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# Synthesis and Biological Evaluation of Biphenyl Amides That Modulate the US28 Receptor

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To prepare and biologically evaluate 38 new potential US28 allosteric modulators, we employed a straightforward synthetic route involving radical arylation. The study was based on a former lead structure but with the dihydroisoquinolinone moiety replaced by substituted biphenyls. The investigation of structure–activity relationships among the new biphenyl-derived ligands led to a preliminary pharmacophore model and the discovery of four promising candidates with full inverse agonist properties.

## Introduction

Infection with human cytomegalovirus (HCMV) is the major cause of morbidity and mortality in immunocompromised newborns, transplant patients, AIDS patients, and some oncology patients.[1] There are five systemic drugs approved for HCMV treatment: ganciclovir, valganciclovir, foscarnet, and cidofovir target the viral DNA polymerase,[2] and fomivirsen acts as an antisense antiviral by blocking the translation of viral mRNA.[3] Because the routine use of these drugs is associated with intolerable toxicities, selection for resistant HCMV strains, and high treatment costs, the development of new anti-HCMV therapeutics is highly desirable. Among the potential drug targets are the viral G-protein-coupled receptors (GPCRs). GPCRs are an excellent drug target; more than 30% of current drugs on the market target this receptor class.[4] HCMV encodes four viral GPCRs, including the US28 receptor.

The US28 receptor possesses significant homology to human chemokine receptors,[5] and participates in many actions that enable viral survival and dissemination in infected hosts as well as causing aggravation of diseases associated with HCMV infection. For example, the US28 receptor scavenges chemokines,[6] which might be a viral strategy for preventing leukocyte recruitment in the infected area, thereby allowing the virus to evade host immune attack on infected cells. The US28 receptor also appears to have high affinity for several CC-type chemokines, as well as for Fractalkine/$CX_3CL1$,[7] which acts as an adhesion molecule on most cell types. Because of its affinity for Fractalkine/$CX_3CL1$, US28 receptors expressed on HCMV-infected cells might enhance cell adhesion and cell–cell interactions, thus contributing to the spread and transmission of the virus.[8] In this context the US28 receptor has also been investigated as a co-receptor for HIV entry.[9] Similarly, the expression of the US28 receptor on the surface of vascular smooth muscle cells (VSMC) induces their migration toward a gradient of CC-type chemokines,[10] which are highly expressed in atherosclerotic lesions.[11] Moreover, constitutive signaling by the US28 receptor may affect transcription of viral and host genes and can activate transcription factors that are necessary for virus reactivation from latency.[12] Therefore, the US28 receptor is an interesting target, and the search for a potent inverse agonist of its constitutive activity is an ongoing challenge.

Several studies have recently been reported on the synthesis and biological evaluation of novel ligands for the US28 receptor. Inhibitors of chemokine binding to the US28 receptor, such as methiothepin (**1**), have been studied by Schall et al. in competitive binding assays that use radiolabeled [$^{125}$I]Fractalkine/$CX_3CL1$ (Figure 1).[13]

The characterization of a broad variety of VUF ligands (e.g., VUF2274 (**2**)) in functional assays, measuring the accumulation of inositol triphosphate in the PLCβ pathway, and the inhibi-

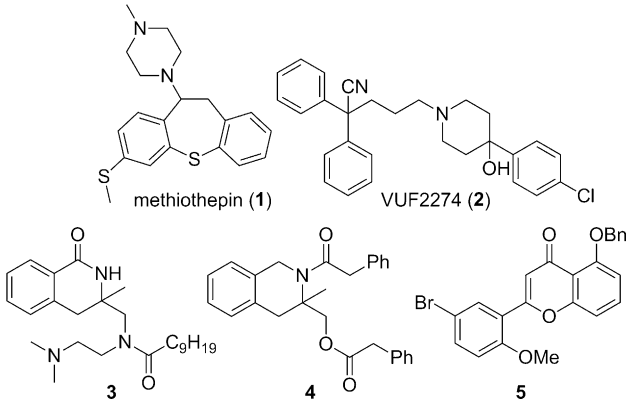


**Figure 1.** Ligands that bind the US28 receptor: methiothepin (**1**),[13] VUF2274 (**2**),[14c] dihydroisoquinolinone **3**, tetrahydroisoquinoline **4**, and flavonoid-based derivative **5**.[15]

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tion of [$^{125}$I]Rantes/CCL5 binding has been reported by Leurs and co-workers.[14] Dihydroisoquinolinones, tetrahydroisoquinolines, and the chalcone- and flavonoid-based derivatives (c.f. ligands **3**, **4**, and **5**) have been described as allosteric modulators of the US28 receptor by our research group and Phanstiel's group.[15] The luciferase-based PathDetect Elk1 gene reporter assay was used to characterize the inverse agonist properties of the compounds.[15] Dihydroisoquinolinone **3** has inverse agonist properties with slightly improved potency and similar activity to VUF2274 (**2**; see Table 1 below for data). To ensure the broad and straightforward accessibility of new compounds for biological testing, it is our general goal to exploit recently developed and efficient synthetic strategies with a broad substrate scope for the preparation of potential ligands.

In our first study on the US28 receptor,[15] we used radical carboamination reactions as a key step to synthesize dihydroisoquinolinones such as amide **3**.[16,17] Given the promising results obtained with ligands of this type, we then considered replacement of the isoquinolinone moiety **6a** with a biphenylamine **6b** for three main reasons: 1) our synthetic access to substructure **6b** allows a broad variation of the substituents $R^1$, 2) the possibility to vary the dihedral angle of the biphenyl unit in **6b** through introduction of suitable substituents, and 3) the straightforward accessibility of biphenylamines **6b** from simple starting materials through only one synthetic step.[18,19] Moreover, biphenyl units are commonly found as structural elements in many pharmaceuticals.[20]

Herein we report the synthesis of a novel class of biphenylamine derivatives and their biological evaluation with regard to inhibition of constitutive signaling of the US28 receptor. The general biphenylamine structure **7** depicted in Figure 2 was varied in eight different ways to gain insight into structure–activity relationships. For better understanding, the groups of structural variations 1–8 correspond to Schemes 1–8 in the following section.

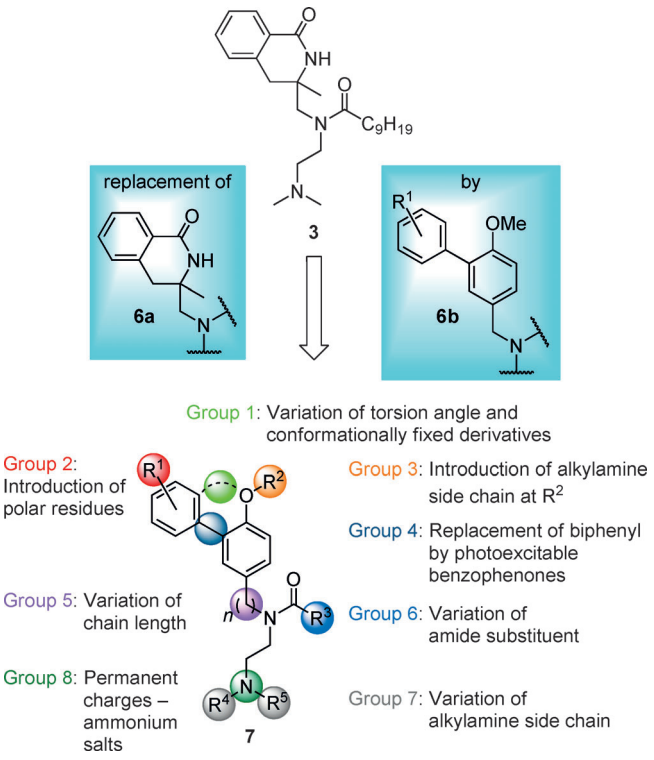
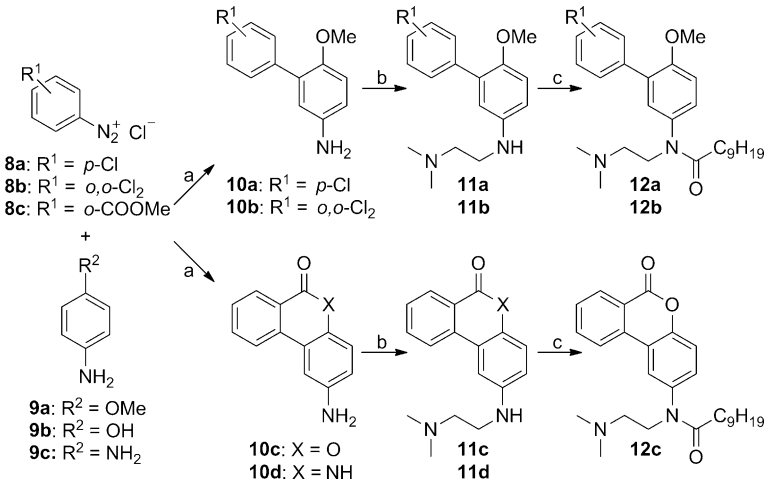



**Figure 2.** General approach to biphenylamine ligands **7**.

## Results and Discussion

### Chemistry

One reason for choosing biphenyls as a structural core motif for the potential US28 receptor ligands was the associated option to vary the torsion or dihedral angle of the aryl–aryl bond through the substitution pattern. In this way, we focused on the preparation of a structurally more diverse library of test compounds than would have been possible through the simple replacement of substituents on a given central unit, such as a benzene core. The synthesis of the first group of compounds started with a reductive titanium(III)-mediated radical aryl–aryl coupling (Scheme 1). By reacting the two aryl diazonium chlorides **8a** and **8b** with 4-anisidine (**9a**), and salt **8c** with 4-aminophenol (**9b**) or 1,4-phenylenediamine (**9c**), a set of four biphenyls **10a–d** were available through a simple synthetic step and without any further protecting group strategy.[19a] Regarding the dihedral angle of these biphenyls, **10a** can be expected to be slightly twisted because of the occupancy of just one out of four *ortho* positions (relative to the aryl–aryl bond) by

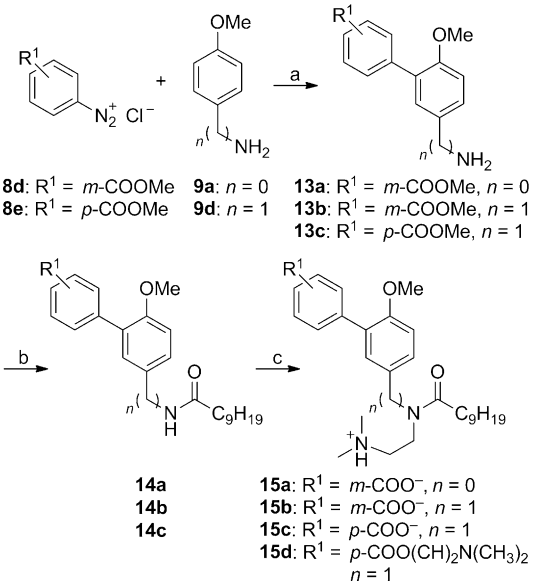



**Scheme 1.** Variation of torsion angle and conformationally fixed derivatives. *Reagents and conditions*: a) $TiCl_3$, HCl/$H_2O$/$CH_3CN$, RT, **8a–c** added over 15 min (**10a**: 57%, **10b**: 31%, **10c**: 34%, **10d**: 18%); b) 2-chloro-*N*,*N*-dimethylethylamine·HCl, $H_2O$, microwave irradiation at 150 °C, 20 min (**11a**: 38%, **11b**: 31%, **11c**: 23%, **11d**: 9%); c) $H_{19}C_9COCl$, $NEt_3$, 1,2-$C_2H_4Cl_2$, 50 °C, 12 h (**12a**: 38%, **12b**: 75%, **12c**: 35%).

the methoxy group. Higher degrees of substitution at the *ortho* positions, such as in the dichloro derivative **10b**, can be expected to lead to increased dihedral angles of ~50°–80°.[21] Because the ester group of the diazonium salt **8c** readily reacts with proximal hydroxy or amino functionalities as present in **9b** and **9c**, aryl–aryl coupling furnished the nearly planar dibenzopyranone **10c** and phenanthridinone **10d** through a subsequent instantaneous cyclization step.

Titanium(III)-mediated radical arylations of 4-anisidine (**9a**) and 4-aminophenol (**9b**) commonly give yields in the range of 40–70%.[19a] The comparatively lower yield obtained for **10b** is most probably because more acetonitrile had to be added to the reaction mixture to solubilize the less polar diazonium salt **8b**.[22] Reactions of acceptor-substituted electron-poor diazonium salts, such as **8c** with **9b** and **9c**, can be complicated if these substrates can be oxidized to the corresponding quinone imines by the diazonium salt. The reagents for the following steps to give **11a–d** and **12a–c** were chosen in a way to maintain structural similarity and thus comparability with dihydroisoquinolinone **3** from our previous study (Figure 2). The alkylation of **10a–d** with 2-chloro-*N*,*N*-dimethylethylamine hydrochloride under microwave irradiation produced moderate to low yields.[23] Amides **12a–c** were finally obtained under standard conditions with decanoyl chloride as the acylating agent.

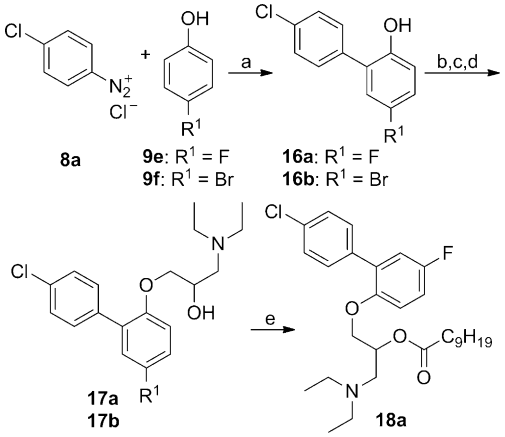
To evaluate the influence of polar substituents on the biphenyl core, the radical aryl–aryl coupling was also conducted with the *meta*- and *para*-methoxycarbonyl-substituted diazonium salts **8d** and **8e** (Scheme 2). Because neither of the two substrates 4-anisidine (**9a**) and 4-methoxybenzylamine (**9d**) is easily oxidized and no acetonitrile had to be added for solubility reasons, the desired biphenyls **13a–c** were obtained in fair yields of 54–63%, which are in the usual range mentioned above. Because the benzylamines **13b** and **13c** could not be alkylated with 2-chloro-*N*,*N*-dimethylethylamine hydrochloride under the aforementioned microwave conditions, the synthetic sequence was modified in the way that **13a–c** were first acylated to give the corresponding amides **14a–c**. Deprotonation of **14a–c** with sodium hydride then allowed attachment of the alkylamino side chain through reaction with 2-chloro-*N*,*N*-dimethylethylamine hydrochloride. Saponification of the ester groups and formation of carboxylates **15a–c** occurred during the aqueous workup after the alkylation step.




**Scheme 2.** Introduction of polar residues. *Reagents and conditions*: a) $TiCl_3$, $HCl/H_2O$, over 15 min, RT, (**13a**: 63%, **13b**: 54%, **13c**: 58%); b) $H_{19}C_9COCl$, $NEt_3$, 1,2-$C_2H_4Cl_2$, 50 °C, 12 h, (**14a**: 58%, **14b**: 33%, **14c**:18%); c) NaH, DMA, 1 h at 0 °C, then 2-chloro-*N*,*N*-dimethylethylamine·HCl, RT, 16 h (**15a**: 13%, **15b**: 18%, **15c**: 5%, **15d**: 20%).

After the alkylation procedure, we were surprised to find the by-product **15d**, which appears to arise from an attack of the carboxylate salt **15c** by the alkylating agent. This side reaction is likely to occur during workup, when the ester has been converted into a more nucleophilic carboxylate.[24,25]

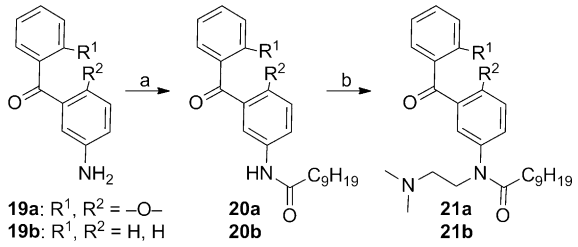
Besides attaching the alkylamino and the decanoyl side chains at the nitrogen atom of the biphenylamine core unit (c.f. structure **7**, Figure 2), we also wanted to explore the biological effects of linking those structural elements via the phenolic oxygen atom, which has so far been protected as a methyl ether. To avoid the presence of an additional polar substituent in the final racemic products **17** and **18**, the typical amino group on the biphenyl core was replaced by less polar fluoro or bromo substituents (Scheme 3). To help clarify the close structural relationship between the biphenyl ether **18a** and previously described compounds such as **12a**, the structure of **18a** has been rotated in Scheme 3. Starting from the biphenyl alcohols **16a** and **16b**, which were again prepared by titanium(III)-mediated aryl–aryl coupling, alkylation was achieved with epichlorohydrin.[26] The reaction with **16a** exclusively gave a β-chloro alcohol, which was converted into the corresponding epoxide by treatment with dilute sodium hydroxide in step c). Under similar conditions, **16b** led directly to the epoxide along with major amounts the β-chloro alcohol. Subse-




**Scheme 3.** Introduction of the alkylamine side chain at the phenolic oxygen atom. *Reagents and conditions*: a) $TiCl_3$, $HCl/H_2O/CH_3CN$, RT, over 15 min (**16a**: 35%, **16b**: 21%); b) epichlorohydrine, pyridine, RT, 24 h (**a**: 71% β-chloro alcohol, **b**: 31% β-chloro alcohol + 13% epoxide, epoxide used for step d); c) 0.71 N NaOH, EtOH, RT, 1 h (**a**: 55% epoxide); d) $NEt_2H$, $H_2O$, RT, 24 h, (**17a**: 53%, **167**: 65%); e) $H_{19}C_9COCl$, $NEt_3$, 1,2-$C_2H_4Cl_2$, 50 °C, 12 h (**18a**: 18%).

quent amination through ring opening of both intermediate epoxides[27] with diethylamine furnished amino alcohols **17a** and **17b**, the former of which was further converted into **18a** under standard acylation conditions.

Related to the compounds **11c**,**d** and **12c** (Scheme 1), which incorporate a more or less planar biphenyl unit, we also investigated replacement of the biphenyl substructure by a benzophenone or xanthone unit (Scheme 4). In case of high affinity



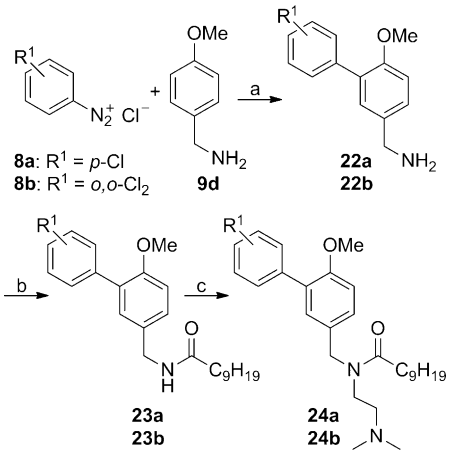

**Scheme 4.** Replacement of biphenyl by photoexcitable benzophenones. *Reagents and conditions*: a) $H_{19}C_9COCl$, $NEt_3$, 1,2-$C_2H_4Cl_2$, 50 °C, 12 h (**20a**: 80%, **20b**: quant); b) NaH, DMA, 0 °C, 1 h, then 2-chloro-*N*,*N*-dimethylethylamine·HCl, RT, 16 h (**21a**: 38%, **21b**: 8%).

for the US28 receptor, such ligands could be valuable tools in photolabeling experiments[28] to determine the proximal amino acids in the binding pocket. Starting from 2-aminoxanthone (**19a**)[29] or 3-aminobenzophenone (**19b**), acylation with decanoyl chloride proceeded without difficulty to give amides **20a** and **20b**. Deprotonation with excess sodium hydride and alkylation with 2-chloro-*N*,*N*-dimethylethylamine then provided the desired target compounds **21a** and **21b**.[30]

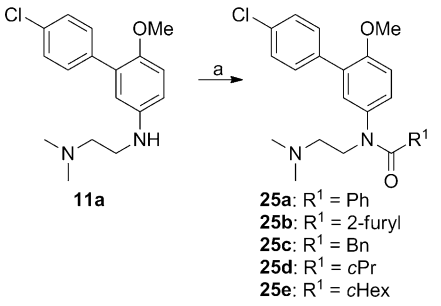
Titanium(III)-mediated radical arylations of phenols and phenyl ethers proceed best when water can be used as the only solvent because this mostly limits undesired hydrogen abstraction by the aryl radicals. With regard to the required solubility in acidic aqueous solutions, aminophenols such as **9a** and **9b** and hydroxy- or methoxybenzylamines such as **9d** represent ideal substrates for this reaction type.[19b] Not surprisingly, fair yields were obtained from the arylation reactions of 4-methoxybenzylamine (**9d**) with the diazonium salts **8a** and **8b** (Scheme 5). The lower yield of **22b** can again be explained by the necessity to add acetonitrile to solubilize the diazonium salt **8b**. In the next steps, the biphenylmethylamines **22a** and **22b** were first acylated with decanoyl chloride to give **23a** and **23b**, and then alkylated under the previously established conditions to obtain the desired target compounds **24a** and **24b**.

Variations of the carbonyl part of the amide were carried out with biphenyl **11a** as the starting material (Scheme 6). Acylation with five acid chlorides under standard conditions gave amides **25a**–**e** in good-to-high yields with the exception of the furoyl derivative **25b**. For the purification of amides **25b**, **25d**, and **25e**, it was particularly useful to remove the carboxylic acid derivatives, which arise from hydrolysis of the acid chlorides during workup, through filtration over aluminum oxide.

