Synthesis, Receptor Affinity, and Antiallodynic Activity of Spirocyclic σ Receptor Ligands with Exocyclic Amino Moiety

Bergkemper, M.; Kronenberg, E.; Thum, S.; Börgel, F.; Daniliuc, C.; Schepmann, D.; Nieto, F. R.; Brust, P.; Reinoso, R. F.; Alvarez, I.; Wünsch, B.;

Originally published:

October 2018

Journal of Medicinal Chemistry 61(2018), 9666-9690

DOI: https://doi.org/10.1021/acs.jmedchem.8b01183

Synthesis, receptor affinity and antiallodynic activity of spirocyclic σ receptor ligands with exocyclic amino moiety

Melanie Bergkemper,[a] Elisabeth Kronenberg,[a] Simone Thum,[a] Frederik Börgel,[a] Constantin Daniliuc,[b] Dirk Schepmann,[a] Francisco Rafael Nieto,[c] Peter Brust,[d] Raquel F. Reinoso,[e] Inés Alvarez,[e] Bernhard Wünsch* [a,f]

[a] Institut für Pharmazeutische und Medizinische Chemie der Universität Münster, Corrensstraße 48, D-48149 Münster, Germany

Tel.: +49-251-8333311; Fax: +49-251-8332144; E-mail: wuensch@uni-muenster.de

[b] Organisch-Chemisches Institut der Westfälischen Wilhelms-Universität Münster, Corrensstraße 40, D-48149 Münster, Germany

[c] Department of Pharmacology and Institute of Neuroscience, School of Medicine and Biomedical Research Center, University of Granada, Avenida de la Investigación 11, 18016 Granada, Spain

[d] Helmholtz-Zentrum Dresden-Rossendorf, Institut für Radiopharmazeutische Krebsforschung, Forschungsstelle Leipzig, Permoserstr. 15, 04318 Leipzig, Germany

[e.] Esteve Pharmaceuticals S.A., Baldiri Reixach 4-8, 08028 Barcelona, Spain.

[f] Cells-in-Motion Cluster of Excellence (EXC 1003 – CiM), Westfälische Wilhelms-Universität Münster, Germany

Abstract

In order to detect novel σ receptor ligands the rigid spiro[[2]benzopyran-1,1'-cyclohexan]-4'-one was connected with amino moieties derived from σ_2 receptor preferring lead compounds resulting in mixtures of *trans*- and *cis*-configured amines

6, 18 and **27**. In a four step synthesis the methyl acetals **6** were converted into fluoroethyl derivatives **13** and **30**. The most promising σ_2 receptor ligand is the methyl acetal **6a** bearing a 2,4-dimethylbenzylamino moiety. The fluoroethyl derivatives **13c** and **13d** reveal high σ_1 affinity, but moderate selectivity over the σ_2 subtype. In mice **13c** and **13d** showed antiallodynic activity, which is stronger than those of the reference σ_1 antagonist BD-1063 (**34**). Since the antiallodynic activity of **13c** could only be partially reversed by the σ_1 agonist PRE-084 (**35**), it is postulated that a second mechanism contributes to its overall antiallodynic effect. In contrast, the antiallodynic effect of its diastereomer **13d** can be totally explained by a σ_1 antagonism.

Keywords

σ receptors; spirocyclic ligands; X-ray crystal structure; Domino reaction; reductive amination; *cis*-*trans*-configuration; structure-affinity relationship; receptor selectivity; stability; antiallodynic activity; σ_1 antagonist.

1. Introduction

Although a lot of research was performed in the field of σ receptors, their biological function is not totally understood. The σ receptor was first described as opioid receptor subtype, since some of the pharmacological effects of the racemic benzomorphan SKF-10,047 (N-allylnormetazocine) could be antagonized by the opioid antagonist naltrexone.[1] Later it was observed that (+)-SKF-10,047 acts as a σ agonist, whereas (-)-SKF-10,047 shows affinity towards MOR (μ opioid receptor) and KOR (κ opioid receptor).[2] Moreover, the effects of (+)-SKF-10,047 could not be blocked by the opioid antagonist naloxone.[3] This led to the classification of σ receptors as an own class of receptors with two subtypes, σ_1 and σ_2 receptors.[4; 5] Their endogenous ligands are still unknown, although different endogenous compounds with affinity towards σ_1 receptors including neuroactive steroids[6–8], *N*,*N*-dimethyltryptamine[9] and sphingosine derivatives[10] were identified.

The σ_1 receptor has been cloned from different tissues like guinea pig liver,[11] mouse kidney[12] and human placental choriocarcinoma cells. The human σ_1 receptor consists of 223 amino acids[13] and has a molecular weight of 25 kDa.[14] Its sequence shows a similarity of 66 % with the yeast Δ^8/Δ^7 sterol isomerase but no similarity to any other mammalian protein. Indeed, sterol isomerase activity could not be observed for the σ_1 receptor.[11] In 2016, the σ_1 receptor was crystallized by Kruse *et al*. showing a trimeric organization of the receptor with one transmembrane domain for each monomer.[15] σ_1 receptors are particularly enriched in mitochondrion-associated endoplasmic reticulum (ER) membranes (MAM)[16] of neuronal[17] and peripheral cells like liver cells[18] or cardiac myocytes.[19] Under stress situations σ_1 receptors can also translocate to the plasma membrane[20] or ER-associated

membranes,[21] where they can regulate other proteins. The cellular mechanisms connected to the σ_1 receptor are not elucidated in detail. The σ_1 receptor seems to act as a chaperone[22] interacting with IP_3 receptor and modulating Ca^{2+}, K^+, Na^+ and Cl^- channels.[23–27] It is involved in pathomechanisms of neurological diseases like addiction,[28] Alzheimer's disease,[29] depression[30] and schizophrenia.[31] Moreover, it has an influence on pain[32] and allodynia, which makes it an interesting target for the therapy of these diseases.

Allodynia belongs to the symptoms of neuropathic pain, which is induced by several CNS diseases like postherpetic neuralgia, multiple sclerosis or stroke. It is characterized by the evocation of pain by stimuli, which normally do not provoke pain. Therapeutic options for the treatment of allodynia are tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, gabapentinoids, opioids, cannabinoids, lamotrigine, mexiletine, lidocaine gel, and botulinum toxin-A. Besides Na^+ channels, protein kinases, glutamate and tyrosine kinase receptors,[33] the σ_1 receptor is involved in the molecular mechanisms, which cause allodynia. The knockout of the σ_1 receptor in mice led to the inhibition of capsaicin-induced mechanical allodynia. The same effect was observed dose-dependently by treatment of wild-type mice with σ_1 receptor antagonists. Moreover, this antiallodynic effect could be blocked by σ_1 receptor agonists.[34] Therefore, σ_1 receptor antagonists offer a new possibility for the treatment of allodynia. The most developed candidate is the σ_1 receptor antagonist S1RA, which shows high activity in different models of neuropathic pain. After successful completion of phase I, the phase II clinical trial for neuropathic pain of S1RA is currently ongoing.[35]

Recently, the identity of the σ_2 receptor and TMEM97, an endoplasmic reticulum-resident transmembrane protein, was demonstrated, which also led to the identification of the gene coding for the σ_2 receptor.[36] The σ_2 receptor has a molecular weight of 21.5 kDa[14] and is located in the central nervous system[37] and in peripheral tissue like liver and kidney.[14] On the cellular level it is located in mitochondria and ER membranes.[38] Although the signal transduction of the σ_2 receptor is not yet fully understood, its influence on cell differentiation and survival is well-known.[38] It seems to have an influence on Ca^{2+} and K^+ channels[39; 40] and interacts with caspase-3 and the mTOR signaling pathway.[41] These findings can explain the apoptotic effect of σ_2 receptor ligands.[42]

Both, the σ_1 and σ_2 receptor, are expressed in fast proliferating cells like prostate cancer, breast carcinoma or leukemia cells. For the σ_2 receptor it was observed that the expression in proliferating cancer cells is 10-fold higher than in quiescent cancer cells, which still show higher expression than the surrounding tissue. Additionally, in stem cells as a type of proliferating cells the σ_2 receptor density is higher than in differentiated cells.[43] Therefore, the σ_2 receptor can be considered as a biomarker for the proliferative status of cells, offering new opportunities for cancer diagnosis and therapy.

Various compound classes with affinity towards σ_1 and σ_2 receptors are described in the literature. Compounds bearing a cyclohexylpiperazine moiety such as PB28 (**1**) show high σ_1 and σ_2 affinity (K_i (σ_1) = 0.38 nM; K_i (σ_2) = 0.68 nM).[44] The 1-(4-fluorophenyl)-substituted indole derivative siramesine (**2**) displays a preference for the σ_2 receptor (K_i (σ_1) = 17 nM; K_i (σ_2) = 0.12 nM).[45] A high selectivity towards the σ_2

receptor was achieved by compounds of type **3** (K_i (σ_1) = 12.9 μM; K_i (σ_2) = 8.2 nM) containing a benzamide and an isoquinoline moiety connected by an aliphatic spacer.(Figure 1).[46] A common feature of these compounds is the conformationally flexible linker between the basic amino moiety and the aromatic system.

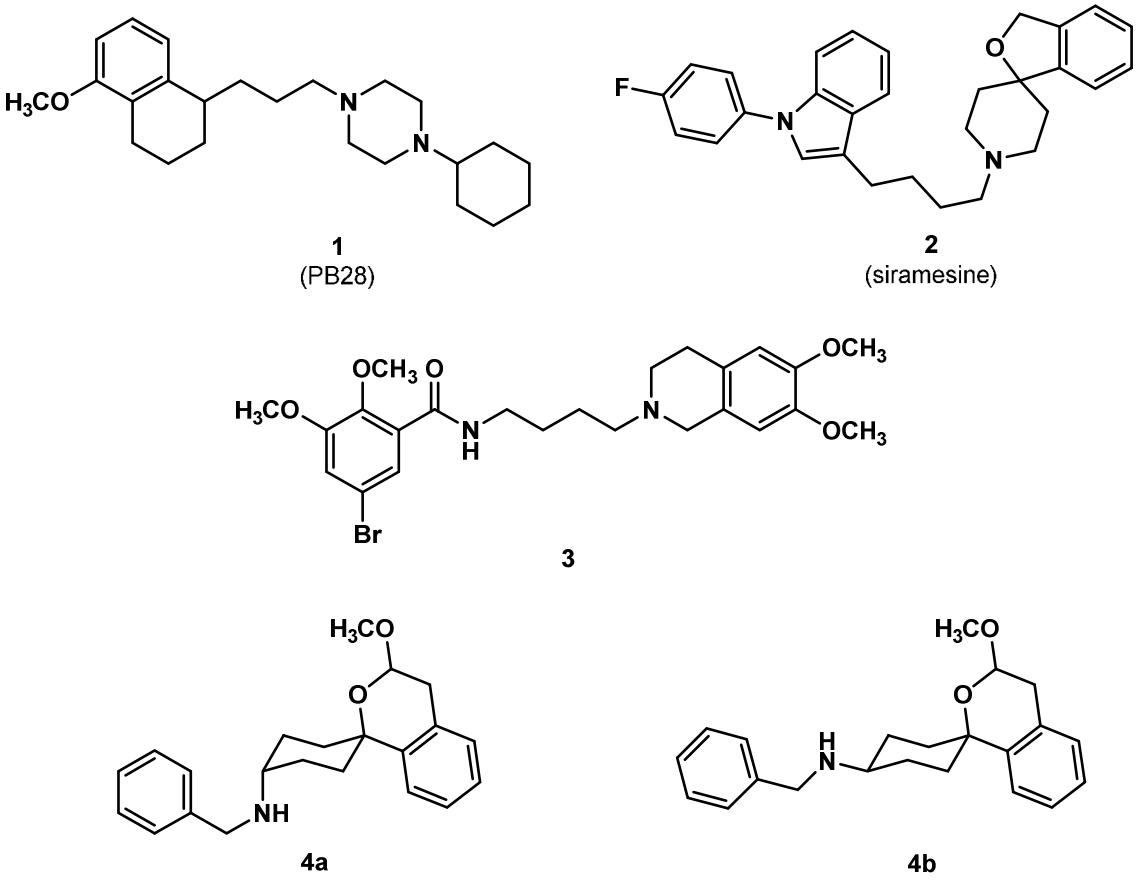
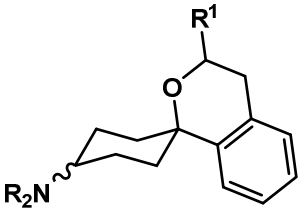


Figure 1. Chemical structures of σ receptor ligands.

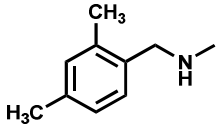
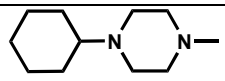
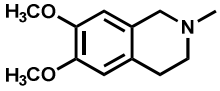
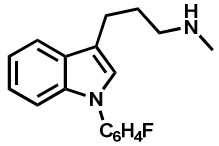
In our group different σ ligands with a spirocyclic ring system as conformationally restricted scaffold were synthesized.[47–52] The spirocyclic 2-benzopyrans **4a** and **4b** with exocyclic amino moiety show moderate affinity towards both σ receptors (**4a**: K_i (σ_1) = 538 nM; K_i (σ_2) > 1000 nM; **4b**: K_i (σ_1) = 158 nM; K_i (σ_2) > 1000 nM).[49] Based on these affinity data, combination of the spirocyclic 2-benzopyran with pharmacophoric moieties of the reference compounds **1** - **3** was envisaged to obtain

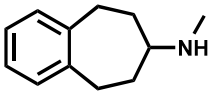
compounds with high σ_1 and/or σ_2 affinity. Furthermore, exchanging the methoxy group in 3-position of the 2-benzopyrans **4a** and **4b** by a fluoroethyl side chain should increase the metabolic stability of the compounds. An overview of all synthesized compounds is shown in Table 1. The influence of the introduction of a fluoroethyl side chain at 3-position of the 2-benzopyran on σ_1 and σ_2 receptor affinity will be investigated. Promising candidates will be selected for further pharmacological characterization in *in vitro* and *in vivo* experiments to determine the antiallodynic activity of these σ receptor ligands.

Table 1: Synthesized spirocyclic compounds with modification of the basic moiety and the residue in 3-position of the 2-benzopyran scaffold.



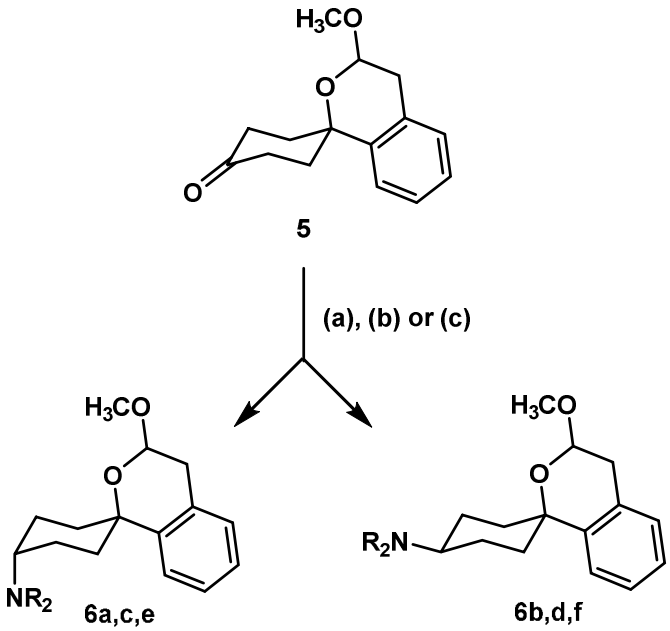
R^1

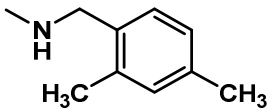
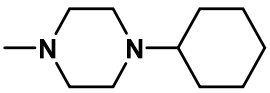
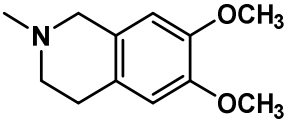
NR_2	OCH_3	OH	CH_2CO_2Et	CH_2CH_2OH	CH_2CH_2F
	**6a,b**	**10a,b**	**11a,b**	**12a,b**	**13a,b**
	**6c,d**	**10c,d**	**11c,d**	**12c,d**	**13c,d**
	**6e,f**	**10e,f**	**11e,f**	**12e,f**	**13e,f**
	**18a,b**	-	-	-	-

	**27a,b**	-	-	- **30a,b**

2. Synthesis

For the synthesis of the designed σ ligands the spirocyclic ketone **5**, which was obtained in four steps starting from 2-bromobenzaldehyde,[49] served as important intermediate. The reductive amination of ketone **5** with 2,4-dimethylbenzylamine (**7**) and $NaBH(OAc)_3$ in THF and HOAc led to the diastereomeric amines **6a** and **6b**, which were separated by fc. Performing this reaction under the same conditions with 1-cyclohexylpiperazine (**8**) led to amines **6c** and **6d**. Because of low solubility of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**9**·HCl) in THF, the synthesis of amines **6e** and **6f** was conducted in CH_2Cl_2 and without HOAc (Scheme 1).



NR_2			
trans	**6a**	**6c**	**6e**
cis	**6b**	**6d**	**6f**

Scheme 1. Synthesis of spirocyclic σ receptor ligands with exocyclic amino moiety. Reagents and reaction conditions: (a) 2,4-dimethylbenzylamine, $NaBH(OAc)_3$, HOAc, THF, 20 h, rt; **6a**, 30 %; **6b**, 44 %. (b) 1-cyclohexylpiperazine, $NaBH(OAc)_3$, HOAc, THF, 23 h, rt; **6c**, 9 %; **6d**, 38 %. (c) 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, $NaBH(OAc)_3$, CH_2Cl_2, 43 h, rt; **6e**, 19 %; **6f**, 37 %.

According to the isolated yields the formation of the diastereomers **6b**, **6d** and **6f** with the amino moiety in equatorial orientation is preferred. This can be explained by stereoelectronic effects during the hydride transfer to intermediate iminium ions. The attack of the hydride in axial orientation at the cyclohexane ring can be stabilized by an overlap of the doubly occupied σ orbital of the newly formed C-H bond and the unoccupied, axial oriented σ^* orbitals of the C-H bonds in α position.[53] Therefore, the axial hydride attack is more favorable than the equatorial approach, which leads to an excess of the diastereomer with the amino moiety in equatorial orientation. Using secondary amines instead of primary amines for the reductive amination, the difference between the yields of the diastereomers is higher.

To determine the configuration of the spirocyclic amines in 1-position of the 2-benzopyran, X-ray crystal structures of the isoquinoline derivatives **6e** and **6f** were recorded exemplarily. As shown in Figure 2, the oxygen atom of the 2-benzopyran of

both diastereomers is in axial orientation and the aromatic moiety is equatorially oriented regarding the cyclohexane chair. Therefore, in compounds **6a**, **6c**, and **6e** with the amino moiety in axial orientation, the O- and N-atoms are *trans*-oriented and therefore the compounds are termed *trans*-configured in this manuscript. On the other side, in compounds **6b**, **6d**, and **6f** O- and N-atoms are *cis*-oriented with respect to the cyclohexane chair and are termed *cis*-diastereomers in this manuscript.

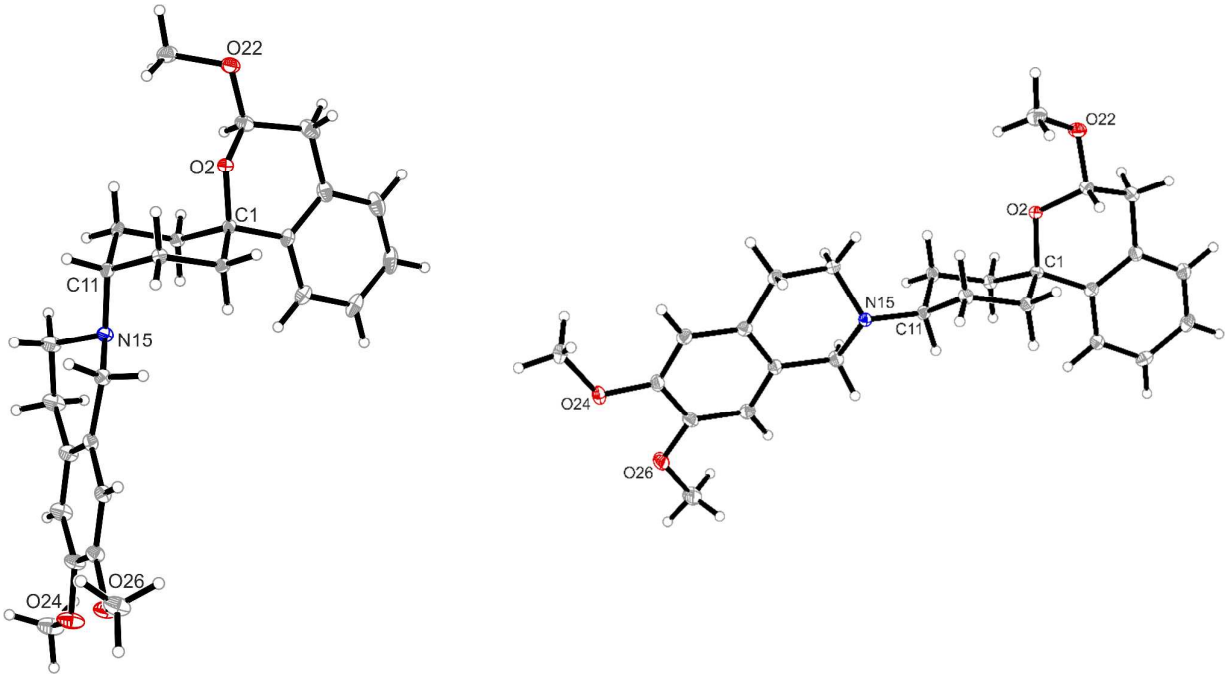
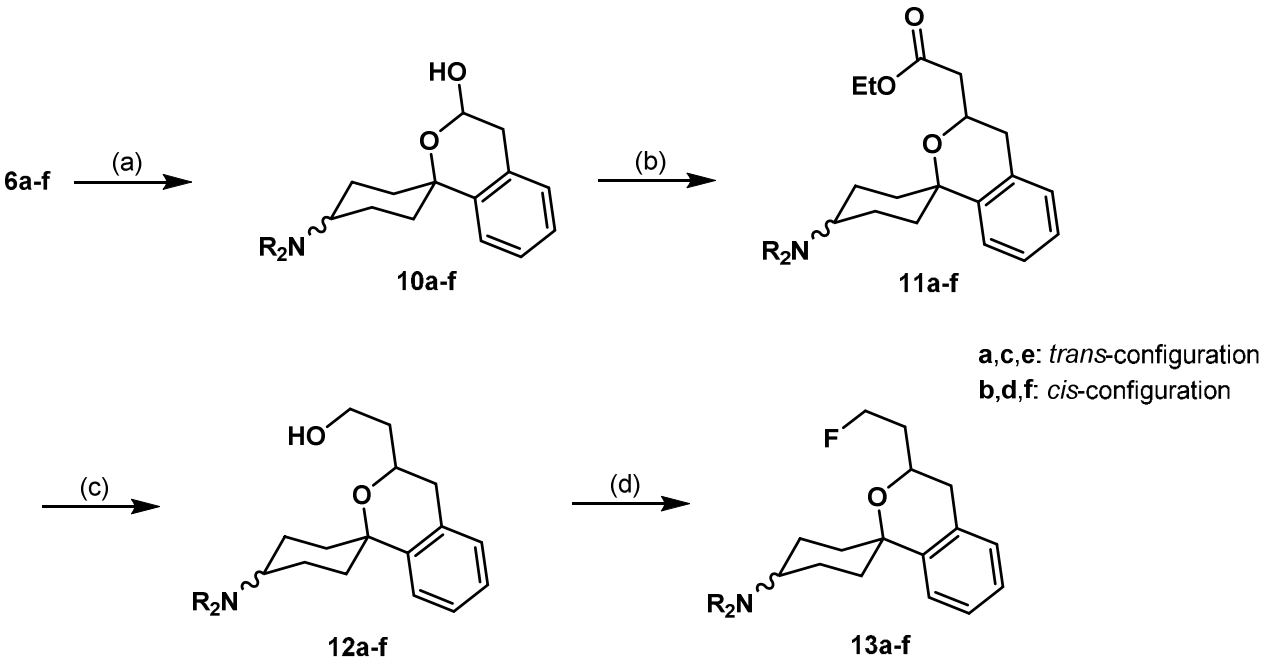


Figure 2. X-ray crystal structures of the *trans*- and *cis*- configured acetalic isoquinoline derivatives **6e** and **f**. Thermal ellipsoids are shown at 30 % and 50 %, respectively. CCDC number: **6e**: 1855388; **6f**: 1855389.

