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Graphical abstract:

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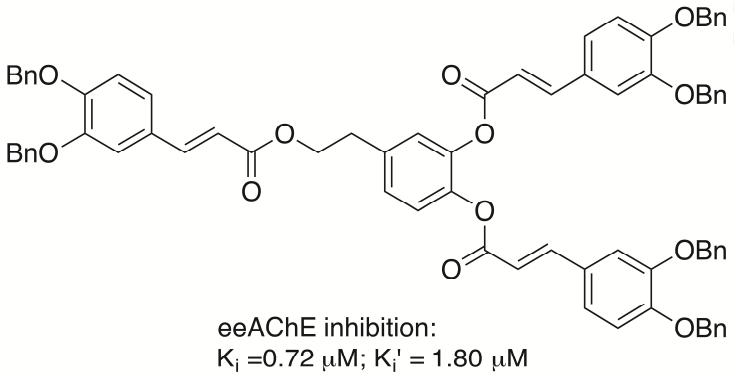


# Caffeic acid phenethyl ester (CAPE)-derivatives act as selective inhibitors of acetylcholinesterase

Josephine M. Gießel, Anne Loesche, Immo Serbian, René Csuk*
Martin-Luther-University Halle-Wittenberg, Organic Chemistry, Kurt-Mothes-Str. 2, D-06120 Halle (Saale), Germany

* Corresponding author: email: rene.csuk@chemie.uni-halle.de; Tel.: +49 345 5525660; Fax.: +49 345 27030

**Keywords:** cinnamic acid phenethyl esters; Caffeic acid phenethyl ester; acetylcholinesterase; butyrylcholinesterase; inhibitors

**Abstract**

Unexpected inhibitory effects against *ee*AChE could be found for a newly synthesized class of caffeic acid phenethyl ester (CAPE) derivatives. Thus, phenethyl-(*E*)-3-(3,5-dimethoxy-4-phenethoxyphenyl)-acrylate ($K_i$ = 1.97 ± 0.38 µM, $K_{i'}$ = 2.44 ± 0.07 µM) and 4-(2-(((*E*)-3-(3,4-bis(benzyloxy)phenyl)acryloyl)oxy)ethyl)-1,2-phenylene (2*E*,2'*E*)-bis(3-(3,4-bis(benzyloxy)phenyl)acrylate) ($K_i$ = 0.72 ± 0.31 µM, $K_{i'}$ = 1.80 ± 0.21 µM) showed very good inhibition of *ee*AChE, while being non cytotoxic for malignant human cancer cells and non-malignant mouse fibroblasts. Also, they are weak inhibitors for BChE (from *equine serum*).

## 1. Introduction

For thousands of years, people have been learning by observing nature, and many modern drugs are derived from secondary natural compounds produced by microorganism, plants or even animals. The latter, however, also often make use of the potential of herbal ingredients. Thus, honey-bees do not only have a sophisticated way to communicate and an elaborate sharing of their tasks, they also hold techniques to protect their beehives against diseases. Thereby, bees seal little holes and gaps around their beehive with propolis. This resin contains many different compounds which protect the beehives from diseases and infections caused by bacteria, fungi and other microorganism.[1] One of these ingredients is caffeic acid phenethyl ester (CAPE, Fig. 1).

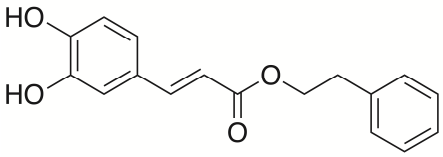


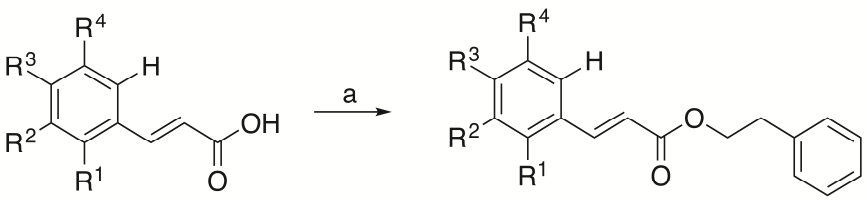

**Fig. 1:** Structure of caffeic acid phenethyl ester (CAPE)

Thus, CAPE is a well-known compound holding a broad range of different biological properties, and this molecule - as well as derivatives thereof - has been studied quite often. Next to inhibitory effects against HIV-1 integrase, cyclooxygenase and lipoxygenase [2], also anti-inflammatory [3], antioxidant and anti-proliferative [4] effects have been shown. Furthermore, there are several studies about the cytotoxic and anticancer effect of CAPE [4-7], and several publications by Lee *et al.* [8, 9] describe for CAPE and derivatives cytotoxic impact. Besides to their cytotoxic activity, Gülçin *et al.* [10] reported CAPE as a picomolar inhibitor of acetylcholinesterase and butyrylcholinesterase. During our ongoing projects, we became interested in the cytotoxic activity of these compounds but also in their ability to inhibit cholinesterases AChE and BChE. Inhibitors of both enzymes are nowadays standard medication for people suffering from neurodegenerative disorders like dementia especially Alzheimer's disease. As a consequence, our products have been tested for their ability to act as inhibitors of AChE (from *electric eel*) and BChE (from *equine serum*) inhibition by Ellman´s and their cytotoxicity by SRB assays.

## 2. Results and discussion

### 2.1 Chemistry

In this project, we investigated the synthesis of CAPE analogues and their biological properties. First of all, esters of 2-phenylethanol with 16 different cinnamic acids were prepared using Mitsunobu reaction [11] conditions. Not unexpectedly, the substitution pattern of the aromatic ring affected the yields of these reactions (Scheme 1, Table 1). Thus, yields were low to moderate for *ortho*- and *meta*-chlorine substituted cinnamic acids, while for cinnamic acids holding electron-donating substituents yields increased.

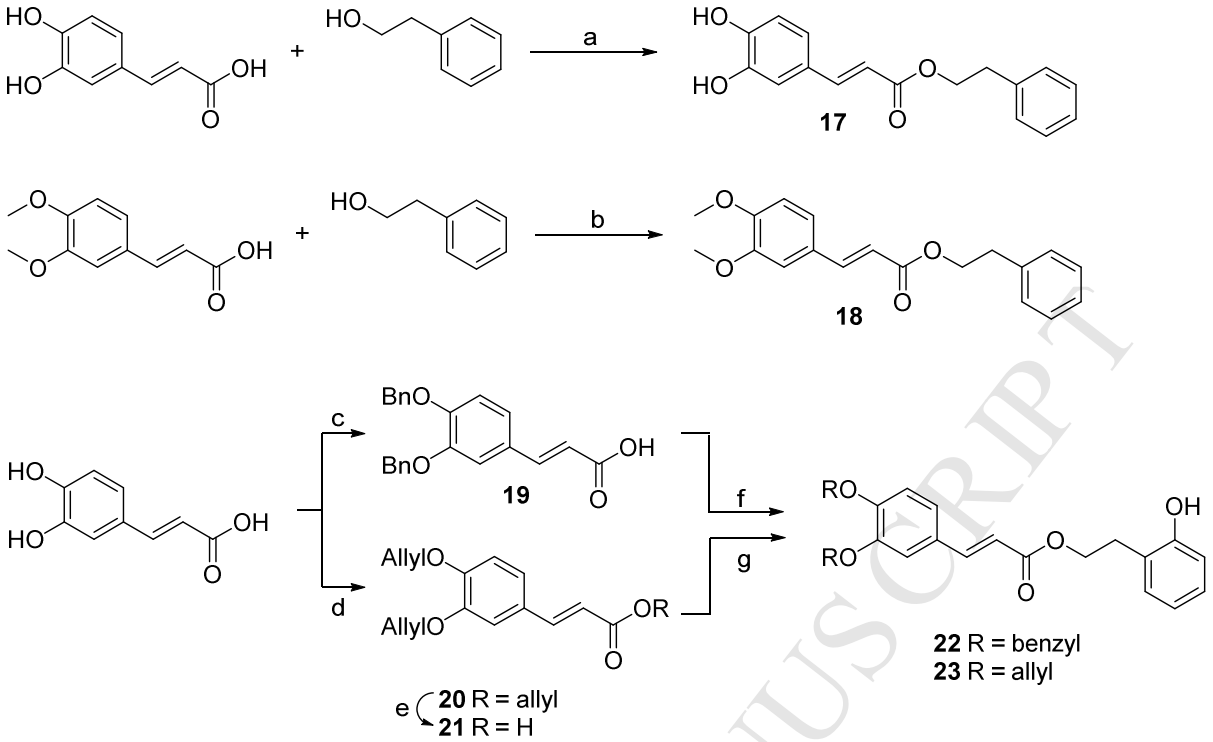


**Scheme 1:** Mitsunobu reaction of cinnamic acid derivatives 1-16: a) corresponding acid, $PPh_3$, THF, 2-phenylethanol, DIAD, 0 °C → rt, overnight, 14 – 99%.

**Table 1:** substitution pattern for compounds **1-16**

| Compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield |
|---|---|---|---|---|---|
| **1** | H | H | H | H | 57 |
| **2** | H | H | F | H | 39 |
| **3** | H | F | H | H | 17 |
| **4** | H | Br | H | H | 34 |
| **5** | Cl | H | H | H | 35 |
| **6** | H | Cl | H | H | 46 |
| **7** | H | H | Cl | H | 73 |
| **8** | H | Me | Me | H | 88 |
| **9** | OMe | H | H | H | 73 |
| **10** | H | OMe | H | H | 88 |
| **11** | H | H | OMe | H | 77 |
| **12** | OMe | H | OMe | H | 39 |
| **13** | H | OMe | H | OMe | 89 |
| **14** | H | OMe | OMe | OMe | 99 |
| **15** | H | OMe | O-$C_2H_4$Ph | OMe | 14 |
| **16** | H | OMe | OAc | H | 31 |

Using standard conditions, **3** and **15** were exceptions to this rule: For the former compound the reaction was very slow while the low yield observed in the reaction of **15** was due to side reactions caused by the *p*-hydroxyl-group. Yields, however, could be improved (67%) for this system by using an excess of 2-phenylethanol. As an alternative, reaction conditions as described by Xie *et al*. [4] were applied (Scheme 2), but yields remained low (9%) for the preparation of **17**.

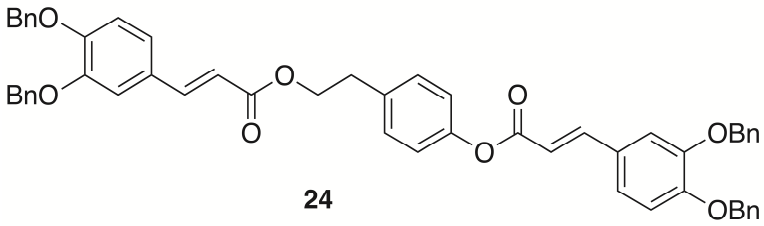



**Scheme 2:** Synthesis of CAPE derivatives **17-23**: a) $Yb(OTF_3)$, $CH_3NO_2$, reflux, 1.5 h, 9%; b) DCC, DMAP, DCM, -20°C → rt, 53%; c) $K_2CO_3$, benzyl chloride, EtOH, reflux, 5 h, 57%; d) $K_2CO_3$, allyl bromide, EtOH, reflux, 5 h, 22%; e) NaOH, EtOH, rt, 51%; f) 2-(*o*-hydroxyphenyl)-ethanol, DCC, DMAP, DCM, -20°C → rt, **22** = 36%; g) 2-(*o*-hydroxyphenyl)-ethanol, DCC, DMAP, DCM, -20°C → rt, **23** = 27%.

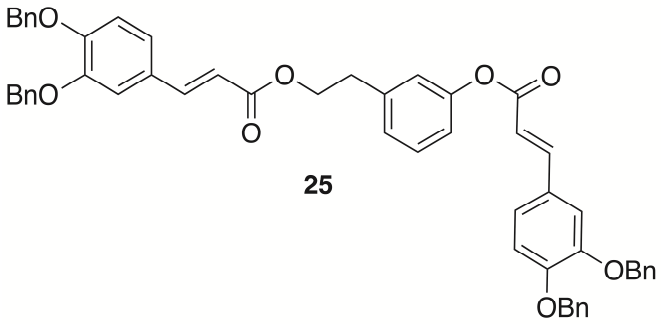
Steglich esterification as described by Eicher *et al.* [12] was used for the synthesis of a 3,4-dimethoxy cinnamic acid derivative, and compound **18** was obtained with a moderate yield of 53%.

Since methoxy groups are not the preferred protective groups for phenols, as their removal often proceeds with low yields, benzyl and allyl protective groups were chosen for the synthesis of several derivatives.

These experiments showed that for benzyl protected caffeic acid higher yields were obtained than for the allyl protected analogues. The possibility to prepare compound **19** in a one-pot-reaction (and the known inhibitory effect of compound **22** for AChE) was decisive to use **19** instead of **21** as a starting material for further derivatizations. As a by-product from these coupling reactions, "dimeric" structures **24-27** were obtained.