4-Aryl-4-hydroxypiperidine and 2,2-diphenylpentanenitrile occur as common structural motifs in a number of known

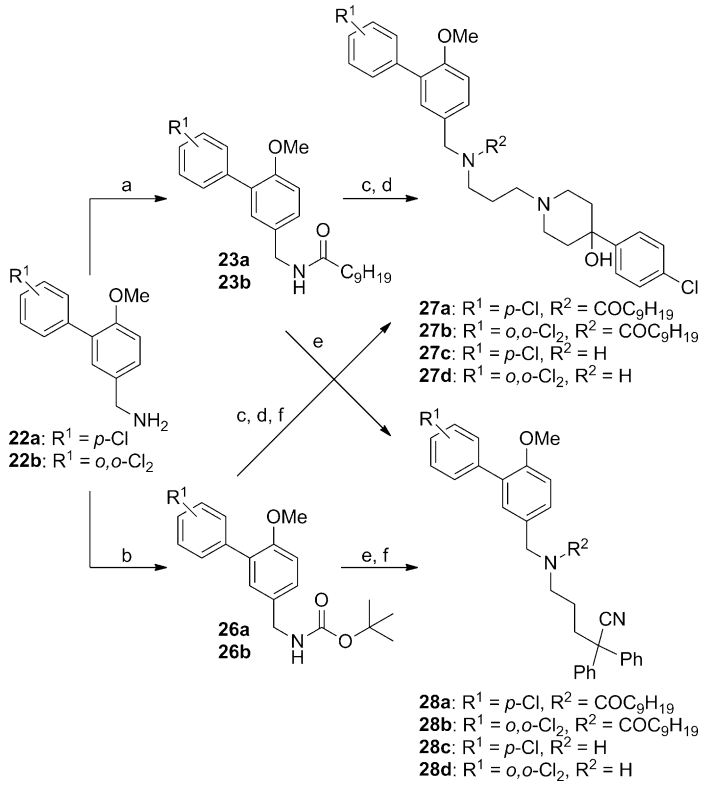



**Scheme 5.** Variation of chain length. *Reagents and conditions*: a) $TiCl_3$, HCl/$H_2O$, over 15 min (**22a**: 65%, **22b**: 48%), b) $H_{19}C_9COCl$, $NEt_3$, 1,2-$C_2H_4Cl_2$, 50 °C, 12 h (**23a**: 32%, **23b**: 14%); c) NaH, DMA, 1 h at 0 °C, then 2-chloro-*N*,*N*-dimethylethylamine·HCl, RT, 16 h (**24a**: 77%, **24b**: 30%).




**Scheme 6.** Variation of the acyl moiety of the amide. *Reagents and conditions*: a) PhCOCl or furan-2-carboxylic acid chloride or $PhCH_2COCl$ or cyclopropanecarboxylic acid chloride or cyclohexanecarboxylic acid chloride, $NEt_3$, 1,2-$C_2H_4Cl_2$, 50 °C, 12 h (**25a**: 73%, **25b**: 22%, **25c**: 68%, **25d**: 49%, **25e**: 88%).

US28 ligands such as VUF2274, VUF5743, and VUF6984.[14c] To investigate the influence of these established building blocks in combination with the biphenylamine unit, two sets of hybrid ligands were prepared (Scheme 7). Depending on whether the final product should be a benzylamide or a benzylamine, the starting materials **22a** and **22b** were either acylated with decanoyl chloride (a) or protected with an acid-sensitive *tert*-butyloxycarbonyl (Boc) group (b) to give the four key intermediates **23a**,**b** and **26a**,**b**. The attachment of the 4-aryl-4-hydroxypiperidine unit to yield compounds **27a**–**d** was carried out in two steps: amides **23a**,**b** and carbamates **26a**,**b** were first N-alkylated with 1-bromo-3-chloropropane (c) to give alkyl chlorides,[31] which were then reacted with 4-(4-chlorophenyl)-4-hydroxypiperidine under iodide catalysis at elevated temperatures (d).[32,33] To obtain the diphenylpentanenitrile-substituted biphenylmethylamines **28a**–**d**, the above-mentioned key intermediates **23a**,**b** and **26a**,**b** were deprotonated with sodium hydride and then treated with 5-bromo-2,2-diphenylpentanenitrile (e).[30,34] After the final Boc deprotection with trifluoroacetic acid (f), benzylamines **28c** and **28d**




**Scheme 7.** Variation of the alkylamine side chain. *Reagents and conditions*: a) $H_{19}C_9COCl$, $NEt_3$, 1,2-$C_2H_4Cl_2$, 50 °C, 12 h (**23a**: 32%, **23b**:14%); b) $Boc_2O$, $NEt_3$, 1,2-$C_2H_4Cl_2$, 50 °C, 12 h (**26a**: 43%, **26b**: 44%); c) NaH, DMF, 1 h at 0 °C, then 1-bromo-3-chloropropane, RT, 16 h (**a**: 14%, **b**: 12%, **c**: 47%, **d**: 57%); d) 4-(4-chlorophenyl)-4-hydroxypiperidine, NaI, $Na_2CO_3$, *n*-butanol, 100 °C, 20 h (**27a**: 14%, **27b**: 25%, **c**: 60%, **d**: 56%); e) NaH, DMF, 1 h at 0 °C, then 5-bromo-2,2-diphenylpentanenitrile, RT, 16 h (**28a**: 66%, **28b**: 22%, **c**: 74%, **d**: 86%); f) TFA, $CH_2Cl_2$, 0 °C, 3 h (**27c**: 100%, **27d**: 100%, **28c**: 38%, **28d**: 16%).

showed unexpectedly high hydrophilicity, which in turn complicated the extraction of these compounds from the aqueous phase and led to relatively low yields in this otherwise simple step. To avoid this difficulty for the related hydroxypiperidines **27c** and **27d**, these compounds were isolated as bis-trifluoroacetate salts.

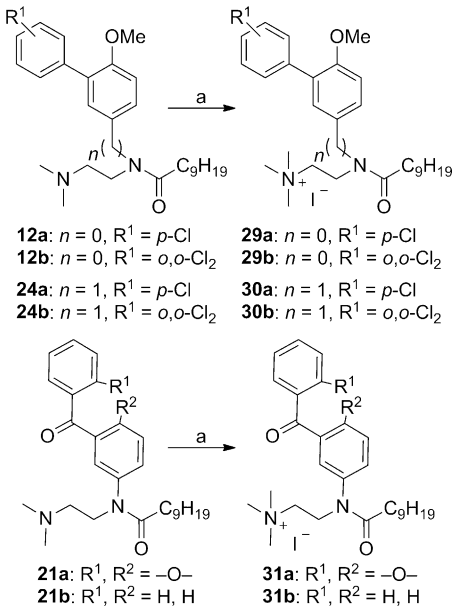
Although the known ligand VUF2274 had been converted into a quaternary ammonium salt that led to a complete loss of binding affinity and activity at the US28 receptor,[14b,35] we wanted to determine whether a comparable structural modification of our ligands would lead to a similar effect. We turned to the synthesis of a set of quaternary ammonium salts (Scheme 8). Starting from anilides **12a** and **12b**, benzylamides **24a** and **24b**, and xanthone and benzophenone derivatives **21a** and **21b**, six ammonium iodides—**29a**,**b**, **30a**,**b**, and **31a**,**b**—could be cleanly prepared through alkylation with methyl iodide.[35]

## Biological evaluation

The ability of compounds to inhibit the constitutive activity of the US28 receptor was tested with a reporter gene assay using the PathDetect *trans*-Elk11 system (Stratagene/Agilent).[15] Transient expression of the US28 receptor in human embryonic kidney (HEK) 293T cells leads to a significant increase in basal accumulation of the reporter gene luciferase. This US28-receptor-mediated accumulation can be efficiently inhibited by various ligands.[15]

Initially the cytotoxicity of all compounds in the HEK293T cell line was investigated with the CellTiter 96 AQueous One Solution Cell Proliferation Assay (Promega). This is a colorimetric method for determining the number of viable cells in cytotoxicity assays. Several compounds demonstrated a negative effect on cell viability at a concentration of 10 μM (Supporting Information, table S1). The VUF hybrids with a 4-(4-chlorophenyl)-4-hydroxypiperidine moiety (**27a**–**d**) were characterized as the highest cytotoxic derivatives. Interestingly, the hydroxy group in this structural element was previously suggested to be a site of potential metabolic toxicity.[36] All compounds showing cytotoxicity (entries: **12c**, **23a**, **25e**, and **27a**–**d**) were omitted from further biological evaluation.

Investigations concerning the influence of the torsion angle of the biphenyls (Scheme 1, Table 1, entries **11a**–**d** and **12a**–**c**) on the potency and inverse agonist activity revealed that there is no significant effect on potency; only some differences in inverse agonist properties were observed (−31% for *para*-chloro (**12a**) and −62% for the *ortho*,*ortho*-dichloro derivative **12b**; Table 1).[37] The conformationally fixed derivatives **11c**,**d** showed negligible activity. The cytotoxicity observed for dibenzopyranone **12c** could be related to ring opening and unselective acylation of various targets.




**Scheme 8.** Permanent charges—ammonium salts. *Reagents and conditions*: a) $CH_3I$, $CH_2Cl_2$, RT, 24 h (100% for all).

**Table 1.** Biological evaluation of compounds in transiently transfected human embryonic kidney (HEK) 293T cells containing the US28 receptor and the components of the PathDetect *trans*-Elk1 reporter gene assay.[a]

| Compd | Scheme/Figure | $EC_{50}$ [μM][b] | $pEC_{50} \pm SEM$[b] | Efficacy [%] |
|---|---|---|---|---|
| **1** | Figure 1 | 0.35 | 6.46 ± 0.46 | 10 ± 3 |
| **2** | | 4.50 | 5.34 ± 0.45 | −22 ± 8 |
| **3** | | 15.0 | 4.82 ± 0.10 | −37 ± 9 |
| **11a** | Scheme 1 | NE | NE | NE |
| **11c** | | NA | NA | −36 ± 2[c] |
| **11d** | | NE | NE | NE |
| **12a** | | 3.01 | 5.52 ± 0.10 | −31 ± 2 |
| **12b** | | 4.11 | 5.39 ± 0.05 | −62 ± 2 |
| **12c** | | TOX | TOX | TOX |
| **15a** | Scheme 2 | NA | NA | −48[c] |
| **15b** | | 1.74 | 5.76 ± 0.09 | −80 ± 5 |
| **15c** | | NA | NA | −31 ± 5[c] |
| **15d** | | NE | NE | NE |
| **17a** | Scheme 3 | NA | NA | −18 ± 5[c] |
| **17b** | | NE | NE | NE |
| **18a** | | 3.39 | 5.47 ± 0.15 | −71 ± 8 |
| **21a** | Scheme 4 | NE | NE | NE |
| **21b** | | NE | NE | NE |
| **23a** | Scheme 5 | TOX | TOX | TOX |
| **23b** | | NA | NA | −49 |
| **24a** | | 2.41 | 5.62 ± 0.03 | −100 ± 2 |
| **24b** | | 10.8 | 4.96 ± 0.04 | −47 ± 2 |
| **25a** | Scheme 6 | NA | NA | −53 ± 4[c] |
| **25b** | | NA | NA | −53 ± 10[c] |
| **25c** | | 3.43 | 5.47 ± 0.10 | −47 ± 7 |
| **25d** | | NA | NA | −50 ± 8[c] |
| **25e** | | TOX | TOX | TOX |
| **27a** | Scheme 7 | TOX | TOX | TOX |
| **27b** | | TOX | TOX | TOX |
| **27c** | | TOX | TOX | TOX |
| **27d** | | TOX | TOX | TOX |
| **28a** | | NA | NA | −23 ± 10[c] |
| **28b** | | NA | NA | −27 ± 10[c] |
| **28c** | | 9.73 | 5.01 ± 0.02 | −91 ± 4 |
| **28d** | | 6.61 | 5.18 ± 0.02 | −59 ± 4 |
| **29a** | Scheme 8 | 4.60 | 5.33 ± 0.15 | −61 ± 8 |
| **29b** | | 4.90 | 5.31 ± 0.01 | −47 ± 4 |
| **30a** | | 4.96 | 5.30 ± 0.01 | −100 ± 2 |
| **30b** | | 4.65 | 5.33 ± 0.03 | −95 ± 2 |
| **31a** | | NE | NE | NE |
| **31b** | | NE | NE | NE |

[a] Functional data were obtained on HEK293T cells that transiently express US28 and components of the PathDetect *trans*-Elk11 reporter gene system.[24] Dose–response curves of 3–5 experiments (performed in triplicate) were normalized and pooled to generate a mean curve from which the $EC_{50}$ value and maximum intrinsic activity of each compound was obtained. The resulting reporter gene assay data were analyzed by nonlinear regression using the algorithms in Prism 5.0 (GraphPad Software, San Diego, CA, USA). [b] Curves were fitted to the sigmoid curve by nonlinear regression analysis in which the $-\log EC_{50}$ values ($pEC_{50} \pm SEM$) were determined. NE = no effect when tested at 10 μM compound; NA = $EC_{50}$ value not available because of incomplete curves, only the efficacy at 10 μM reported; TOX = toxic compound. [c] Efficacy estimated at 10 μM compound.

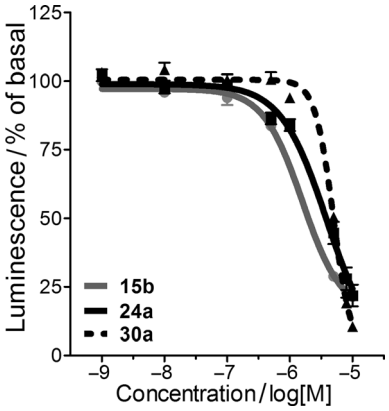



**Figure 3.** Biological characterization of the most potent novel compounds **15b**, **24a**, and **30a**. HEK293T cells were transiently transfected with the US28 receptor and components of the PathDetect *trans*-Elk1 reporter gene assay. Normalized curves from 3–5 experiments, each performed in triplicate, are shown; error bars represent SEM.

Importantly, and almost independent of the substitution pattern of the biphenyl unit, only the derivatives containing a decanoyl side chain acted as inverse agonists. At this early stage the presence of the decanoyl side chain thus appeared to be necessary for the inverse agonist properties of our biphenyl derivatives.

Exchange of the halogen substituents on the biphenyl core for a polar carboxylate group yielded a very active compound (Scheme 2, Table 1, entries **15a–d**). The compound with the best potency and efficacy in this series (**15b**, $EC_{50}$: 1.74 μM, efficacy: −80%, Figure 3) contains the carboxylate group at the *meta* position of the biphenyl group attached to the methoxybenzylamine. Moving the carboxylate group to the *para* position led to a significant loss of potency and efficacy (**15c**, efficacy at 10 μM: −31%). Beside this substitution pattern, we discovered that the distance between the biphenyl core and the nitrogen atom significantly influences the biological properties of the compounds. Elimination of the methylene group between the aryl moiety and the nitrogen atom again resulted in a significant loss of activity (from $n = 1$ (**15b**) to $n = 0$ (**15a**); efficacy −80 and −48%, respectively) and potency (**15b**: 1.74 μM and **15a**: > 10 μM).

Besides attachment to the alkylamino and the decanoyl side chains, as in compounds **12a** and **15a**, and to the nitrogen atom on the biphenylamine unit, we also explored the biologi-

cal effects of linking the biphenyl and those structural elements via a central isopropanolamine core structure (Scheme 3, Table 1, entries **17a**,**b** and **18a**). In this series only **18a** acted as an inverse agonist, with an $EC_{50}$ value of 3.39 μM and an efficacy of −71%. This again underscores the importance of the decanoyl side chain for the potency and inverse agonist activity of the compounds, as this structural element is absent in **17a**,**b**.

Replacement of the biphenyl core with benzophenone or xanthone units, which are commonly used as reactive substructures of photoexcitable ligands, resulted in a complete loss of inverse agonist properties for **21a**,**b** (Scheme 4, Table 1, entries **21a**,**b**). This indicates that the US28 receptor does not tolerate even a minor enlargement of the biphenyl moiety. This effect might be further negatively enhanced by the rigidity of the benzophenone-derived ligands **21a**,**b**, which do not possess a methylene spacer between the aromatic part and the amide.

A comparison of the biological properties of **23a**,**b** and **24a**,**b** unambiguously shows that the presence of the dimethylethylamine side chain is essential for both potency and inverse agonist activity (Scheme 5, Table 1, entries **23a**,**b** and **24a**,**b**). Compounds **23a**,**b**, in which this side chain is absent, were either cytotoxic or had no measurable effects. The derivatives containing the dimethylethylamine side chain (**24a**–**b**), on the other hand, demonstrated good potency and remarkable efficacy, with the *para*-chloro-substituted biphenyl moiety (**24a**, $EC_{50}$: 2.41 μM, efficacy: −100%, Figure 3) being superior to the *ortho*,*ortho*-dichloro derivative (**24b**, $EC_{50}$: 2.03 μM, efficacy: −54%).

To determine whether the US28 receptor would tolerate a variation of the acyl moiety of the amide, we replaced the original decanoyl chain with various aromatic and cyclic aliphatic appendages (Scheme 6, Table 1, entries **25a**–**e**). The cyclohexyl derivative proved to be cytotoxic. Other appendages yielded partial inverse agonists (up to −53%), but only for **25c** was the determination of the $EC_{50}$ value possible (3.43 μM). This indicates the importance of the flexibility of the side chain, which is provided only in **25c** through the presence of a methylene group between the amide bond and the phenyl ring.

4-Aryl-4-hydroxypiperidine and 2,2-diphenylpentanenitrile are known as common structural motifs in a number of US28 ligands such as VUF2274, VUF5743, and VUF6984.[14c] To evaluate these building blocks in combination with the best scaffold we have found thus far, which is a biphenylmethylamine, two sets of hybrid ligands were prepared (Scheme 7, Table 1, entries **27a**–**d** and **28a**–**d**). All compounds that contained the 4-hydroxypiperidine moiety (**27a**–**d**) were highly cytotoxic (Supporting Information, table S1). The second set of compounds incorporating the 2,2-diphenylpentanenitrile scaffold differed significantly in their biological properties. The nitriles **28a**,**b** that contained the nonpolar decanoyl side chain as well as the comparably lipophilic pentanenitrile unit showed only weak partial inverse agonist activity (−23 and −27%, respectively). The nitriles **28c**,**d** lacking the decanoyl side chain regained some potency and efficacy with the unique feature that the *ortho*,*ortho*-dichloro derivative **28d** displayed less efficacy but greater potency (−59%, $EC_{50}$: 6.61 μM) than its *para*-monochlorinated counterpart **28c** (−91%, $EC_{50}$: 9.73 μM). In general, two lipophilic side chains in **28c**,**d** appear not to be tolerated, whereas replacement of the decanoyl part by the lipophilic pentanenitrile results only in a partial loss of activity. This observation could be at least partially explained by the fact that **28c**,**d** contains a basic nitrogen atom, which is not present in **28a**,**b**. A similar structure–activity relationship has been observed before for the biphenylmethylamines **23a**,**b** (without basic nitrogen) and **24a**,**b** (with basic nitrogen).

Although the conversion of VUF2274 into a quaternary ammonium salt led to a complete loss of binding affinity and activity at the US28 receptor,[14b,35] we investigated a similar structural modification of our ligands (Scheme 8, Table 1, Figure 3, entries **29a**,**b**, **30a**,**b**, and **31a**,**b**). Compounds **29a**,**b** and **30a**,**b** had only slightly reduced potency at the US28 receptor while retaining good efficacy (up to −100%). Again, the distance between the biphenyl core and the nitrogen atom dictated the inverse agonist properties of the compounds as already observed for **15a**–**c**. Interestingly, the differences in potency and efficacy between the *para*-chloro- and *ortho*,*ortho*-dichloro-substituted ligands (**29a** vs. **29b**, **30a** vs. **30b**) were negligible for the ammonium salts (Table 1). In the case of benzophenone derivatives the introduction of the permanent charge did not help to improve the biological properties. Benzophenones **21a**,**b** and their charged derivatives **31a**,**b** showed no measurable inverse agonism.

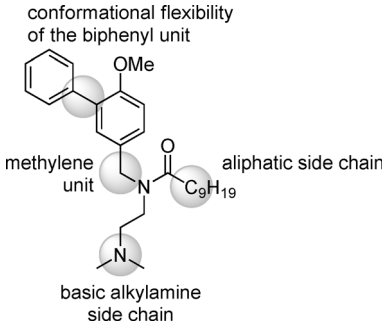



**Figure 4.** Biphenylamine-scaffold-based pharmacophore model depicting crucial structural elements that dictate inverse agonist properties of US28 allosteric modulators.

## Conclusions

We have shown that the biphenyl derivatives, which are readily available through radical arylation reactions of 4-anisidine and 4-methoxybenzylamine, are valuable building blocks for the design and synthesis of novel US28 allosteric modulators with intrinsic negative efficacy (inverse agonism). When we started with the radical reaction, most of the ligands were easily accessible in only three or four simple synthetic steps. Biological evaluation in the reporter gene assay of 38 potential ligands led to the discovery of three promising candidates with potencies of $<5$ μM and efficacies in the range between −80 and

−100% (entries **15b**, **24a**, and **30a**,**b**); these data are superior to those of any published small-molecule US28 ligand. Through multiple variations of side chains and functional groups, crucial structural elements that dictate inverse agonist properties of ligands have been unambiguously determined. The preliminary structure–activity relationship summary (Figure 4) can now serve as a solid foundation for further optimizations.