Hydrolysis of the acetals **6a-f** resulted in the formation of lactols **10a-f**. Afterwards, a tandem reaction with (ethoxycarbonylmethylene)triphenylphosphorane in toluene was performed. The first step in this one pot reaction is the opening of the lactol to afford

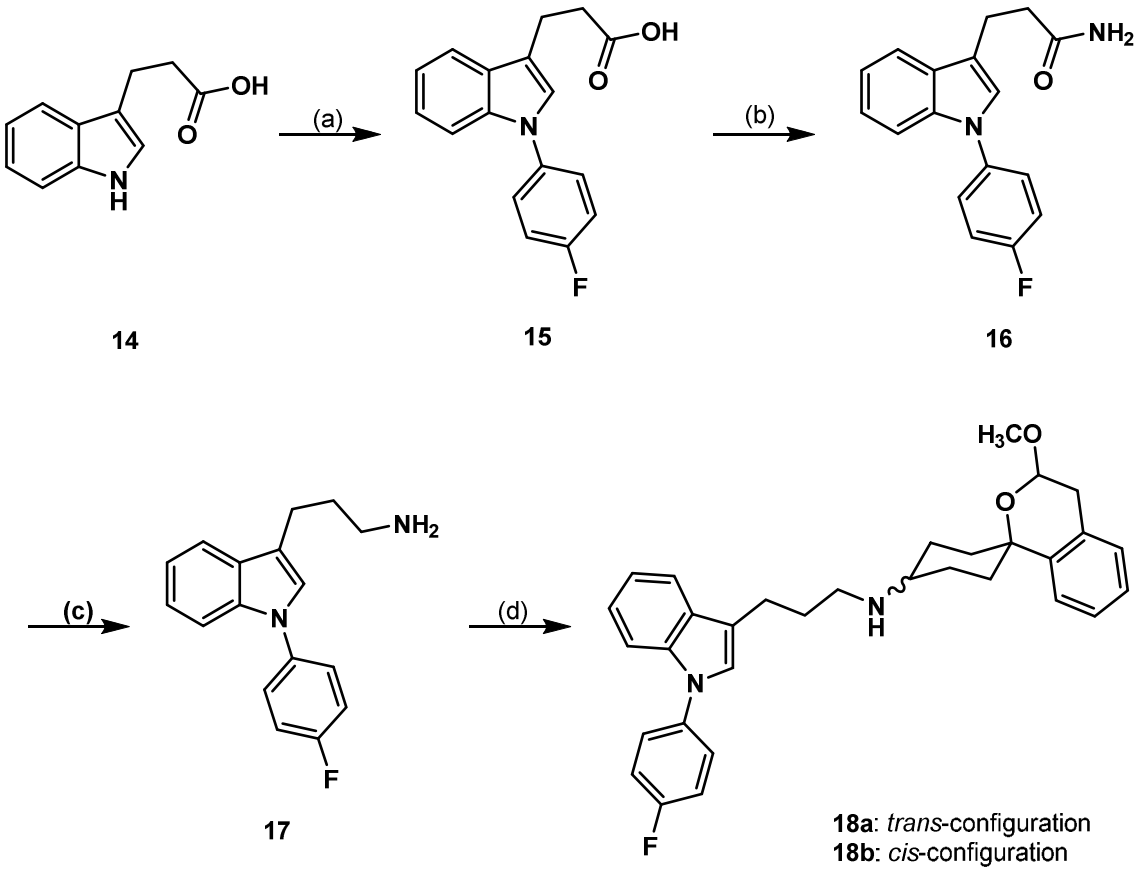
an hydroxy aldehyde, followed by a Wittig reaction and an intramolecular Michael addition at the formed α,β-unsaturated ester.[48] The esters **11a-f** were obtained in yields of 39 - 94 %. The following reduction of the ester with $LiAlH_4$ in Et_2O gave the alcohols **12a-f** in high yields. Fluorination of the alcohols **12a-f** with DAST (diethylaminosulfur trifluoride) led to compounds **13a-f** in yields of 13 - 67 % (Scheme 2).



Scheme 2. Synthesis of spirocyclic σ receptor ligands with fluoroethyl side chain. Reagents and reaction conditions: (a) HCl, THF, 3 - 4 d, rt; **10a**, 71 %; **10b**, 80 %; **10c**, 86 %; **10d**, 81 %; **10e**, 86 %; **10f**, 74 %. (b) $Ph_3P{=}CHCO_2Et$, toluene, 3 - 5 d, reflux; **11a**, 39 %; **11b**, 79 %; **11c**, 52 %; **11d**, 89 %; **11e**, 94 %; **11f**, 77 %. (c) $LiAlH_4$, Et_2O, 2 - 4 h, -20 °C; **12a**, 79 %; **12b**, 82 %; **12c**, 85 %; **12d**, 82 %; **12e**, 71 %; **12f**, 69 %. (d) DAST, CH_2Cl_2, 1 h -78 °C, then 20 h rt; **13a**, 67 %; **13b**, 22 %; **13c**, 67 %; **13d**, 13 %, **13e**, 21 %; **13f**, 27 %.

10-**13a**,**b**: NR_2 = 2,4-dimethylbenzylamino; **10**-**13c**,**d**: NR_2 = 4-cyclohexylpiperazin-1-yl; **10**-**13e**,**f**: NR_2 = 6,7-dimethoxyisoquinolin-2-yl. Structures see Table 1.

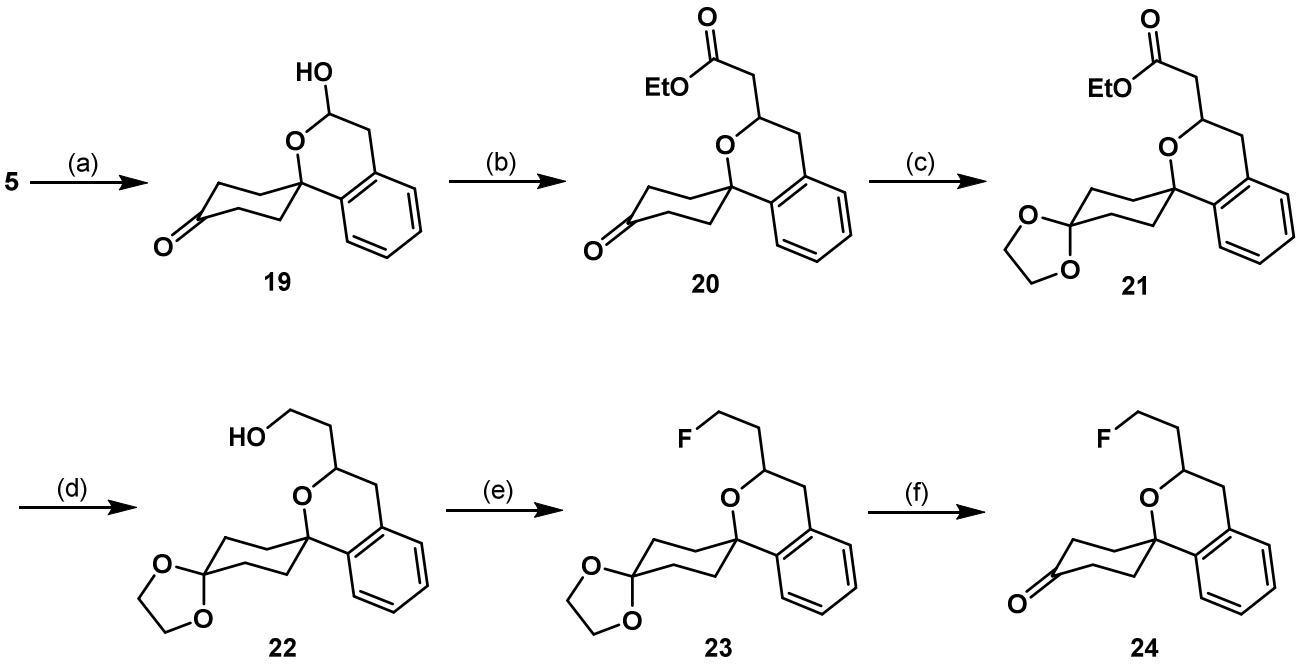
Since compounds with a 1-(4-fluorophenyl)indole moiety like **2** show high affinity towards σ receptors with a preference for the σ_2 subtype,[45] spirocyclic cyclohexylamine derivatives with this residue were envisaged. In the first step of the synthesis 3-(indol-3-yl)propionic acid (**14**) was arylated with 1-bromo-4-fluorobenzene by an Ullmannn reaction to obtain the arylated propionic acid **15** in 78 % yield. Activation of acid **14** with ethyl chloroformate and subsequent treatment with NH_3 provided the primary amide **16** in 97 % yield. Reduction of the amide **16** with $LiAlH_4$ in THF led to the primary amine **17**, which was used for the aforementioned reductive amination of ketone **5**. The diastereomeric amines **18a** and **18b** were separated by fc (Scheme 3).



Scheme 3. Synthesis of spirocyclic σ receptor ligands with [1-(4-fluorophenyl)-(indol-3-yl)]propyl moiety. Reagents and reaction conditions: (a) 1-bromo-4-fluorobenzene, CuI, Cs_2CO_3, DMF, 2 d, reflux; 78 %. (b) $ClCO_2Et$, NH_3, Et_3N, THF, 3 h, 0 °C; 97 %. (c) $LiAlH_4$, THF, 2 h, reflux; 64 %. (d) ketone **5**, $NaBH(OAc)_3$, HOAc, THF, 20 h, rt; **18a**, 30 %; **18b**, 42 %.

In order to get fast access to diverse spirocyclic amines with fluoroethyl side chain, a spirocyclic ketone with fluoroethyl side chain (**24**) was envisaged. The synthesis of **24** was conducted according to the aforementioned synthesis of amines **13a**-**f**. Hydrolysis of the acetalic moiety of ketone **5** led to the lactol **19** in high yield, which was transformed to the ester **20** by (ethoxycarbonylmethylene)triphenylphosphorane and Cs_2CO_3. In order to avoid reduction, the ketone **20** was protected with ethylene

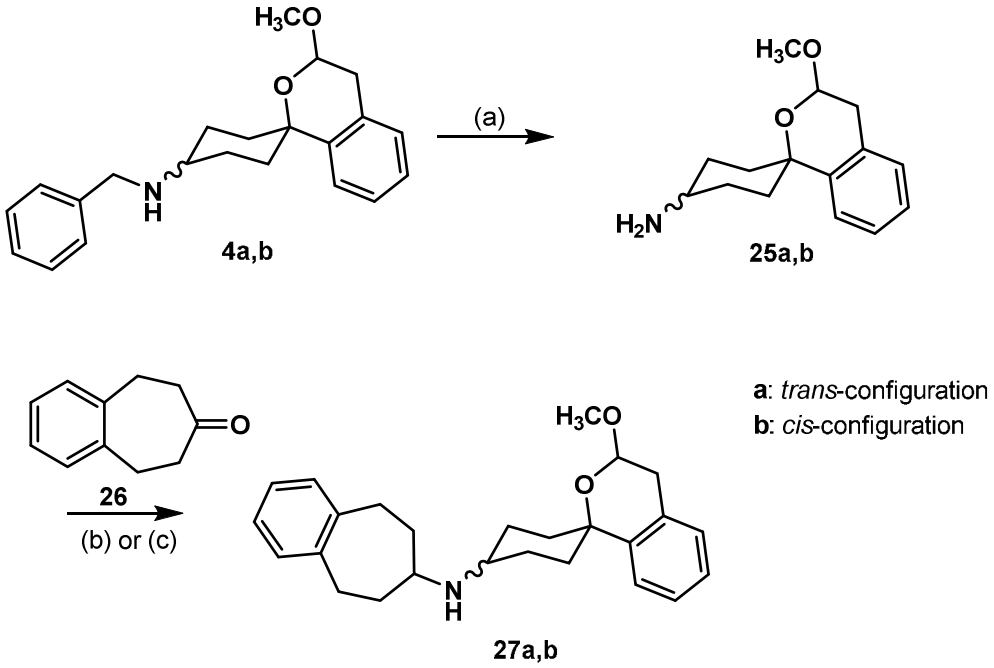
glycol to afford the cyclic ketal **21**. Reduction of the ester **21** was performed with $LiAlH_4$ and gave alcohol **22** in 81 % yield. Compound **23** was obtained after fluorination of the alcohol **22** with DAST. In the last step, the ketal was hydrolyzed with diluted HCl to provide the ketone **24** in a yield of 95 % (Scheme 4).



Scheme 4. Synthesis of the spirocyclic building block **24** with fluoroethyl side chain. Reagents and reaction conditions: (a) HCl, THF, 3 d, rt; 95 %. (b) $Ph_3P{=}CHCO_2Et$, Cs_2CO_3, toluene, 2 d, reflux; 63 %. (c) ethylene glycol, $CH(OCH_3)_3$, *p*-toluenesulfonic acid (*p*-TsOH), CH_2Cl_2, 17 h, RT; 88 %. (d) $LiAlH_4$, Et_2O, 2 h, 81 %. (e) DAST, CH_2Cl_2, 1 h -78 °C, then 20 h rt; 49 %. (f) 2 M HCl, Et_2O, 3 d, 40 °C; 95 %.

Benzo[7]annulenamines **27a**,**b** and tetrahydroisoquinolines **6e**,**f** have comparable sizes, but show different hydrogen bonding properties. To investigate the influence of these different properties on the σ affinity, benzo[7]annulene derivatives **27** with

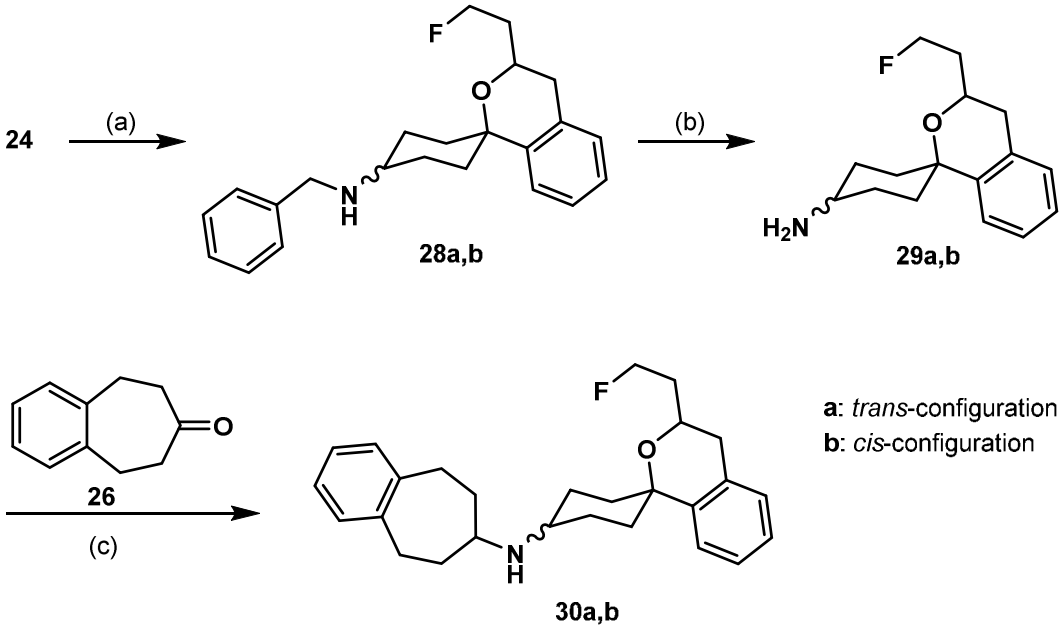
acetalic moiety and **30** with fluoroethyl side chain were synthesized. As shown in Scheme 5, debenzylation of benzylamines **4a** and **4b** with H_2 and Pd/C as catalyst led to the primary amines **25a** and **25b** in 72 % and 89 % yield, respectively. Reductive alkylation of the primary amines **25a** and **25b** with benzo[7]annulenone **26** and $NaBH(OAc)_3$ provided the secondary amines **27a** and **27b** in yields of 48 % and 28 %, respectively.



Scheme 5. Synthesis of spirocyclic σ receptor ligands with benzo[7]annulenyl moiety. Reagents and reaction conditions: (a) H_2, 10 % Pd/C, CH_3OH, 20 h, rt; **25a**, 72 %; **25b**, 89 %. (b) $NaBH(OAc)_3$, HOAc, CH_2Cl_2, 3 h, rt; **27a**, 48 %. (c) $NaBH(OAc)_3$, CH_2Cl_2, 12 h, rt; **27b**, 28 %.

For the synthesis of benzo[7]annulene derivatives **30a** and **30b** with fluoroethyl side chain, ketone **24** was reductively aminated with benzylamine and $NaBH(OAc)_3$. The obtained amines **28a** and **28b** were separated and afterwards debenzylated using

ammonium formate as hydrogen source and Pd/C as catalyst. Reductive alkylation of the primary amines **29a** and **29b** with benzo[7]annulenone **26** and $NaBH(OAc)_3$ led to the secondary amines **30a** and **30b** in yields of 76 % and 81 %, respectively (Scheme 6).



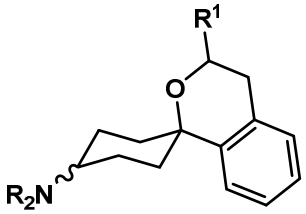
Scheme 6. Synthesis of spirocyclic σ receptor ligands with benzo[7]annulenyl moiety and fluoroethyl side chain. Reagents and reaction conditions: (a) Benzylamine, $NaBH(OAc)_3$, HOAc, THF, 3 h, rt; **28a**, 45 %; **28b**, 45 %. (b) NH_4HCO_2, 10 % Pd/C, CH_3OH, 2 – 4.5 h, 65 °C; **29a**, 96 %; **29b**, 88 %. (c) $NaBH(OAc)_3$, HOAc, CH_2Cl_2, 1 d, rt; **30a**, 76 %; **30b**, 81 %.

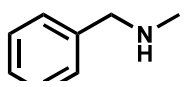
3. σ_1 and σ_2 receptor affinity

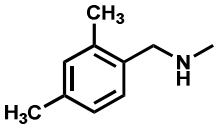
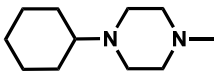
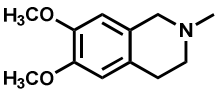
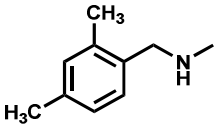
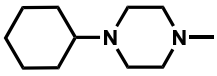
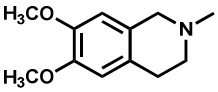
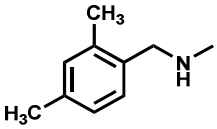
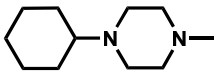
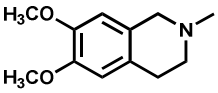
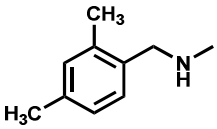
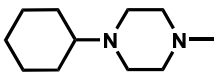
The affinity of all synthesized spirocyclic amines towards σ_1 and σ_2 receptors was determined by radioligand binding assays. The σ_1 assay was performed with homogenates of guinea pig brains as receptor material and [^{3}H]-(+)-pentazocine as σ_1 selective radioligand. Homogenates of rat liver were used as receptor material for

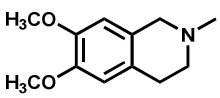
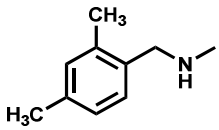
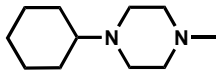
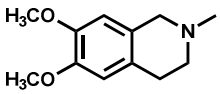
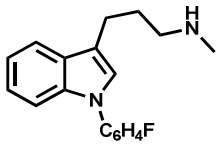
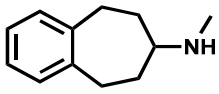
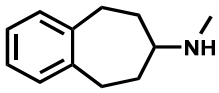
the σ_2 assay. Due to the lack of a σ_2 selective radioligand, the assay was performed with the non-selective radioligand [^{3}H]-1,3-di(o-tolyl)guanidine (DTG) and an excess of non-tritiated (+)-pentazocine to selectively occupy σ_1 receptors.[47; 48] Since the amino acid sequence of the human σ_1 receptor shows 93 % identity with the guinea pig σ_1 receptor, affinity data for the guinea pig and human σ_1 receptor are comparable.[13] Until now, the sequence of the human σ_2 receptor is unknown, but binding studies with σ_2 selective ligands reveal comparable affinity data for rat and human σ_2 receptors.[54; 55] The determined affinities of the synthesized compounds and some reference and lead compounds towards both receptors are summarized in Table 2.