**24**

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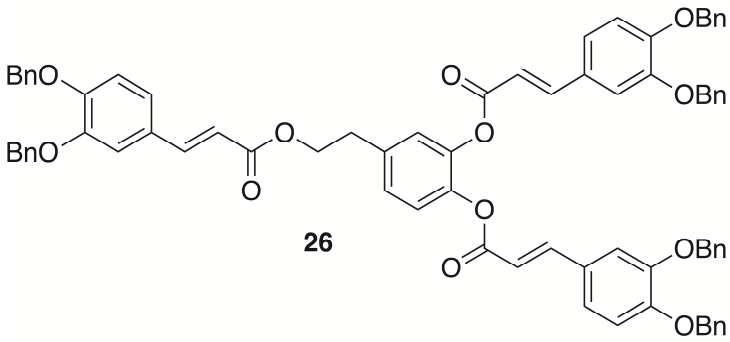
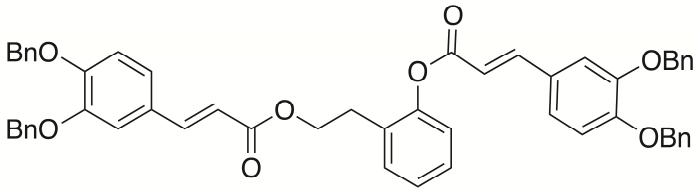



**26**




**27**

**Fig. 2:** "Dimeric" CAPE structures **24**-**27**.

## 2.2 Biological evaluation

### 2.2.1 Inhibition of ChE

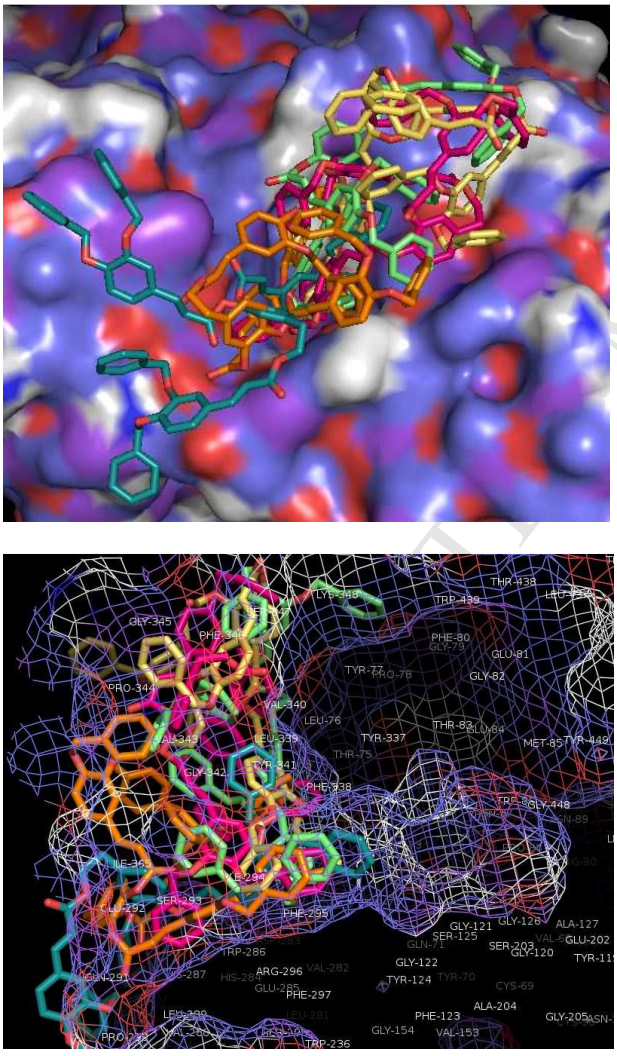
Six compounds were found to be good to excellent inhibitors for *ee*AChE (Tab. 2). They are mixed type inhibitors for this enzyme. Their inhibition constants range from moderate ($K_i$ = 14.21 ± 1.40 µM, $K_{i'}$ = 56.58 ± 7.80) for **6** to very good ($K_i$ = 0.72 ± 0.31 µM, $K_{i'}$ = 1.80 ± 0.21 µM) for compound **26**.

**Table 2:** Ellman's assay; %-inhibition at a concentration of 10 µM of compounds **1-27** (compounds not mentioned in the table were insoluble under the conditions of the assay) with AChE (from *electrophorus electricus*) and BChE (from *equine serum*); the inhibition[11] constants $K_i$ and $K_{i'}$ are given in µM and galantamine hydrobromide (**GH**) was used as a standard; the values are averaged from experiments each performed in triplicate.

| Compound | AChE | | | BChE |
|---|---|---|---|---|
| | Inhibition [%] | $K_i$ [µM] | $K_{i'}$ [µM] | Inhibition [%] |
| **GH** | 87.70 | 0.54 ± 0.01 | -- | 53.00 |
| **1** | 16.21 | | | 18.31 |
| **2** | 13.75 | | | 3.44 |
| **3** | 11.09 | | | 13.59 |
| **4** | 89.89 | 8.82 ± 1.04 | 30.92 ± 2.05 | 14.70 |
| **5** | 19.02 | | | 4.91 |
| **6** | 39.82 | 14.21 ± 1.40 | 56.58 ± 7.80 | 30.77 |
| **7** | 35.30 | | | 7.07 |
| **8** | 14.76 | | | 11.66 |
| **9** | 20.26 | | | 9.27 |
| **10** | 22.16 | | | 5.12 |
| **11** | 16.91 | | | 6.23 |
| **12** | 91.49 | 11.89 ± 0.26 | 34.77 ± 1.92 | 11.90 |
| **13** | 11.32 | | | 7.16 |
| **14** | 9.48 | | | 4.87 |
| **15** | 98.48 | 1.97 ± 0.38 | 2.44 ± 0.07 | 10.71 |
| **16** | 9.59 | | | 8.72 |
| **17** | 35.00 | | | 32.38 |
| **18** | 14.96 | | | 10.13 |
| **19** | 26.64 | | | 11.67 |
| **20** | 23.95 | | | 8.88 |
| **21** | 14.92 | | | 2.80 |
| **22** | 79.01 | 8.55 ± 0.39 | 12.10 ± 0.31 | 23.58 |
| **23** | 9.24 | | | 10.14 |
| **26** | 73.34 | 0.72 ± 0.31 | 1.80 ± 0.21 | 4.11 |

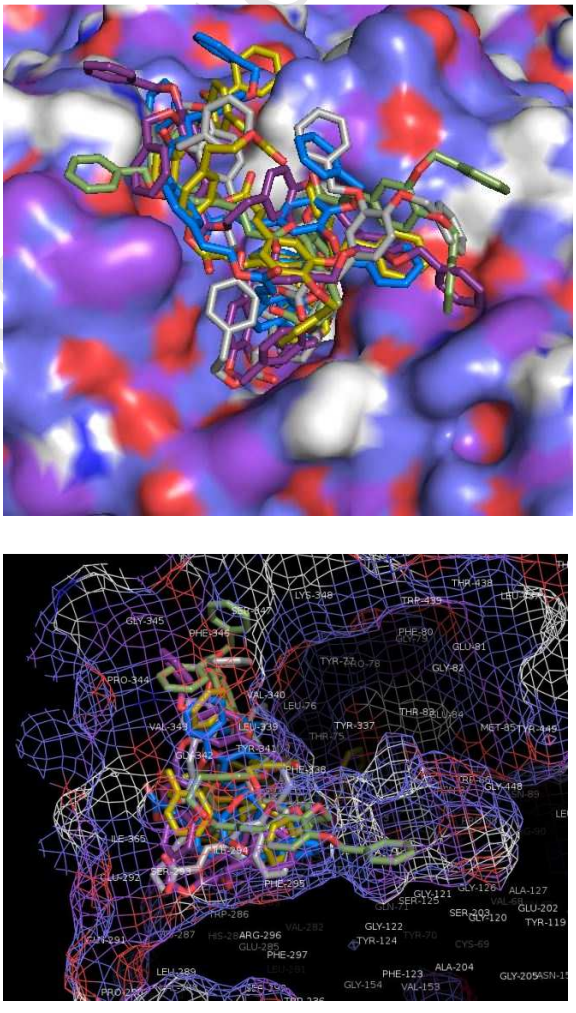
Thus, compound **26** was the best inhibitor of this series of compounds, and with a $K_i$-value of 0.72 ± 0.31 µM, this compound had similar properties on AChE as the gold-standard **GH**. Some molecular modelling calculations were performed to gain some insight in the mode of action of this inhibitor. The results from "blind docking" suggest that compound **26** is blocking the entrance of the active site of AChE. No other possible binding sites were found within 15 GA runs (only top 5 are shown, Fig. 3). To further evaluate these positions, the Grid parameters were changed to give more accurate docking poses for the active site of AChE. The results from these calculations are depicted in Fig. 3.

Blind Docking



**26**_1 yellow; **26**_2 pink; **26**_3 turkis; **26**_4 green; **26**_5 orange

Focused Docking



**26**_1 green; **26**_2 yellow; **26**_3 blue; **26**_4 grey; **26**_5 violett

**Fig. 3.** Results from the molecular modelling calculations (top 5 GA runs shown) revealing that **26** is not able to enter the active site but rather blocks the entrance to it.

### 2.2.2 Cytotoxicity

**Table 3:** Cytotoxicity of compounds **17** and **18**; SRB assay $EC_{50}$ values (in µM) after 96 h of treatment; averaged from three independent experiments performed each in triplicate; confidence interval CI = 95%. Human cancer cell lines: FaDu (hypopharyngeal carcinoma), A2780 (ovarian carcinoma), HT29 (colorectal carcinoma), MCF7 (breast carcinoma), SW1736 (thyroid carcinoma) and non-malignant mouse fibroblasts (NIH 3T3).

| $EC_{50}$[µM] | FaDu | A2780 | HT29 | MCF7 | SW1736 | NIH 3T3 |
|---|---|---|---|---|---|---|
| **17** | 12.1 ± 1.5 | 3.5 ± 0.6 | > 30 | 12.1 ± 1.7 | 4.7 ± 0.3 | 21.4 ± 4.2 |
| **18** | 17.2 ± 2.4 | 17.0 ± 0.3 | 16.7 ± 4.9 | 16.2 ± 4.0 | 16.7 ± 3.7 | 17.7 ± 1.5 |

All compounds were screened for their cytotoxic activity, but only compounds **17** and **18** were cytotoxic for five tested malignant and one non-malignant cell line (NIH 3T3).

## 3. Conclusion

In this study, a small library of 27 derivatives of CAPE was synthesized, and the compounds were tested for their biochemical properties. Furthermore, 4 unexpected “dimeric structures” were found and characterized. Due to the insolubility of these molecules, only **26** coiuld be tested in Ellman´s assay and showed very good mixed type inhibitory effects for AChE, holding $K_i$ = 0.72 ± 0.31 µM and $K_{i'}$ = 1.80 ± 0.21 µM, while being non-cytotoxic for all tested cell lines. Because of the molecule size we supposed that **26** did not fit into the active site of the enzyme, and its mode of action may be to block the entrance to the active side. Out of the synthesized CAPE derivatives, five substances were shown to be good to excellent and selective mixed type inhibitors for the enzyme acetylcholinesterase. We assume that the presence of two benzylic or two 2-phenylethanol groups in these molecules might be the reason for an increased inhibitory effect for AChE, hence paralleling previous results reported by Takao *et al.* [13] All derivatives holding unprotected hydroxyl groups, however, were no inhibitors for cholinesterases. Furthermore, the presence of halogen substituents at the cinnamic moiety did not significantly affect the biological activity of these compounds. These promising results call for further investigations that are presently carried out in our laboratories.

## 4. Experimental part

### 4.1 General

The reagents were bought from commercial suppliers and used without further purification. The solvents were dried according to usual procedures. Melting points were determined on Büchi Melting Point M-565 or LEICA hot stage microscope and are uncorrected, NMR spectra were recorded on a Varian spectrometer Unity 500 ($\delta$ given in ppm, *J* in Hz), mass spectra were obtained on a Finnigan MAT LCQ 7000 (electrospray, voltage 4.1 kV, sheath gas nitrogen) instrument. The optical rotations were measured on a Perkin-Elmer polarimeter at 20 °C. Macherey-Nagel ALUGRAM® Xtra SIL G/$UV_{254}$ pre-coated silica gel 60 F254 plates were used for thin layer chromatography (detection with cerium molybdate spray reagent and UV absorption). IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer Spectrum 1000, and wave numbers are expressed in $cm^{-1}$. The absorption spectra were measured on Perkin Elmer Lambda14 spectrometer. Microanalyses were performed with a Foss-Heraeus Vario EL (CHNS) instrument. The screening assays were performed as previously described. [14-16] Blind Docking was performed on eeAChE (PDB = 1C2O). Grid Center: 35.180, 72.374, -87.078, Grid Points 126,126,126 with spacing of 0.45 Angstroms. Docking parameters are from Autodock 4.2 with GA parameters are: population size = 250; number of evaluations = 25000000; number of generations 27000; GA runs = 15.