## Experimental Section

### *Chemistry*

Solvents and reagents were used as received. $^1$H NMR spectra were recorded on 360 and 600 MHz spectrometers with $CDCl_3$ and $CD_3OD$ used as solvents referenced to TMS ($\delta = 0$ ppm) and $CHCl_3$ ($\delta = 7.26$ ppm). Chemical shifts are reported in parts per million. Coupling constants (*J*) are in Hz. The following abbreviations are used for the description of signals: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quadruplet), m (multiplet), and br (broad). $^{13}$C NMR spectra were recorded at 90.6 and 151 MHz in $CDCl_3$ and $CD_3OD$ referenced to $CDCl_3$ ($\delta = 77.0$ ppm) and $CD_3OD$ ($\delta = 49.5$ ppm). Chemical shifts are given in parts per million. Mass spectra were recorded as electron impact (EI) or electrospray ionization (ESI). Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel plates with short wavelength (254 nm) UV light used to visualize components. Silica gel (Kieselgel 60, 40–63 μm) was used for flash column chromatography.

### *General procedures*

**Radical biaryl synthesis (procedure 1)**:[18b] To a solution of the aniline (10.0 mmol, 2.5 equiv) in $H_2O$ (10 mL) and HCl (3 M, 10 mL), which was degassed with nitrogen and cooled to 0 °C, $NaNO_2$ (10.0 mmol, 2.5 equiv) dissolved in $H_2O$ (5 mL) was added dropwise over a period of 10 min. The reaction mixture was stirred for 20 min. The arenediazonium salt solution (10.0 mL, 0.4 M, 4.00 mmol, 1.0 equiv) was added dropwise to a previously degassed solution of *p*-anisidine/*p*-methoxybenzylamine/*para*-substituted phenol (20.0 mmol, 5.0 equiv) in $H_2O$ (32 mL) and $TiCl_3$ (8.00 mmol, 1 M in 3 N HCl, 8 mL) over a period of 15 min. After 5 min of additional stirring, the base was added when indicated in the individual procedure, and the resulting mixture was extracted with $Et_2O$ (3×100 mL). The combined organic phases were washed with brine and dried over anhydrous $Na_2SO_4$, and the solvent was evaporated under reduced pressure. Purification by distillation and/or column chromatography gave pure biaryl compounds.

**Microwave-assisted N-alkylation of arylamines (procedure 2)**:[23] A mixture of arylamine (3.00 mmol, 1.0 equiv) and 2-chloro-*N*,*N*-dimethylethylamine·HCl (6.00 mmol, 2.0 equiv) in $H_2O$ (2 mL) was irradiated at 150 °C for 20 min. The solution was adjusted to pH 12 with aqueous NaOH (2 M) and then extracted with $Et_2O$ (3×20 mL). The combined organic phases were washed with brine and dried over anhydrous $Na_2SO_4$, and the solvent was evaporated under reduced pressure.

**Acylation of amines or alcohols (procedure 3)**: The amine/alcohol (2.00 mmol, 1.0 equiv) was dissolved in a mixture of 1,2-dichloroethane (10 mL) and $NEt_3$ (4.00 mmol, 2.0 equiv) under argon atmosphere. The acid chloride (4.00 mmol, 2.0 equiv) or anhydride (2.00 mmol, 1.0 equiv) was added dropwise, and the reaction mixture was stirred for 12 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL) and washed with saturated $Na_2CO_3$ solution (50 mL) and brine (50 mL). The organic phase was dried over anhydrous $Na_2SO_4$, and the solvent was evaporated under reduced pressure.

**Alkylation of amides (procedure 4)**: The amide (250 μmol, 1.0 equiv) and NaH (7.50 mmol, 30 equiv) were dissolved in *N*,*N*-dimethylformamide or *N*,*N*-dimethylacetamide (4 mL) under argon atmosphere. The reaction mixture was stirred for 1 h at 0 °C. After addition of the alkyl halide (2.50 mmol, 10 equiv) the solution was stirred for another 4 h at room temperature. The reaction mixture was diluted with $H_2O$, extracted with EtOAc (2×50 mL), and washed with brine. The combined organic phases were dried over anhydrous $Na_2SO_4$, and the solvent was removed under reduced pressure.

**Alkylation with epichlorohydrin (procedure 5)**:[26] The hydroxybiaryl (500 μmol, 1.0 equiv), epichlorohydrin (2.50 mmol, 5.0 equiv), and pyridine (0.1 mL) were stirred at room temperature for 24 h. The unreacted epichlorohydrin and pyridine were removed in vacuo. The residue was dissolved in EtOH (1 mL), and NaOH (30 mg) was added. This reaction mixture was stirred for 1 h, then concentrated under reduced pressure, diluted with $H_2O$ (50 mL), and extracted with EtOAc (3×75 mL). The combined organic phases were washed with brine and dried over anhydrous $Na_2SO_4$, and the solvent was removed under reduced pressure.

**Amination of epoxide (procedure 6)**:[27] The epoxide (60.0 μmol) was dissolved in $H_2O$ (1 mL) at 0 °C, and $NEt_2H$ (2 mL) was added. The mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with $H_2O$ (30 mL) and extracted with $Et_2O$ (3× 30 mL). The combined organic phases were washed with brine and dried over anhydrous $Na_2SO_4$, and the solvent was removed under reduced pressure.

**Alkylation of amines via Finkelstein reaction (procedure 7)**:[32] To a solution of the alkyl halide (100 μmol, 1.0 equiv) and 4-(4-chlorophenyl)-4-hydroxypiperidine (200 μmol, 2.0 equiv) in *n*-butanol (4 mL), $Na_2CO_3$ (100 μmol, 1.0 equiv) and NaI (100 μmol, 1.0 equiv) were added under argon atmosphere. The reaction mixture was stirred at 100 °C for 20 h. After cooling to room temperature the product was filtered, and the filtrate was concentrated under reduced pressure and purified by column chromatography.

**Removal of Boc protecting group (procedure 8)**: The Boc-protected amine was dissolved in trifluoroacetic acid (1 mL) and $CH_2Cl_2$ (3 mL) under an argon atmosphere. The reaction mixture was stirred for 3 h at 0 °C. The solution was made basic (pH ~12) with aqueous NaOH (2 M) before being extracted with $Et_2O$ (2×50 mL). The combined organic phases were washed with brine and dried over anhydrous $Na_2SO_4$, and the solvent was removed under reduced pressure.

**Methylation of tertiary amines (procedure 9)**: The tertiary amine (50.0 μmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (2 mL). $CH_3I$ (1.50 mmol, 30 equiv) was added dropwise, and the reaction mixture was stirred for 24 h. The solvent and excess $CH_3I$ were evaporated under reduced pressure.

### *Compounds*

**4′-Chloro-6-methoxybiphenyl-3-amine (10a)**: Preparations from 4-chloroaniline (1.28 g, 10.0 mmol) and *p*-anisidine (**9a**) (2.46 g, 20.0 mmol) were made according to general procedure 1 described above. The final reaction mixture was made basic with NaOH (4.00 g) and $Na_2SO_3$ (4.00 g) in $H_2O$ (40 mL) prior to extraction. Pu-

rification by Kugelrohr distillation and column chromatography ($CH_2Cl_2$/EtOAc = 30:1) gave the title compound **10a** as a dark solid (533 mg, 2.28 mmol, 57%). $R_f$ = 0.6 ($CH_2Cl_2$/EtOAc = 20:1) [UV]; $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 3.70 (s, 3H), 6.64–6.68 (m, 2H), 6.80–6.84 (m, 1H), 7.35 (d, $J$ = 8.8 Hz, 2H), 7.44 ppm (d, $J$ = 8.8 Hz, 2H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$ = 56.1 ($CH_3$), 113.0 (CH), 115.0 (CH), 117.6 (CH), 127.8 (2×CH), 130.1 ($C_q$), 130.4 (2×CH), 132.5 ($C_q$), 136.7 ($C_q$), 139.9 ($C_q$) 149.4 ppm ($C_q$); MS (EI): $m/z$ (%) = 233 (43) $[M]^+$, 219 (21), 218 (22), 217 (13), 203 (13), 187 (12), 184 (14), 183 (100), 85 (57), 83 (83), 47 (11); HRMS (EI): $C_{13}H_{12}ClNO$ $[M]^+$ calcd: 233.0607, found: 233.0607.

**2′,6′-Dichloro-6-methoxybiphenyl-3-amine (10b)**: Preparations from 2,6-dichloroaniline (1.62 g, 10.0 mmol) and *p*-anisidine (**9a**) (2.46 g, 20.0 mmol) were made according to general procedure 1 described above. For better solubility of 2,6-dichloroaniline, the diazonium salt was prepared in an $CH_3CN$/3 N HCl/$H_2O$ mixture at 2:2:1. The final reaction mixture was basified with NaOH (4.00 g) and $Na_2SO_3$ (4.00 g) in $H_2O$ (40 mL) prior to extraction. Purification by Kugelrohr distillation and column chromatography ($CH_2Cl_2$/EtOAc = 100:1) gave the title compound (**10b**) as a brown oil (332 mg, 1.24 mmol, 31%). $R_f$ = 0.6 ($CH_2Cl_2$/EtOAc = 100:1) [UV]; $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 3.70 (s, 3H), 6.53 (d, $J$ = 2.8 Hz, 1H), 6.78 (dd, $J$ = 2.8 Hz, $J$ = 8.7 Hz, 1H), 6.86 (d, $J$ = 8.7 Hz, 1H), 7.19 (dd, $J$ = 7.6 Hz, $J$ = 8.5 Hz, 1H), 7.37 (d, $J$ = 7.6 Hz, 1H), 7.37 ppm (d, $J$ = 8.5 Hz, 1H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$ = 56.6 ($CH_3$), 113.0 (CH), 116.7 (CH), 118.2 (CH), 127.0 ($C_q$), 127.7 (2×CH), 128.9 (CH), 135.4 (2×$C_q$), 136.7 ($C_q$), 139.3 ($C_q$) 150.2 ppm ($C_q$); MS (EI): $m/z$ (%) = 267 (50) $[M]^+$, 269 (33), 268 (8), 254 (10), 252 (17), 219 (33), 218 (14), 217 (100), 108 (9), 98 (9); HRMS (EI): $C_{13}H_{11}Cl_2NO$ $[M]^+$ calcd: 267.0218, found: 267.0218.

**2-Amino-6*H*-benzo[c]chromen-6-one (10c)**: Preparations from methyl anthranilate (1.51 g, 10.0 mmol) and *p*-aminophenol (**9b**) (2.18 g, 20.0 mmol) were made according to general procedure 1 described above. After completion of the reaction, the resulting mixture was basified to pH 10 using $Na_2CO_3$ and 25% aqueous $NH_3$ prior to extraction. Purification by column chromatography (hexane/EtOAc/AcOH = 10:20:1) gave the title compound (**10c**) as a yellow solid (288 mg, 1.36 mmol, 34%). $R_f$ = 0.6 (hexane/EtOAc/AcOH = 10:20:1) [UV]; $^1$H NMR (360 MHz, $CDCl_3$/$CD_3OD$): $\delta$ = 6.88 (dd, $J$ = 2.6 Hz, $J$ = 8.7 Hz, 1H), 7.19 (d, $J$ = 8.7 Hz, 1H), 7.38 (d, $J$ = 2.7 Hz, 1H), 7.59 (m, 1H), 7.83 (ddd, $J$ = 1.4 Hz, $J$ = 7.3 Hz, $J$ = 8.1 Hz, 1H), 8.08 (d, $J$ = 8.1 Hz, 1H), 8.37 ppm (ddd, $J$ = 0.6 Hz, $J$ = 1.4 Hz, $J$ = 8.0 Hz, 1H); $^{13}$C NMR (90.6 MHz, $CDCl_3$/$CD_3OD$): $\delta$ = 107.7 (CH), 118.5 (CH), 118.6 (CH), 118.6 ($C_q$), 121.3 ($C_q$), 121.8 (CH), 128.9 (CH), 130.6 (CH), 134.9 (CH), 135.0 ($C_q$), 143.5 ($C_q$), 144.6 ($C_q$), 162.2 ppm (CO); MS (EI): $m/z$ (%) = 211 (100) $[M]^+$, 212 (16), 207 (10), 183 (31), 155 (18), 154 (29), 128 (11), 127 (15), 91 (12), 77 (15); HRMS (EI): $C_{13}H_9NO_2$ $[M]^+$ calcd: 211.0633, found: 211.0633.

**2-Aminophenanthridin-6(5*H*)-one (10d)**: Preparation from methyl anthranilate (1.51 g, 10.0 mmol) and 1,4-phenylenediamine (**9c**) (2.16 g, 20.0 mmol) according to general procedure 1 described above. After completion of the reaction, the resulting mixture was basified to pH 10 with $Na_2CO_3$ and 25% aqueous $NH_3$ prior to extraction. Purification by column chromatography (hexane/EtOAc/AcOH = 10:20:1) gave the title compound (**10d**) as a yellow solid (151 mg, 720 μmol, 18%). $R_f$ = 0.4 (hexane/EtOAc/AcOH = 10:20:1) [UV]; $^1$H NMR (360 MHz, $CDCl_3$/$CD_3OD$): $\delta$ = 6.98 (dd, $J$ = 2.4 Hz, $J$ = 8.6 Hz, 1H), 7.19 (d, $J$ = 8.6 Hz, 1H), 7.60 (ddd, $J$ = 1.1 Hz, $J$ = 7.2 Hz, $J$ = 8.1 Hz, 1H), 7.67 (d, $J$ = 2.4 Hz, 1H), 7.82 (ddd, $J$ = 1.5 Hz, $J$ = 7.2 Hz, $J$ = 8.2 Hz, 1H), 8.34 (d, $J$ = 8.2 Hz, 1H), 8.41 ppm (ddd, $J$ = 0.6 Hz, $J$ = 1.5 Hz, $J$ = 8.0 Hz, 1H); $^{13}$C NMR (90.6 MHz, $CDCl_3$/$CD_3OD$): $\delta$ = 106.9 (CH), 116.2 (CH), 117.9 (CH), 118.6 ($C_q$), 121.3 (CH), 124.5 ($C_q$), 126.6 (CH), 126.7 (CH), 127.8 ($C_q$), 131.7 (CH), 134.0 ($C_q$), 142.4 ($C_q$), 161.1 ppm (CO); MS (EI): $m/z$ (%) = 210 (100) $[M]^+$, 211 (16), 209 (6), 182 (9), 181 (16), 154 (9), 128 (4), 127 (7), 105 (5), 91 (8), 77 (6); HRMS (EI): $C_{13}H_{10}N_2O$ $[M]^+$ calcd: 210.0793, found: 210.0793.

***N′*-(4′-Chloro-6-methoxybiphen-3-yl)-*N*,*N*-dimethylethane-1,2-diamine (11a)**: Preparations from compound **10a** (630 mg, 2.70 mmol) were made according to general procedure 2 described above. Purification by column chromatography ($CHCl_3$/MeOH = 20:1) gave the title compound (**4a**) as a violet oil (313 mg, 1.03 mmol, 38%). $R_f$ = 0.5 ($CHCl_3$/MeOH = 3:1) [UV]; $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 2.27 (s, 6H), 2.55–2.60 (m, 2H), 3.12–3.17 (m, 2H), 3.70 (s, 3H), 6.60–6.65 (m, 2H), 6.85–6.89 (m, 1H), 7.35 (d, $J$ = 8.7 Hz, 2H), 7.46 ppm (d, $J$ = 8.7 Hz, 2H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$ = 41.9 ($CH_2$), 45.1 (2×$CH_3$), 56.6 ($CH_2$), 58.1 ($CH_3$), 113.0 (CH), 113.6 (CH), 115.8 (CH), 128.1 (2×CH), 130.4 ($C_q$), 130.8 (2×CH), 132.7 ($C_q$), 137.3 ($C_q$), 134.0 ($C_q$), 149.0 ppm ($C_q$); MS (EI): $m/z$ (%) = 304 (35) $[M]^+$, 248 (8), 247 (10), 246 (25), 245 (20), 230 (11), 202 (9), 139 (8), 59 (22), 58 (100); HRMS (EI): $C_{17}H_{21}ClN_2O$ $[M]^+$ calcd: 304.1342, found: 304.1342.

***N′*-(2′,6′-Dichloro-6-methoxybiphen-3-yl)-*N*,*N*-dimethylethane-1,2-diamine (11b)**: Preparations from compound **10b** (174 mg, 649 μmol) were made according to general procedure 2 described above. Purification by column chromatography ($CHCl_3$/MeOH = 20:1) gave the title compound **11b** as a brown oil (68.1 mg, 201 μmol, 31%). $R_f$ = 0.5 ($CHCl_3$/MeOH = 10:1) [UV]; $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 2.28 (s, 6H), 2.56–2.61 (m, 2H), 3.12–3.17 (m, 2H), 3.69 (s, 3H), 6.45 (d, $J$ = 2.9 Hz, 1H), 6.71 (dd, $J$ = 2.9 Hz, $J$ = 8.8 Hz, 1H), 6.90 (d, $J$ = 8.8 Hz, 1H), 7.19 (dd, $J$ = 7.6 Hz, $J$ = 8.5 Hz, 1H),7.37 (d, $J$ = 7.6 Hz, 1H), 7.37 ppm (d, $J$ = 8.5 Hz, 1H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$ = 41.8 ($CH_2$), 45.2 (2×$CH_3$), 56.8 ($CH_2$), 58.1 ($CH_3$), 113.2 (CH), 114.0 (CH), 115.7 (CH), 127.1 ($C_q$), 127.7 (2×CH), 128.8 (2×$C_q$), 135.5 (CH), 137.1 ($C_q$), 142.5 ($C_q$), 149.2 ppm ($C_q$); MS (EI): $m/z$ (%) = 338 (45) $[M]^+$, 340 (29), 283 (13), 282 (45), 281 (44), 280 (71), 279 (54), 230 (24), 229 (11), 202 (13), 173 (15), 59 (89), 58 (100), 57 (13); HRMS (EI): $C_{17}H_{20}Cl_2N_2O$ $[M]^+$ calcd: 338.0953, found: 338.0953.

**2-(2-Dimethylaminoethylamino)benzo[c]chromen-6-one (11c)**: Preparations from compound **10c** (245 mg, 1.16 mmol) were made according to general procedure 2 described above. Purification by column chromatography ($CHCl_3$/MeOH = 20:1→3:1) gave the title compound (**11c**) as a yellow solid (76.3 mg, 270 μmol, 23%). $R_f$ = 0.3 ($CHCl_3$/MeOH = 3:1) [UV]; $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 2.31 (s, 6H), 2.64 (m, 2H), 3.24 (m, 2H), 6.79 (dd, $J$ = 2.6 Hz, $J$ = 8.8 Hz, 1H), 7.19 (d, $J$ = 2.6 Hz, 1H), 7.20 (d, $J$ = 8.8 Hz, 1H), 7.55 (ddd, $J$ = 1.1 Hz, $J$ = 7.3 Hz, $J$ = 8.0 Hz, 1H), 7.79 (ddd, $J$ = 1.4 Hz, $J$ = 7.3 Hz, $J$ = 8.0 Hz, 1H), 8.06 (d, $J$ = 8.0 Hz, 1H), 8.40 ppm (ddd, $J$ = 0.6 Hz, $J$ = 1.4 Hz, $J$ = 8.0 Hz, 1H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$ = 41.2 ($CH_2$), 44.8 (2×$CH_3$), 57.5 ($CH_2$), 103.9 (CH), 116.2 (CH), 118.1 (CH), 118.1 ($C_q$), 121.2 ($C_q$), 121.3 (CH), 128.2 (CH), 130.3 (CH), 134.2 (CH), 134.8 ($C_q$), 143.6 ($C_q$), 145.2 ($C_q$), 161.3 ppm (CO); MS (EI): $m/z$ (%) = 282 (27) $[M]^+$, 235 (15), 233 (44), 224 (14), 223 (12), 139 (22), 83 (26), 72 (96), 71 (41), 59 (32), 58 (100), 57 (13), 55 (28); HRMS (EI): $C_{17}H_{18}N_2O_2$ $[M]^+$ calcd: 282.1368, found: 282.1368.

**2-(2-Dimethylaminoethylamino)-5*H*-phenanthridin-6-one (11d)**: Preparations from compound **10d** (70 mg, 333 μmol) were made according to general procedure 2 described above. Purification by column chromatography ($CHCl_3$/MeOH = 20:1→3:1) gave the title compound (**11d**) as a yellow solid (8.43 mg, 30.0 μmol, 9%). $R_f$ = 0.2 ($CHCl_3$/MeOH = 3:1) [UV]; $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 2.32 (s, 6H), 2.66 (m, 2H), 3.27 (m, 2H), 6.88 (dd, $J$ = 2.4 Hz, $J$ = 8.6 Hz, 1H),

7.24 (d, $J$=8.6 Hz, 1H), 7.37 (d, $J$=2.4 Hz, 1H), 7.59 (ddd, $J$=1.1 Hz, $J$=7.2 Hz, $J$=8.1 Hz, 1H), 7.76 (ddd, $J$=1.3 Hz, $J$=7.2 Hz, $J$=8.0 Hz, 1H), 8.22 (d, $J$=8.1 Hz, 1H), 8.58 ppm (ddd, $J$=0.4 Hz, $J$=1.3 Hz, $J$=8.0 Hz, 1H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$=41.6 ($CH_2$), 45.1 (2×$CH_3$), 57.9 ($CH_2$), 104.5 (CH), 117.0 (CH), 117.7 (CH), 119.4 ($C_q$), 122.0 (CH), 126.0 ($C_q$), 127.5 (CH), 128.3 (CH), 128.3 ($C_q$), 132.3 (CH), 143.8 ($C_q$), 144.5 ($C_q$), 162.1 ppm (CO); MS (EI): $m/z$ (%)=281 (13) $[M]^+$, 223 (7), 222 (9), 221 (2), 195 (2), 194 (2), 167 (2), 166 (3), 139 (4), 59 (5), 58 (100), 57 (2); HRMS (EI): $C_{17}H_{19}N_3O$ $[M]^+$ calcd: 281.1528, found: 281.1528.