Table 2: σ_1 and σ_2 receptor affinity of spirocyclic amines and reference substances. n = 3, if SEM is given, otherwise n = 1.



compd.	config.	R^1	NR_2	K_i ± SEM [nM]	
				σ_1	σ_2
(+)-pentazocine	-	-	-	5.4 ± 0.5	-
1 (PB28)[44]	-	-	-	0.38 ± 0.10	0.68 ± 0.20
2 (siramesine)[45]	-	-	-	17	0.12
3[46]	-	-	-	12900 ± 111	8.2 ± 1.4
4a	*trans*	OCH_3		538 ± 56	>1000

4b	*cis*	OCH_3		158 ± 5	>1000
6a	*trans*	OCH_3		736	7.6 ± 4.1
6b	*cis*	OCH_3		> 1000*	54 ± 15
6c	*trans*	OCH_3		6.3 ± 0.44	62 ± 17
6d	*cis*	OCH_3		4.4 ± 0.71	213 ± 25
6e	*trans*	OCH_3		639	58 ± 27
6f	*cis*	OCH_3		> 1000	105 ± 8
10a	*trans*	OH		349	181
10b	*cis*	OH		> 1000	66 ± 10
10c	*trans*	OH		77 ± 25	302
10d	*cis*	OH		47 ± 10	27 ± 16
10e	*trans*	OH		583	99 ± 24
10f	*cis*	OH		> 1000	> 1000
11a	*trans*	CH_2CO_2Et		>1000	231
11b	*cis*	CH_2CO_2Et		547	159
11c	*trans*	CH_2CO_2Et		12 ± 2	355
11d	*cis*	CH_2CO_2Et		12 ± 4	51 ± 5
11e	*trans*	CH_2CO_2Et		> 1000	>1000
11f	*cis*	CH_2CO_2Et		> 1000	343
12a	*trans*	CH_2CH_2OH		> 1000	381 ± 113
12b	*cis*	CH_2CH_2OH		548	179
12c	*trans*	CH_2CH_2OH		61 ± 12	172
12d	*cis*	CH_2CH_2OH		28 ± 5	505

12e	*trans*	CH_2CH_2OH		> 1000	>1000
12f	*cis*	CH_2CH_2OH		>1000	>1000
13a	*trans*	CH_2CH_2F		> 1000	302 ± 23
13b	*cis*	CH_2CH_2F		966	> 1000
13c	*trans*	CH_2CH_2F		12 ± 2	45 ± 14
13d	*cis*	CH_2CH_2F		19 ± 2	432 ± 168
13e	*trans*	CH_2CH_2F		807	> 1000
13f	*cis*	CH_2CH_2F		> 1000	505
18a	*trans*	OCH_3		>1000	>1000
18b	*cis*	OCH_3		635	>1000
27a	*trans*	OCH_3		>1000	49 ± 7
27b	*cis*	OCH_3		265	77 ± 5
30a	*trans*	CH_2CH_2F		667	305
30b	*cis*	CH_2CH_2F		198	527

* No correlation between concentration and receptor affinity.

The introduction of two methyl groups in *o*- and *p*-position of the benzyl moiety of lead compounds **4a** and **4b** led to considerably increased σ_2 affinity of amines **6a** ($K_i(\sigma_2)$ = 7.6 nM) and **6b** ($K_i(\sigma_2)$ = 54 nM). Amine **6a** shows very high σ_2 affinity and selectivity over the σ_1 subtype with a K_i-values of 7.6 nM for the σ_2 receptor and 736 nM for the σ_1 receptor. Also, amines **6e** and **6f** with the isoquinolinyl moiety and amines **27a** and **27b** with benzannulenyl moiety display a preference for the σ_2 receptor. In contrast, amines **6c** and **6d** bearing the cyclohexylpiperazinyl moiety show high σ_1 affinity with 10- to 50-fold selectivity over the σ_2 receptor. Unexpectedly,

siramesine derived amines **18a** and **18b** with indolylpropyl moiety show only very low affinity towards both σ receptor subtypes. Due to the very low σ affinity of the methoxy derivatives, **18a** and **18b** were not transformed into the corresponding fluoroethyl derivatives.

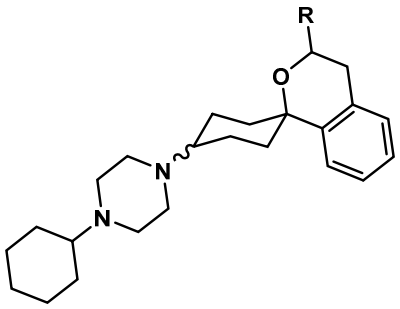
The affinity of the lactols **10a-e** towards both σ receptors is slightly lower than the affinity of the corresponding methyl acetals. Up to a test compound concentration of 1 µM, lactol **10f** did not compete with the radioligands for the σ receptors. With elongation of the side chain the affinity towards both σ receptor subtypes decreased for esters **11a** and **11b** with dimethylbenzylamino moiety and **11e** and **11f** with isoquinolinyl residue. The reduction of the esters to the alcohols **12a**, **12b**, **12e** and **12f** did not change the affinity towards the σ receptors. Also, the fluorination did not lead to increased σ affinity of compounds **13a**, **13b**, **13e** and **13f**. In comparison to the acetals **27a** and **27b** the introduction of the fluoroethyl side chain led to a decrease in σ_2 affinity for the compounds with benzannulenyl moiety **30a** and **30b**.

Esters **11c** and **11d** with cyclohexylpiperazinyl moiety show comparable σ_1 affinity as the acetals **6c** and **6d**. In comparison to ester **11c**, alcohol **12c** shows a small decrease in σ_1 affinity and increase in σ_2 affinity resulting in lower σ_1/σ_2 selectivity. The diastereomeric alcohol **12d** displays a higher σ_1/σ_2 selectivity due to the 10-fold reduced σ_2 affinity of **12d** compared to the σ_2 affinity of the ester **11d**. The fluorinated compound **13c** shows high affinity towards both σ receptors with K_i-values of 12 nM for the σ_1 receptor and 45 nM for the σ_2 receptor. A preference for one of the σ receptors was not observed. However, the diastereomeric fluoroethyl derivative **13d** reveals high σ_1 affinity and selectivity (K_i (σ_1) = 19 nM; K_i (σ_2) = 432 nM).

4. Pharmacological *in vitro* characterization of selected compounds 10d, 11d, 13c and 13d

Due to their high σ_1 and σ_2 affinity, lactol **10d**, ester **11d** and fluoroethyl compounds **13c** and **13d** bearing the cyclohexylpiperazinyl moiety were selected for further characterization *in vitro*. At first, the selectivity over a panel of receptors and transporters was investigated. All four compounds show low affinity towards μ-opiod receptors (MOR), κ-opiod receptors (KOR), δ-opiod receptors (DOR) and the phencyclidine (PCP) binding site of the *N*-methyl-*D*-aspartate (NMDA) receptor (Table 3). However, they display high affinity to the ifenprodil binding site of GluN2B subunit containing NMDA receptors. At a concentration of 1 μM, the compounds **10d**, **11d** and **13c** did not interact with 5-HT_{2B} receptor, norepinephrine transporter (NET), dopamine transporter (DAT) and serotonin transporter (SERT). However, they displayed low affinity towards hERG channel, 5-HT_{1A}, α_{1A} and H_1 receptor (Table 4). Measuring the functional activity at MOR by determination of the intracellular cAMP concentration, only fluoroethyl derivative **13c** showed a very weak effect (EC_{50} = 1757 nM). Nevertheless, **13c** displayed the best selectivity profile for σ receptors.

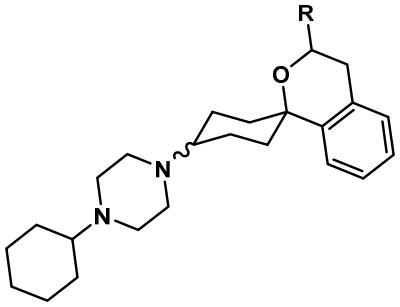
Table 3: Affinity towards σ receptors, opioid receptors, the PCP binding site and the ifenprodil binding site of GluN2B subunit containing NMDA receptors of amines **10d**, **11d**, **13c** and **13d**. n = 3, if SEM is given, otherwise n = 1.



compd.		**10d**	**11d**	**13c**	**13d**
config.		*cis*	*cis*	*trans*	*cis*
R		OH	CH_2CO_2Et	CH_2CH_2F	CH_2CH_2F
	σ_1	47 ± 10	12 ± 4	12 ± 2	19 ± 2
	σ_2	27 ± 16	51 ± 5	45 ± 14	432 ± 168
	MOR	> 1000	458	> 1000	434
K_i [nM]+	KOR	781	> 1000	> 1000	> 1000
	DOR	> 1000	> 1000	> 1000	647
	PCP	> 1000	> 1000	> 1000	> 1000
	GluN2B	34 ± 7	54 ± 6	65 ± 9	31 ± 9

+ Results are the mean of at least two replicates

Table 4: Inhibition of σ, α_1, H_1, 5-HT_{1A} and 5-HT_{2B} receptor, hERG channel, NET, DAT and SERT and functional activity at MOR of amines **10d**, **11d** and **13c**. n = 3, if SEM is given, otherwise n = 1.



compd.		**10d**	**11d**	**13c**
config.		*cis*	*cis*	*trans*
R		OH	CH_2CO_2Et	CH_2CH_2F
K_i [nM]	σ_1	47 ± 10	12 ± 4	12 ± 2
	σ_2	27 ± 16	51 ± 5	45 ± 14
EC_{50} [nM]	MOR	> 10000	> 10000	1757
IC_{50} [nM]	hERG	3207	1753	2620
% Inhibition [1 µM]	α_{1A}	< 50	78	< 50
	H_1	76	98	< 50
	5-HT_{1A}	55	68	62
	5-HT_{2B}	< 50	< 50	< 50
	NET	< 50	< 50	< 50
	DAT	< 50	< 50	< 50
	SERT	< 50	< 50	< 50

In order to determine the chemical stability of compounds **10d**, **11d**, and **13d** they were dissolved in aqueous solution at pH 2 (aqueous HCl) and pH 7.4 (phosphate buffer). The remaining amount of parent compound was determined by HPLC. After a

period of 24 h the parent compounds remained completely intact indicating high chemical stability under these conditions.

Since amines **13c** and **13d** were chosen for *in vivo* tests in mice, the metabolic stability of these compounds during incubation with mouse liver microsomes over a period of 1 h was investigated (Table 4). Imipramine served as reference compound. Using a concentration of 25 µM, both **13c** as well as **13d** showed high metabolic stability. After a period of 60 min 72 % and 70 % of the parent compound remained intact. These findings allow the *in vivo* application of **13c** and **13d** in experiments with a duration of 1 h.

Table 5: Metabolic stability of Imipramine (reference compound) and amines **13c** and **13d** after incubation with mouse liver microsomes for 1 h (n = 3).

Compd.	remaining parent compound ± SEM [%]
Imipramine	17 ± 1.1
13c	71.8 ± 2.4
13d	69.5 ± 1.6

5. *In vivo* activity of amine 13c and 13d in mechanical allodynia assay

For the *in vivo* investigations the fluoroethyl derivatives **13c** and **13d** were selected. **13c** shows promising affinity towards both σ receptor subtypes, a very good selectivity profile over other receptors and transporters and, moreover, does not contain an acid labile acetal or hemiacetal moiety. Its diastereomer **13d** indeed displays high σ_1 receptor affinity and selectivity. Since it has been reported that σ_1

receptors are involved in the development of pain,[32] the effect of amines **13c** and **13d** on mechanical allodynia was analyzed. By using the σ_1 selective **13d** and the dual σ_1/σ_2 ligand **13c** the influence of the different σ receptor binding profile on the antiallodynic activity was determined.

Fluoroethyl derivatives **13c** and **13d**, the σ_1 receptor antagonist BD-1063 (1-[2-(3,4-dichlorophenyl)ethyl]-4-methylpiperazine, **34**)[56] as positive control and their solvent hydroxypropyl-methyl-cellulose (HPMC) as negative control were administered subcutaneously (s.c.) to mice and capsaicin-induced mechanical allodynia was evaluated.[34] As shown in Figure 4, **13c, 13d** and **34** have a strong effect on allodynia. In both assays **13c** and **13d** were more potent than **34**, since lower doses of **13c** and **13d** than **34** were necessary to achieve the same effects.

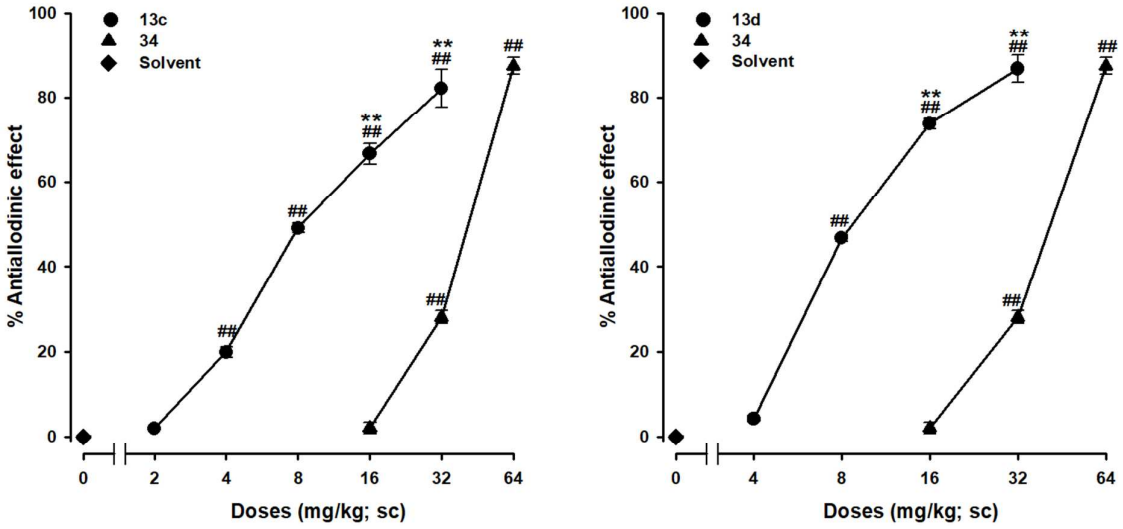


Figure 4. Effects of fluoroethyl derivatives **13c** (left) and **13d** (right) and the reference compound **34** (left and right) on mechanical allodynia induced by intraplantar (i.pl) administration of capsaicin in mice. Animals were treated s.c. with **13c**, **13d**, **34** or their solvent (HPMC, dose 0) 30 min before capsaicin. Each bar and vertical line

represents the mean ± SEM of values obtained in 6–8 animals. One-way analysis of variance followed by the Bonferroni test was used to determine statistically significant differences between values obtained in mice treated with compounds **13c**, **13d** or **34** in comparison with control animals (HPMC-treated, dose 0) value ($^{\#\#}P< 0.01$); and between the values obtained in mice treated with the same dose of **13c** and **34** (left) or the same dose of **13d** and **34** (right) (**P < 0.01).

In order to evaluate the influence of σ_1 affinity on the antiallodynic effects of **13c** and **13d**, the experiment was repeated with pretreatment of the mice with σ_1 agonist PRE-084 (2-morpholin-4-ylethyl 1-phenylcyclohexane-1-carboxylate, **35**, 32 mg/kg).[57] It was observed that for low doses of **13c** (8 – 16 mg/kg), **35** was able to antagonize the antiallodynic effect. At higher doses of **13c** (32 mg/kg), reversion of the antiallodynic effect could not be observed (Figure 5). This indicates an involvement of the σ_1 receptor in the antiallodynic effect of **13c**. However, since the σ_1 agonist **35** was not able to antagonize the effect of **13c** completely at higher doses, the antiallodynic effect of **13c** at least at high doses will be mediated by a second unknown mechanism. In contrast, when compound **13d** was associated to **35** a parallel shift to the right of the dose-response line of **13d** was observed (Figure 5), indicating that the antiallodynic effect of **13d** is probably due only to its interaction with σ_1 receptor.

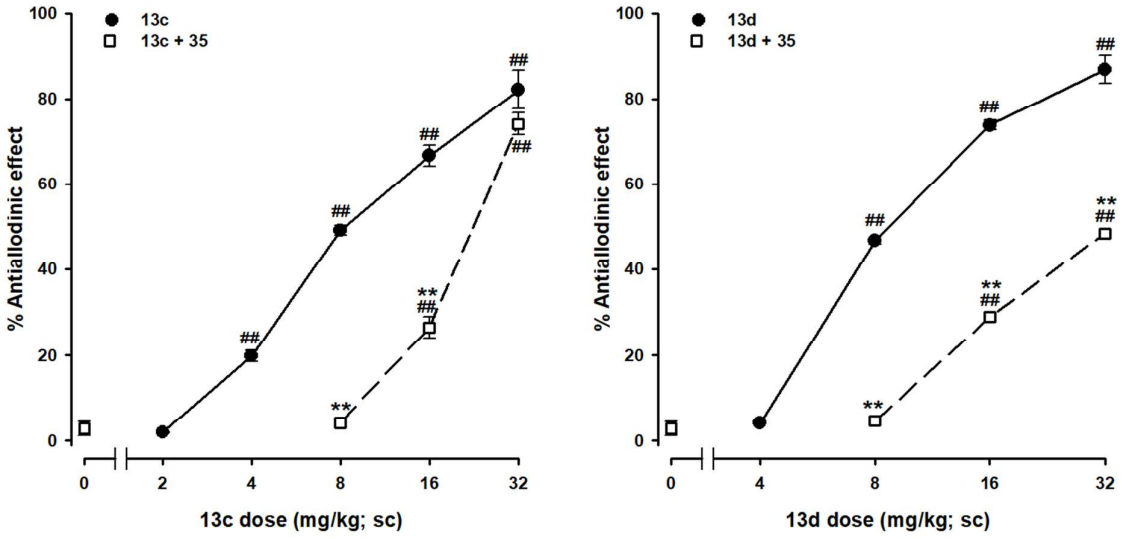


Figure 5. Effects of fluoroethyl derivatives **13c** (left) or **13d** (right) alone and in combination with the σ_1 receptor agonist **35** on mechanical allodynia induced by intraplantar (i.pl) administration of capsaicin in mice. Animals were treated s.c. with **35** 5 min before administration of **13c** or **13d**, which were s.c. administered 30 min before capsaicin. Each bar and vertical line represents the mean ± SEM of values obtained in 6–8 animals. One-way analysis of variance followed by the Bonferroni test was used to determine statistically significant differences between values obtained in mice treated with compounds **13c**, **13d** or their combination with **35** in comparison with the value obtained in control animals (HPMC-treated, dose 0) ($^{\#\#}P< 0.01$); and between the values obtained in mice treated with **13c** and **13c** + **35** (left) or **13d** and **13d** + **35** (right) (**P < 0.01).

6. Conclusion

A series of spirocyclic 2-benzopyrans bearing exocyclic amino moieties derived from ligands preferring the σ_2 receptor subtype was designed, synthesized and evaluated pharmacologically. Whereas compounds with the 4-cyclohexylpiperazinyl moiety

show high σ_1 affinity, ligands bearing the dimethylbenzylamino, 6,7-dimethoxyisoquinolinyl or benzo[7]annulenyl residue display a preference for the σ_2 receptor. The affinity towards both σ receptors decreases with elongation of the side chain in position 3 of the 2-benzopyran system: OCH_3 = OH > CH_2CO_2Et = CH_2CH_2OH = CH_2CH_2F. Introduction of the indolylpropyl moiety derived from the high-affinity σ_2 ligand siramesine led to considerably reduced affinity towards both σ receptors.

Further pharmacological properties of the most promising 4-cyclohexylpiperazinyl derivatives **10d**, **11d** and **13c** were investigated in *in vitro* experiments. In the mouse model of mechanical allodynia the most selective, fluorinated compound **13c** and its diastereomer **13d** showed high antiallodynic activity that can be partially explained by σ_1 receptor antagonism. A second mechanism was postulated to explain the complete antiallodynic effect of **13c**. In contrast, the antiallodynic effect of **13d** can be totally explained by σ_1 receptor antagonism.

7. Experimental

7.1. Chemistry, General

Unless otherwise noted, moisture sensitive reactions were conducted under dry nitrogen. CH_2Cl_2 was distilled over CaH_2. THF was distilled over sodium/benzophenone. Et_2O and toluene were dried over molecular sieve 0.4 Å. Thin layer chromatography (tlc): Silica gel 60 F254 plates (Merck). Flash chromatography (fc): Silica gel 60, 40–64 µm (Merck); parentheses include: diameter of the column (d), length of the stationary phase (l), fraction size (V), eluent. Melting point: Melting point apparatus Mettler Toledo MP50 Melting Point System, uncorrected. MS:

microTOF-Q II (Bruker Daltonics); APCI, atmospheric pressure chemical ionization. IR: FT-IR spectrophotometer MIRacle 10 (Shimadzu) equipped with ATR technique. Nuclear magnetic resonance (NMR) spectra were recorded on Agilent 600-MR (600 MHz for ^{1}H, 151 MHz for ^{13}C) or Agilent 400-MR spectrometer (400 MHz for ^{1}H, 101 MHz for ^{13}C); δ in ppm related to tetramethylsilane and measured referring to $CHCl_3$ (δ = 7.26 ppm (^{1}H NMR) and δ = 77.2 ppm (^{13}C NMR)), CHD_2OD (δ = 3.31 ppm (^{1}H NMR) and δ = 49.0 ppm (^{13}C NMR)) and DMSO-d_6 (δ = 2.54 ppm (^{1}H NMR) and δ = 39.5 ppm (^{13}C NMR)); coupling constants are given with 0.5 Hz resolution; the assignments of ^{13}C and ^{1}H NMR signals were supported by 2-D NMR techniques where necessary. HPLC: Pump: LPG-3400SD, degasser: DG-1210, autosampler: ACC-3000T, UV-detector: VWD-3400RS, interface: DIONEX UltiMate 3000, data acquisition: Chromeleon 7 (Thermo Fisher Scientific); column: LiChrospher® 60 RP-select B (5 µm), LiChroCART® 250-4 mm cartridge; guard column: LiChrospher® 60 RP-select B (5 µm), LiChroCART® 4-4 mm cartridge (No.: 1.50963.0001), manu-CART® NT cartridge holder; flow rate: 1.0 mL/min; injection volume: 5.0 µL; detection at λ = 210 nm; solvents: A: method 1: water with 0.05 % (v/v) trifluoroacetic acid; method 2: water; B: method 1: acetonitrile with 0.05 % (v/v) trifluoroacetic acid; method 2: acetonitrile: gradient elution: (A %): 0-4 min: 90 %, 4-29 min: 90 $\rightarrow$ 0 %, 29-31 min: 0 %, 31-31.5 min: 0 $\rightarrow$ 90 %, 31.5-40 min: 90 %. The purity of all compounds was determined by this method. Unless otherwise mentioned, the purity of all test compounds is higher than 95 %.