Focused Docking was performed on eeAChE (PDB = 1C2O). Grid Center: 35.184, 72.374, -87.072, Grid Points 126,126,126 with spacing of 0.25 Angstroms. Docking parameters are the same as described for the blind docking.

### 4.2 Syntheses

#### 4.2.1 General procedure A

Under Argon atmosphere and at 0 °C, the appropriate carboxylic acid (1 eq.) and triphenylphosphane (1.1 eq.) were dissolved in dry THF (10 mL). 2-Phenylethanol (1 eq.) and DIAD (1.1 eq.) were added. [11] The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure, the residue was dissolved in ethyl acetate (30 mL) and washed with sodium hydrogen carbonate solution (30 mL) and brine (30 mL). The organic phase was dried ($Na_2SO_4$), and the solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate, 4:1). Compounds **1 – 16** were synthesized following procedure A.

#### 4.2.1.1 Phenethyl cinnamate (1)

Compound **1** was obtained as a white solid (0.48 g, 57%); $R_F$ = 0.60 (silica gel, *n*-hexane/ethyl acetate, 4:1); m.p. 56 °C (lit.:[17] 54 °C); IR (ATR): ν = 3029*w*, 1708*s*, 1636*m*, 1578*w*, 1497*w*, 1450*w*, 1383*w*, 1327*w*, 1309*m*, 1255*m*, 1202*m*, 1163*s*, 979*m*, 766*m*, 750*m*, 698*s*, 683*m*, 494*m* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 297 (4.15) nm; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.68 (*d*, *J* = 16.0 Hz, 1H, 3-H), 7.52 (*dd*, *J* = 6.6, 3.1 Hz, 2H, 2´-H) , 7.39 (*d*, *J* = 3.5 Hz, 2H, 3´-H), 7.38 (*d*, *J* = 1.5 Hz, 1H, 4´-H), 7.32 (*d*, *J* = 7.2 Hz, 2H, 3´´´-H), 7.29 – 7.27 (*m*, 2H, 2´´´-H), 7.26 (*d*, *J* = 6.0 Hz, 1H, 4´´´-H), 6.43 (*d*, *J* = 16.0 Hz, 1H, 2-H), 4.44 (*t*, *J* = 7.1 Hz, 2H, 1´´-H), 3.03 (*t*, *J* = 7.1 Hz, 2H, 2´´-H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 167.0 (C-1), 145.0 (C-3), 138.0 (C-1´´´), 134.6 (C-1´), 130.4 (C-4´), 129.1 (C-2´´´), 129.0 (C-3´), 128.7 (C-3´´´), 128.2 (C-2´), 126.7 (C-4´´´), 118.2 (C-2), 65.2 (C-1´´), 35.4 (C-2´´) ppm; MS (ESI, MeOH): m/z (%) = 252.9 ($[M+H]^+$, 86), 275.1 ($[M+Na]^+$, 100), 397.9 ($[3M+Ca]^{2+}$, 33), 524.0 ($[4M+Ca]^{2+}$, 24), 526.9 ($[2M+Na]^+$, 24); analysis calcd for $C_{17}H_{16}O_2$ (252.31): C 80.93, H 6.39; found: C 80.71, H 6.51.

#### 4.2.1.2 Phenethyl (*E*)-3-(4-fluorophenyl)-acrylate (2)

Compound **2** was obtained as a white solid (0.32 g, 39%); $R_F$ = 0.73 (silica gel, *n*-hexane/ethyl acetate, 4:1); m.p. 54 °C; IR (ATR): ν = 1713*m*, 1637*m*, 1597*m*, 1507*m*, 1454*w*, 1414*w*, 1311*m*, 1280*w*, 1228*m*, 1199*m*, 1156*s*, 1096*m*, 995*s*, 831*s*, 770*m*, 739*m*, 700*s*, 512*s*, 495*s* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 280 (4.23) nm; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.63 (*d*, *J* = 16.0 Hz, 1H, 3-H), 7.53 – 7.48 (*m*, 2H, 2´-H) , 7.34 – 7.30 (*m*, 2H, 2´´´-H), 7.25 (*d*, *J* = 7.0 Hz, 2H, 3´´´-H), 7.24 (*t*, *J* = 7.2 Hz, 1H, 4´´´-H), 7.08 (*t*, *J* = 8.6 Hz, 2H, 3´-H), 6.35 (*d*, *J* = 16.0 Hz, 1H, 2-H), 4.4 (*t*, *J* = 7.1 Hz, 2H, 1´´-H), 3.02 (*t*, *J* = 7.1 Hz, 2H, 2´´-H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 166.9 (C-1), 165.1 (C-4´), 143.7 – 143.6 (*m*, C-3), 138.0 (C-1´´´), 130.8 (*d*, *J* = 3.6 Hz, C-1´), 130.1 (*d*, *J* = 8.6 Hz, C-2´), 129.1 (C-3´´´), 128.7 (C-2´´´), 126.7 (C-4´´´), 118.0 (*d*, *J* = 2.1 Hz, C-2), 116.2 (*d*, *J* = 22.0 Hz, C-3´), 65.2 (C-1´´), 35.4 (C-2´´) ppm; $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta$ = -109.66 (*tt*, *J* = 8.5, 5.4 Hz) ppm; MS (ESI, MeOH): m/z (%) = 293.3 ($[M+Na]^+$, 100), 325.3 ($[M+Na+MeOH]^+$, 29); analysis calcd for $C_{17}H_{15}FO_2$ (270.30): C 75.54, H 5.59; found: C 75.39, H 5.84.

#### 4.2.1.3 Phenethyl (*E*)-3-(3-fluorophenyl)-acrylate (3)

Compound **3** was obtained as a colourless oil (0.14 g, 17%); $R_F$ = 0.71 (silica gel, *n*-hexane/ethyl acetate, 4:1); IR (ATR): ν = 3030*w*, 1710*s*, 1640*m*, 1611*w*, 1583*m*, 1486*w*, 1447*m*, 1383*w*, 1318*m*, 1271*m*, 1242*m*, 1224*s*, 1161*s*, 1076*w*, 1054*w*, 1003*m*, 980*m*, 857*m*,

784*m*, 698*s*, 672*s*, 495*m* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 273 (4.19) nm; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.63 (*d*, *J* = 16.0 Hz, 1H, 3-H), 7.39 – 7.35 (*m*, 1H, 5´-H) , 7.34 – 7.31 (*m*, 2H, 2´´´-H), 7.30 – 7.29 (*m*, 1H, 6´-H), 7.28 (*d*, *J* = 2.2 Hz, 2H, 3´´´-H), 7.26 (*t*, *J* = 1.7 Hz, 1H, 4´´´-H), 7.21 (*dt*, *J* = 9.7, 2.2 Hz, 1H, 2´-H), 7.08 (*tdd*, *J* = 8.3, 2.6, 1.0 Hz, 1H, 4´-H), 6.42 (*d*, *J* = 16.0 Hz, 1H, 2-H), 4.44 (*t*, *J* = 7.1 Hz, 2H, 1´´-H), 3.03 (*t*, *J* = 7.1 Hz, 2H, 2´´-H) ppm; $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 166.6 (C-1), 163.1 (*d*, *J* = 246.9 Hz, C-3´), 143.5 (*d*, *J* = 2.7 Hz, C-3), 137.9 (C-1´´´), 136.8 (*d*, *J* = 7.7 Hz, C-1´), 130.6 (*d*, *J* = 8.2 Hz, C-5´), 129.0 (C-3´´´), 128.7 (C-2´´´), 126.7 (C-4´´´), 124.2 (*d*, *J* = 2.9 Hz, C-6´), 119.6 (C-2), 117.3 (*d*, *J* = 21.4 Hz, C-4´), 114.4 (*d*, *J* = 21.9 Hz, C-2´), 65.3 (C-1´´), 35.3 (C-2´´) ppm; $^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta$ = -112.56 (*td*, *J* = 9.0, 5.9 Hz) ppm; MS (ESI, MeOH): m/z (%) = 293.3 ($[M+Na]^+$, 100), 309.3 ($[M+K]^+$, 13), 325.4 ($[M+Na+MeOH]^+$, 35); analysis calcd for $C_{17}H_{15}FO_2$ (270.30): C 75.54, H 5.59; found: C 75.40, H 5.73.

#### 4.2.1.4 Phenethyl (*E*)-3-(3-bromophenyl)-acrylate (4)

Compound **4** was obtained as a white solid (0.25 g, 34%); $R_F$ = 0.70 (silica gel, *n*-hexane/ethyl acetate, 4:1); m.p. 63 °C; IR (ATR): ν = 3056*w*, 1699*s*, 1632*m*, 1561*m*, 1497*w*, 1475*w*, 1453*w*, 1418*w*, 1309*m*, 1300*m*, 1203*m*, 1174*s*, 1164*s*, 1071*s*, 1031*w*, 996*s*, 862*m*, 785*s*, 739*s*, 700*s*, 674*s*, 667*s*, 578*m*, 500*s* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 228 (4.02), 276 (4.07) nm; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.66 (*t*, *J* = 1.8 Hz, 1H, 4´-H), 7.58 (*d*, *J* = 16.0 Hz, 1H, 3-H), 7.50 (*ddd*, *J* = 8.0, 2.0, 1.0 Hz, 1H, 2´-H) , 7.43 (*dt*, *J* = 7.8, 1.3 Hz, 1H, 6´-H), 7.33 – 7.30 (*m*, 2H, 2´´´-H), 7.27 (*d*, *J* = 2.1 Hz, 2H, 3´´´-H), 7.26 – 7.24 (*m*, 1H, 5´-H), 7.24 – 7.22 (*m*, 1H, 4´´´-H), 6.41 (*d*, *J* = 16.0 Hz, 1H, 2-H), 4.43 (*t*, *J* = 7.0 Hz, 2H, 1´´-H), 3.02 (*t*, *J* = 7.1 Hz, 2H, 2´´-H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 166.6 (C-1), 143.2 (C-3), 137.9 (C-1´´´), 136.7 (C-1´), 133.2 (C-2´), 130.9 (C-4´), 130.5 (C-5´), 129.1 (C-3´´´), 128.7 (C-2´´´), 126.8 (C-4´´´), 126.7 (C-6´), 123.2 (C-3´), 119.7 (C-2), 65.3 (C-1´´), 35.3 (C-2´´) ppm; MS (ESI, MeOH): m/z (%) = 355.3 ($[M+Na]^+$, 100), 387.4 ($[M+Na+MeOH]^+$, 71); analysis calcd for $C_{17}H_{15}BrO_2$ (331.21): C 61.65, H 4.57; found: C 61.36, H 4.71.

#### 4.2.1.5 Phenethyl (*E*)-3-(2-chlorophenyl)-acrylate (5)

Compound **5** was obtained as a white solid (0.28 g, 35%); $R_F$ = 0.70 (silica gel, *n*-hexane/ethyl acetate, 4:1); m.p. 35 °C; IR (ATR): ν = 1706*s*, 1441*w*, 1379*w*, 1293*m*, 1271*s*, 1244*s*, 1202*m*, 1172*m*, 1083*w*, 1052*m*, 1017*w*, 986*m*, 953*m*, 753*s*, 699*s*, 571*m*, 494*m* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 230 (4.13), 276 (4.31) nm; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 8.10 (*d*, *J* = 16.0 Hz, 1H, 3-H), 7.61 (*dd*, *J* = 7.5, 2.0 Hz, 1H, 6´-H) , 7.44 – 7.41 (*m*, 1H, 3´-H),

7.34 – 7.31 (*m*, 2H, 2´´´-H), 7.31 (*d*, *J* = 1.9 Hz, 1H, 5´-H), 7.30 – 7.29 (*m*, 2H, 3´´´-H), 7.28 – 7.26 (*m*, 1H, 4´-H), 7.26 – 7.23 (*m*, 1H, 4´´´-H), 6.42 (*d*, *J* = 16.0 Hz, 1H, 2-H), 4.45 (*t*, *J* = 7.0 Hz, 2H, 1´´-H), 3.04 (*t*, *J* = 7.0 Hz, 2H, 2´´-H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 166.5 (C-1), 140.7 (C-3), 138.0 (C-1´´´), 135.1 (C-1´), 132.8 (C-2´), 131.2 (C-5´), 130.3 (C-3´), 129.1 (C-3´´´), 128.7 (C-2´´´), 127.7 (C-6´), 127.2 (C-4´), 126.7 (C-4´´´), 120.8 (C-2), 65.3 (C-1´´), 35.3 (C-2´´) ppm; MS (ESI, MeOH): m/z (%) = 355.3 ($[M+Na]^+$, 100), 387.4 ($[M+Na+MeOH]^+$, 60); analysis calcd for $C_{17}H_{15}BrO_2$ (331.21): C 61.65, H 4.57; found: C 61.31, H 4.75.