**Decanoic acid (4′-chloro-6-methoxybiphen-3-yl)-(2-dimethylaminoethyl)amide (12a)**: Preparations from compound **11a** (47.0 mg, 166 μmol) and decanoyl chloride (100 μL, 482 μmol) were made according to general procedure 3 described above. Purification by column chromatography ($CHCl_3$/MeOH=20:1) and filtration through $Al_2O_3$ gave the title compound (**12a**) as a yellow oil (29.2 mg, 63.6 μmol, 38%). $R_f$=0.6 ($CHCl_3$/MeOH=10:1) [UV]; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$=0.86 (t, $J$=7.1 Hz, 3H), 1.16–1.22 (m, 10H), 1.23–1.29 (m, 2H), 1.52–1.59 (m, 2H), 2.06 (m, 2H), 2.24 (s, 6H), 2.44 (m, 2H), 3.81 (t, $J$=7.1 Hz, 2H), 3.85 (s, 3H), 6.98 (d, $J$=8.4 Hz, 1H), 7.12–7.16 (m, 2H), 7.39 (d, $J$=8.4 Hz, 2H), 7.45 ppm (d, $J$=8.4 Hz, 2H); $^{13}$C NMR: (90.6 MHz, $CDCl_3$): $\delta$=14.1 ($CH_3$), 22.6 ($CH_2$), 25.5 ($CH_2$), 29.2 ($CH_2$), 29.3 ($CH_2$), 29.4 (2×$CH_2$), 31.8 ($CH_2$), 34.3 ($CH_2$), 45.5 (2×$CH_3$), 47.0 ($CH_2$), 55.8 ($CH_3$), 56.7 ($CH_2$), 111.8 (CH), 128.3 (2×CH), 128.6 (CH), 130.4 (CH), 130.4 ($C_q$), 130.7 (2×CH), 133.4 ($C_q$), 135.7 ($C_q$), 135.8 ($C_q$), 155.6 ($C_q$), 173.3 ppm (CO); MS (EI): $m/z$ (%)=459 (1) $[M]^+$, 389 (11), 387 (30), 275 (13), 246 (10), 235 (16), 233 (43), 72 (83), 71 (46), 58 (100), 57 (10).

**Decanoic acid (2′,6′-dichloro-6-methoxybiphen-3-yl)-(2-dimethylaminoethyl)amide (12b)**: Preparations from compound **11b** (60.0 mg, 177 μmol) and decanoyl chloride (100 μL, 482 μmol) were made according to general procedure 3 described above. Purification by column chromatography ($CHCl_3$/MeOH=10:1) and filtration through $Al_2O_3$ gave the title compound (**12b**) as a colorless oil (65.5 mg, 133 μmol, 75%). $R_f$=0.6 ($CHCl_3$/MeOH=10:1) [UV]; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$=0.86 (t, $J$=6.9 Hz, 3H), 1.14–1.28 (m, 12H), 1.50–1.59 (m, 2H), 2.09 (m, 2H), 2.27 (s, 6H), 2.49 (t, $J$=7.1 Hz, 2H), 3.81 (s, 3H), 3.82–3.89 (m, 2H), 6.97 (d, $J$=2.6 Hz, 1H), 7.01 (d, $J$=8.6 Hz, 1H), 7.24 (dd, $J$=2.6 Hz, $J$=8.6 Hz, 1H), 7.25 (dd, $J$=7.5 Hz, $J$=8.6 Hz, 1H), 7.40 (d, $J$=7.5 Hz, 1H), 7.40 ppm (d, $J$=8.6 Hz, 1H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$=14.1 ($CH_3$), 22.6 ($CH_2$), 25.4 ($CH_2$), 29.2 ($CH_2$), 29.3 (2×$CH_2$), 29.4 ($CH_2$), 31.8 ($CH_2$), 34.5 ($CH_2$), 45.3 (2×$CH_3$), 46.4 ($CH_2$), 56.0 ($CH_3$), 56.5 ($CH_2$), 111.9 (CH), 127.0 ($C_q$), 127.8 (2×CH), 129.3 (CH), 129.4 (CH), 131.3 (CH), 135.1 ($C_q$), 135.3 (2×$C_q$), 135.6 ($C_q$), 156.1 ($C_q$), 173.7 ppm (CO); MS (EI): $m/z$ (%)=492 (2) $[M]^+$, 423 (16), 421 (24), 309 (14), 280 (12), 269 (30), 267 (49), 72 (83), 71 (34), 58 (100); HRMS (EI): $C_{27}H_{38}Cl_2N_2O_2$ $[M]^+$ calcd: 492.2310, found: 492.2311.

**Decanoic acid (6-oxo-6*H*-benzo[*c*]chromen-2-yl)-(2-dimethylaminoethyl)amide (12c)**: Preparations from compound **11c** (50.0 mg, 177 μmol) and decanoyl chloride (100 μL, 482 μmol) were made according to general procedure 3 described above. Purification by column chromatography ($CHCl_3$/MeOH=20:1) and filtration through $Al_2O_3$ gave the title compound (**12c**) as a yellow oil (26.8 mg, 61.4 μmol, 35%). $R_f$=0.5 ($CHCl_3$/MeOH=10:1) [UV]; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$=0.84 (t, $J$=7.2 Hz, 3H), 1.15–1.25 (m, 12H), 1.55–1.62 (m, 2H), 2.07 (t, $J$=7.5 Hz, 2H), 2.26 (s, 6H), 2.45 (t, $J$=6.7 Hz, 2H), 3.88 (t, $J$=6.7 Hz, 2H), 7.35 (dd, $J$=2.3 Hz, $J$=8.6 Hz, 1H), 7.43 (d, $J$=8.6 Hz, 1H), 7.66 (t, $J$=7.6 Hz, 1H), 7.89 (dt, $J$=1.1 Hz, $J$=7.6 Hz, 1H), 8.03 (d, $J$=2.3 Hz, 1H), 8.11 (d, $J$=8.0 Hz, 1H), 8.45 ppm (dd, $J$=1.0 Hz, $J$=8.0 Hz, 1H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$=14.1 ($CH_3$), 22.6 ($CH_2$), 25.5 ($CH_2$), 29.2 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 30.9 ($CH_2$), 31.8 ($CH_2$), 34.6 ($CH_2$), 45.5 (2×$CH_3$), 46.9 ($CH_2$), 56.8 ($CH_2$), 119.0 (CH), 119.1 ($C_q$), 121.3 ($C_q$), 121.8 (CH), 123.1 (CH), 129.6 (CH), 130.6 (CH), 130.8 (CH), 134.1 ($C_q$), 135.1 (CH), 139.1 ($C_q$), 150.4 ($C_q$), 160.7 (CO), 173.1 ppm (CO); MS (EI): $m/z$ (%)=436 (1) $[M]^+$, 390 (7), 253 (7), 224 (16), 223 (17), 211 (32), 72 (65), 71 (100), 59 (15), 58 (100), 57 (12); HRMS (EI): $C_{27}H_{36}N_2O_3$ $[M]^+$ calcd: 436.2726, found: 436.2725.

**5′-(*N*-(2-(Dimethylamino)ethyl)decanamido)-2′-methoxybiphenyl-3-carboxylate (15a)**: The intermediate **11a** was prepared from methyl 3-aminobenzoate (1.51 g, 10.0 mmol) and *p*-anisidine (**9a**) (2.46 g, 20.0 mmol) according to general procedure 1 described above. The reaction mixture was basified with NaOH (4.00 g) and $Na_2SO_3$ (4.00 g) in $H_2O$ (40 mL) prior to extraction. Purification by Kugelrohr distillation gave compound **13a** as a black oil (648 mg, 2.52 mmol, 63%). $R_f$=0.3 ($CH_2Cl_2$/EtOAc=40:1) [UV]; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$=3.74 (s, 3H), 3.92 (s, 3H), 6.85–6.90 (m, 3H), 7.45 (t, $J$=7.7 Hz, 1H), 7.71 (d, $J$=7.7 Hz, 1H), 7.99 (d, $J$=7.8 Hz, 1H), 8.17 ppm (t, $J$=1.7 Hz, 1H). **13a** (751 mg, 2.92 mmol) was treated with decanoyl chloride (608 μL, 2.92 mmol; 1:1 equiv due to possible double acylation) according to general procedure 3 described above. Purification by column chromatography (hexane/EtOAc=4:1) gave compound **14a** as an orange solid (697 mg, 1.69 mmol, 58%). $R_f$=0.7 (hexane/EtOAc=2:1) [UV]; $^1$H NMR ($CDCl_3$, 360 MHz): $\delta$=0.87 (t, $J$=6.9 Hz, 3H), 1.20–1.42 (m, 12H), 1.72 (m, 2H), 2.34 (t, $J$=7.6 Hz, 2H), 3.78 (s, 3H), 3.92 (s, 3H), 6.94 (d, $J$=8.8 Hz, 1H), 7.13 (s, 1H), 7.37 (d, $J$=2.7, 1H), 7.45 (t, $J$=7.8 Hz, 1H), 7.57 (dd, $J$=2.7 Hz, $J$=8.8 Hz, 1H), 7.72 (d, $J$=7.8 Hz, 1H), 7.99 (d, $J$=7.8 Hz, 1H), 8.17 ppm (t, $J$=1.8 Hz, 1H). **14a** (697 mg, 1.69 mmol) was treated with 2-chloro-*N*,*N*-dimethylethanamine·HCl (1.83 g, 16.9 mmol) in *N*,*N*-dimethylacetamide according to general procedure 4 described above. Purification by column chromatography ($CHCl_3$/MeOH=5:1) gave the title compound **15a** as an orange oil (102.9 mg, 220 μmol, 13%). $R_f$=0.2 ($CHCl_3$/MeOH=3:1) [UV]; $^1$H NMR ($CDCl_3$, 600 MHz): $\delta$=0.84 (t, $J$=7.1 Hz, 3H), 1.09–1.29 (m, 12H), 1.46–1.54 (m, 2H), 1.97–2.05 (m, 2H), 2.54 (s, 6H), 2.82–2.92 (m, 2H), 3.71 (s, 3H), 3.88–3.98 (m, 2H), 6.83–6.90 (m, 1H), 6.98–7.03 (m, 1H), 7.07–7.18 (m, 1H), 7.22–7.32 (m, 1H), 7.44–7.55 (m, 1H), 7.83–7.93 (m, 1H), 8.00–8.12 ppm (m, 1H); $^{13}$C NMR ($CDCl_3$, 151 MHz): $\delta$=14.1 ($CH_3$), 22.6 ($CH_2$), 25.3 ($CH_2$), 29.3 (2×$CH_2$), 29.4 (2×$CH_2$), 31.8 ($CH_2$), 34.2 ($CH_2$), 43.9 (2×$CH_3$), 45.9 ($CH_2$), 55.1 ($CH_2$), 55.7 ($CH_3$), 111.8 (CH), 127.3 (CH), 127.8 (CH), 128.6 ($C_q$), 130.3 (CH), 130.5 (CH), 131.9 (CH), 132.0 (CH), 134.9 ($C_q$), 135.2 ($C_q$), 136.7 ($C_q$), 155.9 ($C_q$), 173.8 ppm (CO); MS (EI): $m/z$ (%)=467 (2) $[M]^+$, 398 (16), 397 (56), 285 (17), 256 (11), 252 (15), 243 (41), 72 (44), 71 (24), 58 (100).

**5′-((*N*-(2-(Dimethylamino)ethyl)decanamido)methyl)-2′-methoxybiphenyl-3-carboxylate (15b)**: The intermediate **13b** was prepared from methyl 3-aminobenzoate (1.51 g, 10.0 mmol) and *p*-methoxybenzylamine (**9d**) (2.74 g, 20.0 mmol) according to general procedure 1 described above. The reaction mixture was basified with NaOH (4.00 g) and $Na_2SO_3$ (4.00 g) in $H_2O$ (40 mL) prior to extraction. Purification by Kugelrohr distillation gave compound **13b** as a dark-red oil (586 mg, 2.16 mmol, 54%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$=3.80 (s, 3H), 3.85 (s, 2H), 3.92 (s, 3H), 6.95 (d, $J$=8.1 Hz, 1H), 7.26–7.30 (m, 2H), 7.46 (t, $J$=7.7 Hz, 1H), 7.74 (ddd, $J$=1.2 Hz, $J$=1.8 Hz, $J$=7.7 Hz, 1H), 7.99 (d, $J$=7.7 Hz, 1H), 8.19 ppm (t, $J$=1.7 Hz, 1H). **13b** (586 mg, 2.16 mmol) was treated with decanoyl chloride (450 μL, 2.16 mmol; 1:1 equiv due to possible double acylation) according to general procedure 3 described above. Purification by column chromatography (hexane/EtOAc=2:1) gave compound **14b** as an orange oil (303 mg, 713 μmol, 33%). $R_f$=0.3 (hexane/EtOAc=2:1) [UV]; $^1$H NMR ($CDCl_3$, 600 MHz): $\delta$=0.85–0.90

(m, 3H), 1.20–1.35 (m, 12H), 1.62–1.68 (m, 2H), 2.19–2.23 (m, 2H), 3.81 (s, 3H), 3.93 (s, 3H), 4.43 (d, $J$=5.1 Hz, 2H), 6.95 (d, $J$=8.4 Hz, 1H), 7.23 (d, $J$=2.1 Hz, 1H), 7.25–7.29 (m, 1H), 7.47 (t, $J$=7.7 Hz, 1H), 7.70 (d, $J$=7.7 Hz, 1H), 8.00 (td, $J$=1.3 Hz, $J$=7.8 Hz, 1H), 8.16 ppm (t, $J$=1.7 Hz, 1H). **14b** (303 mg, 713 μmol) was treated with 2-chloro-*N*,*N*-dimethylethanamine·HCl (772 mg, 7.13 mmol) in *N*,*N*-dimethylformamide according to general procedure 4 described above. Purification by column chromatography ($CHCl_3$/MeOH=5:1) gave the title compound **15b** as a yellow oil (61.8 mg, 128 μmol, 18%). $R_f$=0.6 ($CHCl_3$/MeOH=3:1) [UV]; $^1$H NMR ($CDCl_3$, 600 MHz): $\delta$=0.85–0.89 (m, 3$H_{maj+min}$), 1.20–1.34 (m, 12$H_{maj+min}$), 1.58–1.69 (m, 2$H_{maj+min}$), 2.28 (s, 6$H_{min}$), 2.34–2.41 (m, 2$H_{maj+min}$), 2.45–2.52 (m, 2$H_{min}$), 2.55 (s, 6$H_{maj}$), 2.81–2.92 (m, 2$H_{maj}$), 3.35–3.40 (m, 2$H_{min}$), 3.55–3.62 (m, 2$H_{maj}$), 3.72 (s, 3$H_{maj}$), 3.77 (s, 3$H_{min}$), 4.50–4.58 (m, 2$H_{maj+min}$), 6.85–6.91 (m, 1$H_{maj+min}$), 7.00–7.08 (m, 2$H_{maj}$), 7.13–7.19 (m, 2$H_{min}$), 7.27–7.34 (m, 1$H_{maj+min}$), 7.49–7.57 (m, 1$H_{maj+min}$), 7.91–7.98 (m, 1$H_{maj+min}$), 7.07–8.18 ppm (m, 1$H_{maj+min}$); $^{13}$C NMR ($CDCl_3$, 91 MHz): $\delta$=14.5 ($CH_3$), 23.7 ($CH_2$), 26.3 ($CH_2$), 30.4 (2×$CH_2$), 30.5 ($CH_2$), 30.6 ($CH_2$), 33.0 ($CH_2$), 34.2 ($CH_2$), 40.5 (2×$CH_3$), 44.7 ($CH_2$), 52.3 ($CH_2$), 56.3 ($CH_3$), 57.2 ($CH_2$), 113.2 (CH), 128.3 (CH), 128.6 (CH), 129.2 ($C_q$), 130.1 (CH), 130.4 (CH), 131.2 ($C_q$), 131.6 ($C_q$), 132.4 (CH), 133.1 (CH), 139.3 ($C_q$), 157.7 ($C_q$), 177.0 ppm (CO); HRMS (ESI): $C_{29}H_{43}N_2O_4$ [$M$+H] calcd: 483.3217, found: 483.3217.

**5′-((*N*-(2-(Dimethylamino)ethyl)decanamido)methyl)-2′-methoxybiphenyl-4-carboxylate (15c)**: The intermediate **13c** was prepared from 4-aminobenzoate (1.51 g, 10.0 mmol) and *p*-methoxybenzylamine (**2d**) (2.74 g, 20.0 mmol) according to general procedure 1 described above. The reaction mixture was basified with NaOH (4.00 g) and $Na_2SO_3$ (4.00 g) in $H_2O$ (40 mL) prior to extraction. Purification by Kugelrohr distillation gave compound **13c** as a dark-red oil (630 mg, 2.32 mmol, 58%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$= 3.79 (s, 3H), 3.82 (s, 2H), 3.93 (s, 3H), 6.96 (d, $J$=8.3 Hz, 1H), 7.29 (d, $J$=2.3 Hz, 1H), 7.31 (dd, $J$=2.3 Hz, $J$=8.3 Hz, 1H), 7.60 (d, $J$= 8.6 Hz, 2H), 8.06 ppm (d, $J$=8.6 Hz, 2H). **13c** (630 mg, 2.32 mmol) was treated with decanoyl chloride (483 μL, 2.16 mmol; 1:1 equiv due to possible double acylation) according to general procedure 3 described above. Purification by column chromatography (hexane/EtOAc=2:1) gave compound **14c** as an orange oil (178 mg, 418 μmol, 18%). $R_f$=0.6 (hexane/EtOAc=1:2) [UV]; $^1$H NMR ($CDCl_3$, 600 MHz): $\delta$=0.87 (t, $J$=7.1 Hz, 3H), 1.20–1.35 (m, 12H), 1.65 (m, 2H), 2.20 (m, 2H), 3.81 (s, 3H), 3.94 (s, 3H), 4.45 (d, $J$=5.5 Hz, 2H), 6.96 (d, $J$=8.3 Hz, 1H), 7.23 (d, $J$=2.3 Hz, 1H), 7.27 (dd, $J$=2.3 Hz, $J$=8.3 Hz, 1H), 7.58 (d, $J$=8.6 Hz, 2H), 8.06 ppm (d, $J$=8.6 Hz, 2H). **14c** (178 mg, 418 μmol) was further treated with 2-chloro-*N*,*N*-dimethylethanamine·HCl (453 mg, 4.18 mmol) in *N*,*N*-dimethylformamide according to general procedure 4 described above. Purification by column chromatography ($CHCl_3$/MeOH=10:1) gave the title compound **15c** as a yellow oil (10.1 mg, 20.9 μmol, 5%). $R_f$= 0.7 ($CHCl_3$/MeOH=3:1) [UV]; $^1$H NMR ($CDCl_3$, 360 MHz): $\delta$=0.84–0.92 (m, 3$H_{maj+min}$), 1.20–1.38 (m, 12$H_{maj+min}$), 1.60–1.71 (m, 2$H_{maj+min}$), 2.32 (s, 6$H_{min}$), 2.37–2.43 (m, 2$H_{min}$), 2.42–2.48 (m, 2$H_{maj+min}$), 2.63 (s, 6$H_{maj}$), 2.92–3.00 (m, 2$H_{maj}$), 3.40–3.47 (m, 2$H_{min}$), 3.62–3.69 (m, 2$H_{maj}$), 3.80 (s, 3$H_{min}$), 3.81 (s, 3$H_{maj}$), 4.60 (s, 2$H_{min}$), 4.63 (s, 2$H_{maj}$), 6.95–7.03 (m, 1$H_{maj+min}$), 7.13–7.17 (m, 2$H_{maj}$), 7.20–7.25 (m, 2$H_{min}$), 7.49–7.57 (m, 2$H_{maj+min}$), 8.01–8.07 ppm (m, 2$H_{maj+min}$); $^{13}$C NMR ($CDCl_3$, 151 MHz): $\delta$=14.1 ($CH_3$), 22.8 ($CH_2$), 25.4 ($CH_2$), 29.5 ($CH_2$), 29.6 (2×$CH_2$), 29.7 ($CH_2$), 32.0 ($CH_2$), 33.5 ($CH_2$), 44.1 (2×$CH_3$), 45.3 ($CH_2$), 51.4 ($CH_2$), 55.5 ($CH_2$), 55.9 ($CH_3$), 112.1 (CH), 127.2 (CH), 128.5 (CH), 129.4 (2×$C_q$), 129.4 (2×CH), 129.5 (2×CH), 130.8 ($C_q$), 141.7 ($C_q$), 156.4 ($C_q$), 175.3 ppm (CO); MS (EI): $m/z$ (%)=482 (20) [$M$]$^+$, 270 (9), 242 (8), 241 (26), 85 (12), 83 (10), 71 (49), 58 (100), 57 (8), 55 (9), 44 (23), 43 (9).

**2-(Dimethylamino)ethyl 5′-((*N*-(2-(dimethylamino)ethyl)decanamido)methyl)-2′-methoxybiphenyl-4-carboxylate (15d)**: Compound **15d** was obtained as a side product in the last synthetic step (general procedure 4) of compound **15c**. Purification by column chromatography ($CHCl_3$/MeOH=10:1) gave the title compound (**15d**) as a colorless oil (46.3 mg, 83.6 μmol, 20%). $R_f$=0.7 ($CHCl_3$/MeOH=3:1) [UV]; $^1$H NMR ($CDCl_3$, 600 MHz): $\delta$=0.85–0.89 (m, 3$H_{maj+min}$), 1.20–1.36 (m, 12$H_{maj+min}$), 1.61–1.72 (m, 2$H_{maj+min}$), 2.23 (s, 12$H_{min}$), 2.34–2.39 (m, 2$H_{maj+min}$), 2.34–2.39 (m, 12$H_{maj}$), 2.40–2.45 (m, 2$H_{min}$), 2.57–2.63 (m, 2$H_{maj}$), 2.76 (t, $J$=5.1 Hz, 2$H_{maj+min}$), 3.34 (t, $J$=7.1 Hz, 2$H_{min}$), 3.55 (t, $J$=6.4 Hz, 2$H_{maj}$), 3.80 (s, 3$H_{min}$), 3.81 (s, 3$H_{maj}$), 4.44–4.49 (m, 2$H_{maj+min}$), 4.60 (d, $J$=4.3 Hz, 2$H_{maj+min}$), 6.93 (d, $J$=8.5 Hz, 1$H_{min}$), 6.98 (d, $J$=8.5 Hz, 1$H_{maj}$), 7.12 (d, $J$=2.1 Hz, 1$H_{maj}$), 7.16 (dd, $J$=2.3 Hz, $J$=8.4 Hz, 1$H_{maj}$), 7.20 (d, $J$=1.9 Hz, 1$H_{min}$), 7.25 (dd, $J$=2.0 Hz, $J$=8.3 Hz, 1$H_{min}$), 7.55–7.59 (m, 2$H_{maj+min}$), 8.05–8.09 ppm (m, 2$H_{maj+min}$).