7.2. Synthetic procedures

7.2.1. *trans*-N-(2,4-Dimethylbenzyl)-3-methoxy-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-amine (6a) and *cis*-N-(2,4-Dimethylbenzyl)-3-methoxy-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexane]-4'-amine (6b)

A solution of ketone **5** (201 mg, 0.82 mmol), 2,4-dimethylbenzylamine (161 mg, 1.19 mmol, 1.5 eq) and acetic acid (50 µL, 0.88 mmol, 1.1 eq) in THF (30 mL) was stirred under N_2 atmosphere at rt. After 2.5 h, $NaBH(OAc)_3$ (310 mg, 1.46 mmol, 1.9 eq) was added and the mixture was stirred for 20 h at rt. 1 M NaOH (20 mL) was added and the aqueous layer was extracted with Et_2O (4 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 3 cm, l = 26 cm, V = 20 mL, cyclohexane/ethyl acetate 90:10 + 1 % *N*,*N*-dimethylethanamine). **6a** was eluted first and **6b** afterwards. **6b** was purified again by fc (d = 2 cm, l = 16 cm, V = 10 mL, cyclohexane/ethyl acetate 80:20 + 1 % *N*,*N*-dimethylethanamine).

trans-**6a**: Pale yellow solid, mp 74 °C, yield 91 mg (30 %). $C_{24}H_{31}NO_2$ (365.6 g/mol). R_f = 0.30 (cyclohexane/ethyl acetate 90:10 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): m/z = 366.2437 (calcd. 366.2428 for $C_{24}H_{32}NO_2$ [MH^+]). ^{1}H NMR (600 MHz, CD_3OD): δ (ppm) = 1.57 (dq, *J* = 13.5/3.1 Hz, 1H, 2'-H_{equ}), 1.74 – 1.79 (m, 2H, 3'-*H*, 5'-*H*), 1.82 (dq, *J* = 13.3/2.8 Hz, 1H, 6'-H_{equ}), 1.98 – 2.16 (m, 3H, 3'-*H*, 5'-*H*, 6'-H_{ax}), 2.29 – 2.34 (m, 1H, 2'-H_{ax}) ,2.30 (s, 1H, 4-CH_3) 2.39 (s, 3H, 2-CH_3), 2.79 (dd, *J* = 15.6/7.5 Hz, 1H, 4-*H*), 2.91 (dd, *J* = 15.6/3.1 Hz, 1H, 4-*H*), 3.01 (quint, *J* = 3.1 Hz, 1H, 4'-H_{equ}), 3.54 (s, 3H, OCH_3), 3.77 (s, 2H, ArCH_2NH), 4.90 (dd, *J* = 7.7/3.1 Hz, 1H, 3-*H*), 6.96 – 7.04 (m, 2H, 3-H_{benzyl}, 5-H_{benzyl}), 7.06 (dd, *J* = 7.6/1.2 Hz, 1H, 5-*H*), 7.13 (td, *J* = 7.4/1.4 Hz, 1H, 6-*H*), 7.16 – 7.20 (m, 1H, 7-*H*), 7.23 (d, *J* = 7.6 Hz, 1H, 6-

H_{benzyl}), 7.33 (dd, J = 7.8/1.3 Hz, 1H, 8-*H*). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, CD_3OD): δ (ppm) = 19.2 (1C, 2-*C*H_3), 21.1 (1C, 4-*C*H_3), 26.6 (1C, *C*-3'), 26.8 (1C, *C*-5'), 31.6 (1C, *C*-6'), 34.3 (1C, *C*-2'), 36.3 (1C, *C*-4), 50.2 (1C, Ar*C*H_2NH), 52.4 (1C, *C*-4'), 56.3 (1C, O*C*H_3), 78.3 (1C, *C*-1), 97.8 (1C, *C*-3), 126.1 (1C, *C*-8), 127.47 (1C, *C*-7), 127.52 (1C, *C*-6), 127.6 (1C, *C*-5_{benzyl}), 130.0 (1C, *C*-5), 130.2 (1C, *C*-6_{benzyl}), 132.0 (1C, *C*-3_{benzyl}), 132.4 (1C, *C*-4a), 136.2 (1C, *C*-1_{benzyl}), 137.4 (1C, *C*-2_{benzyl}), 137.8 (1C, *C*-4_{benzyl}), 143.5 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 3310 (N-H), 2948, 2930, 2851 (C-H_{alkyl}), 1615, 1476 (C=C_{arom}). Purity (HPLC): 96.7 %, t_R = 19.8 min.

cis-**6b**: Pale yellow solid, mp 93 °C, yield 131 mg (44 %). $C_{24}H_{31}NO_2$ (365.6 g/mol). R_f = 0.09 (cyclohexane/ethyl acetate 90:10 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): m/z = 366.2390 (calcd. 366.2428 for $C_{24}H_{32}NO_2$ [MH^+]). ^{1}H NMR (400 MHz, CD_3OD): δ (ppm) = 1.70 (td, J = 13.4/3.5 Hz, 1H, 2'-H_{ax}), 1.74 – 1.83 (m, 1H, 3'-*H*), 1.83 – 1.96 (m, 4H, 3'-*H*, 5'-*H*, 6'-*H*), 1.96 – 2.05 (m, 1H, 6'-*H*), 2.13 (dq, J = 13.6/2.7 Hz, 1H, 2'-H_{equ}), 2.31 (s, 3H, 4-CH_3), 2.36 (s, 3H, 2-CH_3), 2.77 (tt, J = 10.8/3.9 Hz, 1H, 4'-H_{ax}), 2.83 (dd, J = 16.1/7.4 Hz, 1H, 4-*H*), 2.94 (dd, J = 15.7/3.0 Hz, 1H, 4-*H*), 3.59 (s, 3H, OCH_3), 3.83 (s, 2H, ArCH_2NH), 4.93 (dd, J = 7.4/3.2 Hz, 1H, 3-*H*), 6.99 – 7.05 (m, 2H, 3-H_{benzyl}, 5-H_{benzyl}), 7.10 (d, J = 7.6 Hz, 1H, 5-*H*), 7.14 – 7.21 (m, 3H, 6-*H*, 7-*H*, 8-*H*), 7.22 (d, J = 7.5 Hz, 1H, 6-H_{benzyl}). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (101 MHz, CD_3OD): δ (ppm) = 19.1 (1C, 2-*C*H_3), 21.1 (1C, 4-*C*H_3), 29.1 (1C, *C*-5'), 29.1 (1C, *C*-3'), 36.2 (1C, *C*-4), 36.6 (1C, *C*-2'), 39.1 (1C, *C*-6'), 48.7 (1C, Ar*C*H_2NH), 56.5 (1C, O*C*H_3), 57.2 (1C, *C*-4'), 77.5 (1C, *C*-1), 97.8 (1C, *C*-3), 125.7 (1C, *C*-8), 127.5 (1C, *C*-7), 127.6 (1C, *C*-5_{benzyl}), 127.7 (1C, *C*-6), 129.9 (1C, *C*-6_{benzyl}), 130.1 (1C, *C*-5), 132.1 (1C, *C*-3_{benzyl}), 132.6 (1C, *C*-4a), 135.8 (1C, *C*-1_{benzyl}), 137.2 (1C, *C*-2_{benzyl}), 137.9 (1C, *C*-4_{benzyl}), 142.7 (1C, *C*-8a). FT-

IR (neat): ν [cm^{-1}] = 3290 (N-H), 2941, 2918 (C-H_{alkyl}), 1614, 1488 (C=C_{arom}). Purity (HPLC): 95.6 %, t_R = 19.53 min.

7.2.2. *trans*-1-Cyclohexyl-4-(3-methoxy-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-yl)piperazine (6c) and *cis*-1-Cyclohexyl-4-(3-methoxy-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-yl)piperazine (6d)

A solution of ketone **5** (80 mg, 0.32 mmol), 1-cyclohexylpiperazine (76 mg, 0.45 mmol, 1.4 eq) and acetic acid (22 µL, 0.39 mmol, 1.2 eq) in THF (10 mL) was stirred under N_2 atmosphere at rt. After 3 h, $NaBH(OAc)_3$ (129 mg, 0.61 mmol, 1.9 eq) was added and the mixture was stirred for 23 h at rt. 1 M NaOH (20 mL) was added and the aqueous layer was extracted with Et_2O (4 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 2 cm, l = 26 cm, V = 5 mL, cyclohexane/ethyl acetate 66:33 + 2 % *N*,*N*-dimethylethanamine). **6c** was eluted first and **6d** afterwards.

trans-**6c**: Colorless solid, mp 146 °C, yield 13 mg (9 %). $C_{25}H_{38}N_2O_2$ (398.6 g/mol). R_f = 0.34 (cyclohexane/ethyl acetate 90:10 + 2 % *N*,*N*-dimethylethanamine). HR-MS (APCI): m/z = 399.3013 (calcd. 399.3006 for $C_{25}H_{39}N_2O_2$ [MH^+]). ^{1}H NMR (600 MHz, CD_3OD): δ (ppm) = 1.13 – 1.21 (m, 1H ,4-$H_{cyclohexyl}$), 1.13 – 1.37 (m, 4H, 2-$H_{cyclohexyl}$, 3-$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 1.51 (dq, *J* = 13.3/3.1 Hz, 1H, 2'-H_{equ}), 1.64 – 1.71 (m, 1H, 4-$H_{cyclohexyl}$), 1.76 (dq, *J* = 12.6/3.3/2.8/2.3 Hz, 1H, 6'-H_{equ}), 1.82 – 1.88 (m, 2H, 3-$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$), 1.90 – 2.05 (m, 7H, 3'-*H*, 5'-*H*, 6'-H_{ax}, 2-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 2.22 – 2.30 (m, 3H, 2'-H_{ax}, 4'-H_{equ}, 1-$H_{cyclohexyl}$), 2.45 – 2.66 (broad signal, 4H, 2-$H_{piperazine}$ and 6-$H_{piperazine}$ or 3-$H_{piperazine}$ and 5-$H_{piperazine}$), 2.66 – 2.76 (broad signal, 4H, 2-$H_{piperazine}$ and 6-$H_{piperazine}$ or 3-$H_{piperazine}$ and 5-$H_{piperazine}$), 2.78 (dd, *J* = 15.4/7.7 Hz, 1H, 4-*H*), 2.90 (dd, *J* = 15.6/3.2 Hz, 1H, 4-*H*), 3.54 (s, 3H, OCH_3), 4.89

(dd, *J* = 7.5/3.1 Hz, 1H, 3-*H*), 7.04 – 7.08 (m, 1H, 5-*H*), 7.11 – 7.15 (m, 1H, 6-*H*), 7.16 – 7.22 (m, 2H, 7-*H*, 8-*H*). ^{13}C NMR (151 MHz, CD_3OD): δ (ppm) = 24.9 (1C, *C*-3'), 25.0 (1C, *C*-5'), 26.9 (2C, *C*-$2_{cyclohexyl}$, *C*-$6_{cyclohexyl}$), 27.3 (1C, *C*-$4_{cyclohexyl}$), 29.8 (2C, *C*-$3_{cyclohexyl}$, *C*-$5_{cyclohexyl}$), 32.1 (1C, *C*-6'), 34.8 (1C, *C*-2'), 36.2 (1C, *C*-4), 50.6 (2C, *C*-$2_{piperazine}$ and *C*-$6_{piperazine}$ or *C*-$3_{piperazine}$ and *C*-$5_{piperazine}$), 51.4 (2C, *C*-$2_{piperazine}$ and *C*-$6_{piperazine}$ or *C*-$3_{piperazine}$ and *C*-$5_{piperazine}$), 56.3 (1C, O*C*H_3), 59.4 (1C, *C*-4'), 65.0 (1C, *C*-$1_{cyclohexyl}$), 78.4 (1C, *C*-1), 97.9 (1C, *C*-3), 125.9 (1C, *C*-8), 127.4 (1C, *C*-7), 127.5 (1C, *C*-6), 130.0 (1C, *C*-5), 132.5 (1C, *C*-4a), 143.6 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 2947, 2914 (C-H_{alkyl}), 2800, 2758 (N-CH_2), 1486 (C=C_{arom}). Purity (HPLC): 98.1 %, t_R = 14.42 min.

cis-**6d**: Colorless solid, mp 146 °C, yield 48 mg (38 %). $C_{25}H_{38}N_2O_2$ (398.6 g/mol). R_f = 0.17 (cyclohexane/ethyl acetate 90:10 + 2 % *N*,*N*-dimethylethanamine). HR-MS (APCI): m/z = 399.2996 (calcd. 399.3006 for $C_{25}H_{39}N_2O_2$ [MH^+]). ^{1}H NMR (600 MHz, CD_3OD): δ (ppm) = 1.10 – 1.20 (m, 1H, 4-$H_{cyclohexyl}$), 1.20 – 1.35 (m, 4H, 2-$H_{cyclohexyl}$, 3-$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 1.63 – 1.68 (m, 1H, 4-$H_{cyclohexyl}$), 1.68 – 1.74 (m, 1H, 2'-H_{ax}), 1.78 – 1.92 (m, 7H, 3'-*H*, 5'-*H*, 6'-*H*, 2-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 1.92 – 2.03 (m, 3H, 6'-*H*, 3-$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$), 2.14 (dq, *J* = 14.2/3.2 Hz, 1H, 2'-H_{equ}), 2.25 (tt, *J* = 11.0/3.4 Hz, 1H, 1-$H_{cyclohexyl}$), 2.47 (tt, *J* = 10.6/4.3 Hz, 1H, 4'-H_{ax}), 2.61 – 2.76 (broad signal, 8H, $H_{piperazine}$), 2.79 (dd, *J* = 15.6/7.5 Hz, 1H, 4-*H*), 2.91 (dd, *J* = 15.7/3.1 Hz, 1H, 4-*H*), 3.55 (s, 3H, O*C*H_3), 4.90 (dd, *J* = 7.5/3.1 Hz, 1H, 3-*H*), 7.07 (d, *J* = 7.3 Hz, 1H, 5-*H*), 7.11 – 7.16 (m, 1H, 6-*H*), 7.16 – 7.19 (m, 2H, 7-*H*, 8-*H*). ^{13}C NMR (151 MHz, CD_3OD): δ (ppm) = 24.86 (1C, *C*-3' or *C*-5'), 24.89 (1C, *C*-3' or *C*-5'), 26.9 (2C, *C*-$2_{cyclohexyl}$, *C*-$6_{cyclohexyl}$), 27.3 (1C, *C*-$4_{cyclohexyl}$), 29.7 (2C, *C*-$3_{cyclohexyl}$, *C*-$5_{cyclohexyl}$), 36.2 (1C, *C*-4), 36.9 (1C, *C*-2'), 39.4 (1C, *C*-6'), 49.9 (2C, *C*-$3_{piperazine}$, *C*-$5_{piperazine}$), 50.1 (2C, *C*-$2_{piperazine}$, *C*-$6_{piperazine}$), 56.4 (1C, O*C*H_3), 63.9 (1C, *C*-4'), 64.9

(1C, *C*-$1_{cyclohexyl}$), 77.3 (1C, *C*-1), 97.8 (1C, *C*-3), 125.7 (1C, *C*-8), 127.5 (1C, *C*-7), 127.7 (1C, *C*-6), 130.1 (1C, *C*-5), 132.6 (1C, *C*-4a), 142.6 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 2926 (C-H_{alkyl}), 2827, 2798 (N-CH_2), 1489 (C=C_{arom}). Purity (HPLC): 99.7 %, t_R = 13.9 min.

7.2.3. *trans*-6,7-Dimethoxy-2-(3-methoxy-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-yl)-1,2,3,4-tetrahydroisoquinoline (6e) and *cis*-6,7-Dimethoxy-2-(3-methoxy-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-yl)-1,2,3,4-tetrahydroisoquinoline (6f)

A solution of ketone **5** (205 mg, 0.83 mmol) and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (262 mg, 1.14 mmol, 1.4 eq) in CH_2Cl_2 (30 mL) was stirred under N_2 atmosphere at rt. After 4 h, $NaBH(OAc)_3$ (395 mg, 1.87 mmol, 2.3 eq) was added and the mixture was stirred for 43 h at rt. 1 M NaOH (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (4 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 2 cm, l = 20 cm, V = 10 mL, cyclohexane/ethyl acetate 80:20 + 1 % *N*,*N*-dimethylethanamine → 66:33 + 1 % *N*,*N*-dimethylethanamine). **6e** was eluted first and **6f** afterwards. **6f** was purified twice by fc (d = 2 cm, l = 16 cm, V = 10 mL, cyclohexane/ethyl acetate 50:50 + 1 % HCOOH → 66:33 + 1 % *N*,*N*-dimethylethan-amine; d = 2 cm, l = 20 cm, V = 10 mL, cyclohexane/ethyl acetate 80:20 + 1 % *N*,*N*-dimethylethanamine → 60:40 + 1 % *N*,*N*-dimethylethanamine).

trans-**6e**: Yellow solid, mp 158 °C, yield 66 mg (19 %). $C_{26}H_{33}NO_4$ (423.6 g/mol). R_f = 0.67 (cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): m/z = 424.2454 (calcd. 424.2482 for $C_{26}H_{34}NO_4$ [MH^+]). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.48 (dq, *J* = 12.3/2.7 Hz, 1H, 2'-*H*), 1.70 – 1.78 (m, 1H, 6'-*H*),

1.86 – 2.07 (m, 5H, 3'-*H*, 5'-*H*, 6'-*H*), 2.21 (td, *J* = 12.8/3.9 Hz, 1H, 2'-*H*), 2.36 – 2.44 (m, 1H, 4'-H_{equ}), 2.69 – 2.77 (m, 3H, 4-*H*, 3-$H_{isoquinoline}$), 2.77 – 2.82 (m, 2H, 4-$H_{isoquinoline}$), 2.90 (dd, *J* = 15.8/3.1 Hz, 1H, 4-*H*), 3.46 (s, 3H, 3-OCH_3), 3.63 (s, 2H, 1-$H_{isoquinoline}$), 3.72 (s, 3H, 6-OCH_3), 3.74 (s, 3H, 7-OCH_3), 4.90 (dd, *J* = 7.2/3.1 Hz, 1H, 3-*H*), 6.71 (s, 2H, 5-$H_{isoquinoline}$, 8-$H_{isoquinoline}$), 7.03 (dd, *J* = 7.0/2.0 Hz, 1H, 8-*H*), 7.08 (dd, *J* = 7.3/1.8 Hz, 1H, 5-*H*), 7.11 – 7.19 (m, 2H, 6-*H*, 7-*H*). ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) = 23.9 (1C, *C*-3' or *C*-5'), 24.1 (1C, *C*-3' or *C*-5'), 28.7 (1C, *C*-4$_{isoquinoline}$), 30.9 (1C, *C*-6'), 33.3 (1C, *C*-2'), 34.7 (1C, *C*-4), 47.0 (1C, *C*-3$_{isoquinoline}$), 52.9 (1C, *C*-1$_{isoquinoline}$), 55.0 (1C, 3-O*C*H$_3$), 55.45 (1C, 6-O*C*H$_3$ or 7-O*C*H$_3$), 55.50 (1C, 6-O*C*H$_3$ or 7-O*C*H$_3$), 56.5 (1C, *C*-4'), 76.0 (1C, *C*-1), 95.8 (1C, *C*-3), 110.3 (1C, *C*-8$_{isoquinoline}$), 111.6 (1C, *C*-5$_{isoquinoline}$), 124.4 (1C, *C*-8), 126.2 (1C, *C*-4a$_{isoquinoline}$), 126.2 (1C, *C*-6 or *C*-7), 126.3 (1C, *C*-6 or *C*-7), 127.0 (1C, *C*-8a$_{isoquinoline}$), 128.8 (1C, *C*-5), 131.1 (1C, *C*-4a), 142.1 (1C, *C*-8a), 146.9 (1C, *C*-6$_{isoquinoline}$ or *C*-7$_{isoquinoline}$), 147.1 (1C, *C*-6$_{isoquinoline}$ or *C*-7$_{isoquinoline}$). FT-IR (neat): ν [cm^{-1}] = 2943, 2920, 2832 (C-H$_{alkyl}$), 1516, 1447 (C=C$_{arom}$). Purity (HPLC): 98.8 %, t_R = 17.7 min. A sample was recrystallized from CH_2Cl_2 to obtain crystals, which were suitable to for X-ray crystal structure analysis.

cis-**6f**: Yellow solid, mp 180 °C, yield 133 mg (37 %). $C_{26}H_{33}NO_4$ (423.6 g/mol). R_f = 0.22 (cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): m/z = 424.2439 (calcd. 424.2482 for $C_{26}H_{34}NO_4$ [MH$^+$]). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.61 – 1.71 (m, 1H, 2'-*H*), 1.71 – 1.85 (m, 5H, 3'-*H*, 5'-*H*, 6'-*H*), 1.85 – 2.02 (m, 1H, 6'-*H*), 2.02 – 2.11 (m, 1H, 2'-*H*), 2.64 – 2.76 (m, 5H, 4-*H*, 4'-H_{ax}, 4-$H_{isoquinoline}$), 2.80 (t, *J* = 5.7 Hz, 2H, 3-$H_{isoquinoline}$), 2.90 (dd, *J* = 15.9/3.2 Hz, 1H, 4-*H*), 3.47 (s, 3H, 3-OCH_3), 3.70 (s, 8H, 1-$H_{isoquinoline}$, 6-OCH_3, 7-OCH_3), 4.89 (dd, *J* = 7.2/3.1 Hz, 1H, 3-*H*), 6.65 (s, 1H, 5-$H_{isoquinoline}$), 6.66 (s, 1H, 8-$H_{isoquinoline}$), 7.09 (dd, *J*

= 7.3/1.8 Hz, 1H, 5-*H*), 7.12 – 7.21 (m, 2H, 6-*H*, 7-*H*), 7.25 (dd, *J* = 7.4/1.8 Hz, 1H, 8-*H*). ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) = 23.3 (2C, *C*-3', *C*-5'), 28.7 (1C, *C*-$4_{isoquinoline}$), 34.6 (1C, *C*-4), 35.6 (1C, *C*-2'), 37.9 (1C, *C*-6'), 46.7 (1C, *C*-$3_{isoquinoline}$), 50.5 (1C, *C*-$1_{isoquinoline}$), 55.2 (1C, 3-OCH_3), 55.46 (1C, 6-OCH_3 or 7-OCH_3), 55.52 (1C, 6-OCH_3 or 7-OCH_3), 61.4 (1C, *C*-4'), 75.4 (1C, *C*-1), 95.7 (1C, *C*-3), 110.2 (1C, *C*-$8_{isoquinoline}$), 111.7 (1C, *C*-$5_{isoquinoline}$), 124.5 (1C, *C*-8), 126.0 (1C, *C*-$8a_{isoquinoline}$), 126.2 (1C, *C*-6 or *C*-7), 126.3 (1C, *C*-6 or *C*-7), 126.6 (1C, *C*-$4a_{isoquinline}$), 128.9 (1C, *C*-5), 131.3 (1C, *C*-4a), 141.5 (1C, *C*-8a), 146.8 (1C, *C*-$6_{isoquinoline}$ or *C*-$7_{isoquinoline}$), 147.1 (1C, *C*-$6_{isoquinoline}$ or *C*-$7_{isoquinoline}$). FT-IR (neat): ν [cm^{-1}] = 2978, 2940, (C-H_{alkyl}), 1516, 1466, 1450 (C=C_{arom}). Purity (HPLC): 95.3 %, t_R = 17.9 min. A sample was recrystallized from CH_2Cl_2 to obtain crystals, which were suitable to for X-ray crystal structure analysis.