#### 4.2.1.6 Phenethyl (*E*)-3-(3-chlorophenyl)-acrylate (6)

Compound **6** was obtained as a white solid (0.36 g, 46%); $R_F$ = 0.75 (silica gel, *n*-hexane/ethyl acetate, 4:1); m.p. 53 °C; IR (ATR): ν = 3066*w*, 1703*m*, 1636*m*, 1562*w*, 1471*w*, 1455*w*, 1421*w*, 1301*m*, 1206*m*, 1175*s*, 1161*s*, 1077*m*, 993*s*, 861*s*, 786*s*, 745*s*, 697*s*, 684*m*, 672*s*, 500*s* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 230 (4.13), 274 (4.30) nm; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.60 (*d*, *J* = 16.0 Hz, 1H, 3-H), 7.50 (*t*, *J* = 1.9 Hz, 1H, 6´-H) , 7.38 (*tt*, *J* = 6.2, 1.7 Hz, 2H, 2´-H+5´-H), 7.35 (*t*, *J* = 1.7 Hz, 2H, 2´´´-H), 7.33 (*dd*, *J* = 6.7, 1.9 Hz, 2H, 3´´´-H), 7.27 (*q*, *J* = 2.8, 2.2 Hz, 1H, 4´-H), 7.26 – 7.23 (*m*, 1H, 4´´´-H), 6.42 (*d*, *J* = 16.0 Hz, 1H, 2-H), 4.44 (*t*, *J* = 7.1 Hz, 2H, 1´´-H), 3.03 (*t*, *J* = 7.0 Hz, 2H, 2´´-H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 166.6 (C-1), 143.3 (C-3), 137.9 (C-1´´´), 136.4 (C-1´), 135.0 (C-3´), 130.3 (C-5´), 130.2 (C-4´), 129.0 (C-3´´´), 128.7 (C-2´´´), 127.9 (C-6´), 126.7 (C-4´´´), 126.4 (C-2´), 119.7 (C-2), 65.3 (C-1´´), 35.3 (C-2´´) ppm; MS (ESI, MeOH): m/z (%) = 309.3 ($[M+Na]^+$, 100), 341.4 ($[M+Na+MeOH]^+$, 56); analysis calcd for $C_{17}H_{15}ClO_2$ (286.76): C 71.21, H 5.27; found: C 70.97, H 5.39.

#### 4.2.1.7 Phenethyl (*E*)-3-(4-chlorophenyl)-acrylate (7)

Compound **7** was obtained as a white solid (0.58 g, 73%); $R_F$ = 0.77 (silica gel, *n*-hexane/ethyl acetate, 4:1); m.p. 63 °C (lit.:[18] 62 – 64 °C); IR (ATR): ν = 1711*s*, 1634*m*, 1590*w*, 1490*m*, 1455*w*, 1406*w*, 1308*s*, 1203*w*, 1184*w*, 1156*s*, 1110*m*, 1086*s*, 995*s*, 824*s*, 742*m*, 701*s*, 518*m*, 494*s* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 229 (3.77), 286 (4.14) nm; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.61 (*d*, *J* = 16.0 Hz, 1H, 3-H), 7.46 – 7.43 (*m*, 2H, 2´-H) , 7.38 – 7.35 (*m*, 2H, 3´-H), 7.34 – 7.30 (*m*, 2H, 2´´´-H), 7.27 (*t*, *J* = 2.2 Hz, 2H, 3´´´-H), 7.26 – 7.23 (*m*, 1H, 4´´´-H), 6.39 (*d*, *J* = 16.0 Hz, 1H, 2-H), 4.43 (*t*, *J* = 7.1 Hz, 2H, 1´´-H), 3.02 (*t*, *J* = 7.0 Hz, 2H, 2´´-H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 166.8 (C-1), 143.5 (C-3), 138.0 (C-1´´´), 136.4 (C-4´), 133.0 (C-1´), 129.4 (C-2´), 129.3 (C-3´), 129.1 (C-3´´´), 128.7 (C-2´´´),

126.8 (C-4´´´), 118.8 (C-2), 65.3 (C-1´´), 35.4 (C-2´´); MS (ESI, MeOH): m/z (%) = 309.3 ($[M+Na]^+$, 100), 341.4 ($[M+Na+MeOH]^+$, 50); analysis calcd for $C_{17}H_{15}ClO_2$ (286.76): C 71.21, H 5.27; found: C 70.96, H 5.50.

#### 4.2.1.8 Phenethyl (*E*)-3-(3,4-dimethylphenyl)-acrylate (8)

Compound **8** was obtained as a white solid (0.35 g, 88%); $R_F$ = 0.76 (silica gel, *n*-hexane/ethyl acetate, 4:1); m.p. 40 °C; IR (ATR): ν = 3028*w*, 2945*w*, 1707*s*, 1634*m*, 1608*w*, 1571*w*, 1498*w*, 1454*w*, 1407*w*, 1384*w*, 1315*m*, 1260*m*, 1233*m*, 1205*m*, 1154*s*, 1124*w*, 1087*w*, 1054*w*, 1020*w*, 982*m*, 817*m*, 697*m* $cm^{-1}$; UV-vis (MeOH): λ (log ε) = 224 (3.92), 290 (4.12) nm; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.65 (*d*, *J* = 16.0 Hz, 1H, 3-H), 7.34 – 7.32 (*m*, 2H, 2´´´-H), 7.31 (*d*, *J* = 2.0 Hz, 1H, 2´-H), 7.29 (*d*, *J* = 1.9 Hz, 2H, 3´´´-H), 7.28 – 7.26 (*m*, 1H, 6´-H), 7.26 – 7.23 (*m*, 1H, 4´´´-H), 7.15 (*d*, *J* = 7.8 Hz, 1H, 5´-H), 6.39 (*d*, *J* = 16.0 Hz, 1H, 2-H), 4.44 (*t*, *J* = 7.1 Hz, 2H, 1´´-H), 3.03 (*t*, *J* = 7.1 Hz, 2H, 2´´-H), 2.29 (*s*, 6H, 7´-H+8´-H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 167.3 (C-1), 145.2 (C-3), 139.6 (C-3´), 138.1 (C-1´´´), 137.2 (C-4´), 132.2 (C-1´), 130.3 (C-5´), 129.4 (C-2´), 129.1 (C-3´´´), 128.6 (C-2´´´), 126.7 (C-4´´´), 125.9 (C-6´), 116.9 (C-2), 65.0 (C-1´´), 35.4 (C-2´´), 19.9 (C-7´), 19.8 (C-8´) ppm; MS (ESI, MeOH): m/z (%) = 280.9 ($[M+H]^+$, 44), 303.1 ($[M+Na]^+$, 77), 440.0 ($[3M+Ca]^{2+}$, 34), 582.9 ($[2M+Na]^+$, 100); analysis calcd for $C_{19}H_{20}O_2$ (280.37): C 81.40, H 7.19; found: C 81.17, H 6.89.

#### 4.2.1.9 Phenethyl (*E*)-3-(2-methoxyphenyl)-acrylate (9)

Compound **9** was obtained as a colourless oil (0.58 g, 73%); $R_F$ = 0.61 (silica gel, *n*-hexane/ethyl acetate, 4:1); IR (ATR): ν = 1705*s*, 1629*m*, 1598*m*, 1489*m*, 1464*m*, 1437*w*, 1319*m*, 1246*s*, 11159*s*, 1107*m*, 1050*m*, 1024*m*, 989*m*, 749*s*, 699*m* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 232 (4.12), 276 (4.25), 323 (4.01) nm; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.00 (*d*, *J* = 16.2 Hz, 1H, 3-H), 7.51 (*dd*, *J* = 7.7, 1.5 Hz, 1H, 4´-H) , 7.36 (*dd*, *J* = 10.3, 2.0 Hz, 1H, 6´-H), 7.33 – 7.30 (*m*, 2H, 3´´´-H), 7.29 – 7.26 (*m*, 2H, 2´´´-H), 7.25 – 7.22 (*m*, 1H, 4´´´-H), 6.96 (*t*, *J* = 7.5 Hz, 1H, 5´-H), 6.92 (*d*, *J* = 8.3 Hz, 1H, 3´-H), 6.52 (*d*, *J* = 16.2 Hz, 1H, 2-H), 4.43 (*t*, *J* = 7.1 Hz, 2H, 1´´-H), 3.89 (*s*, 3H, 7´-H), 3.03 (*t*, *J* = 7.1 Hz, 2H, 2´´-H) ppm;$^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 167.5 (C-1), 158.5 (C-2´), 140.4 (C-3), 138.2 (C-1´´´), 131.6 (C-6´), 129.1 (C-2´´´), 129.0 (C-4´), 128.6 (C-3´´´), 126.7 (C-4´´´), 123.6 (C-1´), 120.8 (C-5´), 118.7 (C-2), 111.3 (C-3´), 65.0 (C-1´´), 55.6 (C-7´), 35.4 (C-2´´) ppm; MS (ESI, MeOH): m/z (%) = 282.9 ($[M+H]^+$, 67), 305.1 ($[M+Na]^+$, 100), 443.0 ($[3M+Ca]^{2+}$, 14), 586.8 ($[2M+Na]^+$, 33); analysis calcd for $C_{18}H_{18}O_3$ (282.34): C 76.57, H 6.43, found: C 76.37, H 6.61.

#### 4.2.1.10 Phenethyl (*E*)-3-(3-methoxyphenyl)-acrylate (10)

Compound **10** was obtained as a yellowish oil (0.70 g, 88%); $R_F$ = 0.68 (silica gel, *n*-hexane/ethyl acetate, 4:1); IR (ATR): ν = 1708*s*, 1637*m*, 1579*m*, 1488*w*, 1454*m*, 1433*w*, 1308*m*, 1247*s*, 1230*s*, 1161*s*, 1043*m*, 981*m*, 782*m*, 749*m*, 699*m*, 679*m*, 495*m* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 236 (4.20), 279 (4.34) nm; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.65 (*d*, *J* = 16.0 Hz, 1H, 3-H), 7.36 – 7.32 (*m*, 2H, 3´´´-H) , 7.32 – 7.31 (*m*, 1H, 5´-H), 7.28 (*d*, J = 1.4 Hz, 2H, 2´´´-H), 7.24 (*d*, *J* = 7.1 Hz, 1H, 4´´´-H), 7.12 (*dt*, *J* = 7.5, 1.2 Hz, 1H, 6´-H), 7.04 (*dd*, *J* = 2.5, 1.7 Hz, 1H, 2´-H), 6.94 (*ddd*, *J* = 8.3, 2.6, 1.0 Hz, 1H, 4´-H), 6.42 (*d*, *J* = 16.0 Hz, 1H, 2-H), 4.44 (*t*, *J* = 7.1 Hz, 2H, 1´´-H), 3.84 (*s*, 3H, 7´-H), 3.03 (*t*, *J* = 7.1 Hz, 2H, 2´´-H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 166.9 (C-1), 160.0 (C-3´), 144.9 (C-3), 138.0 (C-1´´´), 135.9 (C-1´), 130.0 (C-5´), 129.1 (C-2´´´), 128.7 (C-3´´´), 126.7 (C-4´´´), 120.9 (C-6´), 118.5 (C-2), 116.3 (C-4´), 113.1 (C-2´), 65.2 (C-1´´), 55.4 (C-7´), 35.4 (C-2´´) ppm; MS (ESI, MeOH): m/z (%) = 282.9 ($[M+H]^+$, 44), 305.1 ($[M+Na]^+$, 100), 443.0 ($[3M+Ca]^{2+}$, 21), 586.8 ($[2M+Na]^+$, 30); analysis calcd for $C_{18}H_{18}O_3$ (282.34): C 76.57, H 6.43; found: C 76.32, H 6.60.

#### 4.2.1.11 Phenethyl-(*E*)-3-(4-methoxyphenyl)-acrylate (11)

Compound **11** was obtained as a white solid (0.61 g, 77%); $R_F$ = 0.62 (silica gel, *n*-hexane/ethyl acetate, 4:1); IR (ATR): ν = 1702*m*, 1634*w*, 1600*s*, 1511*s*, 1456*w*, 1444*w*, 1422*w*, 1314*m*, 1250*m*, 1204*m*, 1171*s*, 1028*m*, 986*s*, 962*m*, 830*s*, 816*s*, 742*m*, 701*s*, 539*m*, 520*s*, 506*s*, 490*m* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 232 (4.07), 311 (4.42) nm; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.64 (*d*, *J* = 16.0 Hz, 1H, 3-H), 7.49 – 7.44 (*m*, 2H, 2´-H), 7.35 – 7.31 (*m*, 2H, 3´´´-H) , 7.29 – 7.26 (*m*, 2H, 2´´´-H), 7.26 – 7.22 (*m*, 1H, 4´´´-H), 6.92 – 6.89 (*m*, 2H, 3´-H), 6.31 (*d*, *J* = 16.0 Hz, 1H, 2-H), 4.42 (*t*, *J* = 7.1 Hz, 2H, 1´´-H), 3.84 (*s*, 3H, 5´-H), 3.02 (*t*, *J* = 7.1 Hz, 2H, 2´´-H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 167.2 (C-1), 161.4 (C-4´), 144.5 (C-3), 138.0 (C-1´´´), 129.7 (C-2´), 128.9 (C-2´´´), 128.5 (C-3´´´), 127.2 (C-1´), 126.5 (C-4´´´), 115.5 (C-2), 114.3 (C-3´), 64.8 (C-1´´), 55.4 (C-5´), 35.3 (C-2´´) ppm; MS (ESI, MeOH): m/z (%) = 282.9 ($[M+H]^+$, 89), 305.1 ($[M+Na]^+$, 100), 443.0 ($[3M+Ca]^{2+}$, 16), 586.8 ($[2M+Na]^+$, 44); analysis calcd for $C_{18}H_{18}O_3$ (282.34): C 76.57, H 6.43; found: C 76.26, H 6.70.