**4′-Chloro-5-fluorobiphenyl-2-ol (16a)**: Preparations from 4-chloroaniline (1.28 g, 10.0 mmol) and 4-fluorophenol (**9e**) (2.24 g, 20.0 mmol) were made according to general procedure 1 described above. For better solubility 4-fluorophenol (**9e**) was dissolved in a $H_2O$/$TiCl_3$ (1 M in 3 N HCl)/$CH_3CN$=2:2:1 mixture. Purification by column chromatography ($CH_2Cl_2$/hexane=10:3) gave the title compound **16a** as a brown solid (312 mg, 1.40 mmol, 35%). $R_f$=0.6 ($CH_2Cl_2$/hexane=10:3) [UV]; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$=4.85 (br s, 1H), 6.90 (ddd, $J$=0.7 Hz, $J$=4.7 Hz, $J$=8.6 Hz, 1H), 6.93–6.98 (m, 2H), 7.41 (d, $J$=8.7 Hz, 2H), 7.46 ppm (d, $J$=8.7 Hz, 2H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$=115.7 (d, $J$=23.0 Hz, CH), 116.4 (d, $J$=23.5 Hz, CH), 117.0 (d, $J$=8.2 Hz, CH), 128.0 (d, $J$=7.6 Hz, $C_q$), 129.4 (2×CH), 130.3 (2×CH), 134.4 ($C_q$), 134.7 (d, $J$=1.6 Hz, $C_q$), 148.4 (d, $J$=2.2 Hz, $C_q$) 157.1 ppm (d, $J$=239.1 Hz, $C_q$); MS (EI): $m/z$ (%)=222 (100) [$M$]$^+$, 221 (6), 188 (11), 187 (79), 186 (27), 159 (42), 157 (15), 133 (17), 93 (11), 79 (6), 69 (11); HRMS (EI): $C_{12}H_8ClFO$ [$M$]$^+$ calcd: 222.0248, found: 222.0250.

**5-Bromo-4′-chlorobiphenyl-2-ol (16b)**: Preparations from 4-chloroaniline (1.28 g, 10.0 mmol) and 4-bromophenol (**9f**) (3.46 g, 20.0 mmol) were made according to general procedure 1 described above. For better solubility 4-bromophenol (**9f**) was dissolved in a $H_2O$/$TiCl_3$ (1 M in 3 N HCl)/$CH_3CN$=2:2:1 mixture. Purification by column chromatography ($CH_2Cl_2$/hexane=10:3) gave the title compound (**16b**) as an orange oil (238 mg, 840 μmol, 21%). $R_f$=0.5 ($CH_2Cl_2$/hexane=10:3) [UV]; $^1$H NMR (360 MHz, $CDCl_3$): $\delta$=5.17 (br s, 1H), 6.85 (d, $J$=9.0 Hz, 1H), 7.32–7.37 (m, 2H), 7.40 (d, $J$= 8.8 Hz, 2H), 7.46 ppm (d, $J$=8.8 Hz, 2H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$=112.9 ($C_q$), 117.9 (CH), 128.4 ($C_q$), 129.0 ($C_q$), 129.4 (2× CH), 130.4 (2×CH), 132.0 (CH), 132.7 (CH), 134.4 ($C_q$), 151.6 ppm ($C_q$); MS (EI): $m/z$ (%)=282 (70) [$M$]$^+$, 249 (7), 247 (9), 202 (8), 175 (7), 169 (12), 168 (100), 140 (10), 139 (35), 69 (9); HRMS (EI): $C_{12}H_8BrClO$ [$M$]$^+$ calcd: 281.9447, found: 281.9445.

**(±)-1-(4′-Chloro-5-fluorobiphen-2-yloxy)-3-diethylaminopropan-2-ol (17a)**: Compound **16a** (150 mg, 674 μmol), epichlorohydrin (258 μL, 3.37 mmol) and 1 drop of pyridine were stirred at room temperature for 24 h. The unreacted epichlorohydrin and pyridine were removed in vacuo (first part of general procedure 5 described above). Purification by column chromatography ($CH_2Cl_2$/hexane= 10:3) gave the β-chloro alcohol as a yellow oil (151 mg, 479 μmol, 71%). $R_f$=0.3 ($CH_2Cl_2$/hexane=10:3) [UV]; $^1$H NMR (360 MHz, $CDCl_3$): $\delta$=2.24 (br s, 1H), 3.56 (dd, $J$=5.2 Hz, $J$=11.3 Hz, 1H), 3.60 (dd, $J$=5.2 Hz, $J$=11.3 Hz, 1H), 3.98–4.10 (m, 3H), 6.91–6.97 (m, 1H), 6.98–7.04 (m, 2H), 7.37–7.44 ppm (m, 4H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$=45.7 ($CH_2$), 69.7 (CH), 70.1 ($CH_2$), 114.7 (d, $J$=8.5 Hz, CH), 115.0 (d, $J$=22.8 Hz, CH), 117.3 (d, $J$=23.5 Hz, CH), 128.4 (2×CH), 130.5 (2×CH), 131.7 (d, $J$=7.6 Hz, $C_q$), 133.7 ($C_q$), 135.6 (d, $J$=

1.6 Hz, $C_q$), 151.2 (d, $J$ = 2.3 Hz, $C_q$) 157.7 ppm (d, $J$ = 240.8 Hz, $C_q$); MS (EI): $m/z$ (%) = 314 (38) $[M]^+$, 224 (35), 223 (16), 222 (100), 221 (10), 200 (10), 199 (13), 187 (42), 186 (33), 170 (13), 159 (10), 157 (17), 85 (30), 83 (43); HRMS (EI): $C_{15}H_{13}Cl_2FO_2$ $[M]^+$ calcd: 314.0277, found: 314.0278. The product was reacted according to second part of general procedure 5 to obtain the respective epoxide (73.4 mg, 263 μmol, 55%). The epoxide (126 mg, 452 μmol) was further submitted to the general procedure 6 described above. Purification by column chromatography ($CHCl_3$/MeOH = 20:1) gave the title compound **17a** as a yellow oil (84.3 mg, 240 μmol, 53%). $R_f$ = 0.6 ($CHCl_3$/MeOH = 3:1) [UV]; $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 0.99 (t, $J$ = 7.1, Hz, 6H), 2.40–2.44 (m, 2H), 2.45–2.54 (m, 2H), 2.54–2.65 (m, 2H), 3.82–3.91 (m, 1H), 3.92–3.95 (m, 2H), 6.93 (dd, $J$ = 4.7 Hz, $J$ = 8.7 Hz, 1H), 6.96–7.04 (m, 2H), 7.36 (d, $J$ = 8.8 Hz, 2H), 7.47 ppm (d, $J$ = 8.8 Hz, 2H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$ = 11.8 (2×$CH_3$), 47.3 (2×$CH_2$), 55.8 ($CH_2$), 65.8 ($CH_2$), 71.7 (CH), 114.3 (d, $J$ = 8.3 Hz, CH), 114.8 (d, $J$ = 22.6 Hz, CH), 117.1 (d, $J$ = 23.5 Hz, CH), 128.2 (2×CH), 130.8 (2×CH), 131.3 (d, $J$ = 7.6 Hz, $C_q$), 133.4 ($C_q$), 135.8 (d, $J$ = 1.7 Hz, $C_q$), 151.9 (d, $J$ = 2.3 Hz, $C_q$) 157.4 ppm (d, $J$ = 238.7 Hz, $C_q$); MS (EI): $m/z$ (%) = 351 (27) $[M]^+$, 336 (11), 334 (19), 264 (16), 222 (24), 200 (21), 199 (20), 187 (24), 186 (48), 170 (22), 159 (10), 157 (23), 116 (40), 114 (14), 87 (92), 86 (100), 84 (10), 72 (29), 58 (73), 57 (13), 56 (23); HRMS (EI): $C_{19}H_{23}ClFNO_2$ $[M]^+$ calcd: 351.1401, found: 351.1402.

**(±)-1-(5-Bromo-4′-chlorobiphen-2-yloxy)-3-diethylaminopropan-2-ol (17b)**: Compound **16b** (110 mg, 388 μmol) was treated with epichlorohydrin (150 μL, 1.94 mmol) and pyridine (0.1 mL) according to general procedure 5 described above. Purification by column chromatography ($CH_2Cl_2$/hexane = 10:1) gave, apart from the β-chloro alcohol (31%), the desired epoxide as an orange oil (17.1 mg, 50.4 μmol, 13%). $R_f$ = 0.7 ($CH_2Cl_2$/hexane = 10:1) [UV]; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 2.65 (dd, $J$ = 2.7 Hz, $J$ = 5.0 Hz, 1H), 2.82 (dd, $J$ = 4.1 Hz, $J$ = 5.0 Hz, 1H), 3.22–3.26 (m, 1H), 3.92 (dd, $J$ = 5.3 Hz, $J$ = 11.2 Hz, 1H), 4.23 (dd, $J$ = 2.7 Hz, $J$ = 11.2 Hz, 1H), 6.86 (d, $J$ = 8.6 Hz, 1H), 7.38 (d, $J$ = 8.7 Hz, 2H), 7.40 (dd, $J$ = 2.3 Hz, $J$ = 8.6 Hz, 1H), 7.42 (d, $J$ = 2.3 Hz, 1H), 7.44 ppm (d, $J$ = 8.7 Hz, 2H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$ = 44.4 ($CH_2$), 50.0 (CH), 69.3 ($CH_2$), 113.9 ($C_q$), 114.8 (CH), 128.3 (2×CH), 130.7 (2×CH), 131.5 (CH), 132.0 ($C_q$), 133.3 (CH), 133.5 ($C_q$), 135.3 ($C_q$) 154.4 ppm ($C_q$); MS (EI): $m/z$ (%) = 338 (80) $[M]^+$, 286 (15), 284 (56), 282 (44), 216 (20), 204 (26), 203 (13), 202 (81), 173 (11), 168 (49), 151 (10), 140 (11), 139 (66), 138 (12), 57 (84); HRMS (EI): $C_{15}H_{12}BrClO_2$ $[M]^+$ calcd: 337.9709, found: 337.9709. The epoxide (14.0 mg, 41.2 μmol) was further treated with $NEt_2H$ (2 mL) according to general procedure 6 described above. Purification by column chromatography ($CHCl_3$/MeOH = 20:1) gave the title compound **17b** as a brown oil (11.1 mg, 26.8 μmol, 65%). $R_f$ = 0.5 ($CHCl_3$/MeOH = 3:1) [UV]; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 1.01 (t, $J$ = 7.2, Hz, 6H), 2.45–2.48 (m, 2H), 2.52 (qd, $J$ = 7.1 Hz, $J$ = 14.0 Hz, 2H), 2.64 (qd, $J$ = 7.2 Hz, $J$ = 14.5 Hz, 2H), 3.91–3.99 (m, 3H), 6.87 (d, $J$ = 9.3 Hz, 1H), 7.36 (d, $J$ = 8.8 Hz, 2H), 7.39–7.42 (m, 2H), 7.44 ppm (d, $J$ = 8.8 Hz, 2H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$ = 11.5 (2×$CH_3$), 47.4 (2×$CH_2$), 56.0 ($CH_2$), 65.6 ($CH_2$), 71.0 (CH), 113.6 ($C_q$), 114.5 (CH), 128.2 (2×CH), 130.8 (2×CH), 131.5 (CH), 131.8 ($C_q$), 133.1 (CH), 133.4 ($C_q$), 135.5 ($C_q$), 154.8 ppm ($C_q$); MS (EI): $m/z$ (%) = 411 (10) $[M]^+$, 396 (14), 284 (26), 282 (22), 204 (15), 202 (42), 168 (44), 151 (12), 139 (40), 116 (36), 114 (15), 87 (92), 86 (100), 84 (11), 72 (29), 58 (78), 57 (15), 56 (24); HRMS (EI): $C_{19}H_{23}BrClNO_2$ $[M]^+$ calcd: 411.0601, found: 411.0601.

**(±)-1-((4′-Chloro-5-fluorobiphen-2-yl)oxy)-3-(diethylamino)propan-2-yl decanoate (18a)**: Preparations from compound **17a** (75.0 mg, 233 μmol) and decanoyl chloride (100 μL, 482 μmol) were made according to general procedure 3 described above. Purification by column chromatography (hexane/EtOAc = 4:1) gave the title compound **18a** as a colorless oil (21.2 mg, 41.9 μmol, 18%). $R_f$ = 0.8 (hexane/EtOAc = 2:1) [UV]; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 0.88 (t, $J$ = 7.1, Hz, 3H), 0.95 (t, $J$ = 7.1 Hz, 6H), 1.22–1.31 (m, 12H), 1.51–1.57 (m, 2H), 2.15–2.25 (m, 2H), 2.47–2.55 (m, 4H), 2.54–2.61 (m, 2H), 4.03 (dd, $J$ = 5.3 Hz, $J$ = 10.1 Hz, 1H), 4.11 (dd, $J$ = 3.6 Hz, $J$ = 10.1 Hz, 1H), 5.13–5.18 (m, 1H), 6.91 (dd, $J$ = 4.6 Hz, $J$ = 9.0 Hz, 1H), 6.98 (ddd, $J$ = 3.1 Hz, $J$ = 7.8 Hz, $J$ = 8.9 Hz, 1H), 7.02 (dd, $J$ = 3.1 Hz, $J$ = 9.0 Hz, 1H), 7.36 (d, $J$ = 8.7 Hz, 2H), 7.45 ppm (d, $J$ = 8.7 Hz, 2H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$ = 11.6 (2×$CH_3$), 14.1 ($CH_3$), 22.6 ($CH_2$), 24.8 ($CH_2$), 29.1 ($CH_2$), 29.2 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 31.8 ($CH_2$), 34.4 ($CH_2$), 47.8 (2×$CH_2$), 52.7 ($CH_2$), 68.9 ($CH_2$), 70.2 (CH), 114.0 (d, $J$ = 8.4 Hz, CH), 114.7 (d, $J$ = 22.7 Hz, CH), 117.1 (d, $J$ = 23.6 Hz, CH), 128.1 (2×CH), 130.8 (2×CH), 131.2 (d, $J$ = 7.5 Hz, $C_q$), 133.3 ($C_q$), 135.6 (d, $J$ = 1.6 Hz, $C_q$), 151.6 (d, $J$ = 2.3 Hz, $C_q$), 157.3 (d, $J$ = 239.8 Hz, $C_q$), 173.1 ppm (CO); HRMS (ESI): $C_{29}H_{42}ClFNO_3$ $[M+H]$ calcd: 506.2832, found: 506.2834.

***N*-(2-(Dimethylamino)ethyl)-*N*-(9-oxo-9*H*-xanthen-2-yl)decanamide (21a)**: The starting material **19a** was synthesized according to procedure described by Szajnman et al.[29] A solution of xanthone (1.00 g, 5.10 mmol, 1.0 equiv) in concentrated $H_2SO_4$ (3 mL) was cooled to 0 °C before fuming $HNO_3$ (180 μL, 2.56 mmol, 0.5 equiv) in concentrated $H_2SO_4$ (0.6 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 40 min and then poured onto crushed ice. The solid was filtered off, washed with cold $H_2O$ until pH 7 was attained, and dried with a high-vacuum pump. The crude product contained unsubstituted xanthone, 1-nitroxanthone, 2-nitroxanthone, and 2,7-dinitroxanthone. 2-Nitroxanthone (114 mg, 473 μmol) was isolated by column chromatography (hexane/EtOAc = 5:1; $R_f$ = 0.3) and was further dissolved in EtOAc (20 mL) in the presence of Pd/C as catalyst (40.0 mg). After being stirred under 40 atm $H_2$ overnight in the autoclave, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. Purification by column chromatography (hexane/EtOAc = 2:1) gave compound **19a** as a yellow solid (75.4 mg, 357 μmol, 7% over two steps). $R_f$ = 0.4 (hexane/EtOAc = 1:1) [UV]; $^1$H NMR: (600 MHz, $CDCl_3$): $\delta$ = 7.30 (dd, $J$ = 2.9 Hz, $J$ = 8.9 Hz, 1H), 7.39 (ddd, $J$ = 1.1 Hz, $J$ = 7.1 Hz, $J$ = 8.0 Hz, 1H), 7.43 (d, $J$ = 8.9 Hz, 1H), 7.51 (d, $J$ = 8.6 Hz, 1H), 7.61 (d, $J$ = 2.9 Hz, 1H), 7.75 (ddd, $J$ = 1.7 Hz, $J$ = 7.1 Hz, $J$ = 8.6 Hz, 1H), 8.30 ppm (dd, $J$ = 1.7 Hz, $J$ = 8.0 Hz, 1H). **19a** (70.0 mg, 331 μmol) was further treated with decanoyl chloride (68.7 μL, 331 μmol; 1:1 equiv due to possible double acylation) according to general procedure 3 described above. Purification by column chromatography (hexane/EtOAc = 4:1) and filtration through $Al_2O_3$ gave compound **20a** as a yellow solid (96.8 mg, 265 μmol, 80%). $R_f$ = 0.6 (hexane/EtOAc = 2:1) [UV]; $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 0.88 (t, $J$ = 6.8 Hz, 3H), 1.20–1.48 (m, 12H), 1.70–1.82 (m, 2H), 2.39–2.49 (m, 2H), 7.39 (t, $J$ = 7.5 Hz, 1H), 7.51 (d, $J$ = 8.5 Hz, 2H), 7.71–7.77 (m, 1H), 8.09 (s, 1H), 8.33 (dd, $J$ = 1.6 Hz, $J$ = 8.0 Hz, 1H), 8.45 ppm (d, $J$ = 8.5 Hz, 1H). **20a** (90.0 mg, 245 μmol) was further treated with 2-chloro-*N*,*N*-dimethylethanamine·HCl (352 mg, 2.45 mmol) in *N*,*N*-dimethylformamide according to general procedure 4 described above. Purification by column chromatography ($CHCl_3$/MeOH = 20:1) gave the title compound **21a** as a colorless solid (41.0 mg, 93.9 μmol, 38%). $R_f$ = 0.4 ($CHCl_3$/MeOH = 10:1) [UV]; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 0.84 (t, $J$ = 7.1 Hz, 3H), 1.14–1.27 (m, 12H), 1.53–1.60 (m, 2H), 2.04 (t, $J$ = 7.5 Hz, 2H), 2.27 (s, 6H), 2.49 (t, $J$ = 6.9 Hz, 2H), 3.90 (t, $J$ = 6.9 Hz, 2H), 7.44 (t, $J$ = 7.5 Hz, 1H), 7.55 (d, $J$ = 8.0 Hz, 1H), 7.58 (d, $J$ = 8.8 Hz, 1H), 7.64 (dd, $J$ = 2.5 Hz, $J$ = 8.8 Hz, 1H), 7.78 (ddd, $J$ = 1.6 Hz, $J$ = 7.2 Hz, $J$ = 8.6 Hz, 1H), 8.19 (d, $J$ = 2.5 Hz, 1H), 8.37 ppm (dd, $J$ = 1.6 Hz, $J$ = 8.0 Hz, 1H); $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 14.0 ($CH_3$), 22.6 ($CH_2$),

25.3 ($CH_2$), 29.2 (2×$CH_2$), 29.3 (2×$CH_2$), 31.8 ($CH_2$), 34.6 ($CH_2$), 45.4 (2×$CH_3$), 46.8 ($CH_2$), 56.5 ($CH_2$), 118.0 (CH), 119.6 (CH), 121.5 (CH), 122.4 ($C_q$), 124.4 (CH), 126.1 (CH), 126.8 (CH), 135.2 (CH), 135.3 ($C_q$), 138.7 ($C_q$), 155.0 ($C_q$), 156.1 ($C_q$), 173.0 (CO), 176.6 ppm (CO); HRMS (ESI): $C_{27}H_{37}N_2O_3$ [$M$+H] calcd: 437.2799, found: 437.2808.