7.2.4. *trans*-4'-[(2,4-Dimethylbenzyl)amino]-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-3-ol (10a)

A solution of acetal **6a** (254 mg, 0.69 mmol) and 0.2 M HCl (17 mL, 3.5 mmol, 5.0 eq) in THF (20 mL) was stirred at rt for 3 d. 1 M NaOH (10 mL) was added and the aqueous layer was extracted with Et_2O (4 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 2 cm, l = 20 cm, V = 10 mL, cyclohexane/ethyl acetate 80:20 + 1 % *N*,*N*-dimethylethanamine). Pale yellow solid, mp 142 °C, yield 173 mg (71 %). $C_{23}H_{29}NO_2$ (351.5 g/mol). R_f = 0.11 (cyclohexane/ethyl acetate 80:20 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): m/z = 352.2277 (calcd. 352.2271 for $C_{23}H_{30}NO_2$ [MH^+]). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.60 – 1.74 (m, 3H, 2'-*H*, 3'-*H*, 5'-*H*), 1.74 – 1.81 (m, 1H, 6'-*H*), 1.94 – 2.15 (m, 3H, 3'-*H*, 5'-*H*, 6'-*H*), 2.25 –

2.40 (m, 1H, 2'-*H*), 2.32 (s, 1H, 4-CH_3), 2.41 (s, 3H, 2-CH_3), 2.85 (dd, *J* = 15.5/8.0 Hz, 1H, 4-*H*), 3.01 (dd, *J* = 15.5/3.0 Hz, 1H, 4-*H*), 3.03 – 3.07 (m, 1H, 4'-H_{equ}), 3.75 (s, 2H, ArCH_2NH), 5.28 (dd, *J* = 7.8/2.9 Hz, 1H, 3-*H*), 6.98 – 7.04 (m, 2H, 3-H_{benzyl}, 5-H_{benzyl}), 7.06 – 7.11 (m, 1H, 5-*H*), 7.13 – 7.26 (m, 4H, 6-*H,* 7-*H,* 8-*H*, 6-H_{benzyl}). Signals for the NH and OH protons are not observed in the spectrum. ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 19.2 (1C, 2-*C*H_3), 21.2 (1C, 4-*C*H_3), 26.1 (1C, *C*-3' or *C*-5'), 26.3 (1C, *C*-3' or *C*-5'), 30.6 (1C, *C*-6'), 33.5 (1C, *C*-2'), 37.3 (1C, *C*-4), 49.9 (1C, Ar*C*H_2NH), 51.4 (1C, *C*-4'), 77.9 (1C, *C*-1), 89.7 (1C, *C*-3), 125.2 (1C, *C*-8), 126.6 (1C, *C*-6 or *C*-7), 126.7 (2C, *C*-6 or *C*-7, *C*-5$_{benzyl}$), 129.1 (1C, *C*-6$_{benzyl}$), 129.2 (1C, *C*-5), 131.2 (1C, *C*-4a), 131.3 (1C, *C*-3$_{benzyl}$), 136.1 (1C, *C*-1$_{benzyl}$), 136.7 (1C, *C*-2$_{benzyl}$), 136.8 (1C, *C*-4$_{benzyl}$), 142.5 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 3337 (N-H/O-H), 2924 (C-H_{alkyl}), 1454, 1435 (C=C_{arom}). Purity (HPLC): 98.6 %, t_R = 19.5 min.

7.2.5. *cis*-4'-[(2,4-Dimethylbenzyl)amino]-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-3-ol (10b)

A solution of acetal **6b** (201 mg, 0.55 mmol) and 2 M HCl (3 mL, 6.0 mmol, 11 eq) in THF (10 mL) was stirred at rt for 3 d. 1 M NaOH (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 2 cm, l = 16 cm, V = 10 mL, cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine). Colorless solid, mp 177 °C, yield 156 mg (80 %). $C_{23}H_{29}NO_2$ (351.5 g/mol). R_f = 0.03 (cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): m/z = 352.2254 (calcd. 352.2271 for $C_{23}H_{30}NO_2$ [MH^+]). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.62 (td, *J* = 13.6/3.6 Hz, 1H, 2'-H_{ax}), 1.68 – 1.81 (m, 1H, 3'-*H*), 1.81 – 1.93 (m, 4H, 3'-*H*, 5'-*H*, 6'-*H*), 1.93 –

2.01 (m, 1H, 6'-*H*), 2.07 (dq, *J* = 13.9/3.0 Hz, 1H, 2'-H_{equ}), 2.30 (s, 3H, 4-CH_3), 2.34 (s, 3H, 2-CH_3), 2.69 (m, 1H, 4'-H_{ax}), 2.83 (dd, *J* = 15.6/7.7 Hz, 1H, 4-*H*), 2.97 (dd, *J* = 15.7/3.1 Hz, 1H, 4-*H*), 3.82 (s, 2H, ArCH_2NH), 5.26 (dd, *J* = 7.7/3.0 Hz, 1H, 3-*H*), 6.96 – 7.02 (m, 2H, 3-H_{benzyl}, 5-H_{benzyl}), 7.07 – 7.13 (m, 2H, 5-*H*, 8-*H*), 7.14 – 7.23 (m, 3H, 6-*H*, 7-*H*, 6-H_{benzyl}). Signals for the NH and OH protons are not observed in the spectrum. ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 19.1 (1C, 2-*C*H_3), 21.1 (1C, 4-*C*H_3), 28.7 (1C, *C*-3'), 28.8 (1C, *C*-5'), 35.6 (1C, *C*-6'), 36.9 (1C, *C*-4), 38.3 (1C, *C*-2'), 48.5 (1C, Ar*C*H_2NH), 56.2 (1C, *C*-4'), 77.4 (1C, *C*-1), 89.5 (1C, *C*-3), 124.6 (1C, *C*-8), 126.6 (1C, *C*-6 or *C*-7), 126.7 (1C, *C*-5_{benzyl}), 126.8 (1C, *C*-6 or *C*-7), 128.8 (1C, *C*-6_{benzyl}), 129.4 (1C, *C*-5), 131.3 (1C, *C*-3_{benzyl}), 131.7 (1C, *C*-4a), 135.3 (1C, *C*-1_{benzyl}), 136.2 (1C, *C*-2_{benzyl}), 136.8 (1C, *C*-4_{benzyl}), 141.7 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 3256 (N-H), 2932 (C-H_{alkyl}), 1454, 1366 (C=C_{arom}). Purity (HPLC): 99.5 %, t_R = 17.5 min.

7.2.6. *trans*-4'-(4-Cyclohexylpiperazin-1-yl)-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-3-ol (10c)

A solution of acetal **6c** (174 mg, 0.44 mmol) and 0.2 M HCl (11 mL, 2.2 mmol, 5 eq) in THF (10 mL) was stirred at rt for 3 d. 1 M NaOH (5 mL) was added and the aqueous layer was extracted with Et_2O (4 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 2 cm, l = 15 cm, V = 10 mL, cyclohexane/ethyl acetate 50:50 + 2 % *N*,*N*-dimethylethanamine). Pale yellow solid, mp 214 °C, yield 145 mg (86 %). $C_{24}H_{36}N_2O_2$ (384.6 g/mol). R_f = 0.10 (cyclohexane/ethyl acetate 50:50 + 2 % *N*,*N*-dimethylethanamine). HR-MS (APCI): m/z = 385.2885 (calcd. 385.2850 for $C_{24}H_{37}N_2O_2$ [MH^+]). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.07 – 1.19 (m, 1H, 4-

$H_{cyclohexyl}$), 1.19 – 1.34 (m, 4H, 2-$H_{cyclohexyl}$, 3-$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 1.58 (dq, J = 13.7/3.5/3.0 Hz, 1H, 2'-H_{equ}), 1.62 – 1.67 (m, 1H, 4-$H_{cyclohexyl}$), 1.70 (dq, J = 13.4/3.0 Hz, 1H, 6'-H_{equ}), 1.78 – 1.91 (m, 5H, 3'-*H*, 5'-*H*, 2-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 1.91 – 2.04 (m, 4H, 3'-*H* or 5'-*H*, 6'-H_{ax}, 3-$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$), 2.22 (td, J = 13.2/3.6 Hz, 1H, 2'-H_{ax}), 2.25 – 2.36 (m, 2H, 4'-H_{equ}, 1-$H_{cyclohexyl}$), 2.69 (broad signal, 7H, $H_{piperazine}$), 2.85 (dd, J = 15.5/7.8 Hz, 2H, 4-*H*, $H_{piperazine}$), 3.00 (dd, J = 15.5/2.9 Hz, 1H, 4-*H*), 5.28 (dd, J = 7.8/3.5 Hz, 1H, 3-*H*), 7.08 (d, J = 7.5 Hz, 1H, 5-*H*), 7.15 – 7.24 (m, 3H, 6-*H*, 7-*H*, 8-*H*). A signal for the OH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 24.0 (1C, *C*-3' or *C*-5'), 24.2 (1C, *C*-3' or *C*-5'), 26.0 (2C, *C*-$2_{cyclohexyl}$, *C*-$6_{cyclohexyl}$), 26.4 (1C, *C*-$4_{cyclohexyl}$), 29.2 (2C, *C*-$3_{cyclohexyl}$, *C*-$5_{cyclohexyl}$), 31.0 (1C, *C*-6'), 34.1 (1C, *C*-2'), 37.3 (1C, *C*-4), 49.9 (2C, *C*-$2_{piperazine}$ and *C*-$6_{piperazine}$ or *C*-$3_{piperazine}$ and *C*-$5_{piperazine}$), 50.5 (2C, *C*-$2_{piperazine}$ and *C*-$6_{piperazine}$ or *C*-$3_{piperazine}$ and *C*-$5_{piperazine}$), 57.5 (1C, *C*-4'), 63.8 (1C, *C*-$1_{cyclohexyl}$), 78.0 (1C, *C*-1), 89.7 (1C, *C*-3), 125.2 (1C, *C*-8), 126.6 (2C, *C*-6, *C*-7), 129.2 (1C, *C*-5), 131.3 (1C, *C*-4a), 142.6 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 3325 (O-H), 2959, 2932, 2805 (C-H_{alkyl}), 1454 (C=C_{arom}). Purity (HPLC): 97.4 %, t_R = 12.7 min.

7.2.7. *cis*-4'-(4-Cyclohexylpiperazin-1-yl)-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-3-ol (10d)

A solution of acetal **6d** (273 mg, 0.68 mmol) and 0.5 M HCl (7 mL, 3.5 mmol, 5 eq) in THF (10 mL) was stirred at rt for 4 d. 1 M NaOH (8 mL) was added and the aqueous layer was extracted with Et_2O (4 x 8 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 3 cm, l = 18 cm, V = 20 mL, cyclohexane/ethyl acetate 50:50 + 2 % *N*,*N*-dimethylethanamine). Colorless solid, mp 204 °C, yield 211 mg (81 %). $C_{24}H_{36}N_2O_2$

(384.6 g/mol). R_f = 0.03 (cyclohexane/ethyl acetate 50:50 + 2 % *N*,*N*-dimethylethanamine). HR-MS (APCI): m/z = 385.2874 (calcd. 385.2850 for $C_{24}H_{37}N_2O_2$ [MH^+]). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.05 – 1.16 (m, 1H, 4-$H_{cyclohexyl}$), 1.17 – 1.34 (m, 4H, 2-$H_{cyclohexyl}$, 3-$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 1.58 – 1.67 (m, 2H, 2'-H_{ax}, 4-$H_{cyclohexyl}$), 1.75 – 1.86 (m, 5H, 3'-*H*, 5'-*H*, 2-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 1.86 – 1.97 (m, 4H, 5'-*H*, 6'-H_{ax}, 3-$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$), 1.99 (dq, *J* = 9.6/3.0/2.6 Hz, 1H, 6'-H_{equ}), 2.11 (dq, *J* = 14.3/3.3 Hz, 1H, 2'-H_{equ}), 2.27 (broad signal, 1H, 1-$H_{cyclohexyl}$), 2.40 – 2.48 (m, 1H, 4'-H_{ax}), 2.58 – 2.81 (broad signal, 8H, $H_{piperazine}$), 2.85 (dd, *J* = 15.6/7.7 Hz, 1H, 4-*H*), 2.99 (dd, *J* = 15.6/2.9 Hz, 1H, 4-*H*), 5.29 (dd, *J* = 7.9/3.1 Hz, 1H, 3-*H*), 7.07 – 7.14 (m, 2H, 5-*H*, 8-*H*), 7.14 – 7.22 (m, 2H, 6-*H*, 7-*H*). A signal for the OH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 24.0 (1C, *C*-5'), 24.2 (1C, *C*-3'), 26.0 (2C, *C*-$2_{cyclohexyl}$, *C*-$6_{cyclohexyl}$), 26.4 (1C, *C*-$4_{cyclohexyl}$), 29.01 (1C, *C*-$3_{cyclohexyl}$ or *C*-$5_{cyclohexyl}$), 29.03 (1C, *C*-$3_{cyclohexyl}$ or *C*-$5_{cyclohexyl}$), 36.2 (1C, *C*-2'), 37.0 (1C, *C*-4), 38.9 (1C, *C*-6'), 49.4 (2C, *C*-$2_{piperazine}$ and *C*-$6_{piperazine}$ or *C*-$3_{piperazine}$ and *C*-$5_{piperazine}$), 49.5 (2C, *C*-$2_{piperazine}$ and *C*-$6_{piperazine}$ or *C*-$3_{piperazine}$ and *C*-$5_{piperazine}$), 63.1 (1C, *C*-4'), 63.8 (1C, *C*-$1_{cyclohexyl}$), 76.8 (1C, *C*-1), 89.5 (1C, *C*-3), 124.7 (1C, *C*-8), 126.6 (1C, *C*-7), 126.8 (1C, *C*-6), 129.4 (1C, *C*-5), 131.6 (1C, *C*-4a), 141.5 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 3352 (O-H), 2928 (C-H_{alkyl}), 1454 (C=C_{arom}). Purity (HPLC): 97.7 %, t_R = 12.7 min.

7.2.8. *trans*-4'-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-3,4-dihydro-spiro[[2]benzopyran-1,1'-cyclohexan]-3-ol (10e)

A solution of acetal **6e** (154 mg, 0.36 mmol) and 0.2 M HCl (9 mL, 1.8 mmol, 5 eq) in THF (10 mL) was stirred at rt for 3 d. 1 M NaOH (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were dried

(Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 2 cm, l = 19 cm, V = 10 mL, cyclohexane/ethyl acetate 80:20 + 1 % *N*,*N*-dimethylethanamine → cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine). Colorless solid, mp 174 °C, yield 127 mg (86 %). $C_{25}H_{31}NO_4$ (409.5 g/mol). R_f = 0.31 (cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): m/z = 410.2294 (calcd. 410.2326 for $C_{25}H_{32}NO_4$ [MH^+]). ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) = 1.46 (dq, *J* = 12.9/2.9 Hz, 1H, 2'-H_{equ}), 1.72 (dq, *J* = 13.2/2.8 Hz, 1H, 6'-H_{equ}), 1.84 – 1.91 (m, 1H, 6'-H_{ax}), 1.91 – 1.99 (m, 4H, 3'-*H*, 5'-*H*), 2.17 (ddd, *J* = 12.9/10.6/6.4 Hz, 1H, 2'-H_{ax}), 2.36 (quint, *J* = 3.0 Hz, 1H, 4'-H_{equ}), 2.68 (dd, *J* = 15.7/8.2 Hz, 1H, 4-*H*), 2.71 – 2.76 (m, 2H, 3-$H_{isoquinoline}$), 2.76 – 2.80 (m, 2H, 4-$H_{isoquinoline}$), 2.82 (dd, *J* = 15.7/2.8 Hz, 1H, 4-*H*), 3.61 (s, 2H, 1-$H_{isoquinoline}$), 3.70 (s, 3H, 7-OCH_3), 3.73 (s, 3H, 6-OCH_3), 5.11 (ddd, *J* = 8.6/5.9/2.9 Hz, 1H, 3-*H*), 6.41 (d, *J* = 5.9 Hz, 1H, O*H*), 6.70 (s, 1H, 5-$H_{isoquinoline}$), 6.70 (s, 1H, 8-$H_{isoquinoline}$), 7.00 (dd, *J* = 7.5/1.6 Hz, 1H, 8-*H*), 7.06 (dd, *J* = 6.1/1.6 Hz, 1H, 5-*H*), 7.09 – 7.15 (m, 2H, 6-*H*, 7-*H*). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) = 23.8 (1C, *C*-3'), 23.9 (1C, *C*-5'), 28.7 (1C, *C*-4$_{isoquinoline}$), 30.3 (1C, *C*-6'), 33.7 (1C, *C*-2'), 36.8 (1C, *C*-4), 47.0 (1C, *C*-3$_{isoquinoline}$), 52.9 (1C, *C*-1$_{isoquinoline}$), 55.4 (1C, 7-O*C*H_3), 55.5 (1C, 6-O*C*H_3), 56.6 (1C, *C*-4'), 76.3 (1C, *C*-1), 88.3 (1C, *C*-3), 110.3 (1C, C-8$_{isoquinoline}$), 111.6 (1C, C-5$_{isoquinoline}$), 124.5 (1C, *C*-8), 126.11 (1C, *C*-6), 126.14 (1C, *C*-7), 126.2 (1C, C-4a$_{isoquinoline}$), 127.1 (1C, C-8a$_{isoquinoline}$), 128.9 (1C, *C*-5), 132.1 (1C, *C*-4a), 142.5 (1C, *C*-8a), 146.9 (1C, C-7$_{isoquinoline}$), 147.1 (1C, C-6$_{isoquinoline}$). FT-IR (neat): ν [cm^{-1}] = 3360 (O-H), 2928, 2882, 2808 (C-H_{alkyl}), 1520, 1454 (C=C_{arom}). Purity (HPLC): 95.4 %, t_R = 15.2 min.

7.2.9. *cis*-4'-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-3,4-dihydro-spiro[[2]benzopyran-1,1'-cyclohexan]-3-ol (10f)

A solution of acetal **6f** (97 mg, 0.23 mmol) and 0.2 M HCl (6 mL, 1.2 mmol, 5.2 eq) in THF (10 mL) was stirred at rt for 3 d. 1 M NaOH (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 2 cm, l = 19 cm, V = 10 mL, cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine → ethyl acetate + 1 % *N*,*N*-dimethylethanamine). Pale yellow solid, mp 202 °C, yield 69 mg (74 %). $C_{25}H_{31}NO_4$ (409.5 g/mol). R_f = 0.06 (cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): m/z = 410.2278 (calcd. 410.2326 for $C_{25}H_{32}NO_4$ [MH^+]). ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) = 1.59 (td, *J* = 13.6/3.8 Hz, 1H, 2'-H_{ax}), 1.61 – 1.68 (m, 2H, 3'-*H*, 5'-*H*), 1.74 – 1.78 (m, 1H, 6'-*H*), 1.80 – 1.94 (m, 3H, 3'-*H*, 5'-*H*, 6'-*H*), 2.02 (dq, *J* = 13.7/3.2 Hz, 1H, 2'-H_{equ}), 2.58 – 2.64 (m, 1H, 4'-H_{ax}), 2.64 – 2.70 (m, 3H, 4-*H*, 4-$H_{isoquinoline}$), 2.75 (t, *J* = 5.8 Hz, 2H, 3-$H_{isoquinoline}$), 2.81 (dd, *J* = 15.8/2.9 Hz, 1H, 4-*H*), 3.64 (s, 2H, 1-$H_{isoquinoline}$), 3.68 (s, 6H, 6-OCH_3, 7-OCH_3), 5.09 (ddd, *J* = 8.6/5.9/2.9 Hz, 1H, 3-*H*), 6.41 (d, *J* = 5.9 Hz, 1H, O*H*), 6.62 (s, 2H, 5-$H_{isoquinoline}$, 8-$H_{isoquinoline}$), 7.05 (dd, *J* = 7.5/1.5 Hz, 1H, 5-*H*), 7.11 (td, *J* = 7.3/1.5 Hz, 1H, 6-*H*), 7.14 (td, *J* = 7.5/1.7 Hz, 1H, 7-*H*), 7.20 (dd, *J* = 7.7/1.5 Hz, 1H, 8-*H*). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) = 23.2 (1C, *C*-3' or *C*-5'), 23.3 (1C, *C*-3' or *C*-5'), 29.1 (1C, C-4$_{isoquinoline}$), 35.2 (1C, *C*-2'), 36.7 (1C, *C*-4), 38.3 (1C, *C*-6'), 46.9 (1C, C-3$_{isoquinoline}$), 50.7 (1C, C-1$_{isoquinoline}$), 55.48 (1C, 6-O*C*H$_3$ or 7-O*C*H$_3$), 55.52 (1C, 6-O*C*H$_3$ or 7-O*C*H$_3$), 61.6 (1C, *C*-4'), 75.6 (1C, *C*-1), 88.2 (1C, *C*-3), 110.2 (1C, C-8$_{isoquinoline}$), 111.8 (1C, C-5$_{isoquinoline}$), 124.6 (1C, *C*-8), 126.1 (1C, *C*-7), 126.2 (1C, *C*-6), 126.3 (1C, C-4a$_{isoquinoline}$), 127.4 (1C, C-8a$_{isoquinoline}$), 129.0 (1C, *C*-5), 132.2 (1C, *C*-4a), 142.0 (1C, *C*-8a), 146.8 (1C, *C*-

$6_{isoquinoline}$ or *C*-$7_{isoquinoline}$), 147.0 (1C, *C*-$6_{isoquinoline}$ or *C*-$7_{isoquinoline}$). FT-IR (neat): ν [cm^{-1}] = 3102 (O-H), 2931, 2939 (C-H_{alkyl}), 1516, 1466 (C=C_{arom}). Purity (HPLC): 97.9 %, t_R = 15.7 min.