#### 4.2.1.12 Phenethyl (*E*)-3-(2,4-dimethoxyphenyl)-acrylate (12)

Compound **12** was obtained as a white solid (0.27 g, 39%); $R_F$ = 0.32 (silica gel, *n*-hexane/ethyl acetate, 4:1); m.p. 52 °C; IR (film): ν = 1702*m*, 1602*s*, 1504*m*, 1455*m*, 1300*s*, 1251*m*, 1210*s*, 1153*s*, 1117*s*, 1029*s*, 824*m*, 699*m* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 252 (3.99), 318 (4.10), 358 (4.22) nm; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.91 (*d*, *J* = 16.1 Hz, 1H, 3-H), 7.44 (*d*, *J* = 8.6 Hz, 1H, 3´-H), 7.34 – 7.31 (*m*, 1H, 4´´´-H), 7.29 (*dd*, *J* = 9.2, 2.0 Hz, 2H, 2´´´-H), 7.25 – 7.21 (*m*, 2H, 3´´´-H), 6.50 (*dd*, *J* = 8.6, 2.4 Hz, 1H, 6´-H), 6.45 (*d*, *J* = 2.3 Hz, 1H, 5´-H), 6.42 (*d*, *J* = 16.1 Hz, 1H, 2-H), 4.41 (*t*, *J* = 7.1 Hz, 2H, 1´´-H), 3.87 (*s*, 3H, 8´-H), 3.84 (*s*, 3H, 7´-H), 3.02 (*t*, *J* = 7.1 Hz, 2H, 2´´-H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 167.9 (C-1), 162.9 (C-4´), 160.0 (C-2´), 140.3 (C-3), 138.2 (C-1´´´), 130.5 (C-3´), 129.1 (C-4´´´), 128.6 (C-2´´´), 126.6 (C-3´´´), 116.8 (C-1´), 116.0 (C-2), 105.4 (C-6´), 98.6 (C-5´), 64.9 (C-1´´), 55.6 (C-8´), 55.5 (C-7´), 35.5 (C-2´´) ppm; MS (ESI, MeOH): m/z (%) = 313.0 ($[M+H]^+$, 46), 335.1 ($[M+Na]^+$, 67), 488.1 ($[3M+Ca]^{2+}$, 21), 646.9 ($[2M+Na]^+$, 100); analysis calcd for $C_{19}H_{20}O_4$ (312.36): C 73.06, H 6.45; found: C 72.77, H 6.69.

#### 4.2.1.13 Phenethyl (*E*)-3-(3,5-dimethoxyphenyl)-acrylate (13)

Compound **13** was obtained as a colourless oil (0.34 g, 89%); $R_F$ = 0.54 (silica gel, *n*-hexane/ethyl acetate, 4:1); IR (ATR): ν = 2957*w*, 2839*w*, 1708*m*, 1638*w*, 1591*s*, 1498*w*, 1455*m*, 1427*m*, 1386*w*, 1302*w*, 1278*s*, 1239*m*, 1205*m*, 1152*s*, 1062*m*, 1002*w*, 979*m*, 835*m*, 699*m*, 674*m* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 226 (4.12), 287 (4.03) nm; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.59 (*d*, *J* = 16.0 Hz, 1H, 3-H), 7.36 – 7.30 (*m*, 2H, 2´´´-H), 7.27 (*d*, *J* = 5.7 Hz, 2H, 3´´´-H), 7.25 (*d*, *J* = 4.5 Hz, 1H, 4´´´-H), 6.66 (*d*, *J* = 2.3 Hz, 2H, 2´-H), 6.50 (*t*, *J* = 2.2 Hz, 1H, 4´-H), 6.39 (*d*, *J* = 16.0 Hz, 1H, 2-H), 4.43 (*t*, *J* = 7.1 Hz, 2H, 1´´-H), 3.81 (*s*, 3H, 5´-H), 3.84 (*s*, 3H, 7´-H), 3.03 (*t*, *J* = 7.1 Hz, 2H, 2´´-H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 166.9 (C-1), 161.2 (C-3´), 145.0 (C-3), 138.0 (C-1´´´), 136.4 (C-1´), 129.1 (C-3´´´), 128.7 (C-2´´´), 126.7 (C-4´´´), 118.7 (C-2), 106.1 (C-2´), 102.7 (C-4´), 65.2 (C-1´´), 55.6 (C-5´), 35.4 (C-2´´) ppm; MS (ESI, MeOH): m/z (%) = 313.1 ($[M+H]^+$, 52), 335.0 ($[M+Na]^+$, 82), 488.0 ($[3M+Ca]^{2+}$, 35), 646.8 ($[2M+Na]^+$, 100); analysis calcd for $C_{19}H_{20}O_4$ (312.36): C 73.06, H 6.45; found: C 72.84, H 6.65.

#### 4.2.1.14 Phenethyl (*E*)-3-(3,4,5-trimethoxyphenyl)-acrylate (14)

Compound **14** was obtained as a white solid (0.36 g, 99%); $R_F$ = 0.21 (silica gel, *n*-hexane/ethyl acetate, 4:1); m.p. 97°C; IR (ATR): ν = 1705*m*, 1631*w*, 1582*m*, 1505*w*, 1451*w*, 1419*w*, 1305*w*, 1269*m*, 1248*m*, 1165*m*, 1148*m*, 1127*s*, 991*m*, 975*m*, 842*m*, 817*m*, 754*m*, 703*m* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 310 (4.27) nm; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ =

7.59 (*d*, *J* = 15.9 Hz, 1H, 3-H), 7.31 (*d*, *J* = 2.8 Hz, 2H, 2´´´-H), 7.24 (*d*, *J* = 4.1 Hz, 2H, 3´´´-H), 7.23 – 7.22 (*m*, 1H, 4´´´-H), 6.74 (*s*, 2H, 2´-H), 6.33 (*d*, *J* = 15.9 Hz, 1H, 2-H), 4.44 (*t*, *J* = 7.1 Hz, 2H, 1´´-H), 3.89 (*s*, 6H, 5´-H), 3.88 (*s*, 3H, 6´-H), 3.03 (*t*, *J* = 7.1 Hz, 2H, 2´´-H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 167.0 (C-1), 153.6 (C-3´), 145.0 (C-3), 140.3 (C-4´), 138.0 (C-1´´´), 130.1 (C-1´), 129.1 (C-3´´´), 128.7 (C-2´´´), 126.7 (C-4´´´), 117.4 (C-2), 105.5 (C-2´), 65.1 (C-1´´), 61.1 (C-6´), 56.3 (C-5´), 35.4 (C-2´´) ppm; MS (ESI, MeOH): m/z (%) = 221.1 ($[M-C_8H_9]^+$), 343.0 ($[M+H]^+$, 60), 365.1 ($[M+Na]^+$); analysis calcd for $C_{20}H_{22}O_5$ (342.39): C 70.16, H 6.48; found: C 69.82, H 6.63.

**4.2.1.15 Phenethyl (*E*)-3-(3,5-dimethoxy-4-phenethoxyphenyl)-acrylate (15)**

Compound **15** was obtained as a colourless oil (0.13 g, 14%); $R_F$ = 0.33 (silica gel, *n*-hexane/ethyl acetate, 4:1); IR (ATR): ν = 1707*m*, 1635*m*, 1581*m*, 1500*m*, 1454*m*, 1418*m*, 1271*s*, 1241*s*, 1150*s*, 1124*s*, 999*m*, 827*m*, 745*m*, 698*s*, 492*m* cm$^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 250 (4.20), 337 (4.33) nm; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.59 (*d*, *J* = 15.9 Hz, 1H, 3-H), 7.35 – 7.32 (*m*, 2H, 4´´-H+4´´´´-H), 7.30 (*dd*, *J* = 6.7, 2.1 Hz, 2H, 2´´´´-H), 7.28 (*d*, *J* = 1.6 Hz, 4H, 2´´-H+3´´´´-H), 7.25 – 7.18 (*m*, 2H, 3´´-H), 6.73 (*s*, 2H, 2´-H), 6.32 (*d*, *J* = 15.9 Hz, 1H, 2-H), 4.44 (*t*, *J* = 7.1 Hz, 2H, 1´´´-H), 4.23 (*t*, *J* = 7.6 Hz, 2H, 6´-H), 3.84 (*s*, 6H, 5´-H), 3.10 (*t*, J = 7.6 Hz, 2H, 7´-H), 3.03 (*t*, *J* = 7.0 Hz, 2H, 2´´´-H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ =167.0 (C-1), 153.8 (C-3´), 145.0 (C-3), 139.4 (C-4´), 138.4 (C-1´´), 138.0 (C-1´´´´), 130.0 (C-1´), 129.2 (C-4´´), 129.1 (C-4´´´´), 128.7 (C-2´´), 128.5 (C-2´´´´), 126.7 (C-3´´), 126.4 (C-3´´´´), 117.3 (C-2), 105.5 (C-2´), 74.2 (C-6´), 65.1 (C-1´´´), 56.3 (C-5´), 36.7 (C-7´), 35.4 (C-2´´´) ppm; MS (ESI, MeOH): m/z (%) = 433.0 ($[M+H]^+$, 56), 450.0 ($[M+NH_4]^+$, 14), 455.1 ($[M+Na]^+$, 41), 470.9 ($[M+K]^+$, 2), 668.1 ($[3M+Ca]^{2+}$, 16), 886.9 ($[2M+Na]^+$, 100); analysis calcd for $C_{27}H_{28}O_5$ (432.52): C 74.98, H 6.53; found: C 74.59, H 6.77.

**4.2.1.16 Phenethyl (*E*)-3-(4-acetoxy-3-methoxyphenyl)-acrylate (16)**

Compound **16** was obtained as a white solid (0.11 g, 31%); $R_F$ = 0.37 (silica gel, *n*-hexane/ethyl acetate, 4:1); m.p. 79 °C; IR (ATR): ν = 2956*w*, 1758*m*, 1707*m*, 1634*m*, 1601*w*, 1510*m*, 1466*w*, 1454*w*, 1419*m*, 1372*w*, 1333*m*, 1302*w*, 1261*m*, 1214*m*, 1200*m*, 1172*s*, 1149*s*, 1123*m*, 1030*m*, 1012*m*, 983*m*, 906*m*, 868*m*, 831*m*, 695*m*, 648*m*, 492*m* cm$^{-1}$; UV-vis (MeOH): λ (log ε) = 211 (4.45), 280 (4.47) nm; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.62 (*d*, *J* = 16.0 Hz, 1H, 3-H), 7.32 (*d*, *J* = 7.2 Hz, 1H, 6´-H), 7.27 (*d*, *J* = 1.8 Hz, 2H, 2´´´-H), 7.26 – 7.24 (*m*, 2H, 3´´´-H), 7.11 (*d*, *J* = 1.2 Hz, 1H, 5´-H), 7.09 (*t*, J = 1.9 Hz, 1H, 2´-H), 7.05 (*d*, *J* = 7.9 Hz, 1H,

4´´´-H), 6.37 (*d*, *J* = 16.0 Hz, 1H, 2-H), 4.43 (*t*, *J* = 7.1 Hz, 2H, 1´´´-H), 3.86 (*s*, 3H, 7´-H), 3.03 (*t*, *J* = 7.1 Hz, 2H, 2´´´-H), 2.32 (*s*, 3H, 9´-H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 168.9 (C-8´), 166.9 (C-1), 151.6 (C-3´) 144.3 (C-3), 141.6 (C-4´), 138.0 (C-1´´´), 133.6 (C-1´), 129.1 (C-2´´´), 128.7 (C-6´), 126.7 (C-3´´´), 123.4 (C-4´´´), 121.4 (C-5´), 118.7 (C-2), 111.4 (C-2´), 65.2 (C-1´´), 56.1 (C-7´), 35.4 (C-2´´), 20.8 (C-9´) ppm; MS (ESI, MeOH): m/z (%) = 340.9 ($[M+H]^+$, 23), 357.9 ($[M+NH_4]^+$, 5), 363.0 ($[M+Na]^+$, 40), 702.8 ($[2M+Na]^+$, 100); analysis calcd for $C_{20}H_{20}O_5$ (340.38): C 70.58, H 5.92; found: C 70.36, H 6.18.