***N*-(3-Benzoylphenyl)-*N*-(2-(dimethylamino)ethyl)decanamide (21 b)**: The intermediate **20 b** was prepared from 3-aminobenzophenone (700 mg, 3.55 mmol) and decanoyl chloride (737 μL, 3.55 mmol; 1:1 equiv caused by to possible double acylation) according to general procedure 3 described above. The reaction gave **20 b** (1.42 g) in quantitative yield as a yellow solid, which was used further without purification. $R_f$ = 0.8 (hexane/EtOAc = 2:1) [UV]; $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 0.87 (t, $J$ = 6.9 Hz, 3H), 1.20–1.40 (m, 12H), 1.67–1.77 (m, 2H), 2.37 (m, 2H), 7.40–7.52 (m, 4H), 7.56–7.62 (m, 1H), 7.77–7.83 (m, 3H), 7.98 ppm (d, $J$ = 8.0 Hz, 1H). In a second step, **20 b** (1.25 g, 3.55 mmol) was treated with 2-chloro-*N*,*N*-dimethylethanamine·HCl (1.45 g, 10.1 mmol) in *N*,*N*-dimethylformamide according to general procedure 4 described above. Purification by column chromatography ($CHCl_3$/MeOH = 10:1) gave the title compound **21 b** as a colorless solid (125 mg, 296 μmol, 8%). $R_f$ = 0.7 ($CHCl_3$/MeOH = 5:1) [UV]; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 0.85 (t, $J$ = 7.1 Hz, 3H), 1.15–1.23 (m, 10H), 1.23–1.28 (m, 2H), 1.53–1.59 (m, 2H), 2.05 (t, $J$ = 7.4 Hz, 2H), 2.29 (s, 6H), 2.48–2.55 (m, 2H), 3.88 (t, $J$ = 6.5 Hz, 2H), 7.48 (d, $J$ = 8.0 Hz, 1H), 7.51 (t, $J$ = 7.8 Hz, 2H), 7.55 (t, $J$ = 7.8 Hz, 1H), 7.61–7.65 (m, 2H), 7.78–7.81 ppm (m, 3H); $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 14.1 ($CH_3$), 22.7 ($CH_2$), 25.4 ($CH_2$), 29.3 (2×$CH_2$), 29.4 (2×$CH_2$), 31.9 ($CH_2$), 34.6 ($CH_2$), 45.3 (2×$CH_3$), 46.8 ($CH_2$), 56.5 ($CH_2$), 128.5 (2×CH), 129.4 (CH), 129.7 (CH), 129.8 (CH), 130.0 (2×CH), 132.4 (CH), 132.9 (CH), 137.1 ($C_q$), 139.2 ($C_q$), 142.9 ($C_q$), 173.0 (CO), 195.5 ppm (CO); HRMS (ESI): $C_{27}H_{39}N_2O_2$ [$M$+H] calcd: 423.3006, found: 423.3008.

**Decanoic acid (4′-chloro-6-methoxybiphen-3-ylmethyl)amide (23 a)**: Biphenyl **22 a** was prepared from 4-chloroaniline (1.28 g, 10.0 mmol) and *p*-methoxybenzylamine (**9 d**) (2.74 g, 20.0 mmol) according to general procedure 1 described above. The final reaction mixture was basified with NaOH (4.00 g) and $Na_2SO_3$ (4.00 g) in $H_2O$ (40 mL) prior to extraction. Purification by Kugelrohr distillation gave compound **22 a** as a dark oil (644 mg, 2.60 mmol, 65%). $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 3.79 (s, 3H), 3.85 (s, 2H), 6.94 (d, $J$ = 8.4 Hz, 1H), 7.23–7.31 (m, 2H), 7.36 (d, $J$ = 8.8 Hz, 2H), 7.46 ppm (d, $J$ = 8.8 Hz, 2H). Compound **22 a** (551 mg, 2.22 mmol) was further treated with decanoyl chloride (462 μL, 2.22 mmol; 1:1 equiv possibly caused by possible double acylation) according to general procedure 3 described above. Purification by column chromatography (hexane/EtOAc = 4:1→2:1) gave the title compound **23 a** as a yellow oil (286 mg, 710 μmol, 32%). $R_f$ = 0.4 (hexane/EtOAc = 2:1) [UV]; $^1$H NMR: (360 MHz, $CDCl_3$): $\delta$ = 0.87 (t, $J$ = 6.9 Hz, 3H), 1.21–1.35 (m, 12H), 1.59–1.69 (m, 2H), 2.19 (m, 2H), 3.79 (s, 3H), 4.41 (d, $J$ = 5.6 Hz, 2H), 5.74 (br s, 1H), 6.93 (d, $J$ = 8.4 Hz, 1H), 7.19 (d, $J$ = 2.3 Hz, 1H), 7.24 (dd, $J$ = 2.3 Hz, $J$ = 8.4 Hz, 1H), 7.36 (d, $J$ = 8.8 Hz, 2H), 7.43 ppm (d, $J$ = 8.8 Hz, 2H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$ = 14.1 ($CH_3$), 22.6 ($CH_2$), 25.8 ($CH_2$), 29.2 ($CH_2$), 29.3 (2×$CH_2$), 29.4 ($CH_2$), 31.8 ($CH_2$), 36.8 ($CH_2$), 43.0 ($CH_2$), 55.7 ($CH_3$), 111.5 (CH), 128.2 (2×CH), 128.4 (CH), 129.7 ($C_q$), 130.2 (CH), 130.7 (2×CH), 130.9 ($C_q$), 133.0 ($C_q$), 136.5 ($C_q$), 155.8 ($C_q$), 172.9 ppm (CO); MS (EI): $m/z$ (%) = 401 (77) [$M$]$^+$, 291 (16), 290 (9), 289 (45), 246 (18), 234 (9), 233 (52), 232 (27), 231 (100), 216 (9), 195 (8), 181 (16), 152 (9); HRMS (EI): $C_{24}H_{32}ClNO_2$ [$M$]$^+$ calcd: 401.2122, found: 401.2121.

**Decanoic acid (2′,6′-dichloro-6-methoxybiphen-3-ylmethyl)amide (8 b)**: Biphenyl **22 b** was synthesized from 2,6-dichloroaniline (1.62 g, 10.0 mmol) and *p*-methoxybenzylamine (**9 d**) (2.74 g, 20.0 mmol) according to general procedure 1 described above. For better solubility of 2,6-dichloroaniline, the diazonium salt was prepared in an $CH_3CN$/3 N HCl/$H_2O$ = 2:2:1 mixture. After completion of the reaction, the resulting mixture was basified with NaOH (4.00 g) and $Na_2SO_3$ (4.00 g) in $H_2O$ (40 mL) prior to extraction. Purification by Kugelrohr distillation gave compound **7 b** as a dark oil (542 g, 1.92 mmol, 48%). $^1$H NMR: (360 MHz, $CDCl_3$): $\delta$ = 3.77 (s, 3H), 3.86 (s, 2H), 6.98 (d, $J$ = 8.4 Hz, 1H), 7.07 (d, $J$ = 2.3 Hz, 1H), 7.21 (dd, $J$ = 7.5 Hz, $J$ = 8.6 Hz, 1H), 7.30–7.40 ppm (m, 3H). Compound **22 b** (560 mg, 1.98 mmol) was further treated with decanoyl chloride (412 μL, 1.98 mmol; 1:1 equiv due to possible double acylation) according to general procedure 3 described above. Purification by column chromatography (hexane/EtOAc = 4:1→2:1) gave the title compound **23 b** as a yellow solid (119 mg, 272 μmol, 14%). $R_f$ = 0.4 (hexane/EtOAc = 2:1) [UV]; $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 0.88 (t, $J$ = 6.9 Hz, 3H), 1.21–1.35 (m, 12H), 1.57–1.68 (m, 2H), 2.21 (m, 2H), 3.77 (s, 3H), 4.39 (s, 2H), 6.98 (d, $J$ = 8.5 Hz, 1H), 7.03 (d, $J$ = 2.3 Hz, 1H), 7.24 (dd, $J$ = 7.5 Hz, $J$ = 8.6 Hz, 1H), 7.32 (dd, $J$ = 2.3 Hz, $J$ = 8.5 Hz, 1H), 7.39 (d, $J$ = 7.5 Hz, 1H), 7.39 ppm (d, $J$ = 8.6 Hz, 1H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$ = 14.1 ($CH_3$), 22.8 ($CH_2$), 26.0 ($CH_2$), 29.4 (2×$CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$), 32.0 ($CH_2$), 36.7 ($CH_2$), 42.9 ($CH_2$), 56.1 ($CH_3$), 111.6 (CH), 126.5 ($C_q$), 128.0 (2×CH), 129.3 (CH), 129.6 (CH), 130.5 (CH), 130.6 ($C_q$), 135.6 (2×$C_q$), 136.5 ($C_q$), 156.3 ($C_q$), 174.4 ppm (CO); MS (EI): $m/z$ (%) = 435 (30) [$M$]$^+$, 325 (17), 323 (24), 282 (7), 280 (11), 269 (10), 268 (11), 267 (64), 266 (17), 265 (100), 215 (9); HRMS (EI): $C_{24}H_{31}Cl_2NO_2$ [$M$]$^+$ calcd: 435.1732, found: 435.1732.

**Decanoic acid (4′-chloro-6-methoxybiphen-3-ylmethyl)-(2-dimethylaminoethyl)amide (24 a)**: Preparations from compound **23 a** (100 mg, 249 μmol) and 2-chloro-*N*,*N*-dimethylethanamine·HCl (270 mg, 2.49 mmol) in *N*,*N*-dimethylacetamide were made according to general procedure 4 described above. Purification by column chromatography ($CHCl_3$/MeOH = 10:1) and filtration through $Al_2O_3$ gave the title compound **24 a** as an orange oil (90.7 mg, 192 μmol, 77%). By the addition of trifluoroacetic acid only one stereoisomer was obtained. $R_f$ = 0.5 ($CHCl_3$/MeOH = 10:1) [UV]; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 0.87 (t, $J$ = 7.1 Hz, 3H), 1.21–1.36 (m, 12H), 1.59–1.67 (m, 2H), 2.48 (m, 2H), 2.95 (s, 3H), 2.96 (s, 3H), 3.32–3.37 (m, 2H), 3.71 (t, $J$ = 6.4 Hz, 2H), 3.82 (s, 3H), 4.58 (s, 2H), 6.97 (d, $J$ = 8.5 Hz, 1H), 7.03 (d, $J$ = 2.3 Hz, 1H), 7.10 (dd, $J$ = 2.3 Hz, $J$ = 8.5 Hz, 1H), 7.38 (d, $J$ = 8.5 Hz, 2H), 7.41 ppm (d, $J$ = 8.5 Hz, 2H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$ = 14.1 ($CH_3$), 22.7 ($CH_2$), 25.0 ($CH_2$), 29.3 ($CH_2$), 29.4 (3×$CH_2$), 31.9 ($CH_2$), 33.1 ($CH_2$), 40.9 ($CH_2$), 43.5 (2×$CH_3$), 50.9 ($CH_2$), 54.9 ($CH_2$), 55.8 ($CH_3$), 111.9 (CH), 127.3 (CH), 127.8 ($C_q$), 128.3 (2×CH), 128.9 (CH), 130.3 ($C_q$), 130.7 (2×CH), 133.3 ($C_q$), 136.2 ($C_q$), 156.3 ($C_q$), 175.2 ppm (CO); MS (EI): $m/z$ (%) = 472 (8) [$M$]$^+$, 233 (11), 232 (5), 231 (31), 181 (9), 85 (5), 72 (13), 71 (99), 59 (8), 58 (100), 57 (5); HRMS (EI): $C_{28}H_{41}ClN_2O_2$ [$M$]$^+$ calcd: 472.2857, found: 472.2858.

**Decanoic acid (2′,6′-dichloro-6-methoxybiphen-3-ylmethyl)-(2-dimethylaminoethyl)amide (24 b)**: Preparations from compound **23 b** (68.0 mg, 156 μmol) and 2-chloro-*N*,*N*-dimethylethanamine·HCl (169 mg, 1.56 mmol) in *N*,*N*-dimethylacetamide were made according to general procedure 4 described above. Purification by column chromatography ($CHCl_3$/MeOH = 20:1) and filtration through $Al_2O_3$ gave the title compound **24 b** as a yellow oil (23.8 mg, 46.8 μmol, 30%). By addition of trifluoroacetic acid only one stereoisomer was obtained. $R_f$ = 0.5 ($CHCl_3$/MeOH = 10:1) [UV]; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 0.87 (t, $J$ = 7.1 Hz, 3H), 1.20–1.31 (m, 12H), 1.59–1.65 (m, 2H), 2.43 (m, 2H), 2.85 (s, 6H), 3.12 (t, $J$ = 6.6 Hz, 2H), 3.74 (t, $J$ = 6.6 Hz, 2H), 3.78 (s, 3H), 4.58 (br s, 2H), 6.86 (d, $J$ = 2.2 Hz, 1H), 7.01 (d, $J$ = 8.4 Hz, 1H), 7.24 (dd, $J$ = 7.8 Hz, $J$ = 8.4 Hz, 1H), 7.26 (dd, $J$ = 2.2 Hz, $J$ = 8.4 Hz, 1H), 7.39 ppm (d, $J$ =

8.1 Hz, 2H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$ = 14.1 ($CH_3$), 22.7 ($CH_2$), 25.0 ($CH_2$), 29.3 ($CH_2$), 29.4 (3×$CH_2$), 31.8 ($CH_2$), 33.2 ($CH_2$), 41.1 ($CH_2$), 43.4 (2×$CH_3$), 51.3 ($CH_2$), 55.0 ($CH_2$), 55.9 ($CH_3$), 111.9 (CH), 126.8 ($C_q$), 127.5 ($C_q$), 127.9 (2×CH), 129.0 (2×CH), 129.3 (CH), 135.3 (2×$C_q$), 136.0 ($C_q$), 156.7 ($C_q$), 175.0 ppm (CO); MS (EI): *m/z* (%) = 506 (52) $[M]^+$, 438 (18), 436 (28), 280 (10), 269 (27), 268 (22), 267 (100), 266 (34), 265 (100), 231 (14), 229 (16), 217 (13), 215 (34), 195 (18), 166 (11), 165 (15), 152 (10), 85 (13), 73 (11), 72 (100), 71 (100), 59 (37), 58 (100), 57 (25), 55 (11); HRMS (EI): $C_{28}H_{40}Cl_2N_2O_2$ $[M]^+$ calcd: 506.2467, found: 506.2467.

***N*-(4′-Chloro-6-methoxybiphen-3-yl)-*N*-(2-dimethylaminoethyl)-benzamide (25a)**: Preparations from compound **11a** (47.0 mg, 166 μmol) and benzoyl chloride (100 μL, 868 μmol) were made according to general procedure 3 described above. Purification by column chromatography ($CHCl_3$/MeOH = 20:1) gave the title compound **25a** as a yellow oil (49.7 mg, 122 μmol, 73%). $R_f$ = 0.3 ($CHCl_3$/MeOH = 10:1) [UV]; $^1$H NMR: (600 MHz, $CDCl_3$): $\delta$ = 2.32 (s, 6H), 2.59–2.66 (m, 2H), 3.76 (s, 3H), 4.02–4.10 (m, 2H), 6.80 (d, *J* = 8.6 Hz, 1H), 6.91–6.95 (m, 1H), 7.06 (d, *J* = 7.1 Hz, 1H), 7.15–7.26 (m, 5H), 7.29–7.33 ppm (m, 4H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$ = 45.5 (2×$CH_3$), 48.1 ($CH_2$), 55.7 ($CH_3$), 56.3 ($CH_2$), 111.5 (CH), 127.7 (CH), 127.8 (2×CH), 128.2 (2×CH), 128.6 (2×CH), 129.4 (CH), 129.8 ($C_q$), 130.3 (CH), 130.3 ($C_q$), 130.6 (2×CH), 133.3 ($C_q$), 135.7 ($C_q$), 136.4 ($C_q$), 154.7 ($C_q$), 170.5 ppm (CO); MS (EI): *m/z* (%) = 408 (1) $[M]^+$, 339 (30), 338 (20), 337 (89), 202 (16), 105 (94), 77 (48), 72 (96), 71 (46), 59 (18), 58 (100); HRMS (EI): $C_{24}H_{25}ClN_2O_2$ $[M]^+$ calcd: 408.1605, found: 408.1606.

**Furan-2-carboxylic acid (4′-chloro-6-methoxybiphen-3-yl)-(2-dimethylaminoethyl)amide (25b)**: Preparations from compound **11a** (47.0 mg, 166 μmol) and furan-2-carboxylic acid chloride (100 μL, 1.01 mmol) were made according to general procedure 3 described above. Purification by column chromatography ($CHCl_3$/MeOH = 20:1) and filtration through $Al_2O_3$ gave the title compound **25b** as a yellow oil (14.8 mg, 37.1 μmol, 22%). $R_f$ = 0.5 ($CHCl_3$/MeOH = 10:1) [UV]; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 2.33 (s, 6H), 2.62 (t, *J* = 3.1 Hz, 2H), 3.86 (s, 3H), 4.00 (t, *J* = 7.1 Hz, 2H), 5.81 (s, 1H), 6.21–6.24 (m, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 7.18 (d, *J* = 2.7 Hz, 1H), 7.21 (dd, *J* = 2.7 Hz, *J* = 8.6 Hz, 1H), 7.35–7.38 (m, 3H), 7.40 ppm (d, *J* = 8.8 Hz, 2H); $^{13}$C NMR (90.6 MHz, $CDCl_3$): $\delta$ = 45.4 (2×$CH_3$), 48.0 ($CH_2$), 55.9 ($CH_3$), 56.3 ($CH_2$), 111.0 (CH), 111.9 (CH), 116.4 (CH), 128.3 (2×CH), 128.6 (CH), 130.5 ($C_q$), 130.6 (CH), 130.7 (2×CH), 133.5 ($C_q$), 135.3 ($C_q$), 135.6 ($C_q$), 144.4 (CH), 147.1 ($C_q$), 156.0 ($C_q$), 159.2 ppm (CO); MS (EI): *m/z* (%) = 399 (1) $[M]^+$, 329 (51), 328 (30), 327 (100), 202 (23), 139 (11), 95 (100), 72 (100), 71 (71), 59 (32), 58 (100), 57 (13).

***N*-(4′-Chloro-6-methoxybiphen-3-yl)-*N*-(2-dimethylaminoethyl)-2-phenylacetamide (25c)**: Preparations from compound **11a** (47.0 mg, 166 μmol) and phenylacetyl chloride (100 μL, 756 μmol) were made according to general procedure 3 described above. Purification by column chromatography ($CHCl_3$/MeOH = 20:1) gave the title compound **25c** as a yellow oil (47.6 mg, 113 μmol, 68%). $R_f$ = 0.5 ($CHCl_3$/MeOH = 10:1) [UV]; $^1$H NMR: (360 MHz, $CDCl_3$): $\delta$ = 2.27 (s, 6H), 2.50 (t, *J* = 7.0 Hz, 2H), 3.49 (s, 2H), 3.83 (t, *J* = 7.0 Hz, 2H), 3.85 (s, 3H), 6.96 (d, *J* = 12.1 Hz, 1H), 6.97 (d, *J* = 0.6 Hz, 1H), 7.04–7.08 (m, 2H), 7.12 (dd, *J* = 2.7 Hz, *J* = 8.6 Hz, 1H), 7.18–7.24 (m, 3H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.36 ppm (d, *J* = 8.8 Hz, 2H); $^{13}$C NMR: (151 MHz, $CDCl_3$): $\delta$ = 32.9 ($CH_2$), 36.7 (2×$CH_3$), 38.4 ($CH_2$), 47.3 ($CH_3$), 47.6 ($CH_2$), 103.3 (CH), 118.0 (CH), 119.7 (2×CH), 119.8 (2×CH), 120.2 (CH), 120.4 (2×CH), 121.8 ($C_q$), 122.1 (3×CH), 124.8 ($C_q$), 126.6 ($C_q$), 126.9 ($C_q$), 127.0 ($C_q$), 147.3 ($C_q$), 162.7 ppm (CO); MS (EI): *m/z* (%) = 422 (1) $[M]^+$, 353 (26), 352 (18), 351 (74), 246 (11), 233 (20), 202 (14), 91 (50), 72 (100), 71 (52), 59 (15), 58 (100); HRMS (EI): $C_{25}H_{27}ClN_2O_2$ $[M]^+$ calcd: 422.1761, found: 422.1761.

**Cyclopropanecarboxylic acid (4′-chloro-6-methoxybiphen-3-yl)-(2-dimethylaminoethyl)-amide (25d)**: Preparation from compound **11a** (47.0 mg, 166 μmol) and cyclopropanecarboxylic acid chloride (100 μL, 1.10 mmol) according to general procedure 3 described above. Purification by column chromatography ($CHCl_3$/MeOH = 20:1) and filtration through $Al_2O_3$ gave the title compound **25d** as a colorless solid (30.5 mg, 81.8 μmol, 49%). $R_f$ = 0.4 ($CHCl_3$/MeOH = 10:1) [UV]; $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 0.58–0.65 (m, 2H), 0.97–1.03 (m, 2H), 1.33–1.42 (m, 1H), 2.24 (s, 6H), 2.45 (m, 2H), 3.84 (m, 2H), 3.84 (s, 3H), 6.99 (d, *J* = 9.1 Hz, 1H), 7.22–7.27 (m, 2H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.46 ppm (d, *J* = 8.7 Hz, 2H); $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 8.4 (2×$CH_2$), 12.7 (CH), 45.6 (2×$CH_3$), 47.3 ($CH_2$), 55.8 ($CH_3$), 56.6 ($CH_2$), 111.8 (CH), 128.3 (2×CH), 128.7 (CH), 130.4 ($C_q$), 130.5 (CH) 130.7 (2×CH), 133.4 ($C_q$), 135.7 ($C_q$), 135.8 ($C_q$), 155.5 ($C_q$), 173.6 ppm (CO); MS (EI): *m/z* (%) = 372 (1) $[M]^+$, 303 (15), 302 (10), 301 (48), 233 (22), 72 (90), 71 (48), 69 (34), 59 (15), 58 (100), 57 (15); HRMS (EI): $C_{21}H_{25}ClN_2O_2$ $[M]^+$ calcd: 372.1605, found: 372.1605.