7.2.10. Ethyl *trans*-2-{4'-[(2,4-dimethylbenzyl)amino]-3,4-dihydrospiro[[2]benzo-pyran-1,1'-cyclohexan]-3-yl}acetate (11a)

A solution of lactol **10a** (154 mg, 0.44 mmol) and (ethoxycarbonylmethylene)-triphenylphosphorane (308 mg, 0.89 mmol, 2.0 eq) in toluene (25 mL) was heated to reflux under N_2 atmosphere for 5 d. After cooling to rt, the mixture was concentrated in vacuo and the residue was purified by fc (d = 3 cm, l = 20 cm, V = 20 mL, cyclohexane/ethyl acetate 95:5 + 2 % *N*,*N*-dimethylethanamine). Yellow oil, yield 72 mg (39 %). $C_{27}H_{35}NO_3$ (421.6 g/mol). R_f = 0.14 (cyclohexane/ethyl acetate 90:10 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 422.2688 (calcd. 422.2690 for $C_{27}H_{36}NO_3$ [MH^+]). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.30 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.45 – 1.52 (m, 1H, 2'-*H*), 1.55 – 1.70 (m, 2H, 3'-*H,* 5'-*H*), 1.81 – 1.92 (m, 2H, 5'-*H,* 6'-*H*), 1.94 – 2.05 (m, 2H, 3'-*H,* 6'-*H*), 2.28 – 2.38 (m, 1H, 2'-*H*), 2.32 (s, 3H, 4-CH_3), 2.41 (s, 3H, 2-CH_3), 2.56 – 2.68 (m, 2H, CH_2CO_2Et), 2.68 – 2.80 (m, 2H, 4-*H*), 2.96 – 3.00 (m, 1H, 4'-H_{equ}), 3.74 (s, 2H, $ArCH_2NH$), 4.11 – 4.29 (m, 3H, 3-*H*, OCH_2CH_3), 6.98 – 7.06 (m, 3H, 5-*H*, 3-$H_{benzyl,}$ 5-H_{benzyl}), 7.09 – 7.15 (m, 1H, 6-*H*), 7.15 – 7.21 (m, 2H, 7-*H*, 8-*H*), 7.21 – 7.26 (m, 1H, 6-CH_{benzyl}). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 14.4 (1C, OCH_2CH_3), 19.2 (1C, 2-CH_3), 21.1 (1C, 4-CH_3), 26.0 (2C, *C*-3', *C*-5'), 29.3 (1C, *C*-6'), 33.5 (1C, *C*-2'), 35.3 (1C, *C*-4), 41.8 (1C, CH_2CO_2Et), 49.9 (1C, $ArCH_2NH$), 51.5 (1C,

C-4'), 60.7 (1C, O*C*H_2CH$_3$), 65.3 (1C, *C*-3), 76.4 (1C, *C*-1), 125.6 (1C, *C*-8), 126.1 (1C, *C*-6), 126.4 (1C, *C*-7), 126.7 (1C, *C*-5_{benzyl}), 128.7 (1C, *C*-5), 129.1 (1C, *C*-6_{benzyl}), 131.3 (1C, *C*-3_{benzyl}), 132.9 (1C, *C*-4a), 136.3 (1C, *C*-1_{benzyl}) 136.7 (1C, *C*-2_{benzyl}), 136.8 (1C, *C*-4_{benzyl}), 143.1 (1C, *C*-8a), 171.7 (1C, *C*=O). FT-IR (neat): ν [cm^{-1}] = 3063 (N-H), 2955, 2924 (C-H_{alkyl}), 1732 (C=O), 1450, 1369 (C=C_{arom}). Purity (HPLC): 98.1 %, t_R = 21.8 min.

7.2.11. Ethyl *cis*-2-{4'-[(2,4-dimethylbenzyl)amino]-3,4-dihydrospiro[[2]benzo-pyran-1,1'-cyclohexan]-3-yl}acetate (11b)

A solution of lactol **10b** (164 mg, 0.47 mmol) and (ethoxycarbonylmethylene)-triphenylphosphorane (330 mg, 0.95 mmol, 2.0 eq) in toluene (30 mL) was heated to reflux under N_2 atmosphere for 3 d. After cooling to rt, the mixture was concentrated in vacuo and the residue was purified by fc (d = 3 cm, l = 20 cm, V = 20 mL, cyclohexane/ethyl acetate 80:20 + 1 % *N*,*N*-dimethylethanamine). Yellow oil, yield 156 mg (79 %). $C_{27}H_{35}NO_3$ (421.6 g/mol). R_f = 0.18 (cyclohexane/ethyl acetate 80:20 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 422.2690 (calcd. 422.2690 for $C_{27}H_{36}NO_3$ [MH$^+$]). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.54 – 1.60 (m, 2H, 2'-*H*, 3'-*H*), 1.66 – 1.75 (m, 1H, 5'-*H*), 1.77 – 1.93 (m, 4H, 3'-*H*, 5'-*H*, 6'-*H*), 2.21 (dt, *J* = 10.7/2.9 Hz, 1H, 2'-*H*), 2.30 (s, 3H, 4-C*H*$_3$), 2.34 (s, 3H, 2-C*H*$_3$), 2.58 (dd, *J* = 15.0/5.0 Hz, 1H, C*H*$_2$CO$_2$Et), 2.63 – 2.80 (m, 4H, 4-*H*, 4'-*H*$_{ax}$, C*H*$_2$CO$_2$Et), 3.80 (s, 2H, ArC*H*$_2$NH), 4.14 – 4.27 (m, 3H, 3-*H*, OC*H*$_2$CH$_3$), 6.97 – 7.00 (m, 2H, 3-*H*$_{benzyl}$, 5-*H*$_{benzyl}$), 7.06 (dd, *J* = 7.5/1.3 Hz, 1H, 5-*H*), 7.09 (dd, *J* = 7.7/1.4 Hz, 1H, 8-*H*), 7.13 (td, *J* = 7.4/1.4 Hz, 1H, 6-*H*), 7.16 – 7.20 (m, 1H, 7-*H*), 7.21 (d, *J* = 7.9 Hz, 1H, 6-*H*$_{benzyl}$). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 14.4 (1C, OCH$_2$*C*H$_3$), 19.1 (1C, 2-

CH_3), 21.1 (1C, 4-*C*H_3), 28.6 (2C, *C*-3', *C*-5'), 34.3 (1C, *C*-2'), 35.2 (1C, *C*-4), 38.5 (1C, *C*-6'), 41.6 (1C, *C*$H_2$$CO_2$Et), 48.4 (1C, Ar*C*$H_2$NH), 56.4 (1C, *C*-4'), 60.8 (1C, O*C*$H_2$$CH_3$), 65.3 (1C, *C*-3), 75.7 (1C, *C*-1), 125.1 (1C, *C*-8), 126.2 (1C, *C*-6), 126.3 (1C, *C*-7), 126.7 (1C, *C*-5_{benzyl}), 128.7 (1C, *C*-6_{benzyl}), 128.9 (1C, *C*-5), 131.3 (1C, *C*-3_{benzyl}), 133.3 (1C, *C*-4a), 135.6 (1C, *C*-1_{benzyl}), 136.3 (1C, *C*-2_{benzyl}), 136.6 (1C, *C*-4_{benzyl}), 142.3 (1C, *C*-8a), 171.6 (1C, *C*=O). FT-IR (neat): ν [cm^{-1}] = 3063 (N-H), 2924 (C-H_{alkyl}), 1732 (C=O), 1447, 1373 (C=C_{arom}). Purity (HPLC): 95.2 %, t_R = 21.8 min.

7.2.12. Ethyl *trans*-2-{4'-(4-cyclohexylpiperazin-1-yl)-3,4-dihydrospiro[[2]benzo-pyran-1,1'-cyclohexan]-3-yl}acetate (11c)

A solution of lactol **10c** (120 mg, 0.31 mmol) and (ethoxycarbonylmethylene)-triphenylphosphorane (216 mg, 0.62 mmol, 2.0 eq) in toluene (10 mL) was heated to reflux under N_2 atmosphere for 5 d. After cooling to rt, the mixture was concentrated in vacuo and the residue was purified by fc (d = 2.5 cm, l = 20 cm, V = 10 mL, cyclohexane/ethyl acetate 80:20 + 2 % *N*,*N*-dimethylethanamine). Yellow solid, mp 135 °C, yield 73 mg (52 %). $C_{28}H_{42}N_2O_3$ (454.7 g/mol). R_f = 0.18 (cyclohexane/ethyl acetate 80:20 + 2 % *N*,*N*-dimethylethanamine). HR-MS (APCI): m/z = 455.3303 (calcd. 455.3268 for $C_{28}H_{43}N_2O_3$ [MH^+]). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.07 – 1.19 (m, 1H, 4-$H_{cyclohexyl}$), 1.19 – 1.34 (m, 7H, OCH_2CH_3, 2-$H_{cyclohexyl}$, 3-$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 1.38 – 1.45 (m, 1H, 2'-*H*), 1.60 – 1.69 (m, 1H, 4-$H_{cyclohexyl}$), 1.70 – 1.93 (m, 8H, 3'-*H*, 5'-*H*, 6'-*H*, 2-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 1.93 – 2.04 (m, 2H, 3-$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$), 2.16 – 2.23 (m, 2H, 2'-*H*, 4'-H_{eq}), 2.23 – 2.33 (m, 1H, 1-$H_{cyclohexyl}$), 2.47 – 2.79 (m, 12H, 4-*H*, CH_2CO_2Et, $H_{piperazine}$), 4.09 – 4.28 (m, 3H, 3-*H*, OCH_2CH_3), 7.04 (d, *J* = 7.3 Hz, 1H, 5-*H*), 7.09 – 7.15 (m, 1H, 6-*H*), 7.15 – 7.23 (m, 2H, 7-*H*, 8-*H*). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 14.4 (1C, OCH_2CH_3), 23.86

(1C, *C*-3'), 23.91 (1C, *C*-5'), 26.0 (2C, *C*-$2_{cyclohexyl}$, *C*-$6_{cyclohexyl}$), 26.4 (1C, *C*-$4_{cyclohexyl}$), 29.2 (2C, *C*-$3_{cyclohexyl}$, *C*-$5_{cyclohexyl}$), 29.6 (1C, *C*-6'), 34.0 (1C, *C*-2'), 35.3 (1C, CH_2CO_2Et), 41.7 (1C, *C*-4), 49.9 (2C, *C*-$2_{piperazine}$ and *C*-$6_{piperazine}$ or *C*-$3_{piperazine}$ and *C*-$5_{piperazine}$), 50.5 (2C, *C*-$2_{piperazine}$ and *C*-$6_{piperazine}$ or *C*-$3_{piperazine}$ and *C*-$5_{piperazine}$), 57.5 (1C, *C*-4'), 60.7 (1C, OCH_2CH_3), 63.8 (1C, *C*-$1_{cyclohexyl}$), 65.4 (1C, *C*-3), 76.5 (1C, *C*-1), 125.6 (1C, *C*-8), 126.1 (1C, *C*-6), 126.3 (1C, *C*-7), 128.7 (1C, *C*-5), 133.0 (1C, *C*-4a), 143.2 (1C, *C*-8a), 171.7 (1C, *C*=O). FT-IR (neat): ν [cm^{-1}] = 2928, 2805 (C-H_{alkyl}), 1736 (C=O), 1450 (C=C_{arom}). Purity (HPLC): 97.5 %, t_R = 16.8 min.

7.2.13. Ethyl *cis*-2-{4'-(4-cyclohexylpiperazin-1-yl)-3,4-dihydrospiro[[2]benzo-pyran-1,1'-cyclohexan]-3-yl}acetate (11d)

A solution of lactol **10d** (174 mg, 0.45 mmol) and (ethoxycarbonylmethylene)-triphenylphosphorane (326 mg, 0.94 mmol, 2.1 eq) in toluene (20 mL) was heated to reflux under N_2 atmosphere for 4 d. After cooling to rt, the mixture was concentrated in vacuo and the residue was purified twice by fc (d = 3 cm, l = 20 cm, V = 10 mL, cyclohexane/ethyl acetate 66:33 + 2 % *N*,*N*-dimethylethanamine; d = 2 cm, l = 21 cm, V = 10 mL, cyclohexane/ethyl acetate 80:20 + 2 % *N*,*N*-dimethylethanamine). Yellow solid, mp 117 °C, yield 182 mg (89 %). $C_{28}H_{42}N_2O_3$ (454.7 g/mol). R_f = 0.17 (cyclohexane/ethyl acetate 66:33 + 2 % *N*,*N*-dimethylethanamine). HR-MS (APCI): m/z = 455.3256 (calcd. 455.3268 for $C_{28}H_{43}N_2O_3$ [MH^+]). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.05 – 1.15 (m, 1H, 4-$H_{cyclohexyl}$), 1.16 – 1.26 (m, 4H, 2-$H_{cyclohexyl}$, 3-$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 1.28 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.51 – 1.58 (m, 1H, 2'-*H*), 1.59 – 1.65 (m, 1H, 4-$H_{cyclohexyl}$), 1.65 – 1.75 (m, 3H, 3'-*H*, 5'-*H*), 1.75 – 1.88 (m, 5H, 5'-*H*, 6'-*H*, 2-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 1.88 – 1.95 (m, 2H, 3-$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$), 2.20 – 2.28 (m, 2H, 2'-*H*, 1-$H_{cyclohexyl}$), 2.38 – 2.47 (m, 1H, 4'-H_{ax}), 2.57 (dd,

J = 15.0/4.7 Hz, 1H, C*H*$_2$CO$_2$Et), 2.60 – 2.70 (m, 9H, C*H*$_2$CO$_2$Et, *H*$_{piperazine}$), 2.70 – 2.77 (m, 2H, 4-*H*), 4.12 – 4.25 (m, 3H, 3-*H*, OC*H*$_2$CH$_3$), 7.05 (d, *J* = 7.5 Hz, 1H, 5-*H*), 7.09 (d, *J* = 7.7 Hz, 1H, 8-*H*), 7.12 (td, *J* = 7.4/1.4 Hz, 1H, 6-*H*), 7.17 (t, *J* = 7.7 Hz, 1H, 7-*H*). ^{13}C NMR (151 MHz, CDCl$_3$): δ (ppm) = 14.4 (1C, OCH$_2$*C*H$_3$), 23.7 (1C, *C*-5'), 23.8 (1C, *C*-3'), 26.1 (2C, *C*-2$_{cyclohexyl}$, *C*-6$_{cyclohexyl}$), 26.4 (1C, *C*-4$_{cyclohexyl}$), 29.1 (2C, *C*-3$_{cyclohexyl}$, *C*-5$_{cyclohexyl}$), 34.9 (1C, *C*-2'), 35.2 (1C, *C*-4), 39.1 (1C, *C*-6'), 41.6 (1C, *C*H$_2$CO$_2$Et), 49.4 (2C, *C*-2$_{piperazine}$ and *C*-6$_{piperazine}$ or *C*-3$_{piperazine}$ and *C*-5$_{piperazine}$), 49.5 (2C, *C*-2$_{piperazine}$ and *C*-6$_{piperazine}$ or *C*-3$_{piperazine}$ and *C*-5$_{piperazine}$), 60.7 (1C, OC*H*$_2$CH$_3$), 63.2 (1C, *C*-4'), 63.8 (1C, *C*-1$_{cyclohexyl}$), 65.3 (1C, *C*-3), 75.6 (1C, *C*-1), 125.1 (1C, *C*-8), 126.2 (1C, *C*-6), 126.3 (1C, *C*-7), 128.9 (1C, *C*-5), 133.2 (1C, *C*-4a), 142.2 (1C, *C*-8a), 171.5 (1C, C=O). FT-IR (neat): ν [cm^{-1}] = 2978, 2928, 2855 (C-H$_{alkyl}$), 1728 (C=O), 1450 (C=C$_{arom}$). Purity (HPLC): 97.2 %, t_R = 16.4 min.

7.2.14. Ethyl *trans*-2-{4'-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-3-yl}acetate (11e)

A solution of lactol **10e** (160 mg, 0.39 mmol) and (ethoxycarbonylmethylene)-triphenylphosphorane (272 mg, 0.78 mmol, 2.0 eq) in toluene (12 mL) was heated to reflux under N_2 atmosphere for 4 d. After cooling to rt, the mixture was concentrated in vacuo and the residue was purified by fc (d = 3 cm, l = 19 cm, V = 20 mL, cyclohexane/ethyl acetate 90:10 + 1 % *N*,*N*-dimethylethanamine). Yellow oil, yield 175 mg (94 %). $C_{29}H_{37}NO_5$ (479.6 g/mol). R_f = 0.31 (cyclohexane/ethyl acetate 80:20 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 480.2755 (calcd. 480.2744 for $C_{29}H_{38}NO_5$ [MH$^+$]). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) = 1.31 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 1.43 – 1.51 (m, 1H, 2'-*H*), 1.76 – 2.04 (m, 6H, 3'-*H*, 5'-*H*, 6'-*H*), 2.30 (dt, *J* = 14.0/8.7 Hz, 1H, 2'-*H*), 2.36 – 2.41 (m, 1H, 4'-*H*$_{equ}$), 2.56 – 2.68 (m, 2H,

CH_2CO_2Et), 2.69 – 2.76 (m, 2H, 4-*H*), 2.76 – 2.81 (m, 2H, 3-$H_{isoquinoline}$), 2.82 – 2.90 (m, 2H, 4-$H_{isoquinoline}$), 3.66 (s, 2H, 1-$H_{isoquinoline}$), 3.86 (s, 3H, 7-OCH_3), 3.88 (s, 3H, 6-OCH_3), 4.11 – 4.23 (m, 2H, OCH_2CH_3), 4.23 – 4.31 (m, 1H, 3-*H*), 6.59 (s, 1H, 8-$H_{isoquinoline}$), 6.65 (s, 1H, 5-$H_{isoquinoline}$), 7.03 (d, *J* = 6.7 Hz, 1H, 5-*H*), 7.07 – 7.17 (m, 3H, 6-*H*, 7-*H*, 8-*H*). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 14.5 (1C, OCH_2CH_3), 24.3 (2C, *C*-3', *C*-5'), 29.4 (1C, *C*-$4_{isoquinoline}$), 29.6 (1C, *C*-6'), 34.0 (1C, *C*-2'), 35.3 (1C, *C*-4), 41.8 (1C, CH_2CO_2Et), 47.5 (1C, *C*-$3_{isoquinoline}$), 53.5 (1C, *C*-$1_{isoquinoline}$), 56.1 (2C, 6-OCH_3, 7-OCH_3), 57.2 (1C, *C*-4'), 60.7 (1C, OCH_2CH_3), 65.4 (1C, *C*-3), 76.6 (1C, *C*-1), 109.9 (1C, *C*-$8_{isoquinoline}$), 111.3 (1C, *C*-$5_{isoquinoline}$), 125.8 (1C, *C*-6 or *C*-8), 126.1 (1C, *C*-6 or *C*-8), 126.3 (1C, *C*-7), 127.1 (1C, *C*-$4a_{isoquinoline}$), 127.8 (1C, *C*-$8a_{isoquinoline}$), 128.6 (1C, *C*-5), 132.9 (1C, *C*-4a), 143.0 (1C, *C*-8a), 147.4 (1C, *C*-$7_{isoquinoline}$), 147.5 (1C, *C*-$6_{isoquinoline}$), 171.7 (1C, *C*=O). FT-IR (neat): ν [cm^{-1}] = 2967, 2920 (C-H_{alkyl}), 1736 (C=O), 1520, 1454 (C=C_{arom}). Purity (HPLC): 98.4 %, t_R = 20.0 min.