**4.2.1.17 Phenethyl (*E*)-3-(3,4-dihydroxyphenyl)-acrylate (17)**

Caffeic acid (0.5 g, 2.78 mmol) and 2-phenylethanol (0.35 mL, 2.78 mmol) were dissolved in nitromethane (62.5 mL). $Yb(OTf)_3$ (0.017 g, 0.028 mmol) was added, and the suspension was stirred for 5 min in an ultrasonic bath followed by an additional 1.5 h stirring under reflux.[4] The reaction mixture was stirred at room temperature overnight and washed with $NaHCO_3$-solution (2%, 15 mL) and brine (15 mL). The organic phase was dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel; chloroform/methanol, 99:1), and compound **17** was obtained as a white solid (0.07 g, 9%); $R_F$ = 0.04 (silica gel; chloroform/methanol, 99:1); m.p. 128 – 130 °C (lit.:[19] 126 – 128 °C); IR (KBr): ν = 3480*s*, 1685*m*, 1636*m*, 1602*s*, 1535*w*, 1442*w*, 1363*w*, 1302*m*, 1279*s*, 1182*s* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 250 (4.06), 320 (4.21), 353 (4.28) nm; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.56 (*d*, *J* = 15.9 Hz, 1H, 3-H), 7.34 – 7.30 (*m*, 2H, 2´´´-H), 7.27 – 7.22 (*m*, 3H, 3´´´-H+4´´´-H), 7.07 (*d*, *J* = 2.0 Hz, 1H, 5´-H), 7.01 (*dd*, *J* = 8.2, 2.0 Hz, 1H, 2´-H), 6.87 (*d*, *J* = 8.2 Hz, 1H, 6´-H), 6.25 (*d*, *J* = 15.9 Hz, 1H, 2-H), 4.42 (*t*, *J* = 7.1 Hz, 2H, 1´´-H), 3.01 (*t*, *J* = 7.1 Hz, 2H, 2´´-H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 167.8 (C-1), 146.5 (C-4´), 145.2 (C-3´), 143.9 (C-3), 138.0 (C-1´´´), 129.1 (C-3´´´), 128.7 (C-2´´´), 127.7 (C-1´), 126.8 (C-4´´´), 122.7 (C-6´), 115.7 (C-2), 115.6 (C-5´), 144.6 (C-2´), 65.3 (C-1´´), 35.4 (C-2´´) ppm; MS (ESI, MeOH): m/z (%) = 285.0 ($[M+H]^+$, 45), 302.2 ($[M+NH_4]^+$, 23), 307.1 ($[M+Na]^+$, 100), 446.1 ($[3M+K+H]^{2+}$, 44), 580.1 ($[4M+Na+H]^{2+}$, 23), 588.0 ($[4M+K+H]^{2+}$, 50), 590.8 ($[2M+Na]^+$, 42), 599.9 ($[4M+Zn]^{2+}$, 48); analysis calcd for $C_{17}H_{16}O_4$ (284.31): C 71.82, H 5.67; found: C 71.69, H 5.83.

**4.2.1.18 Phenethyl (*E*)-3-(3,4-dimethoxyphenyl)-acrylate (18)**

At -20 °C (*E*)-3,4-dimethoxy cinnamic acid (1.00 g, 4.8 mmol) und 2-phenylethanol (0.44 mL, 3.69 mmol) were dissolved in dry DCM (18.5 mL). DCC (0.953 g, 4.62 mmol) and DMAP (0.067 g, 0.55 mmol) were added, and the reaction mixture was stirred at room

temperature overnight. The precipitate was filtrated off, and the solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel; dichloromethane), and compound **18** was obtained as a white solid (0.798 g, 53%); $R_F$ = 0.7 (silica gel; dichloromethane); m.p. 97 – 99 °C; IR (KBr): ν = 3455*w*, 3062*w*, 3003*m*, 2959*m*, 2937*m*, 2886*m*, 2838*m*, 1852*w*, 1702*s*, 1636*s*, 1597*s*, 1582*m*, 1515*s*, 1472*m*, 1462*m*, 1447*m*, 1415*w*, 1378*w*, 1340*m*, 1312*m*, 1290*w*, 1258*s*, 1236*s*, 1202*w*, 1178*s*, 1162*s*, 1139*s*, 1075*m*, 1040*m*, 1021*s*, 1000*m*, 854*m*, 810*m*, 757*m*, 706*m* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 253 (4.13), 320 (4.20), 355 (4.33) nm; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.62 (*d*, *J* = 15.9 Hz, 1H, 3-H), 7.35 – 7.22 (*m*, 5H, 2´´´-H+3´´´-H+4´´´), 7.10 (*dd*, *J* = 8.3, 1.9 Hz, 1H, 2´-H), 7.05 (*d*, *J* = 1.8 Hz, 1H, 5´-H), 6.87 (*d*, *J* = 8.3 Hz, 1H, 6´-H), 6.30 (*d*, *J* = 15.9 Hz, 1H, 2-H), 4.43 (*t*, *J* = 7.1 Hz, 2H, 1´´-H), 3.91 (*s*, 6H, 7´-H+8´-H), 3.02 (*t*, *J* = 7.1 Hz, 2H, 2´´-H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 167.3 (C-1), 151.3 (C-4´), 149.4 (C-3´), 144.9 (C-3), 138.0 (C-1´´´), 129.0 (C-3´´´), 128.7 (C-2´´´), 127.6 (C-1´), 126.7 (C-4´´´), 122.8 (C-6´), 115.9 (C-2), 111.2 (C-5´), 109.8 (C-2´), 65.0 (C-1´´), 56.1 (C-8´), 56.0 (C-7´), 35.4 (C-2´´) ppm; MS (ESI, MeOH): m/z (%) = 313.1 ($[M+H]^+$, 30), 335.1 ($[M+Na]^+$, 100); analysis calcd for $C_{19}H_{20}O_4$ (312.36): C 73.06, H 6.45; found: C 72.88, H 6.64.

**4.2.1.19 (*E*) 3-(3,4-Bis(benzyloxy)phenyl)-acrylic acid (19)**

Caffeic acid (2.00 g, 11.1 mmol) and $K_2CO_3$ (9.14 g, 66 mmol) were dissolved in ethanol (74 mL), and benzyl chloride (3.84 mL, 4.22 g, 33.3 mmol) was added carefully. After 5 h of stirring under reflux, the reaction was cooled to room temperature, and KOH (1.85 g, 33 mmol) was added, and the mixture was stirred overnight. The solvent was removed under reduced pressure; the residue was solved in water (200 mL) and washed with ethyl acetate (70 mL). The aqueous phase was acidified with hydrochloric acid to pH = 5 and washed with ethyl acetate (3 x 100 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and the solvent was removed until a precipitate was formed. This suspension was stored in the fridge overnight and filtrated. Compound **19** was obtained as an off-white solid (2.28 g, 57%); $R_F$ = 0.04 (silica gel; chloroform/methanol, 99:1); m.p. 199 – 202 °C (lit.:[20] 201 – 202 °C); IR (KBr): ν = 3442*m*, 3036*w*, 1670*s*, 1623*m*, 1596*m*, 1510*m*, 1453*w*, 1433*m*, 1382*w*, 1308*m*, 1268*s*, 1206*m*, 1169*w*, 1140*m*, 1021*m*, 695*m* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 252 (3.87), 322 (3.92), 352 (3.99) nm; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.66 (*d*, *J* = 15.8 Hz, 1H, 3-H), 7.48 – 7.42 (*m*, 4H, 3´´´-H+4´´´-H), 7.41 – 7.29 (*m*, 6H, 3´´-H+4´´-H+5´´-H+5´´´-H), 7.14 (*d*, *J* = 1.9 Hz, 1H, 5´-H), 7.09 (*dd*, *J* = 8.3, 2.0 Hz, 1H, 2´-H), 6.93 (*d*, *J* = 8.3 Hz, 1H, 6´-H), 6.24 (*d*, *J* = 15.9 Hz, 1H, 2-H), 5.20 (*d*, *J* = 8.4 Hz, 4H, 1´´-H+1´´´-H)

ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.2 (C-1), 151.6 (C-4´), 149.2 (C-3´), 146.9 (C-3), 137.0 (C-2´´´), 136.8 (C-2´´), 128.7 (C-4´´´), 128.6 (C-4´´), 128.1 (C-5´´´), 127.6 (C-1´), 127.5 (C-5´´), 127.4 (C-3´´´), 127.3 (C-3´´), 123.5 (C-2), 115.0 (C-6´), 114.4 (C-5´), 114.1 (C-2´), 71.6 (C-1´´´), 71.1 (C-1´´) ppm; MS (ESI, MeOH): m/z (%) = 361.1 ($[M+H]^+$, 10), 383.1 ($[M+Na]^+$, 100), 742.8 ($[2M+Na]^+$, 13); analysis calcd for $C_{23}H_{20}O_4$ (360.41): C 76.65, H 5.59; found: C 76.37, H 5.81.

#### 4.2.1.20 Allyl (*E*)-3-(3,4-bis(allyloxy)phenyl)-acrylate (20)

Caffeic acid (1.00 g, 5.55 mmol) and $K_2CO_3$ (0.92 g, 6.66 mmol) were dissolved in ethanol (8 mL). Allyl bromide (1.73 mL, 2.42 g, 19.98 mmol) was added dropwise. After stirring for 5 h under reflux, the mixture was cooled to room temperature, and the solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel; dichloromethane), and compound **20** was obtained as white needles (0.37 g, 22%); $R_F$ = 0.84 (silica gel; dichloromethane); m.p. 48 – 51 °C; IR (KBr): ν = 3449*m*, 3067*w*, 3018*w*, 2927*w*, 1706*s*, 1649*w*, 1629*w*, 1596*m*, 1512*s*, 1458*m*, 1424*m*, 1411*w*, 1342*w*, 1270*s*, 1223*s*, 1174*m*, 1143*s*, 1020*m*, 996s, 924*m*, 810*m* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 253 (4.09), 323 (4.17), 354 (4.26) nm; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.62 (*d*, *J* = 15.9 Hz, 1H, 3-H), 7.09 (*d*, *J* = 2.0 Hz, 1H, 6´-H), 7.07 (*dd*, *J* = 3.1, 2.0 Hz, 1H, 2´-H), 6.87 (*d*, *J* = 8.8 Hz, 1H, 5´-H), 6.30 (*d*, *J* = 15.9 Hz, 1H, 2-H), 6.13 – 5.94 (*m*, 3H, 2´´-H+2´´´-H+2´´´´-H), 5.46 – 5.38 (*m*, 3H, 3´´$_{trans}$-H+3´´´$_{trans}$-H+3´´´´$_{trans}$-H)), 5.36 – 5.24 (*m*, 3H, 3´´$_{cis}$-H+3´´´$_{cis}$-H+3´´´´$_{cis}$-H), 4.70 (*dt*, *J* = 5.7, 1.4 Hz, 2H, 1´´´´-H), 4.63 (*dtd*, *J* = 4.0, 2.8, 1.5 Hz, 4H, 1´´-H+1´´´-H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 166.9 (C-1), 150.8 (C-4´), 148.7 (C-3´), 145.0 (C-3), 133.2 (C-2´´´), 133.0 (C-2´´), 132.5 (C-2´´´´), 127.7 (C-1´), 122.8 (C-2), 118.3 (C-3´´´), 118.1 (C-3´´), 118.0 (C-3´´´´), 115.7 (C-5´), 113.6 (C-6´), 112.9 (C-2´), 70.1 (C-1´´´), 69.9 (C-1´´), 65.2 (C-1´´´´) ppm; MS (ESI, MeOH): m/z (%) = 301.0 ($[M+H]^+$, 81), 323.1 ($[M+Na]^+$, 100), 622.9 ($[2M+Na]^+$, 21); analysis calcd for $C_{18}H_{20}O_4$ (300.35): C 71.98, H 6.71; found: C 71.77, H 6.96.