**Cyclohexanecarboxylic acid (4′-chloro-6-methoxybiphen-3-yl)-(2-dimethylaminoethyl)amide (25e)**: Preparations from compound **11a** (47.0 mg, 166 μmol) and cyclohexanecarboxylic acid chloride (100 μL, 748 μmol) were made according to general procedure 3 described above. Purification by column chromatography ($CHCl_3$/MeOH = 20:1) and filtration through $Al_2O_3$ gave the title compound **25e** as a colorless oil (60.6 mg, 146 μmol, 88%). $R_f$ = 0.4 ($CHCl_3$/MeOH = 10:1) [UV]; $^1$H NMR: (360 MHz, $CDCl_3$): $\delta$ = 0.92–1.06 (m, 2H), 1.12–1.27 (m, 1H), 1.46–1.60 (m, 3H), 1.61–1.72 (m, 4H), 2.13–2.20 (m, 1H), 2.22 (s, 6H), 2.43 (m, 2H), 3.78 (m, 2H), 3.86 (s, 3H), 6.98 (d, *J* = 8.1 Hz, 1H), 7.11–7.16 (m, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.44 ppm (d, *J* = 8.8 Hz, 2H); $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 25.5 (2×$CH_2$), 25.6 ($CH_2$), 29.4 (2×$CH_2$), 41.5 (CH), 45.5 (2×$CH_3$), 47.1 ($CH_2$), 55.7 ($CH_3$), 56.5 ($CH_2$), 111.7 (CH), 128.3 (2×CH), 128.4 (CH), 130.2 (CH), 130.2 ($C_q$) 130.6 (2×CH), 133.3 ($C_q$), 135.6 ($C_q$), 135.7 ($C_q$), 155.5 ($C_q$), 176.3 ppm (CO); MS (EI): *m/z* (%) = 414 (1) $[M]^+$, 345 (23), 344 (16), 343 (66), 246 (10), 235 (14), 233 (45), 202 (12), 83 (27), 72 (88), 71 (36), 59 (11), 58 (100), 55 (28); HRMS (EI): $C_{24}H_{31}ClN_2O_2$ $[M]^+$ calcd: 414.2074, found: 414.2075.

**Decanoic acid (4′-chloro-6-methoxybiphen-3-ylmethyl)-{3-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]propyl}amide (27a)**: Compound **23a** (240 mg, 597 μmol) and 1-bromo-3-chloropropane (500 μL, 5.05 mmol) were reacted in *N*,*N*-dimethylformamide according to general procedure 4 described above. The intermediate was purified by column chromatography (hexane/EtOAc = 4:1; $R_f$ = 0.4) and reacted further with 4-(4-chlorophenyl)-4-hydroxypiperidine (40.0 mg, 189 μmol) according to general procedure 7 described above. Purification by column chromatography ($CHCl_3$/MeOH = 20:1→3:1) gave the title compound **27a** as a yellow oil (7.81 mg, 11.9 μmol, 2% over two steps). By addition of trifluoroacetic acid, only one stereoisomer was obtained. $R_f$ = 0.5 ($CHCl_3$/MeOH = 10:1) [UV]; $^1$H NMR: (600 MHz, $CDCl_3$): $\delta$ = 0.87 (t, *J* = 7.1 Hz, 3H), 1.21–1.33 (m, 12H), 1.60–1.65 (m, 2H), 1.98 (d, *J* = 14.4 Hz, 2H), 2.09 (br s, 2H), 2.46–2.54 (m, 4H), 3.10 (br s, 2H), 3.29–3.38 (m, 2H), 3.46–3.53 (m, 4H), 3.82 (s, 3H), 4.57 (s, 2H), 6.98 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 1.9 Hz, 1H), 7.11 (dd, *J* = 1.9 Hz, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.42 ppm (d, *J* = 8.6 Hz, 2H); $^{13}$C NMR: (151 MHz, $CDCl_3$): $\delta$ = 14.1 ($CH_3$), 22.5 ($CH_2$), 22.6 ($CH_2$), 25.5 ($CH_2$), 29.2 ($CH_2$), 29.3 ($CH_2$), 29.4 (2×$CH_2$), 31.8 ($CH_2$), 33.3 ($CH_2$), 35.5 (2×$CH_2$), 42.8 ($CH_2$), 49.2 (2×$CH_2$), 50.8 ($CH_2$), 55.1 ($CH_2$), 55.8 ($CH_3$), 69.1 ($C_q$), 111.9 (CH), 125.8 (2×CH), 127.1 (CH), 127.4 ($C_q$), 128.3 (2×CH),

128.7 (CH), 129.0 (2×CH), 130.3 ($C_q$), 130.7 (2×CH), 133.4 ($C_q$), 134.1 ($C_q$), 136.1 ($C_q$), 143.7 ($C_q$), 156.3 ($C_q$), 176.2 ppm (CO); MS (EI): *m/z* (%) = 652 (21) $[M]^+$, 238 (14), 233 (27), 232 (14), 231 (74), 226 (33), 225 (15), 224 (100), 210 (18), 206 (17), 192 (14), 191 (14), 189 (40), 181 (10), 154 (13), 127 (12), 99 (22), 97 (13), 84 (13), 71 (12), 57 (19), 56 (22), 55 (12); HRMS (EI): $C_{38}H_{50}Cl_2N_2O_3$ $[M]^+$ calcd: 652.3199, found: 652.3199.

**Decanoic acid {3-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-propyl}-(2′,6′-dichloro-6-methoxybiphen-3-ylmethyl)amide (27 b)**: Compound **23 b** (218 mg, 500 μmol) and 1-bromo-3-chloropropane (500 μL, 5.05 mmol) were reacted in *N*,*N*-dimethylformamide according to general procedure 4 described above. The intermediate was purified by column chromatography (hexane/EtOAc = 4:1; $R_f$ = 0.4) and reacted further with 4-(4-chlorophenyl)-4-hydroxypiperidine (40.0 mg, 189 μmol) according to general procedure 7 described above. Purification by column chromatography ($CHCl_3$/MeOH = 20:1→3:1) gave the title compound (**27 b**) as a colorless oil (10.3 mg, 15.0 μmol, 3% over two steps). By addition of trifluoroacetic acid only one stereoisomer was obtained. $R_f$ = 0.5 ($CHCl_3$/MeOH = 10:1) [UV]; $^1$H NMR: (600 MHz, $CDCl_3$): $\delta$ = 0.87 (t, *J* = 7.1 Hz, 3H), 1.20–1.31 (m, 12H), 1.58–1.65 (m, 2H), 1.92 (d, *J* = 14.2 Hz, 2H), 2.00–2.07 (m, 2H), 2.53–2.65 (m, 4H), 2.98–3.05 (m, 2H), 3.20–3.29 (m, 2H), 3.44–3.49 (m, 4H), 3.78 (s, 3H), 4.55 (s, 2H), 6.87 (d, *J* = 2.2 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 7.23 (dd, *J* = 2.2 Hz, *J* = 8.4 Hz, 1H), 7.24 (t, *J* = 8.1 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.42 ppm (d, *J* = 8.6 Hz, 2H); $^{13}$C NMR: (90.6 MHz, $CDCl_3$): $\delta$ = 14.1 ($CH_3$), 22.7 (2×$CH_2$), 25.3 ($CH_2$), 29.3 ($CH_2$), 29.4 (2×$CH_2$), 29.5 ($CH_2$), 31.9 ($CH_2$), 33.4 ($CH_2$), 35.5 (2×$CH_2$), 42.7 ($CH_2$), 48.9 (2×$CH_2$), 50.6 ($CH_2$), 55.1 ($CH_2$), 56.0 ($CH_3$), 69.3 ($C_q$), 111.8 (CH), 125.9 (2×CH), 126.7 ($C_q$), 127.8 ($C_q$), 127.9 (2×CH), 128.4 (CH), 128.8 (CH), 128.9 (2×CH), 129.2 (CH), 133.9 ($C_q$), 135.4 (2×$C_q$), 136.1 ($C_q$), 144.1 ($C_q$), 156.5 ($C_q$), 175.0 ppm (CO); MS (EI): *m/z* (%) = 686 (22) $[M]^+$, 267 (45), 266 (14), 265 (66), 252 (12), 238 (17), 226 (35), 225 (16), 224 (100), 210 (17), 206 (18), 192 (18), 191 (21), 190 (13), 189 (62), 154 (21), 127 (13), 112 (11), 99 (32), 97 (13), 57 (15), 56 (20); HRMS (EI): $C_{38}H_{49}Cl_3N_2O_3$ $[M]^+$ calcd: 686.2827, found: 686.2808.

**1-{3-[(4′-Chloro-6-methoxybiphen-3-ylmethyl)amino]propyl}-4-(4-chlorophenyl)piperidin-4-ol (27 c)**: Compound **22 a** (500 mg, 2.02 mmol) and di-*tert*-butyl dicarbonate (500 μL, 2.18 mmol) were reacted according to general procedure 3 described above. Purification by column chromatography (hexane/EtOAc = 4:1) gave compound **26 a** as a yellow oil (301 mg, 865 μmol, 43%). $R_f$ = 0.4 (hexane/EtOAc = 4:1) [UV]; $^1$H NMR: (360 MHz, $CDCl_3$): $\delta$ = 1.46 (s, 9H), 3.79 (s, 3H), 4.28 (d, *J* = 4.8 Hz, 2H), 6.92 (d, *J* = 8.3 Hz, 1H), 7.19 (d, *J* = 2.1 Hz, 1H), 7.22–7.26 (m, 1H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.44 ppm (d, *J* = 8.8 Hz, 2H). Compound **26 a** (226 mg, 650 μmol) was further treated with 1-bromo-3-chloropropane (500 μL, 5.05 mmol) in *N*,*N*-dimethylformamide according to general procedure 4 described above. The intermediate was purified by column chromatography (hexane/EtOAc = 4:1; $R_f$ = 0.5) and reacted further with 4-(4-chlorophenyl)-4-hydroxypiperidine (120 mg, 567 μmol) according to general procedure 7 described above. Purification by column chromatography ($CHCl_3$/MeOH = 20:1; $R_f$ = 0.5) gave pure Boc-protected product. The removal of Boc protection via general procedure 8 described above gave the title compound **27 c** as an orange oil (90.9 mg, 182 μmol, 28% over three steps). $R_f$ = 0.3 ($CHCl_3$/MeOH/$NEt_3$ = 100:5:1) [UV]; $^1$H NMR: (600 MHz, $CDCl_3$): $\delta$ = 1.78 (d, *J* = 13.3 Hz, 2H), 2.11–2.24 (m, 4H), 2.95–3.10 (m, 6H), 3.14–3.22 (m, 2H), 3.75 (s, 3H), 3.97 (s, 2H), 6.90 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.34–7.37 (m, 2H), 7.41 ppm (d, *J* = 8.4 Hz, 2H); $^{13}$C NMR: (151 MHz, $CDCl_3$): $\delta$ = 21.2 ($CH_2$), 35.7 (2×$CH_2$), 45.1 ($CH_2$), 48.8 (2×$CH_2$), 51.0 ($CH_2$), 54.8 ($CH_2$), 55.6 ($CH_3$), 69.0 ($C_q$), 111.7 (CH), 123.4 ($C_q$), 126.0 (2×CH), 128.3 (2×CH), 128.6 (2×CH), 129.9 ($C_q$), 130.6 (CH), 130.7 (2×CH), 132.2 (CH), 133.4 (2×$C_q$), 135.7 ($C_q$), 145.1 ($C_q$), 157.2 ppm ($C_q$); HPLC–MS: *m/z* (%) = 499.4 $[M+H]$.

**4-(4-Chlorophenyl)-1-{3-[(2′,6′-dichloro-6-methoxybiphen-3-ylmethyl)amino]propyl}piperidin-4-ol (27 d)**: Compound **22 b** (560 mg, 1.98 mmol) and di-*tert*-butyl dicarbonate (500 μL, 2.18 mmol) were reacted according to general procedure 3 described above. Purification by column chromatography (hexane/EtOAc = 4:1) gave compound **26 b** as a pink solid (330 mg, 863 μmol, 44%). $R_f$ = 0.5 (hexane/EtOAc = 4:1) [UV]; $^1$H NMR: (360 MHz, $CDCl_3$): $\delta$ = 1.46 (s, 9H), 3.76 (s, 3H), 4.28 (d, *J* = 4.7 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 2.2 Hz, 1H), 7.21 (dd, *J* = 7.5 Hz, *J* = 8.4 Hz, 1H), 7.32 (dd, *J* = 2.2 Hz, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.37 ppm (d, *J* = 8.5 Hz, 1H). Compound **19 b** (190 mg, 497 μmol) was treated with 1-bromo-3-chloropropane (500 μL, 5.05 mmol) in *N*,*N*-dimethylformamide according to general procedure 4 described above. The intermediate was purified by column chromatography (hexane/EtOAc = 4:1; $R_f$ = 0.4) and reacted further with 4-(4-chlorophenyl)-4-hydroxypiperidine (120 mg, 567 μmol) according to general procedure 7 described above. Purification by column chromatography ($CHCl_3$/MeOH = 20:1; $R_f$ = 0.4) gave the pure Boc-protected product. The removal of Boc protection via general procedure 8 described above gave the title compound **27 d** as a yellow oil (84.9 mg, 159 μmol, 32% over three steps). $R_f$ = 0.3 ($CHCl_3$/MeOH/$NEt_3$ = 100:5:1) [UV]; $^1$H NMR: (600 MHz, $CD_3OD$): $\delta$ = 1.86 (d, *J* = 14.2 Hz, 2H), 2.10–2.17 (m, 2H), 2.24 (dt, *J* = 4.0 Hz, *J* = 14.2 Hz, 2H), 3.07 (m, 2H), 3.18 (m, 2H), 3.33 (t, *J* = 11.8 Hz, 2H), 3.43 (d, *J* = 11.8 Hz, 2H), 3.69 (s, 3H), 4.14 (s, 2H), 7.09 (d, *J* = 8.6 Hz, 1H), 7.17 (d, *J* = 2.3 Hz, 1H), 7.23 (dd, *J* = 7.7 Hz, *J* = 8.5 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 7.48 ppm (dd, *J* = 2.3 Hz, *J* = 8.6 Hz, 1H); $^{13}$C NMR: (151 MHz, $CD_3OD$): $\delta$ = 22.3 ($CH_2$), 36.6 (2×$CH_2$), 45.3 ($CH_2$), 50.5 (2×$CH_2$), 51.9 ($CH_2$), 55.0 ($CH_2$), 56.4 ($CH_3$), 69.2 ($C_q$), 113.0 (CH), 124.2 ($C_q$), 127.4 (2×CH), 128.2 ($C_q$), 129.1 (2×CH), 129.6 (2×CH), 130.9 (CH), 133.2 (CH), 133.5 (CH), 134.4 ($C_q$), 136.6 (2×$C_q$), 137.2 ($C_q$), 146.9 ($C_q$), 159.4 ppm ($C_q$); HPLC–MS: *m/z* (%) = 535.1 $[M+H]$.

**Decanoic acid (4′-chloro-6-methoxybiphen-3-ylmethyl)-(4-cyano-4,4-diphenylbutyl)amide (28 a)**: Preparations from compound **23 a** (100 mg, 249 μmol) and 5-bromo-2,2-diphenylpentanenitrile (314 mg, 1.00 mmol) in *N*,*N*-dimethylformamide were made according to general procedure 4 described above. Purification by column chromatography (hexane/EtOAc = 4:1) gave the title compound **28 a** as a yellow oil (105 mg, 165 μmol, 66%). $R_f$ = 0.4 (hexane/EtOAc = 1:4) [UV]; $^1$H NMR: (360 MHz, $CDCl_3$): $\delta$ = 0.83–0.92 (m, 3$H_{maj+min}$), 1.20–1.32 (m, 12$H_{maj+min}$), 1.58–1.72 (m, 5$H_{maj+min}$), 2.24–2.39 (m, 3$H_{maj+min}$), 3.26 (t, *J* = 7.4 Hz, 2$H_{min}$), 3.44 (t, *J* = 7.0 Hz, 2$H_{maj}$), 3.79 (s, 3$H_{min}$), 3.80 (s, 3$H_{maj}$), 4.43 (s, 2$H_{maj}$), 4.49 (s, 2$H_{min}$), 6.88 (d, *J* = 8.4 Hz, 1$H_{min}$), 6.93 (d, *J* = 8.4 Hz, 1$H_{maj}$), 7.00 (d, *J* = 2.2 Hz, 1$H_{maj}$), 7.06 (d, *J* = 2.3 Hz, 1$H_{min}$), 7.06 (dd, *J* = 2.2 Hz, *J* = 8.4 Hz, 1$H_{maj}$), 7.13 (dd, *J* = 2.3 Hz, *J* = 8.4 Hz, 1$H_{min}$), 7.26–7.35 (m, 10$H_{maj+min}$), 7.35–7.38 (m, 2$H_{maj+min}$), 7.38–7.43 ppm (m, 2$H_{maj+min}$); $^{13}$C NMR: (151 MHz, $CDCl_3$): $\delta$ = 13.9 ($CH_{3\,maj+min}$), 22.5 ($CH_{2\,maj+min}$), 23.8 ($CH_{2\,maj}$), 24.6 ($CH_{2\,min}$), 25.4 ($CH_{2\,maj+min}$), 29.1 ($CH_{2\,maj}$), 29.2 ($CH_{2\,min}$), 29.3 (3×$CH_{2\,maj+min}$), 31.7 ($CH_{2\,maj+min}$), 33.1 ($CH_{2\,min}$), 33.3 ($CH_{2\,maj}$), 36.5 ($CH_{2\,min}$), 36.6 ($CH_{2\,maj}$), 44.2 ($C_{q\,maj}$), 46.1 ($C_{q\,min}$), 47.2 ($CH_{2\,min}$), 49.7 ($CH_{2\,maj}$), 51.2 ($CH_{2\,min}$), 51.5 ($CH_{2\,maj}$), 55.5 ($CH_{3\,min}$), 55.6 ($CH_{3\,maj}$), 111.3 ($CH_{min}$), 111.5 ($CH_{maj}$), 121.8 ($CN_{min}$), 122.1 ($CN_{maj}$), 126.5 (4×$CH_{min}$), 126.6 (4×$CH_{maj}$), 127.7 (2×$CH_{maj}$), 128.0 (2×$CH_{min}$), 128.0 (2×$CH_{min}$), 128.1 (2×$CH_{maj}$), 128.5 ($C_{q\,maj}$), 128.6 ($C_{q\,min}$), 128.7 ($C_{q\,maj}$), 128.8 ($C_{q\,min}$), 128.8 (4×$CH_{maj}$), 128.9 (4×$CH_{min}$), 129.4 ($C_q$

$_{min}$), 129.8 ($C_{q\ maj}$), 129.9 ($C_{q\ min}$), 130.2 ($C_{q\ maj}$), 130.6 (2×$CH_{maj}$), 130.7 (2×$CH_{min}$), 132.8 ($C_{q\ min}$), 133.0 ($C_{q\ maj}$), 136.2 ($C_{q\ maj}$), 136.4 ($C_{q\ min}$), 139.5 ($CH_{min}$), 139.8 ($CH_{maj}$), 155.5 ($C_{q\ min}$), 155.7 ($C_{q\ maj}$), 173.0 ($CO_{min}$), 173.5 ppm ($CO_{maj}$), one CH is missing due to overlap of signals; MS (EI): *m/z* (%) = 634 (53) $[M]^+$, 522 (11), 442 (23), 400 (13), 330 (15), 249 (12), 248 (17), 246 (51), 233 (54), 232 (28), 231 (100), 181 (16), 70 (14), 57 (13); HRMS (EI): $C_{41}H_{47}ClN_2O_2$ $[M]^+$ calcd: 634.3326, found: 634.3325.

**Decanoic acid (4-cyano-4,4-diphenylbutyl)-(2′,6′-dichloro-6-methoxybiphen-3-ylmethyl)amide (28b)**: Preparations from compound **23b** (50 mg, 115 μmol) and 5-bromo-2,2-diphenylpentanenitrile (90 mg, 287 μmol) in *N*,*N*-dimethylformamide were made according to general procedure 4 described above. Purification by column chromatography (hexane/EtOAc = 4:1) gave the title compound **28b** as a yellow oil (16.9 mg, 25.3 μmol, 22%). $R_f$ = 0.2 (hexane/EtOAc = 4:1) [UV]; $^1$H NMR: (360 MHz, $CDCl_3$): $\delta$ = 0.83–0.91 (m, 3$H_{maj+min}$), 1.19–1.33 (m, 12$H_{maj+min}$), 1.57–1.73 (m, 5$H_{maj+min}$), 2.23–2.40 (m, 3$H_{maj+min}$), 3.22 (t, *J* = 7.6 Hz, 2$H_{min}$), 3.44 (t, *J* = 6.9 Hz, 2$H_{maj}$), 3.76 (s, 3$H_{min}$), 3.77 (s, 3$H_{maj}$), 4.43 (s, 2$H_{maj}$), 4.49 (s, 2$H_{min}$), 6.83 (d, *J* = 2.1 Hz, 1$H_{maj}$), 6.87 (d, *J* = 2.1 Hz, 1$H_{min}$), 6.91 (d, *J* = 8.5 Hz, 1$H_{min}$), 6.96 (d, *J* = 8.5 Hz, 1$H_{maj}$), 7.13–7.40 ppm (m, 14$H_{maj+min}$); $^{13}$C NMR: (90.6 MHz, $CDCl_3$): $\delta$ = 14.1 ($CH_{3\,maj+min}$), 22.7 ($CH_{2\,maj+min}$), 23.8 ($CH_{2\,maj}$), 24.5 ($CH_{2\,min}$), 25.5 ($CH_{2\,maj}$), 25.6 ($CH_{2\,min}$), 29.3 ($CH_{2\,maj+min}$), 29.5 (3×$CH_{2\,maj+min}$), 31.9 ($CH_{2\,maj+min}$), 33.3 ($CH_{2\,min}$), 33.5 ($CH_{2\,maj}$), 36.6 ($CH_{2\,min}$), 36.8 ($CH_{2\,maj}$), 44.1 ($C_{q\ maj}$), 45.6 ($C_{q\ min}$), 46.9 ($CH_{2\,min}$), 49.7 ($CH_{2\,maj}$), 51.4 ($CH_{2\,min}$), 51.6 ($CH_{2\,maj}$), 55.9 ($CH_{3\,min}$), 56.0 ($CH_{3\,maj}$), 111.3 ($CH_{min}$), 111.7 ($CH_{maj}$), 122.0 ($CN_{min}$), 122.3 ($CN_{maj}$), 126.1 ($C_{q\,min}$), 126.5 ($C_{q\,maj}$), 126.7 (4×$CH_{min}$), 126.8 (4×$CH_{maj}$), 127.8 (2×$CH_{maj+min}$), 127.9 (2×$CH_{maj}$), 128.0 (2×$CH_{min}$), 128.1 ($CH_{maj}$), 128.4 ($CH_{min}$), 128.9 (4×$CH_{maj}$), 128.9 ($CH_{min}$), 129.0 ($CH_{maj}$), 129.0 (4×$CH_{min}$), 129.2 ($CH_{maj}$), 129.5 ($CH_{min}$), 130.0 ($C_{q\ maj}$), 131.0 ($C_{q\ min}$), 135.4 (2×$C_{q\ maj}$), 135.5 (2×$C_{q\ min}$), 136.2 ($C_{q\ maj}$), 136.4 ($C_{q\ min}$), 139.7 (2×$C_{q\ min}$), 140.1 (2×$C_{q\ maj}$), 156.1 ($C_{q\ min}$), 156.2 ($C_{q\ maj}$), 173.1 ($CO_{min}$), 173.8 ppm ($CO_{maj}$); MS (EI): *m/z* (%) = 668 (44) $[M]^+$, 556 (11), 478 (16), 476 (23), 434 (11), 364 (13), 282 (30), 280 (48), 269 (17), 268 (16), 267 (97), 266 (26), 265 (100), 249 (11), 215 (14), 165 (10), 112 (11), 70 (18); HRMS (EI): $C_{41}H_{46}Cl_2N_2O_2$ $[M]^+$ calcd: 668.2936, found: 668.2936.