7.2.15. Ethyl *cis*-2-{4'-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-3-yl}acetate (11f)

A solution of lactol **10f** (175 mg, 0.43 mmol) and (ethoxycarbonylmethylene)-triphenylphosphorane (305 mg, 0.88 mmol, 2.1 eq) in toluene (12 mL) was heated to reflux under N_2 atmosphere for 5 d. After cooling to rt, the mixture was concentrated in vacuo and the residue was purified by fc (d = 3 cm, l = 19 cm, V = 20 mL, cyclohexane/ethyl acetate 80:20 + 1 % *N*,*N*-dimethylethanamine). Yellow oil, yield 157 mg (77 %). $C_{29}H_{37}NO_5$ (479.6 g/mol). R_f = 0.09 (cyclohexane/ethyl acetate 80:20 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 480.2752 (calcd. 480.2744 for $C_{29}H_{38}NO_5$ [MH^+]). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.31 (t, *J* = 7.1 Hz, 3H,

OCH_2CH_3), 1.55 – 1.65 (m, 1H, 2'-H_{ax}), 1.73 – 1.99 (m, 6H, 3'-*H*, 5'-*H*, 6'-*H*), 2.28 (dq, *J* = 14.2/3.1 Hz, 1H, 2'-H_{equ}), 2.61 (dd, *J* = 15.1/4.6 Hz, 1H, CH_2CO_2Et), 2.65 – 2.79 (m, 4H, 4-*H*, 4'-H_{ax}, CH_2CO_2Et), 2.79 – 2.92 (m, 4H, 3-$H_{isoquinoline}$, 4-$H_{isoquinoline}$), 3.77 (s, 2H, 1-$H_{isoquinoline}$), 3.84 (s, 3H, 6-OCH_3 or 7-OCH_3), 3.84 (s, 3H, 6-OCH_3 or 7-OCH_3), 4.16 – 4.23 (m, 2H, OCH_2CH_3), 4.23 – 4.31 (m, 1H, 3-*H*), 6.53 (s, 1H, 8-$H_{isoquinoline}$), 6.59 (s, 1H, 5-$H_{isoquinoline}$), 7.07 (d, *J* = 7.1 Hz, 1H, 5-*H*), 7.10 – 7.13 (m, 1H, 8-*H*), 7.13 – 7.16 (m, 1H, 6-*H*), 7.16 – 7.22 (m, 1H, 7-*H*). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 14.4 (1C, OCH_2CH_3), 23.3 (1C, *C*-3' or *C*-5'), 23.6 (1C, *C*-3' or *C*-5'), 29.4 (1C, *C*-$4_{isoquinoline}$), 34.9 (1C, *C*-2'), 35.2 (1C, *C*-4), 39.1 (1C, *C*-6'), 41.7 (1C, CH_2CO_2Et), 46.9 (1C, *C*-$3_{isoquinoline}$), 51.4 (1C, *C*-$1_{isoquinoline}$), 56.06 (1C, 6-OCH_3 or 7-OCH_3), 56.08 (1C, 6-OCH_3 or 7-OCH_3), 60.7 (1C, OCH_2CH_3), 62.7 (1C, *C*-4'), 65.3 (1C, *C*-3), 75.6 (1C, *C*-1), 109.8 (1C, *C*-$8_{isoquinoline}$), 111.6 (1C, *C*-$5_{isoquinoline}$), 125.1 (1C, *C*-8), 126.3 (1C, *C*-6), 126.4 (1C, *C*-7), 126.7 (1C, *C*-$4a_{isoquinoline}$), 127.3 (1C, *C*-$8a_{isoquinoline}$), 128.9 (1C, *C*-5), 133.2 (1C, *C*-4a), 142.1 (1C, *C*-8a), 147.3 (1C, *C*-$7_{isoquinoline}$), 147.6 (1C, *C*-$6_{isoquinoline}$), 171.6 (1C, *C*=O). FT-IR (neat): ν [cm^{-1}] = 2928 (C-H_{alkyl}), 1732 (C=O), 1516, 1450 (C=C_{arom}). Purity (HPLC): 96.0 %, t_R = 20.1 min.

7.2.16. *trans*-2-{4'-[(2,4-Dimethylbenzyl)amino]-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-3-yl}ethanol (12a)

A solution of $LiAlH_4$ (22 mg, 0.59 mmol, 3.1 eq) in THF (5 mL) was added slowly to a solution of ester **11a** (82 mg, 0.19 mmol) in Et_2O (10 mL) at -20 °C under N_2 atmosphere. After stirring for 4 h, H_2O (10 mL) was added, the precipitate was filtered off and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 1.5 cm, l = 18 cm, V = 5 mL, cyclohexane/ethyl

acetate 90:10 + 1 % *N*,*N*-dimethylethanamine → 70:30 + 1 % *N*,*N*-dimethylethanamine). Yellow oil, yield 58 mg (79 %). $C_{25}H_{33}NO_2$ (379.5 g/mol). R_f = 0.11 (cyclohexane/ethyl acetate 80:20 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 380.2568 (calcd. 380.2584 for $C_{25}H_{34}NO_2$ [MH^+]). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.49 – 1.56 (m, 1H, 2'-*H*), 1.64 – 1.78 (m, 2H, 3'-*H*, 5'-*H*), 1.85 – 1.98 (m, 5H, 3'-*H*, 5'-*H*, 6'-*H*, CH_2CH_2OH), 2.00 – 2.10 (m, 1H, 6'-*H*), 2.32 (s, 3H, 4-CH_3), 2.34 – 2.44 (m, 1H, 2'-*H*), 2.41 (s, 3H, 4-CH_3), 2.61 (dd, *J* = 15.8/2.7 Hz, 1H, 4-*H*), 2.84 (dd, *J* = 15.7/11.4 Hz, 1H, 4-*H*), 3.01 – 3.10 (m, 1H, 4'-H_{eq}), 3.75 (s, 2H, ArCH_2NH), 3.86 – 3.93 (m, 2H, CH$_2$CH_2OH), 4.00 – 4.06 (m, 1H, 3-*H*), 6.99 – 7.03 (m, 2H, 3-H_{benzyl}, 5-H_{benzyl}), 7.05 (d, *J* = 7.6 Hz, 1H, 5-*H*), 7.11 – 7.15 (m, 1H, 6-*H*), 7.15 – 7.20 (m, 2H, 7-*H*, 8-*H*), 7.22 – 7.26 (m, 1H, 6-H_{benzyl}). Signals for the NH and OH protons are not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 19.2 (1C, 2-CH_3), 21.2 (1C, 4-CH_3), 26.3 (2C, *C*-3', *C*-5'), 29.3 (1C, *C*-6'), 33.4 (1C, *C*-2'), 35.5 (1C, *C*-4), 38.0 (1C, CH_2CH$_2$OH), 49.9 (1C, ArCH_2NH), 51.2 (1C, *C*-4'), 61.5 (1C, CH$_2$CH_2OH), 68.5 (1C, *C*-3), 76.7 (1C, *C*-1), 125.7 (1C, *C*-8), 126.2 (1C, *C*-6), 126.3 (1C, *C*-7), 126.7 (1C, *C*-5$_{benzyl}$), 128.7 (1C, *C*-5), 129.1 (1C, *C*-6$_{benzyl}$), 131.3 (1C, *C*-3$_{benzyl}$), 133.0 (1C, *C*-4a), 136.1 (1C, *C*-1$_{benzyl}$), 136.7 (1C, *C*-2$_{benzyl}$), 136.9 (1C, *C*-4$_{benzyl}$), 142.8 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 3426 (O-H/N-H), 2920 (C-H_{alkyl}), 1435, 1373 (C=C_{arom}), 1061 (C-O). Purity (HPLC): 98.2 %, t_R = 18.3 min.

7.2.17. *cis*-2-{4'-[(2,4-Dimethylbenzyl)amino]-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-3-yl}ethanol (12b)

$LiAlH_4$ (55 mg, 1.44 mmol, 2.9 eq) was added slowly to a solution of ester **11b** (211 mg, 0.50 mmol) in Et_2O (10 mL) at -20 °C under N_2 atmosphere. After stirring for 2 h, H_2O (10 mL) was added, the precipitate was filtered off and the aqueous layer

was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 3 cm, l = 16 cm, V = 20 mL, cyclohexane/ethyl acetate 10:20 + 1 % *N*,*N*-dimethylethanamine → ethyl acetate + 1 % *N*,*N*-dimethylethanamine). Pale yellow solid, mp 89 °C, yield 157 mg (82 %). $C_{25}H_{33}NO_2$ (379.5 g/mol). R_f = 0.06 (cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 380.2568 (calcd. 380.2568 for $C_{25}H_{34}NO_2$ [MH^+]). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.53 – 1.66 (m, 3H, 2'-*H*, 3'-*H*, 5'-*H*), 1.80 – 1.85 (m, 1H, 6'-*H*), 1.85 – 1.99 (m, 5H, 3'-*H*, 5'-*H*, 6'-*H*, CH_2CH$_2$OH), 2.20 (dt, *J* = 10.8/3.0 Hz, 1H, 2'-*H*), 2.30 (s, 3H, 4-CH_3), 2.34 (s, 3H, 2-CH_3), 2.63 (dd, *J* = 15.9/2.7 Hz, 1H, 4-*H*), 2.65 – 2.71 (m, 1H, 4'-H_{ax}), 2.82 (dd, *J* = 15.9/11.1 Hz, 1H, 4-*H*), 3.81 (s, 2H, ArCH_2NH), 3.86 – 3.95 (m, 2H, CH$_2$CH_2OH), 4.01 (ddt, *J* = 11.4/8.6/3.1 Hz, 1H, 3-*H*), 6.97 – 7.01 (m, 2H, 3-H_{benzyl}, 5-H_{benzyl}), 7.05 – 7.11 (m, 2H, 5-*H*, 8-*H*), 7.14 (td, *J* = 7.4/1.5 Hz, 1H, 6-*H*), 7.17 (t, *J* = 7.5 Hz, 1H, 7-*H*), 7.21 (d, *J* = 8.2 Hz, 1H, 6-H_{benzyl}). Signals for the NH and OH protons are not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 19.1 (1C, 2-*C*H$_3$), 21.1 (1C, 4-*C*H$_3$), 29.0 (1C, C-3' or C-5'), 29.1 (1C, C-3' or C-5'), 34.4 (1C, *C*-2'), 35.5 (1C, *C*-4), 38.1 (1C, *C*H$_2$CH$_2$OH), 38.4 (1C, *C*-6'), 48.4 (1C, Ar*C*H$_2$NH), 56.0 (1C, *C*-4'), 60.8 (1C, CH$_2$*C*H$_2$OH), 67.6 (1C, *C*-3), 75.8 (1C, *C*-1), 125.1 (1C, *C*-8), 126.26 (1C, *C*-6 or *C*-7), 126.27 (1C, *C*-6 or *C*-7), 126.7 (1C, *C*-5$_{benzyl}$), 128.6 (1C, *C*-6$_{benzyl}$), 128.9 (1C; *C*-5), 131.3 (1C, *C*-3$_{benzyl}$), 133.5 (1C, *C*-4a), 135.6 (1C, *C*-1$_{benzyl}$), 136.3 (1C, *C*-2$_{benzyl}$), 136.6 (1C, *C*-4$_{benzyl}$), 142.1 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 3364 (O-H/N-H), 2924 (C-H_{alkyl}), 1454 (C=C_{arom}), 1061 (C-O). Purity (HPLC): 99.8 %, t_R = 18.7 min.

7.2.18. *trans*-2-{4'-(4-Cyclohexylpiperazin-1-yl)-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-3-yl}ethanol (12c)

A solution of $LiAlH_4$ (15 mg, 0.38 mmol, 2.9 eq) in THF (2 mL) was added slowly to a solution of ester **11c** (60 mg, 0.13 mmol) in Et_2O (5 mL) at -20 °C under N_2 atmosphere. After stirring for 5 h, H_2O (8 mL) was added, the precipitate was filtered off and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 1.5 cm, l = 18 cm, V = 10 mL, cyclohexane/ethyl acetate 50:50 + 2 % *N*,*N*-dimethylethanamine). Colorless solid, mp 185 °C, yield 45 mg (85 %). $C_{26}H_{40}N_2O_2$ (412.6 g/mol). R_f = 0.11 (cyclohexane/ethyl acetate 50:50 + 2 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 413.3154 (calcd. 413.3163 for $C_{26}H_{41}N_2O_2$ [MH^+]). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.08 – 1.18 (m, 1H, 4-$H_{cyclohexyl}$), 1.19 – 1.31 (m, 4H, 2-$H_{cyclohexyl}$, 3-$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 1.45 (dq, *J* = 13.3/3.0 Hz, 1H, 2'-H_{equ}), 1.61 – 1.68 (m, 1H, 4-$H_{cyclohexyl}$), 1.70 – 1.78 (m, 2H, 3'-*H*, 5'-*H*), 1.78 – 1.86 (m, 3H, 6'-*H*, 2-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 1.86 – 2.02 (m, 7H, CH_2CH$_2$OH, 3'-*H*, 5'-*H*, 6'-*H*, 3-$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$), 2.20 – 2.31 (m, 3H, 2'-H_{ax}, 4'-H_{equ}, 1-$H_{cyclohexyl}$), 2.40 – 2.77 (broad signal, 8H, 4-*H*, $H_{piperazine}$), 2.83 (dd, *J* = 15.8/11.1 Hz, 1H, 4-*H*), 2.86 – 2.93 (broad signal, 1H, $H_{piperazine}$) 3.86 – 3.93 (m, 2H, CH$_2$CH_2OH), 4.02 (ddt, *J* = 11.6/8.6/3.1 Hz, 1H, 3-*H*), 7.04 (d, *J* = 7.5 Hz, 1H, 5-*H*), 7.13 (td, *J* = 7.2/1.7 Hz, 1H, 6-*H*), 7.15 – 7.22 (m, 2H, 7-*H*, 8-*H*). A signal for the OH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 24.2 (1C, *C*-3' or *C*-5'), 24.3 (1C, *C*-3' or *C*-5'), 26.0 (2C, *C*-$2_{cyclohexyl}$, *C*-$6_{cyclohexyl}$), 26.4 (1C, *C*-$4_{cyclohexyl}$), 29.2 (2C, *C*-$3_{cyclohexyl}$, *C*-$5_{cyclohexyl}$), 29.7 (1C, *C*-6'), 34.0 (1C, *C*-2'), 35.6 (1C, *C*-4), 38.0 (1C, *C*H$_2$CH$_2$OH), 49.9 (2C, *C*-$2_{piperazine}$ and *C*-$6_{piperazine}$ or *C*-$3_{piperazine}$ and *C*-$5_{piperazine}$), 50.5 (2C, *C*-$2_{piperazine}$ and *C*-$6_{piperazine}$ or *C*-$3_{piperazine}$ and *C*-

$5_{piperazine}$), 57.3 (1C, *C*-4'), 61.4 (1C, CH_2CH_2OH), 63.7 (1C, *C*-$1_{cyclohexyl}$), 68.4 (1C, *C*-3), 76.8 (1C, *C*-1), 125.6 (1C, *C*-8), 126.1 (1C, *C*-6), 126.3 (1C, *C*-7), 128.6 (1C, *C*-5), 133.2 (1C, *C*-4a), 143.0 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 3198 (O-H), 2978, 2932, 2816 (C-H_{alkyl}), 1450 (C=C_{arom}). Purity (HPLC, method 1): 99.5 %, t_R = 14.0 min.

7.2.19. *cis*-2-{4'-(4-Cyclohexylpiperazin-1-yl)-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-3-yl}ethanol (12d)

A solution of $LiAlH_4$ (30 mg, 0.79 mmol, 2.8 eq) in THF (2 mL) was added slowly to a solution of ester **11d** (125 mg, 0.28 mmol) in Et_2O (6 mL) at -20 °C under N_2 atmosphere. After stirring for 4 h, H_2O (15 mL) was added, the precipitate was filtered off and the aqueous layer was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified twice by fc (d = 2 cm, l = 17 cm, V = 10 mL, cyclohexane/ethyl acetate 33:66 + 2 % *N*,*N*-dimethylethanamine → ethyl acetate + 2 % *N*,*N*-dimethylethanamine; d = 1.5 cm, l = 10 cm, V = 3 mL, cyclohexane/ethyl acetate 66:33 + 2 % *N*,*N*-dimethylethanamine → 33:66 + 2 % *N*,*N*-dimethylethanamine). Colorless solid, mp 128 °C, yield 94 mg (82 %). $C_{26}H_{40}N_2O_2$ (412.6 g/mol). R_f = 0.08 (cyclohexane/ethyl acetate 33:66 + 2 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 413.3137 (calcd. 413.3163 for $C_{26}H_{41}N_2O_2$ [MH^+]). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.04 – 1.16 (m, 1H, 4-$H_{cyclohexyl}$), 1.17 – 1.31 (m, 4H, 2-$H_{cyclohexyl}$, 3-$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 1.53 – 1.68 (m, 2H, 2'-*H*, 4-$H_{cyclohexyl}$), 1.67 – 1.85 (m, 6H, 3'-*H*, 5'-*H*, 2-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 1.85 – 1.98 (m, 6H, C$H_2$$CH_2$OH, 6'-*H*, 3-

$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$), 2.19 – 2.30 (m, 2H, 2'-*H*, 1-$H_{cyclohexyl}$), 2.48 (tt, *J* = 11.3/3.8 Hz, 1H, 4'-H_{ax}), 2.62 (dd, *J* = 16.0/2.8 Hz, 1H, 4-*H*), 2.65 – 2.76 (broad signal, 8H, $H_{piperazine}$), 2.81 (dd, *J* = 15.9/11.1 Hz, 1H, 4-*H*), 3.87 – 3.92 (m, 2H, CH_2CH_2OH), 3.96 – 4.05 (m, 1H, 3-*H*), 7.05 (d, *J* = 6.8 Hz, 1H, 5-*H*), 7.09 (dd, *J* = 7.3/1.8 Hz, 1H, 8-*H*), 7.11 – 7.20 (m, 2H, 6-*H*, 7-*H*). A signal for the OH proton is not observed in the spectrum. ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 23.8 (1C, *C*-3' or *C*-5'), 23.8 (1C, *C*-3' or *C*-5'), 26.0 (2C, *C*-$2_{cyclohexyl}$, *C*-$6_{cyclohexyl}$), 26.4 (1C, *C*-$4_{cyclohexyl}$), 29.06 (1C, *C*-$3_{cyclohexyl}$ or *C*-$5_{cyclohexyl}$), 29.07 (1C, *C*-$3_{cyclohexyl}$ or *C*-$5_{cyclohexyl}$), 34.9 (1C, *C*-2'), 35.5 (1C, *C*-4), 38.1 (1C, CH_2CH_2OH), 38.8 (1C, *C*-6'), 49.3 (2C, *C*-$2_{piperazine}$ and *C*-$6_{piperazine}$ or *C*-$3_{piperazine}$ and *C*-$5_{piperazine}$), 49.4 (2C, *C*-$2_{piperazine}$ and *C*-$6_{piperazine}$ or *C*-$3_{piperazine}$ and *C*-$5_{piperazine}$), 61.1 (1C, CH_2CH_2OH), 63.0 (1C, *C*-4'), 63.8 (1C, *C*-$1_{cyclohexyl}$), 68.1 (1C, *C*-3), 75.8 (1C, *C*-1), 125.1 (1C, *C*-8), 126.30 (1C, *C*-6 or *C*-7), 126.32 (1C, *C*-6 or *C*-7), 128.9 (1C, *C*-5), 133.4 (1C, *C*-4a), 141.9 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 3225 (O-H), 2970, 2928, 2851 (C-H_{alkyl}), 1447 (C=C_{arom}). Purity (HPLC, method 1): 99.2 %, t_R = 13.5 min.

7.2.20. *trans*-2-{4'-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-3-yl}ethanol (12e)

$LiAlH_4$ (36 mg, 0.93 mmol, 2.7 eq) was added slowly to a solution of ester **11e** (163 mg, 0.34 mmol) in Et_2O (9 mL) at -20 °C under N_2 atmosphere. After stirring for 3 h, H_2O (10 mL) was added, the precipitate was filtered off and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 3 cm, l = 17 cm, V = 20 mL, cyclohexane/ethyl acetate 66:33 + 1 % *N*,*N*-dimethyl-ethanamine). Pale yellow solid, mp 160 °C, yield 105 mg (71 %). $C_{27}H_{35}NO_4$

(437.6 g/mol). R_f = 0.23 (cyclohexane/ethyl acetate 66:33 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 438.2686 (calcd. 438.2639 for $C_{27}H_{36}NO_4$ [MH^+]). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.48 – 1.55 (m, 1H, 2'-*H*), 1.80 – 2.09 (m, 8H, 3'-*H*, 5'-*H*, 6'-*H*, CH_2CH_2OH), 2.28 – 2.38 (m, 1H, 2'-*H*), 2.40 – 2.52 (m, 1H, 4'-H_{equ}), 2.62 (dd, *J* = 15.9/2.6 Hz, 1H, 4-*H*), 2.75 – 2.93 (m, 5H, 4-*H*, 3-$H_{isoquinoline}$, 4-$H_{isoquinoline}$), 3.62 – 3.72 (m, 2H, 1-$H_{isoquinoline}$), 3.86 (s, 3H, 7-OCH_3), 3.88 (s, 3H, 6-OCH_3), 3.89 – 3.95 (m, 2H, CH_2CH_2OH), 4.04 (ddt, *J* = 11.0/8.2/2.9 Hz, 1H, 3-*H*), 6.59 (s, 1H, 8-$H_{isoquinoline}$), 6.65 (s, 1H, 5-$H_{isoquinoline}$), 7.03 (d, *J* = 7.7 Hz, 1H, 5-*H*), 7.09 – 7.17 (m, 3H, 6-*H*, 7-*H*, 8-*H*). A signal for the OH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 24.6 (2C, *C*-3', *C*-5'), 29.4 (1C, *C*-$4_{isoquinoline}$), 29.7 (1C, *C*-6'), 33.9 (1C, *C*-2'), 35.6 (1C, *C*-4), 38.0 (1C, *C*H_2CH_2OH), 47.4 (1C, *C*-$3_{isoquinoline}$), 53.5 (1C, *C*-$1_{isoquinoline}$), 56.1 (2C, 6-OCH_3, 7-OCH_3), 57.0 (1C, *C*-4'), 61.4 (1C, CH_2CH_2OH), 68.5 (1C, *C*-3), 76.9 (1C, *C*-1), 109.9 (1C, *C*-$8_{isoquinoline}$), 111.3 (1C, *C*-$5_{isoquinoline}$), 125.9 (1C, *C*-6 or *C*-8), 126.2 (1C, *C*-6 or *C*-8), 126.3 (1C, *C*-7), 127.0 (1C, *C*-$4a_{isoquinoline}$), 127.6 (1C, *C*-$8a_{isoquinoline}$), 128.5 (1C, *C*-5), 133.0 (1C, *C*-4a), 142.7 (1C, *C*-8a), 147.4 (1C, *C*-$7_{isoquinoline}$), 147.6 (1C, *C*-$6_{isoquinoline}$). FT-IR (neat): ν [cm^{-1}] = 3437 (O-H), 2920 (C-H_{alkyl}), 1516, 1450 (C=C_{arom}). Purity (HPLC): 96.1 %, t_R = 16.4 min.