#### 4.2.1.21 (*E*) 3-(3,4-Bis(allyloxy)phenyl) acrylic acid (21)

Compound **20** (0.66 g, 2.2 mmol) and NaOH (0.18 g, 4.4 mmol) were dissolved in ethanol (5 mL). The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the crude product was purified by column chromatography (silica gel; dichloromethane), and compound **21** was obtained as a white solid (0.29 g, 51%); $R_F$ = 0.06 (silica gel; dichloromethane); m.p. 95 – 98 °C (lit.:[21] 159 – 160 °C); IR (KBr): ν = 3448*m*,

1666*s*, 1623*s*, 1597*s*, 1510*s*, 1426*s*, 1370*m*, 1307*m*, 1263*s*, 1204*m*, 1173*w*, 1136*m*, 1005*m* $cm^{-1}$; UV-vis (MeOH): λ (log ε) = 315 (4.13), 350 (4.17) nm; $^{1}H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ = 7.48 (*d*, *J* = 15.9 Hz, 1H, 3-H), 7.32 (*d*, *J* = 1.9 Hz, 1H, 5´-H), 7.17 (*dd*, *J* = 8.3, 1.9 Hz, 1H, 2´-H), 6.98 (*d*, *J* = 8.4 Hz, 1H, 6´-H), 6.41 (*d*, *J* = 15.9 Hz, 1H, 2-H), 6.10 – 5.98 (m, 2H, 2´´-H+2´´´-H), 5.40 (*ddq*, *J* = 17.3, 5.3, 1.7 Hz, 2H, 3´´$_{trans}$-H+3´´´$_{trans}$-H), 5.25 (*dp*, *J* = 10.5, 1.5 Hz, 2H, 3´´$_{cis}$-H+3´´´$_{cis}$-H), 4.60 (*ddt*, *J* = 6.6, 5.3, 1.6 Hz, 4H, 1´´-H+1´´´-H) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ = 167.7 (C-1), 149.8 (C-4´), 147.9 (C-3´), 143.9 (C-3), 133.8 (C-2´´´), 133.5 (C-2´´), 127.3 (C-1´), 122.6 (C-2), 117.5 (C-3´´´), 117.4 (C-3´´), 116.9 (C-5´), 113.4 (C-6´), 112.4 (C-2´), 68.9 (C-1´´´), 68.8 (C-1´´) ppm; MS (ESI, MeOH): m/z (%) = 259.0 ($[M-H]^-$, 100), 519.1 ($[2M-H]^-$, 56), 541.1 ($[2M-2H+Na]^-$, 11); analysis calcd for $C_{15}H_{16}O_4$ (260.29): C 69.22, H 6.20; found: C 68.97, H 6.48.

**4.2.1.22 General procedure B**

Under Argon atmosphere and at -20 °C top of a solution of the carboxylic acid (1.3 eq.) in dry DCM (5 mL / mmol), the corresponding phenethyl alcohol (1 eq.), DCC (1.25 eq.) and DMAP (0.15 eq.) were added. The reaction mixture was stirred overnight at room temperature. The precipitate was filtrated off, and the solvent was removed *in vacuo*; the residue was purified by column chromatography (silica gel; dichloromethane). [11, 12]

Compounds **22 – 27** were synthesized following procedure B.

**4.2.1.23 2-Hydroxyphenethyl (*E*)-3-(3,4-bis(benzyloxy)phenyl)-acrylate (22)**

Compound **22** was obtained as a colourless oil (0.18 g, 36%); $R_F$ = 0.44 (silica gel; dichloromethane); m.p. 97 °C; IR (film): ν = 3440*m*, 1682*m*, 1633*s*, 1596*m*, 1510*m*, 1455*m*, 1384*w*, 1263*s*, 1168*m*, 1136*m*, 1015*w* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 240 (4.27), 323 (4.32), 355 (4.41) nm; $^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.60 (*d*, *J* = 15.9 Hz, 1H, 3-H), 7.48 – 7.39 (*m*, 5H, 3´´´-H+4´´´-H+5´´´-H), 7.39 – 7.29 (*m*, 5H, 3´´-H+4´´-H+5´´-H), 7.18 – 7.13 (*m*, 2H, 4$^{v}$-H+6$^{v}$-H), 7.12 (*d*, *J* = 2.1 Hz, 1H, 6´-H), 7.07 (*dd*, *J* = 8.3, 2.1 Hz, 1H, 2´-H), 6.92 (*d*, *J* = 8.3 Hz, 1H, 5´-H), 6.88 (*dd*, *J* = 11.4, 4.3 Hz, 2H, 3$^{v}$-H+5$^{v}$-H), 6.24 (*d*, *J* = 15.9 Hz, 1H, 2-H), 5.20 (*s*, 2H, 1´´´-H), 5.18 (*s*, 2H, 1´´-H), 4.38 (*t*, *J* = 7.1 Hz, 2H, 1´´´´-H), 3.02 (*t*, *J* = 7.1 Hz, 2H, 2´´´´-H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 167.8 (C-1), 154.7 (C-2$^{v}$), 151.4 (C-4´), 149.1 (C-3´), 145.5 (C-3), 137.0 (C-2´´´), 136.9 (C-2´´), 131.0 (C-6$^{v}$), 128.7 (C-4´´´), 128.5 (C-4´´), 128.1 (C-5´´+C-5´´´), 127.8 (C-1´), 127.5 (C-3´´+C-3´´´), 127.3 (C-4$^{v}$), 123.7 (C-1$^{v}$), 123.2 (C-6´), 120.8 (C-5$^{v}$), 116.2 (C-3$^{v}$), 115.6 (C-2), 114.4 (C-5´), 114.0 (C-2´), 71.6 (C-1´´´), 71.1 (C-1´´), 64.6 (C-1´´´´), 30.5 (C-2´´´´) ppm; MS (ESI, MeOH): m/z (%)

= 481.0 ($[M+H]^+$, 5), 503.2 ($[M+Na]^+$, 100), 983.0 ($[2M+Na]^+$, 51); analysis calcd for $C_{31}H_{28}O_5$ (480.56): C 77.48, H 5.87; found: C 77.21, H 6.03.

#### 4.2.1.24 2-Hydroxyphenethyl (*E*)-3-(3,4-bis(allyloxy)phenyl)-acrylate (23)

Compound **23** was obtained as a white solid (0.09 g, 27%); $R_F$ = 0.32 (silica gel; dichloromethane); m.p. 119 °C; IR (KBr): ν = 3383*s*, 2927*w*, 1684*s*, 1628*s*, 1594*m*, 1578*w*, 1509*s*, 1458*m*, 1426*m*, 1348*w*, 1307*m*, 1264*s*, 1230*m*, 1196*s*, 1170*s*, 1132*s*, 1114*w*, 1064*w*, 1008*m*, 974*m* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 254 (3.99), 355 (4.19) nm; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.63 (*d*, *J* = 15.9 Hz, 1H, 3-H), 7.14 (*ddd*, *J* = 8.0, 4.5. 1.7 Hz, 2H, $4^v$-H+$6^v$-H), 7.09 – 7.07 (*m*, 2H, $3^v$-H+$5^v$-H), 6.90 – 7.84 (*m*, 3H, 2´-H+5´-H+6´-H), 6.27 (*d*, *J* = 15.9 Hz, 1H, 2-H), 6.14 – 6.02 (*m*, 2H, 2´´-H+2´´´-H), 5.46 – 5.41 (*m*, 2H, $3´´_{trans}$-H+$3´´´_{trans}$-H), 5.32 – 5.29 (*m*, 2H, $3´´_{cis}$-H+$3´´´_{cis}$-H), 4.64 (*ddd*, *J* = 5.5, 2.8, 1.4 Hz, 4H, 1´´-H+1´´´-H), 4.39 (*t*, *J* = 7.1 Hz, 2H, 1´´´´-H), 3.03 (*t*, *J* = 7.1 Hz, 2H, 2´´´´-H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 167.9 (C-1), 154.7 (C-$2^v$), 151.0 (C-4´), 148.8 (C-3´), 145.6 (C-3), 133.2 (C-2´´´), 133.0 (C-2´´), 131.0 (C-$6^v$), 128.5 (C-$4^v$), 127.6 (C-1´), 123.7 (C-$1^v$), 123.0 (C-$5^v$), 120.8 (C-5´), 118.2 (C-3´´´), 118.1 (C-3´´), 116.2 (C-6´), 115.4 (C-2), 113.6 (C-2´), 113.0 (C-$3^v$), 70.2 (C-1´´´), 69.9 (C-1´´), 64.6 (C-1´´´´), 30.5 (C-2´´´´) ppm; MS (ESI, MeOH): m/z (%) = 381.0 ($[M+H]^+$, 19), 403.1 ($[M+Na]^+$, 100), 783.1 ($[2M+Na]^+$, 83); analysis calcd for $C_{23}H_{24}O_5$ (380.44): C 72.61, H 6.36; found: C 72.44, H 6.50.

#### 4.2.1.25 4-{2-[((*E*)-3-(3,4-Bis(benzyloxy)phenyl)acryloyl)oxy]ethyl}phenyl (*E*)-3-(3,4-bis(benzyloxy)phenyl)-acrylate (24)

Compound **24** was obtained after column chromatography (silica gel; dichloromethane) as a white solid (0.14 g, 15%); $R_F$ = 0.51 (silica gel; dichloromethane); m.p. 172 – 175 °C; IR (KBr): ν = 3446*w*, 3033*w*, 1731*m*, 1710*m*, 1630*s*, 1596*m*, 1578*w*, 1508*s*, 1454*m*, 1432*m*, 1383*w*, 1350*w*, 1303*m*, 1264*s*, 1199*m*, 1161*s*, 1128*s*, 1006*m*, 741*m*, 694*m* $cm^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 248 (4.33), 356 (4.48) nm; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.74 (*d*, *J* = 15.9 Hz, 1H, 3-H), 7.56 (*d*, *J* = 15.9 Hz, 1H, $3^v$´-H), 7.49 – 7.42 (*m*, 8H), 7.41 – 7.35 (*m*, 8H), 7.33 (*dd*, *J* = 6.9, 3.9 Hz, 4H), 7.28 (*d*, *J* = 8.5 Hz, 2H), 7.19 – 7.05 (*m*, 6H), 6.93 (*dd*, *J* = 11.8, 8.4 Hz, 2H), 6.42 (*d*, *J* = 15.9 Hz, 1H, 2-H), 6.23 (*d*, *J* = 15.9 Hz, 1H, $2^v$´-H), 5.20 (*t*, *J* = 7.1 Hz, 8H, 1´´-H+1´´´-H+$1^v$´´´-H+$1´^x$), 4.41 (*t*, *J* = 7.0 Hz, 2H, $1´^v$-H), 3.02 (*t*, *J* = 7.1 Hz, 2H, $2´^v$-H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 167.5 (C-$1^v$´), 166.0 (C-1), 154.7 (C-4´), 151.6 (C-$4^v$´´), 149.7 (C-3´), 149.1 (C-$3^v$´´), 146.5 (C-$3^v$´), 144.9 (C-3), 136.9 (C-2´´+C-2´´´+C-$2^v$´´´+C-$2´^v$), 130.0, 128.8, 128.7, 128.7, 128.2, 128.1, 127.5, 127.5, 127.4, 127.3,

123.1, 121.8, 115.3 (C-2$^{v}$´), 115.2 (C-2), 114.5 + 114.4 (C-5´+C-5$^{v}$´´), 114.1 + 114.0 (C-2´+C-2$^{v}$´´), 71.5 + 71.1 (C-1´´+C-1´´´+C-1$^{v}$´´´+C-1´$^{v}$), 64.9 (C-1$^{v}$´), 34.8 (C-2$^{v}$´) ppm; MS (ESI, MeOH/$CH_2Cl_2$): m/z (%) = 823.1 ([M+H]$^+$, 32), 840.1 ([M+$NH_4$]$^+$, 24), 845.3 ([M+Na]$^+$, 100), 1668.3 ([2M+Na]$^+$, 94); analysis calcd for $C_{54}H_{46}O_8$ (822.95): C 78.81, H 5.63; found: C 78.59, H 5.89.