**5-[(4′-Chloro-6-methoxybiphen-3-ylmethyl)amino]-2,2-diphenylpentanenitrile (28c)**: Preparations from compound **26a** (52.0 mg, 149 μmol; for synthesis see compound **27c**) and 5-bromo-2,2-diphenylpentanenitrile (175 mg, 557 μmol) in *N*,*N*-dimethylformamide were made according to the general procedures 4 and 8 described above. Purification by column chromatography ($CHCl_3$/MeOH = 20:1) gave the title compound **28c** as a yellow oil (20.1 mg, 41.7 μmol, 28% over two steps). $R_f$ = 0.5 ($CHCl_3$/MeOH = 10:1) [UV]; $^1$H NMR: (360 MHz, $CDCl_3$): $\delta$ = 1.67–1.77 (m, 2H), 2.42–2.49 (m, 2H), 2.74 (t, *J* = 6.7 Hz, 2H), 3.73–3.78 (m, 2H), 3.75 (s, 3H), 6.89 (d, *J* = 8.3 Hz, 1H), 7.22–7.38 (m, 14H), 7.44 ppm (d, *J* = 8.7 Hz, 2H); $^{13}$C NMR: (90.6 MHz, $CDCl_3$): $\delta$ = 23.9 ($CH_2$), 36.9 ($CH_2$), 46.7 ($C_q$), 51.2 ($CH_2$), 51.5 ($CH_2$), 55.6 ($CH_3$), 111.5 (CH), 122.1 (CN), 126.7 ($C_q$), 126.8 (4×CH), 128.0 (2×CH), 128.2 (2×CH), 128.9 (4×CH), 129.6 (CH), 129.8 (CH), 130.8 (2×CH), 131.5 (CH), 133.1 ($C_q$), 136.2 ($C_q$), 139.8 (2×$C_q$), 156.3 ppm ($C_q$); MS (EI): *m/z* (%) = 480 (26) $[M]^+$, 479 (11), 478 (16), 321 (9), 260 (17), 234 (9), 233 (47), 232 (25), 231 (100), 192 (9), 181 (19), 165 (19); HRMS (EI): $C_{31}H_{29}ClN_2O$ $[M]^+$ calcd: 480.1968, found: 480.1968.

**5-[(2′,6′-Dichloro-6-methoxybiphen-3-ylmethyl)amino]-2,2-diphenylpentanenitrile (28d)**: Preparations from compound **26b** (57.0 mg, 149 μmol; for synthesis see compound **27d**) and 5-bromo-2,2-diphenylpentanenitrile (175 mg, 557 μmol) in *N*,*N*-dimethylformamide were made according to the general procedures 4 and 8 described above. Purification by column chromatography ($CHCl_3$/MeOH = 20:1) gave the title compound **28d** as a yellow oil (10.8 mg, 20.9 μmol, 14% over two steps). $R_f$ = 0.6 ($CHCl_3$/MeOH = 10:1) [UV]; $^1$H NMR: (600 MHz, $CDCl_3$): $\delta$ = 1.61–1.68 (m, 2H), 2.45–2.49 (m, 2H), 2.69 (t, *J* = 6.9 Hz, 2H), 3.75 (s, 2H), 3.77 (s, 3H), 6.96 (d, *J* = 8.5 Hz, 1H), 7.02 (d, *J* = 2.2 Hz, 1H), 7.22 (dd, *J* = 7.8 Hz, *J* = 8.4 Hz, 1H), 7.24–7.28 (m, 3H), 7.30–7.34 (m, 4H), 7.36–7.40 ppm (m, 6H); $^{13}$C NMR: (90.6 MHz, $CDCl_3$): $\delta$ = 25.5 ($CH_2$), 37.3 ($CH_2$), 47.7 ($C_q$), 51.6 ($CH_2$), 52.3 ($CH_2$), 55.9 ($CH_3$), 111.4 (CH), 122.3 (CN), 126.0 ($C_q$), 126.9 (5×CH), 127.8 (2×CH), 127.9 (2×CH), 128.9 (4×CH), 129.0 (CH), 129.9 (CH), 130.9 (CH), 135.5 (2×$C_q$), 136.5 ($C_q$), 140.1 (2×$C_q$), 156.0 ppm ($C_q$); MS (EI): *m/z* (%) = 514 (20) $[M]^+$, 294 (13), 269 (12), 268 (11), 267 (66), 266 (18), 265 (100), 235 (45), 234 (20), 233 (21), 215 (12), 207 (12), 206 (10), 195 (10), 193 (27), 192 (41), 190 (11), 180 (12), 166 (13), 165 (50), 156 (16), 129 (15), 105 (18), 104 (36), 91 (15); HRMS (EI): $C_{31}H_{28}Cl_2N_2O$ $[M]^+$ calcd: 514.1579, found: 514.1579.

**2-(*N*-(4′-Chloro-6-methoxybiphen-3-yl)decanamido)-*N*,*N*,*N*-trimethylethanaminium iodide (29a)**: Preparations from compound **12a** (25.3 mg, 55.1 μmol) were made according to general procedure 9 described above. The title compound **29a** was obtained as a brown oil (26.1 mg, 55.1 μmol, 100%). $R_f$ = 0.3 ($CHCl_3$/MeOH = 10:1) [UV]; $^1$H NMR: (600 MHz, $CDCl_3$): $\delta$ = 0.86 (t, *J* = 7.2 Hz, 3H), 1.15–1.22 (m, 10H), 1.23–1.28 (m, 2H), 1.49–1.54 (m, 2H), 2.08 (m, 2H), 3.48 (s, 9H), 3.83 (m, 2H), 3.85 (s, 3H), 4.02–4.28 (m, 2H), 7.08 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 2.7 Hz, 1H), 7.36 (dd, *J* = 2.7 Hz, *J* = 8.8 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.52 ppm (d, *J* = 8.7 Hz, 2H); $^{13}$C NMR: (90.6 MHz, $CDCl_3$): $\delta$ = 14.0 ($CH_3$), 22.6 ($CH_2$), 25.1 ($CH_2$), 29.1 ($CH_2$), 29.2 (2×$CH_2$), 29.3 ($CH_2$), 31.7 ($CH_2$), 34.1 ($CH_2$), 44.2 ($CH_2$), 54.0 (3×$CH_3$), 56.0 ($CH_3$), 63.5 ($CH_2$), 112.8 (CH), 128.3 (2×CH), 128.9 (CH), 129.4 (CH), 130.9 (2×CH), 131.1 ($C_q$), 133.5 ($C_q$), 134.0 ($C_q$), 135.2 ($C_q$), 156.3 ($C_q$), 174.7 ppm (CO); HRMS (ESI): $C_{28}H_{42}ClN_2O_2^+$ $[M+H]$ calcd: 473.2935, found: 473.2936.

**2-(*N*-(2′,6′-Dichloro-6-methoxybiphen-3-yl)decanamido)-*N*,*N*,*N*-trimethylethanaminium iodide (29b)**: Preparations from compound **12b** (25.2 mg, 51.1 μmol) were made according to general procedure 9 described above. The title compound **29b** was obtained as a brown oil (26.0 mg, 51.1 μmol, 100%). $R_f$ = 0.4 ($CHCl_3$/MeOH = 10:1) [UV]; $^1$H NMR: (600 MHz, $CDCl_3$): $\delta$ = 0.86 (t, *J* = 7.1 Hz, 3H), 1.14–1.23 (m, 10H), 1.24–1.30 (m, 2H), 1.48–1.54 (m, 2H), 2.12 (m, 2H), 3.53 (s, 9H), 3.82 (s, 3H), 3.86 (m, 2H), 4.09–4.29 (m, 2H), 6.90 (d, *J* = 2.7 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 1H), 7.26 (dd, *J* = 7.7 Hz, *J* = 8.5 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.55 ppm (dd, *J* = 2.8 Hz, *J* = 8.8 Hz, 1H); $^{13}$C NMR: (151 MHz, $CDCl_3$): $\delta$ = 14.0 ($CH_3$), 22.6 ($CH_2$), 25.1 ($CH_2$), 29.2 (3×$CH_2$), 29.3 ($CH_2$), 31.8 ($CH_2$), 34.3 ($CH_2$), 44.1 ($CH_2$), 54.1 (3×$CH_3$), 56.2 ($CH_3$), 63.8 ($CH_2$), 113.0 (CH), 127.4 ($C_q$), 127.9 (2×CH), 129.5 (CH), 129.9 (CH), 130.1 (CH), 133.4 ($C_q$), 135.0 ($C_q$), 135.2 (2×$C_q$), 156.8 ($C_q$), 174.9 ppm (CO); HRMS (ESI): $C_{28}H_{41}Cl_2N_2O_2$ $[M+H]$ calcd: 507.2540, found: 507.2549.

**2-(*N*-((4′-Chloro-6-methoxybiphen-3-yl)methyl)decanamido)-*N*,*N*,*N*-trimethylethanaminium iodide (30a)**: Preparations from compound **24a** (15.0 mg, 31.7 μmol) were made according to general procedure 9 described above. The title compound **30a** was obtained as a brown oil (15.5 mg, 31.7 μmol, 100%). $R_f$ = 0.4 ($CHCl_3$/MeOH = 10:1) [UV]; $^1$H NMR: (600 MHz, $CDCl_3$): $\delta$ = 0.87 (t, *J* = 7.1 Hz, 3H), 1.21–1.32 (m, 12H), 1.60–1.66 (m, 2H), 2.43 (m, 2H), 3.37 (s, 9H), 3.75 (t, *J* = 6.8 Hz, 2H), 3.81 (s, 3H), 3.95 (t, *J* = 6.8 Hz, 2H), 4.81–4.82 (br s, 2H), 6.98 (d, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 7.27 (dd, *J* = 2.4 Hz, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 8.6 Hz, 2H), 7.45 ppm (d, *J* = 8.6 Hz, 2H); $^{13}$C NMR: (90.6 MHz, $CDCl_3$): $\delta$ = 14.1 ($CH_3$), 22.6 ($CH_2$), 25.1 ($CH_2$), 29.2 ($CH_2$), 29.4 (3×$CH_2$), 31.8 ($CH_2$), 33.1 ($CH_2$), 39.4 ($CH_2$), 50.7 ($CH_2$), 54.0 (3×$CH_3$), 55.8 ($CH_3$), 62.6

($CH_2$), 111.9 (CH), 127.3 (CH), 127.8 ($C_q$), 128.3 (2×CH), 129.0 (CH), 130.0 ($C_q$), 130.8 (2×CH), 133.2 ($C_q$), 136.2 ($C_q$), 156.2 ($C_q$), 174.7 ppm (CO); HRMS (ESI): $C_{29}H_{44}ClN_2O_2^+$ [$M+H$] calcd: 487.3086, found: 487.30861.

**2-(*N*-((2′,6′-Dichloro-6-methoxybiphen-3-yl)methyl)decanamido)-*N*,*N*,*N*-trimethylethanaminium iodide (30 b)**: Preparations from compound **24 b** (5.00 mg, 9.85 μmol) were made according to general procedure 9 described above. The title compound **30 b** was obtained as a brown oil (5.15 mg, 9.85 μmol, 100%). $R_f$ = 0.4 ($CHCl_3$/MeOH = 10:1) [UV]; $^1$H NMR: (600 MHz, $CDCl_3$): $\delta$ = 0.87 (t, $J$ = 7.1 Hz, 3H), 1.20–1.32 (m, 12H), 1.59–1.65 (m, 2H), 2.44 (m, 2H), 3.31 (s, 9H), 3.68 (t, $J$ = 6.9 Hz, 2H), 3.79 (s, 3H), 3.81 (m, 2H), 4.77 (br s, 2H), 6.90 (d, $J$ = 2.3 Hz, 1H), 7.05 (d, $J$ = 8.5 Hz, 1H), 7.25 (dd, $J$ = 7.7 Hz, $J$ = 8.4 Hz, 1H), 7.39 (d, $J$ = 8.1 Hz, 2H), 7.44 ppm (dd, $J$ = 2.3 Hz, $J$ = 8.5 Hz, 1H); $^{13}$C NMR: (151 MHz, $CDCl_3$): $\delta$ = 14.1 ($CH_3$), 22.6 ($CH_2$), 25.0 ($CH_2$), 29.2 ($CH_2$), 29.3 ($CH_2$), 29.4 (2×$CH_2$), 31.8 ($CH_2$), 33.3 ($CH_2$), 40.0 ($CH_2$), 51.2 ($CH_2$), 54.0 (3×$CH_3$), 56.0 ($CH_3$), 63.1 ($CH_2$), 112.0 (CH), 126.6 ($C_q$), 127.4 ($C_q$), 127.9 (2×CH), 128.9 (CH), 129.3 (CH), 129.6 (CH), 135.2 (2×$C_q$), 135.9 ($C_q$), 156.6 ($C_q$), 174.7 ppm (CO); HRMS (ESI): $C_{29}H_{43}Cl_2N_2O_2^+$ [$M+H$] calcd: 521.2696, found: 521.2698.

***N*,*N*,*N*-Trimethyl-2-(*N*-(9-oxo-9*H*-xanthen-2-yl)decanamido)ethanaminium iodide (31 a)**: Preparations from compound **21 a** (25.0 mg, 57.3 μmol) were made according to general procedure 9 described above. The title compound **31 a** was obtained as a yellow solid (25.9 mg, 57.3 μmol, 100%). $R_f$ = 0.4 ($CHCl_3$/MeOH = 10:1) [UV]; $^1$H NMR: (600 MHz, $CDCl_3$): $\delta$ = 0.82 (t, $J$ = 7.1 Hz, 3H), 1.10–1.19 (m, 10H), 1.19–1.24 (m, 2H), 1.48–1.55 (m, 2H), 2.06 (t, $J$ = 7.6 Hz, 2H), 3.52 (s, 9H), 3.94 (t, $J$ = 6.8 Hz, 2H), 4.23–4.29 (m, 2H), 7.43 (t, $J$ = 7.5 Hz, 1H), 7.53 (d, $J$ = 8.4 Hz, 1H), 7.68 (d, $J$ = 8.8 Hz, 1H), 7.77 (ddd, $J$ = 1.7 Hz, $J$ = 7.2 Hz, $J$ = 8.6 Hz, 1H), 7.94 (dd, $J$ = 2.7 Hz, $J$ = 8.8 Hz, 1H), 8.08 (d, $J$ = 2.7 Hz, 1H), 8.28 ppm (dd, $J$ = 1.5 Hz, $J$ = 7.9 Hz, 1H); $^{13}$C NMR: (90.6 MHz, $CDCl_3$): $\delta$ = 14.1 ($CH_3$), 22.6 ($CH_2$), 25.1 ($CH_2$), 29.1 ($CH_2$), 29.2 ($CH_2$), 29.3 (2×$CH_2$), 31.8 ($CH_2$), 34.4 ($CH_2$), 44.4 ($CH_2$), 54.2 (3×$CH_3$), 63.4 ($CH_2$), 118.2 (CH), 121.2 (CH), 121.3 ($C_q$), 122.5 ($C_q$), 124.6 (CH), 125.4 (CH), 126.6 (CH), 135.5 (CH), 135.6 (CH), 137.2 ($C_q$), 155.5 ($C_q$), 156.1 ($C_q$), 174.3 (CO), 176.4 ppm (CO); HRMS (ESI): $C_{28}H_{39}N_2O_3$ [$M+H$] calcd: 451.2955, found: 451.2967.

**2-(*N*-(3-Benzoylphenyl)decanamido)-*N*,*N*,*N*-trimethylethanaminium iodide (31 b)**: Preparations from compound **21 b** (25.0 mg, 59.2 μmol) were made according to general procedure 9 described above. The title compound **31 b** was obtained as a brown oil (25.9 mg, 59.2 μmol, 100%). $R_f$ = 0.4 ($CHCl_3$/MeOH = 10:1) [UV]; $^1$H NMR: (600 MHz, $CDCl_3$): $\delta$ = 0.86 (t, $J$ = 7.1 Hz, 3H), 1.15–1.22 (m, 10H), 1.23–1.29 (m, 2H), 1.50–1.56 (m, 2H), 2.08 (t, $J$ = 7.6 Hz, 2H), 3.50 (s, 9H), 3.90 (t, $J$ = 6.8 Hz, 2H), 4.18–4.22 (m, 2H), 7.50–7.54 (m, 2H), 7.60–7.64 (m, 2H), 7.66 (t, $J$ = 7.8 Hz, 1H), 7.74 (d, $J$ = 7.8 Hz, 1H), 7.78 (d, $J$ = 7.8 Hz, 1H), 7.82 ppm (d, $J$ = 7.8 Hz, 2H); $^{13}$C NMR: (90.6 MHz, $CDCl_3$): $\delta$ = 14.1 ($CH_3$), 22.6 ($CH_2$), 25.1 ($CH_2$), 29.2 (2×$CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 31.8 ($CH_2$), 34.4 ($CH_2$), 44.2 ($CH_2$), 54.2 (3×$CH_3$), 63.4 ($CH_2$), 128.6 (2×CH), 128.9 (CH), 130.1 (2×CH), 130.4 (CH), 130.8 (CH), 132.7 (CH), 133.0 (CH), 136.8 ($C_q$), 139.6 ($C_q$), 141.6 ($C_q$), 174.1 (CO), 195.3 ppm (CO); HRMS (ESI): $C_{28}H_{41}N_2O_2$ [$M+H$] calcd: 437.3162, found: 437.3166.

### *Biology*

*Reporter gene assay*: The efficacy of each compound on the US28 receptor was investigated with the luciferase-based reporter gene assay PathDetect *trans*-Elk11 (Agilent, Stratagene).[38] Briefly, human embryonic kidney (HEK) 293T cells were transiently transfected with 0.1 μg Elk1, 5 μg Luc, and 5 μg US28 vector or an empty pcDNA3 vector (mock cells). The US28 receptor that we used was cloned from the clinically relevant and highly endotheliotropic HCMV strain TB40/E (Genbank Accession No. ABV71518.1).[39] Five hours after transfection, the cells were washed with DMEM/F-12 containing 1% FBS, harvested, seeded in a white half-area 96-well plate (20000 cells per well) and incubated with the indicated concentrations of test compounds. The incubation buffer consisted of DMEM/F-12, 1% FBS, 2 mM L-glutamine, 1% penicillin–streptomycin, and 1% DMSO. The cells were incubated at 37 °C under a humidified atmosphere with 5% $CO_2$ for an additional 20–24 h. The luciferase substrate BrightGlo (Promega)[40] was used according to the manufacturers' instructions. The luminescence intensity was acquired with a microplate reader Victor$^3$V (PerkinElmer). The basal luminescence of mock transfected cells was ~500 RLU, and the basal luminescence of US28 transfected cells up to 8–10-fold higher (4000–5000 RLU). Data were analyzed by nonlinear regression with the algorithms in Prism 5.0 (GraphPad Software, San Diego, CA, USA). The dose–response curves of 3–8 experiments performed in triplicate were normalized and pooled to generate a mean sigmoidal curve from which the $EC_{50}$ value and the maximum intrinsic activity of each compound was obtained.

*Cytotoxicity assay*: To estimate the general toxicity of each novel compound the CellTiter 96 AQueous One Solution Cell Proliferation Assay (Promega) was performed. Briefly, HEK293T cells were seeded in half-area 96-well plates at 10000 cells per well, and the compounds were added at a concentration of 10 μM. After addition of the compounds and DMSO (0.1%) as the negative control, the cells were incubated at 37 °C in 5% $CO_2$ for 24 h. Then the MTS reagent (Promega Cell Titer 96 AQueous One Solution Cell Proliferation Reagent) was added (10 μL), and incubated for an additional 2 h. The absorbance at 490 nm was measured on a Victor$^3$V (PerkinElmer) plate reader. The control run using solely 0.1% DMSO in the media drug showed no toxicity over the 24 h period. The data are shown in Supporting Information table S1. The one-way ANOVA test for repeated measures followed by Tukey's multiple comparison test was used to determine the significance of the observed cytotoxicity on the HEK293T cells.

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