reaction time was 3 h.

Compound **(*Z*)-8g**: 26.8 mg (88%). Colorless oil. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.55–1.70 (m, 2H, NCH$_2$C*H*$_{2,ax}$C*H*$_{2,ax}$), 1.72–1.86 (m, 1H, NCH$_2$C*H*$_{2,eq}$CH$_2$), 1.86–1.95 (m, 1H, NCH$_2$CH$_2$C*H*$_{2,eq}$), 2.31–2.42 (m, 1H, NC*H*$_{2,ax}$CH$_2$CH$_2$), 2.46–2.56 (m, 1H, NC*H*$_{2,ax}$CH), 2.59–2.65 (m, 1H, NCH$_2$C*H*), 2.75–2.89 (m, 2H, NC*H*$_2$CH$_2$O), 2.90–3.03 (m, 1H, NC*H*$_{2,eq}$CH$_2$CH$_2$), 3.03–3.61 (m, 1H, NC*H*$_{2,eq}$CH), 4.01 (s, 2H, ArCH$_2$Ar), 4.04 (t, J = 5.4 Hz, 2H, NCH$_2$C*H*$_2$O), 5.38 (d, J = 7.2 Hz, 1H, OCHC*H*), 6.18 (d, J = 7.2 Hz, 1H, OC*H*CH), 7.09–7.13 (m, 4H, OCHCHCCH$_{ar}$CH$_{ar}$C*H*$_{ar}$C*H*$_{ar}$ and CH$_2$CC*H*$_{ar}$CH$_{ar}$CH$_{ar}$CH$_{ar}$C*H*-$_{ar}$), 7.14–7.22 (m, 2H, OCHCHCCH$_{ar}$C*H*$_{ar}$ and CH$_2$CCH$_{ar}$CH$_{ar}$C*H*$_{ar}$CH-$_{ar}$CH$_{ar}$), 7.25 (t, J = 7.4 Hz, 2H, CH$_2$CCH$_{ar}$C*H*$_{ar}$CH$_{ar}$C*H*$_{ar}$CH$_{ar}$), 7.90 (d, J = 7.6 Hz, 1H, OCHCHCC*H*$_{ar}$) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2): δ 22.58 (NCH$_2$CH$_2$CH$_2$), 26.57 (NCH$_2$CH$_2$CH$_2$), 39.72 (ArCH$_2$Ar), 40.78 (NCH$_2$CH), 53.73 (NCH$_2$CH$_2$CH$_2$), 55.69 (NCH$_2$CH), 57.18 (NCH$_2$CH$_2$O), 70.71 (NCH$_2$CH$_2$O), 103.7 (OCHCH), 126.3 (OCH-CHC$_{ar}$C$_{ar}$HC$_{ar}$H), 126.6 (CH$_2$C$_{ar}$C$_{ar}$HC$_{ar}$HC$_{ar}$HC$_{ar}$HC$_{ar}$H), 126.7 (OCH-CHC$_{ar}$C$_{ar}$HC$_{ar}$HC$_{ar}$H), 128.7 (2 C, CH$_2$C$_{ar}$C$_{ar}$HC$_{ar}$HC$_{ar}$HC$_{ar}$HC$_{ar}$H), 129.0 (2 C, CH$_2$C$_{ar}$C$_{ar}$HC$_{ar}$HC$_{ar}$HC$_{ar}$HC$_{ar}$H), 130.1 (OCHCHC$_{ar}$C$_{ar}$H), 130.6 (OCHCHC$_{ar}$C$_{ar}$HC$_{ar}$HC$_{ar}$HC$_{ar}$H), 134.3 (OCHCHC$_{ar}$), 137.8 (OCHCHC$_{ar}$C$_{ar}$CH$_2$), 141.4 (OCHCHC$_{ar}$C$_{ar}$CH$_2$C$_{ar}$), 146.5 (OCHCH), 176.5 (COOH) ppm. M ($C_{23}H_{27}NO_3$) 365.48. MS (CI, CH_5^+) m/z (%): 366 (100, [M+H]$^+$), 156 (62), 142 (37). HRMS (EI+): M$^+$ calcd for $C_{23}H_{27}NO_3$ 365.1991; found: 365.1995.

Supplementary data

Supplementary data (experimental data for **14a-d**, **14f–i**, **15a-d**, **15f**, **16a-d**, **16f**, **10a-d**, **10f**, **11a–g**, **11g**, **22b–f**, **23c–g**, (*E*)-**7b**, (*E*)-**7c**, **7d-g**, (*E*)-**8a**, (*E*)-**8c**, (*E*)-**8d**, (*E*)-**8e**, (*E*)-**8f**, (*E*)-**8g**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2013.02.056.

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