#### 4.2.1.26 3-{2-[((*E*)-3-(3,4-Bis(benzyloxy)phenyl)acryloyl)oxy]ethyl}phenyl (*E*)-3-(3,4-bis(benzyloxy)phenyl)-acrylate (25)

After column chromatography (silica gel; dichloromethane) compound **25** was obtained as a white solid (0.42 g, 48%); $R_F$ = 0.48 (silica gel; dichloromethane); m.p. 80 °C; IR (KBr): ν = 3448*w*, 3034*w*, 2864*w*, 1725*m*, 1699*s*, 1629*m*, 1596*m*, 1511*s*, 1454*m*, 1434*m*, 1383*m*, 1306*m*, 1270*s*, 1241*s*, 1150*s*, 1134*s*, 1016*m*, 984*m*, 800*m*, 739*m*, 695*s* cm$^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 248 (4.38), 358 (4.53) nm; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.74 (*d*, *J* = 15.9 Hz, 1H, 3-H), 7.56 (*d*, *J* = 15.9 Hz, 1H, 3$^{v}$´-H), 7.46 (*ddd*, *J* = 8.8, 4.4, 1.7 Hz, 6H), 7.43 – 7.40 (*m*, 2H), 7.37 (*dd*, *J* = 7.1, 1.2 Hz, 6H), 7.35 – 7.32 (*m*, 4H), 7.32 (*d*, *J* = 5.1 Hz, 2H), 7.18 – 7.13 (*m*, 3H), 7.11 (*dd*, *J* = 8.4, 2.1 Hz, 1H), 7.09 – 7.03 (*m*, 4H), 6.94 (*d*, *J* = 8.4 Hz, 1H), 6.90 (*d*, *J* = 8.3 Hz, 1H), 6.42 (*d*, *J* = 15.9 Hz, 1H, 2-H), 6.24 (*d*, *J* = 15.9 Hz, 1H, 2$^{v}$´-H), 5.29 + 5.21 + 5.19 + 5.17 (*s*, 8H, 1´´-H+1´´´-H+1$^{v}$´´´-H+1´$^{x}$), 4.43 (*t*, *J* = 6.9 Hz, 2H, 1´$^{v}$-H), 3.03 (*t*, *J* = 6.9 Hz, 2H, 2´$^{v}$-H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 167.2 (C-1$^{v}$´), 165.7 (C-1), 151.6 (C-4´), 151.1 (C-4$^{v}$´´), 149.2 (C-3´), 149.1 (C-3$^{v}$´´), 146.5 (C-3$^{v}$´), 144.8 (C-3), 139.8, 137.0 + 136.9 + 136.8 + 136.8 (C-2´´+C-2´´´+C-2$^{v}$´´´+C-2´$^{v}$), 129.6, 128.7, 128.7, 128.7, 128.6, 128.2, 128.1, 128.0, 127.7, 127.5, 127.4, 127.3, 126.4, 123.4, 123.1, 120.0, 116.1 (C-2$^{v}$´), 115.2 (C-2), 114.4 + 114.3 (C-5´+C-5$^{v}$´´), 114.1 + 114.0 (C-2´+C-2$^{v}$´´), 71.5 + 71.1 (C-1´´+C-1´´´+C-1$^{v}$´´´+C-1´$^{v}$), 64.6 (C-1$^{v}$´), 35.2 (C-2$^{v}$´) ppm; MS (ESI, MeOH/$CH_2Cl_2$): m/z (%) = 822.9 ([M+H]$^+$, 30), 840.2 ([M+$NH_4$]$^+$, 13), 845.3 ([M+Na]$^+$, 100), 1667.1 ([2M+Na]$^+$, 35); analysis calcd for $C_{54}H_{46}O_8$ (822.95): C 78.81, H 5.63; found: C 78.69, H 5.91.

#### 4.2.1.27 4-{2-[((*E*)-3-(3,4-bis(benzyloxy)phenyl)acryloyl)oxy]ethyl}-1,2-phenylene (2*E*,2'*E*)-bis(3-(3,4-bis(benzyloxy)phenyl)-acrylate) (26)

Compound **26** was obtained as a white solid (0.07 g, 6%); $R_F$ = 0.27 (silica gel; dichloromethane); m.p. 100 °C; IR (KBr): ν = 3448*w*, 3031*w*, 2864*w*, 1719*s*, 1629*m*, 1597*m*, 1509*s*, 1454*m*, 1431*m*, 1382*m*, 1304*m*, 1259*s*, 1168*s*, 1133*s*, 1007*m*, 982*m*, 840*m*, 802*m*, 734*m*, 695*s* cm$^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 248 (4.53), 357 (4.66) nm; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.70 (*dd*, *J* = 15.9, 3.4 Hz, 2H), 7.57 (*d*, *J* = 15.9 Hz, 1H, 3-H), 7.47 – 7.27 (*m*,

37H), 7.24 – 7.13 (*m*, 4H), 7.10 – 6.98 (*m*, 4H), 6.90 (*d*, *J* = 8.4 Hz, 1H), 6.85 (*dd*, *J* = 8.4, 4.6 Hz, 2H), 6.37 (*dd*, *J* = 15.9, 2.3 Hz, 2H), 6.25 (*d*, *J* = 15.9 Hz, 1H, 2-H), 5.30 (*s*, 1H), 5.19 – 5.04 (*m*, 5H), 4.44 (*t*, *J* = 6.8 Hz, 2H, 1´$^{v}$-H), 3.04 (*t*, *J* = 6.8 Hz, 2H, 2´$^{v}$-H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 167.2, 164.9, 151.6, 151.2, 149.1, 147.1, 147.0, 144.9, 142.5, 141.3, 137.0, 136.9, 136.8, 136.7, 128.7, 128.6, 128.1, 128.0, 127.5, 127.4, 127.4, 127.3, 127.2, 124.2, 123.6, 123.5, 123.1, 116.0, 114.4, 114.2, 114.0, 113.9, 71.5, 71.4, 71.1, 71.0, 64.5 (C-1$^{v}$´), 34.8 (C-2$^{v}$´) ppm; MS (ESI, MeOH/$CH_2Cl_2$): m/z (%) = 1199.3 ([M+$NH_4$]$^+$, 19), 1203.4 ([M+Na]$^+$, 100), 1219. 4 ([M+K]$^+$, 41); analysis calcd for $C_{77}H_{64}O_{12}$ (1181,35): C 78.29, H 5.46; found: C 77.99, H 5.64.

#### 4.2.1.28 2-{2-[((*E*)-3-(3,4-bis(benzyloxy)phenyl)acryloyl)oxy]ethyl}phenyl (*E*)-3-(3,4-bis(benzyloxy)phenyl)-acrylate (27)

Compound **27** was obtained as a white solid (0.35 g, 40%); $R_F$ = 0.49 (silica gel; dichloromethane); m.p. 96 – 99 °C; IR (KBr): ν = 3448*w*, 3030*w*, 1714*m*, 1631*s*, 1596*m*, 1511*s*, 1492*m*, 1454*m*, 1433*m*, 1383*m*, 1303*m*, 1263*s*, 1217*m*, 1168*s*, 1134*s*, 1018*m*, 1000*m*, 750*m*, 695*m* cm$^{-1}$; UV-vis ($CHCl_3$): λ (log ε) = 248 (4.43), 354 (4.57) nm; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.77 (*d*, *J* = 15.9 Hz, 1H, 3-H), 7.54 (*d*, *J* = 15.9 Hz, 1H, 3$^{v}$´-H), 7.49 – 7.41 (*m*, 8H), 7.41 – 7.28 (*m*, 11H), 7.23 (*td*, *J* = 7.4, 1.2 Hz, 2H), 7.19 – 7.14 (*m*, 4H), 7.10 (*dt*, J = 4.7, 2.2 Hz, 2H), 7.02 (*dd*, *J* = 8.3, 2.0 Hz, 1H), 6.90 (*dd*, *J* = 14.3, 8.4 Hz, 2H), 6.47 (*d*, *J* = 15.9 Hz, 1H, 2-H), 6.22 (*d*, *J* = 15.9 Hz, 1H, 2$^{v}$´-H), 5.20 + 5.18 + 5.17 + 5.15 (*s*, 8H, 1´´-H+1´´´-H+1$^{v}$´´´-H+1´$^{x}$), 4.42 (*t*, *J* = 6.9 Hz, 2H, 1´$^{v}$-H), 2-99 (*t*, *J* = 6.9 Hz, 2H, 2´$^{v}$-H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 167.2 (C-1$^{v}$´), 165.6 (C-1), 151.6 (C-4´), 151.2 (C-4$^{v}$´´), 149.6 (C-3´), 149.2 (C-3$^{v}$´´), 146.8 (C-3$^{v}$´), 144.7 (C-3), 137.0 + 136.9 + 136.8 + 136.8 (C-2´´+C-2´´´+C-2$^{v}$´´´+C-2´$^{v}$), 130.9, 130.2, 128.7, 128.7, 128.1, 128.0, 127.5, 127.4, 127.3, 126.2, 123.5, 123.0, 122.7, 116.1 (C-2$^{v}$´), 114.9 (C-2), 114.4 + 114.0 (C-5´+C-5$^{v}$´´), 113.9 + 113.8 (C-2´+C-2$^{v}$´´), 71.5 + 71.1 (C-1´´+C-1´´´+C-1$^{v}$´´´+C-1´$^{v}$), 63.9 (C-1$^{v}$´), 30.0 (C-2$^{v}$´) ppm; MS (ESI, MeOH/$CH_2Cl_2$): m/z (%) = 823.1 ([M+H]$^+$, 5), 840.1 ([M+$NH_4$]$^+$, 18), 845.2 ([M+Na]$^+$, 100), 1668.1 ([2M+Na]$^+$, 86); analysis calcd for $C_{54}H_{46}O_8$ (822.95): C 78.81, H 5.63; found: C 78.60, H 5.81.

### 4.3 Biological assays

4.3.1 Solutions

Preparation of 50 mM Tris-HCl buffer solutions: Tris(hydroxymethyl)-amino-methane (606 mg) was dissolved in bi-distilled water (100 mL) and adjusted with HCl to a pH of 8.0±0.1.

The buffer was freshly prepared and stored in the refrigerator. AChE solution 2.005 U/mL: the enzyme (271 U/mg, 0.037 mg) was dissolved in freshly prepared buffer pH 8.0 (5 mL) containing $NaN_3$ (0.98 mg). BChE solution 2.040 U/mL: the enzyme (7.54 U/mg, 1.353 mg) was dissolved in freshly prepared buffer pH 8.0 (5 mL) containing $NaN_3$ (0.98 mg). DTNB solution 3 mM: DTNB (23.8 mg) was dissolved in freshly prepared buffer pH 8.0 (20 mL) containing NaCl (116.8 mg) and $MgCl_2$ (38.0 mg). ATChI solution 15 mM: ATChI (43.4 mg) was dissolved in bi-distilled water (10 mL). All solutions were stored in Eppendorf caps in the refrigerator or freezer, if necessary. The pure compounds were initially dissolved in DMSO, galantamine hydrobromide as standard for AChE and BChE was dissolved in bi-distilled water. The final concentrations for the enzymatic assay were obtained by diluting the stock solution with bi-distilled water. No inhibition was detected by residual DMSO or methanol (<0.5%).

4.2.2 Ellman´s assay

A mixture of the DTNB solution (125 mL), enzyme (25 mL) and compounds solutions (25 mL, 3 different concentrations and once water) was prepared and incubated at 30 °C for 20 min. The substrate (25 mL, 4 different concentrations) was added to start the enzymatic reaction. The absorbance data were recorded under a controlled temperature of 30 °C for 30 min at 1 min intervals. The used substrate concentrations in the test were as follows: [ATChI]=[BTChI]=0.9375 mM, 0.625 mM, 0.325 mM, 0.1875 mM. The mode of inhibition as well as $K_i$ and $K_{i'}$ were determined using Lineweaver-Burk, Dixon and Cornish-Bowden plots. Data were fitted using the Origin 6.1G software (Origin-Lab Corp., Northampton, MA, U.S.A.).

4.2.3 Cell lines and culture conditions

The cell lines used are human cancer cell lines: 518A2 (melanoma), A549 (alveolar basal epithelial adenocarcinoma), A2780 (ovarian carcinoma), MCF-7 (breast adenocarcinoma), and non-malignant mouse fibroblasts NIH 3T3. Cultures were maintained as monolayers in RPMI 1640 medium with L-glutamine (Capricorn Scientific GmbH, Ebsdorfergrund, Germany) supplemented with 10% heat inactivated fetal bovineserum (Sigma-Aldrich Chemie GmbH, Steinheim, Germany) and penicillin/streptomycin (Capricorn Scientific GmbH, Ebsdorfergrund, Germany) at 37 °C in a humidified atmosphere with 5% $CO_2$.

4.2.4 Cytotoxic assay

The cytotoxicity of the compounds was evaluated using the sulforhodamine-B (Kiton-Red S, ABCR) micro culture colorimetric assay. Cells were seeded into 96-well plates on day 0 at appropriate cell densities to prevent confluence of the cells during the period of experiment. After 24 h, the cells were treated with six different concentrations (1, 3, 7, 12, 20, and 30 μM) minimum. The final concentration of DMSO/DMF never exceeded 0.5%, which was non-toxic to the cells. After a 96h treatment, the supernatant medium from the 96-well plates was discarded, the cells were fixed with 10% trichloroacetic acid (TCA) and allowed to rest at 4 °C. After 24 h fixation, the cells were washed in a strip washer and dyed with SRB solution (100 μL, 0.4% in 1% acetic acid) for about 20 min. After dying, the plates were washed four times with 1% acetic acid to remove the excess of the dye and allowed to air-dry overnight. Tris base solution (200 μL, 10 mM) was added to each well and absorbance was measured at λ = 570 nm using a 96-well plate reader (Tecan Spectra, Crailsheim, Germany). The EC50 values were averaged from three independent experiments performed each in triplicate calculated from semi logarithmic dose response curves applying a non-linear 4 P Hills-slope equation (GraphPad Prism5; variables top and bottom were set to 100 and 0, respectively).

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Highlights

* Novel caffeic acid phenethyl ester (CAPE) derivatives were synthesized
* Ellman's assays showed several of them as inhibitors of AChE
* Thus, the best inhibitor gave $K_i = 0.72 \pm 0.31$ µM, $K_{i'} = 1.80 \pm 0.21$ µM) for AChE
* Almost no inhibition was observed for BChE
* The compounds were not cytotoxic for human tumor and non-malignant NIH 3T3 cells