7.2.21. *cis*-2-{4'-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-3,4-dihydro-spiro[[2]benzopyran-1,1'-cyclohexan]-3-yl}ethanol (12f)

A solution of $LiAlH_4$ (32 mg, 0.85 mmol, 2.9 eq) in THF (5 mL) was added slowly to a solution of ester **11f** (137 mg, 0.29 mmol) in Et_2O (9 mL) at -20 °C under N_2 atmosphere. After stirring for 3.5 h, H_2O (10 mL) was added, the precipitate was filtered off and the aqueous layer was extracted with ethyl acetate (4 x 10 mL). The

combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 2 cm, l = 18 cm, V = 10 mL, cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine → ethyl acetate + 1 % *N*,*N*-dimethylethanamine). Yellow solid, mp 148 °C, yield 88 mg (69 %). $C_{27}H_{35}NO_4$ (437.6 g/mol). R_f = 0.06 (cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 438.2673 (calcd. 438.2639 for $C_{27}H_{36}NO_4$ [MH^+]). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.60 – 1.70 (m, 1H, 2'-*H*), 1.81 – 1.90 (m, 4H, 3'-*H*, 5'-*H*), 1.90 – 2.03 (m, 4H, 6'-*H*, C*H*$_2$CH$_2$OH), 2.25 – 2.33 (m, 1H, 2'-*H*), 2.64 (dd, *J* = 15.9/2.6 Hz, 1H, 4-*H*), 2.70 – 2.79 (m, 2H, 4'-H_{ax}), 2.80 – 2.97 (m, 5H, 4-*H*, 3-$H_{isoquinoline}$, 4-$H_{isoquinoline}$), 3.81 (s, 2H, 1-$H_{isoquinoline}$), 3.84 (s, 6H, 6-OC*H*$_3$, 7-OC*H*$_3$), 3.90 – 4.00 (m, 2H, CH$_2$C*H*$_2$OH), 4.00 – 4.09 (m, 1H, 3-*H*), 6.55 (s, 1H, 8-$H_{isoquinoline}$), 6.60 (s, 1H, 5-$H_{isoquinoline}$), 7.07 (d, *J* = 7.3 Hz, 1H 5-*H*), 7.10 – 7.22 (m, 3H, 6-*H*, 7-*H*, 8-*H*). A signal for the OH proton is not observed in the spectrum. ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 23.7 (1C, *C*-5'), 23.8 (1C, *C*-3'), 29.4 (1C, *C*-4$_{isoquinoline}$), 35.0 (1C, *C*-2'), 35.5 (1C, *C*-4), 38.1 (1C, *C*H$_2$CH$_2$OH), 39.0 (1C, *C*-6'), 46.9 (1C, *C*-3$_{isoquinoline}$), 51.5 (1C, *C*-1$_{isoquinoline}$), 56.06 (1C, 6-O*C*H$_3$ or 7-O*C*H$_3$), 56.14 (1C, 6-O*C*H$_3$ or 7-O*C*H$_3$), 61.2 (1C, CH$_2$*C*H$_2$OH), 62.7 (1C, *C*-4'), 68.3 (1C, *C*-3), 75.9 (1C, *C*-1), 109.8 (1C, *C*-8$_{isoquinoline}$), 111.6 (1C, *C*-5$_{isoquinoline}$), 125.1 (1C, *C*-8), 126.3 (1C, *C*-6 or *C*-7), 126.4 (1C, *C*-6 or *C*-7), 126.6 (1C, *C*-4a$_{isoquinoline}$), 127.0 (1C, *C*-8a$_{isoquinoline}$), 128.9 (1C, *C*-5), 133.4 (1C, *C*-4a), 141.8 (1C; *C*-8a), 147.4 (1C, *C*-7$_{isoquinoline}$), 147.6 (1C, *C*-6$_{isoquinoline}$). FT-IR (neat): ν [cm^{-1}] = 3179 (O-H), 2943, 2920, 2851 (C-H_{alkyl}), 1516, 1443 (C=C_{arom}). Purity (HPLC): 96.3 %, t_R = 16.7 min.

7.2.22. *trans*-N-(2,4-Dimethylbenzyl)-3-(2-fluoroethyl)-3,4-dihydrospiro[[2]benzo-pyran-1,1'-cyclohexan]-4'-amine (13a)

A solution of alcohol **12a** (36 mg, 0.09 mmol) in CH_2Cl_2 (4 mL) was added dropwise to a solution of DAST (0.03 mL, 0.23 mmol, 2.6 eq) in CH_2Cl_2 (5 mL) under N_2 atmosphere at -78 °C. After 90 min, the mixture was warmed to rt and stirred for 20 h. 1 M NaOH (3 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 1 cm, l = 18 cm, V = 5 mL, cyclohexane/ethyl acetate 90:10 + 1 % *N*,*N*-dimethylethanamine → 80:20 + 1 % *N*,*N*-dimethylethanamine). Pale yellow solid, mp 67 °C, yield 24 mg (67 %). $C_{25}H_{32}FNO$ (381.5 g/mol). R_f = 0.56 (cyclohexane/ethyl acetate 80:20 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 382.2541 (calcd. 382.2541 for $C_{25}H_{33}FNO_2$ [MH^+]). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.50 (dq, *J* = 13.4/3.0 Hz, 1H, 2'-*H*), 1.60 – 1.72 (m, 2H, 3'-*H*, 5'-*H*), 1.81 – 1.94 (m, 3H, 5'-*H*, 6'-*H*, CH_2CH_2F), 1.94 – 2.18 (m, 3H, 3'-*H*, 6'-*H*, CH_2CH_2F), 2.31 – 2.41 (m, 1H, 2'-*H*), 2.33 (s, 3H, 4-CH_3), 2.43 (s, 3H, 2-CH_3), 2.66 (dd, *J* = 15.8/3.1 Hz, 1H, 4-*H*), 2.75 (dd, *J* = 15.8/10.7 Hz, 1H, 4-*H*), 3.02 (quint, *J* = 3.0 Hz, 1H, 4'-H_{equ}), 3.75 (s, 2H, ArCH_2NH), 3.97 (ddt, *J* = 10.6/9.3/3.3 Hz, 1H, 3-*H*), 4.60 (ddd, *J* = 9.0/5.7/4.3 Hz, 0.5H, CH_2CH_2F), 4.72 (m, 2 x 0.5H, CH_2CH_2F), 4.84 (td, *J* = 9.0/4.5 Hz, 0.5H, CH_2CH_2F), 6.99 – 7.04 (m, 2H, 3-H_{benzyl}, 5-H_{benzyl}), 7.06 (m, 1H, 5-*H*), 7.10 – 7.16 (m, 1H, 6-*H*), 7.16 – 7.20 (m, 2H, 7-*H*, 8-*H*), 7.24 (d, *J* = 7.5 Hz, 1H, 6-H_{benzyl}). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 19.1 (1C, 2-CH_3), 21.2 (1C, 4-CH_3), 26.1 (1C, *C*-3'), 26.3 (1C, *C*-5'), 29.3 (1C, *C*-6'), 33.6 (1C, *C*-2'), 35.8 (1C, *C*-4), 37.1 (d, *J* = 19.4 Hz, 1C, *C*H_2CH_2F), 49.9 (1C, Ar*C*H_2NH), 51.4 (1C, *C*-4'), 63.7 (d, *J* = 5.0 Hz, 1C, *C*-3), 76.1 (1C, *C*-1), 81.1 (d, *J* = 163.7 Hz, 1C, CH_2*C*H_2F), 125.6 (1C, *C*-8), 126.0 (1C, *C*-6), 126.3 (1C, *C*-7), 126.7 (1C, *C*-5$_{benzyl}$), 128.7 (1C, *C*-5), 129.0 (1C, *C*-6$_{benzyl}$), 131.3 (1C, *C*-3$_{benzyl}$), 133.3 (1C, *C*-4a), 136.2 (1C, *C*-1$_{benzyl}$),

136.69 (1C, *C*-2_{benzyl}), 136.73 (1C, *C*-4_{benzyl}), 143.3 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 3306 (N-H), 2947, 2924 (C-H_{alkyl}), 1447 (C=C_{arom}). Purity (HPLC): 98.1 %, t_R = 21.4 min.

7.2.23. *cis*-N-(2,4-Dimethylbenzyl)-3-(2-fluoroethyl)-3,4-dihydrospiro[[2]benzo-pyran-1,1'-cyclohexan]-4'-amine (13b)

A solution of alcohol **12b** (70 mg, 0.18 mmol) in CH_2Cl_2 (6 mL) was added dropwise to a solution of DAST (0.07 mL, 0.53 mmol, 2.9 eq) in CH_2Cl_2 (5 mL) under N_2 atmosphere at -78 °C. After 90 min, the mixture was warmed to rt and stirred for 20 h. 1 M NaOH (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (4 x 8 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified twice by fc (d = 2 cm, l = 18 cm, V = 10 mL, cyclohexane/ethyl acetate 90:10 + 1 % *N*,*N*-dimethylethanamine; d = 1.5 cm, l = 23 cm, V = 5 mL, cyclohexane/ethyl acetate 80:20 + 1 % *N*,*N*-dimethylethanamine). Colorless oil, yield 15 mg (22 %). $C_{25}H_{32}FNO$ (381.5 g/mol). R_f = 0.40 (cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 382.2526 (calcd. 382.2541 for $C_{25}H_{33}FNO_2$ [MH^+]). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.51 – 1.63 (m, 2H, 2'-*H*, 3'-*H*), 1.66 – 1.94 (m, 5H, 3'-*H*, 5'-*H*, 6'-*H*), 1.94 – 2.15 (m, 2H, C$H_2$$CH_2$F), 2.15 – 2.22 (m, 1H, 2'-*H*), 2.31 (s, 3H, 4-CH_3), 2.35 (s, 3H, 2-CH_3), 2.63 – 2.71 (m, 2H, 4'-H_{ax}, 4-*H*), 2.76 (dd, *J* = 15.8/10.8 Hz, 1H, 4-*H*), 3.82 (s, 2H, ArCH_2NH), 3.95 (ddt, *J* = 10.7/9.0/3.4 Hz, 1H, 3-*H*), 4.65 (dddd, *J* = 46.8/9.4/5.4/4.4 Hz, 1H, CH_2CH_2F), 4.76 (dtd, *J* = 47.5/9.0/4.4 Hz, 1H, CH_2CH_2F), 6.97 – 7.03 (m, 2H, 3-H_{benzyl}, 5-H_{benzyl}), 7.05 – 7.11 (m, 2H, 5-*H*, 8-*H*), 7.11 – 7.18 (m, 2H, 6-*H*, 7-*H*), 7.18 – 7.24 (m, 1H, 6-H_{benzyl}). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 19.1 (1C, 2-CH_3),

21.1 (1C, 4-*C*H_3), 28.89 (1C, *C*-3'), 28.94 (1C, *C*-5'), 34.2 (1C, *C*-2'), 35.7 (1C, *C*-4), 37.0 (d, *J* = 19.4 Hz, 1C, *C*H_2CH_2F), 38.6 (1C, *C*-6'), 48.5 (1C, Ar*C*H_2NH), 56.3 (1C, *C*-4'), 64.0 (d, *J* = 4.9 Hz, 1C, *C*-3), 75.4 (1C, *C*-1), 81.1 (d, *J* = 163.6 Hz, 1C, CH_2*C*H_2F), 125.1 (1C, *C*-8), 126.2 (1C, *C*-6 or *C*-7), 126.3 (1C, *C*-6 or *C*-7), 126.7 (1C, *C*-5_{benzyl}), 128.7 (1C, *C*-6_{benzyl}), 128.9 (1C, *C*-5), 131.3 (1C, *C*-3_{benzyl}), 133.7 (1C, *C*-4a), 135.6 (1C, *C*-1_{benzyl}), 136.3 (1C, *C*-2_{benzyl}), 136.7 (1C, *C*-4_{benzyl}), 142.5 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 3017 (N-H), 2924, 2855 (C-H_{alkyl}), 1447 (C=C_{arom}). Purity (HPLC): 97.4 %, t_R = 21.4 min.

7.2.24. *trans*-1-Cyclohexyl-4-[3-(2-fluoroethyl)-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-yl]piperazine (13c)

A solution of alcohol **12c** (35 mg, 0.09 mmol) in CH_2Cl_2 (4 mL) was added dropwise to a solution of DAST (0.03 mL, 0.23 mmol, 2.6 eq) in CH_2Cl_2 (3 mL) under N_2 atmosphere at -78 °C. After 1 h, the mixture was warmed to rt and stirred for 23 h. 1 M NaOH (3 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 1 cm, l = 18 cm, V = 5 mL, cyclohexane/ethyl acetate 66:33 + 2 % *N*,*N*-dimethylethanamine). Colorless solid, mp 167 °C, yield 24 mg (67 %). $C_{26}H_{39}FN_2O$ (414.6 g/mol). R_f = 0.35 (cyclohexane/ethyl acetate 66:33 + 2 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 415.3103 (calcd. 415.3119 for $C_{26}H_{40}FN_2O_2$ [MH^+]). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.07 – 1.20 (m, 1H, 4-$H_{cyclohexyl}$), 1.20 – 1.34 (m, 4H, 2-$H_{cyclohexyl}$, 3-$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 1.38 – 1.46 (m, 1H, 2'-*H*), 1.61 – 1.68 (m, 1H, 4-$H_{cyclohexyl}$), 1.69 – 1.92 (m, 8H, 3'-*H*, 5'-*H*, 6'-*H*, 2-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 1.92 – 2.15 (m, 4H, CH_2CH_2F, 3-

$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$), 2.20 – 2.34 (m, 3H, 2'-*H*, 4'-H_{equ}, 1-$H_{cyclohexyl}$), 2.48 – 2.80 (m, 10H, 4-*H*, $H_{pperazine}$), 3.95 (ddt, *J* = 10.6/9.3/3.3 Hz, 1H, 3-*H*), 4.59 (ddd, *J* = 9.4/5.6/4.3 Hz, 0.5H, CH_2CH_2F), 4.67 – 4.74 (m, 2 x 0.5H, CH_2CH_2F), 4.83 (td, *J* = 9.0/4.4 Hz, 0.5H, CH_2CH_2F), 7.05 (d, *J* = 7.5 Hz, 1H, 5-*H*), 7.12 (td, *J* = 6.9/6.1/2.3 Hz, 1H, 6-*H*), 7.15 – 7.22 (m, 2H, 7-*H*, 8-*H*). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 24.0 (1C, *C*-3' or *C*-5'), 24.1 (1C, *C*-3' or *C*-5'), 26.0 (2C, *C*-$2_{cyclohexyl}$, *C*-$6_{cyclohexyl}$), 26.4 (1C, *C*-$4_{cyclohexyl}$), 29.1 (2C, *C*-$3_{cyclohexyl}$, *C*-$5_{cyclohexyl}$), 29.6 (1C, *C*-6'), 34.1 (1C, *C*-2'), 35.9 (1C, *C*-4), 37.1 (d, *J* = 19.4 Hz, 1C, CH_2CH_2F), 49.9 (2C, *C*-$2_{piperazine}$ and *C*-$6_{piperazine}$ or *C*-$3_{piperazine}$ and *C*-$5_{piperazine}$), 50.5 (2C, *C*-$2_{piperazine}$ and *C*-$6_{piperazine}$ or *C*-$3_{piperazine}$ and *C*-$5_{piperazine}$), 57.5 (1C, *C*-4'), 63.8 (1C, *C*-$1_{cyclohexyl}$), 63.9 (d, *J* = 5.0 Hz, 1C, *C*-3), 76.2 (1C, *C*-1), 81.1 (d, *J* = 163.6 Hz, 1C, CH_2CH_2F), 125.6 (1C, *C*-8), 126.0 (1C, *C*-6), 126.2 (1C, *C*-7), 128.7 (1C, *C*-5), 133.4 (1C, *C*-4a), 143.4 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 2916, 2851, 2801 (C-H_{alkyl}), 1451 (C=C_{arom}). Purity (HPLC): 93.6 %, t_R = 16.6 min.

7.2.25. *cis*-1-Cyclohexyl-4-[3-(2-fluoroethyl)-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-yl]piperazine (13d)

A solution of alcohol **12d** (64 mg, 0.15 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of DAST (0.05 mL, 0.38 mmol, 2.5 eq) in CH_2Cl_2 (5 mL) under N_2 atmosphere at -78 °C. After 1 h, the mixture was warmed to rt and stirred for 20 h. 1 M NaOH (4 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 2 cm, l = 15 cm, V = 10 mL, cyclohexane/ethyl acetate 66:33 + 2 % *N*,*N*-dimethylethanamine; d = 1.5 cm, l = 20 cm, V = 5 mL, cyclohexane/ethyl acetate 95:5 + 1 % *N*,*N*-dimethylethanamine →

80:20 + 1 % *N*,*N*-dimethylethanamine; d = 2 cm, l = 16 cm, V = 5 mL, cyclohexane/ethyl acetate 90:10 + 1 % *N*,*N*-dimethylethanamine). Yellow solid, mp 152 °C, yield 9 mg (13 %). $C_{26}H_{39}FN_2O$ (414.6 g/mol). R_f = 0.17 (cyclohexane/ethyl acetate 66:33 + 2 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 415.3155 (calcd. 415.3119 for $C_{26}H_{40}FN_2O_2$ [MH^+]). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.04 – 1.17 (m, 1H, 4-$H_{cyclohexyl}$), 1.17 – 1.32 (m, 4H, 2-$H_{cyclohexyl}$, 3-$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 1.51 – 1.60 (m, 1H, 2'-*H*), 1.60 – 1.71 (m, 1H, 4-$H_{cyclohexyl}$), 1.71 – 1.90 (m, 8H, 3'-*H*, 5'-*H*, 6'-*H*, 2-$H_{cyclohexyl}$, 6-$H_{cyclohexyl}$), 1.90 – 2.14 (m, 4H, CH_2CH_2F, 3-$H_{cyclohexyl}$, 5-$H_{cyclohexyl}$), 2.16 – 2.25 (m, 1H, 2'-*H*), 2.25 – 2.34 (m, 1H, 1-$H_{cyclohexyl}$), 2.42 – 2.52 (m, 1H, 4'-H_{ax}), 2.60 – 2.85 (m, 10H, 4-*H*, $H_{piperazine}$), 3.94 (ddt, *J* = 10.3/8.9/3.4 Hz, 1H, 3-*H*), 4.58 (ddd, *J* = 8.9/5.6/4.5 Hz, 0.5H, CH_2CH_2F), 4.66 – 4.73 (m, 2 x 0.5H, CH_2CH_2F), 4.82 (td, *J* = 9.1/4.4 Hz, 0.5H CH_2CH_2F), 7.06 (d, *J* = 7.4 Hz, 1H, 5-*H*), 7.08 – 7.11 (m, 1H, 8-*H*), 7.11 – 7.15 (m, 1H, 6-*H*), 7.15 – 7.20 (m, 1H, 7-*H*). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 23.7 (1C, *C*-5'), 23.9 (1C, *C*-3'), 26.0 (2C, *C*-$2_{cyclohexyl}$, *C*-$6_{cyclohexyl}$), 26.4 (1C, *C*-$4_{cyclohexyl}$), 29.0 (2C, *C*-$3_{cyclohexyl}$, *C*-$5_{cyclohexyl}$), 34.8 (1C, *C*-2'), 35.7 (1C, *C*-4), 37.0 (d, *J* = 19.3 Hz, 1C, CH_2CH_2F), 39.0 (1C, *C*-6'), 49.3 (4C, $C_{piperazine}$), 63.2 (1C, *C*-4'), 63.8 (1C, *C*-$1_{cyclohexyl}$), 64.0 (d, *J* = 4.9 Hz, 1C, *C*-3), 75.3 (1C, *C*-1), 81.1 (d, *J* = 163.8 Hz, 1C, CH_2CH_2F), 125.1 (1C, *C*-8), 126.2 (1C, *C*-6 or *C*-7), 126.3 (1C, *C*-6 or *C*-7), 128.9 (1C, *C*-5), 133.6 (1C, *C*-4a), 142.3 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 2924, 2851, 2824 (C-H_{alkyl}), 1450 (C=C_{arom}). Purity (HPLC): 94.2 %, t_R = 15.5 min.

7.2.26. *trans*-6,7-Dimethoxy-2-[3-(2-fluoroethyl)-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-yl]-1,2,3,4-tetrahydroisoquinoline (13e)

A solution of alcohol **12e** (62 mg, 0.14 mmol) in CH_2Cl_2 (6 mL) was added dropwise to a solution of DAST (0.06 mL, 0.45 mmol, 3.2 eq) in CH_2Cl_2 (8 mL) under N_2 atmosphere at -78 °C. After 1.5 h, the mixture was warmed to rt and stirred for 21 h. 1 M NaOH (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (4 x 8 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified twice by fc (d = 1.5 cm, l = 22 cm, V = 5 mL, cyclohexane/ethyl acetate 80:20 + 1 % *N*,*N*-dimethylethanamine; d = 1.5 cm, l = 23 cm, V = 5 mL, cyclohexane/ethyl acetate 90:10 + 2 % *N*,*N*-dimethylethanamine). Colorless solid, mp 125 °C, yield 15 mg (21 %). $C_{27}H_{34}FNO_3$ (439.6 g/mol). R_f = 0.23 (cyclohexane/ethyl acetate 80:20 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 440.2627 (calcd. 440.2595 for $C_{27}H_{35}FNO_3$ [MH^+]). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.44 – 1.52 (m, 1H, 2'-*H*), 1.77 – 2.19 (m, 8H, 3'-*H*, 5'-*H*, 6'-*H*, CH_2CH_2F), 2.26 – 2.40 (m, 1H, 2'-*H*), 2.40 – 2.47 (m, 1H, 4'-H_{equ}), 2.65 (dd, *J* = 15.9/3.0 Hz, 1H, 4-*H*), 2.73 (dd, *J* = 15.9/5.1 Hz, 1H, 4-*H*), 2.77 – 2.83 (m, 2H, 3-$H_{isoquinoline}$), 2.83 – 2.91 (m, 2H, 4-$H_{isoquinoline}$), 3.68 (s, 2H, 1-$H_{isoquinoline}$), 3.86 (s, 3H, 7-OCH_3), 3.88 (s, 3H, 6-OCH_3), 3.91 – 4.06 (m, 1H, 3-*H*), 4.61 (dt, *J* = 9.3/5.0 Hz, 0.5H, CH_2CH_2F), 4.69 – 4.78 (m, 2 x 0.5H, CH_2CH_2F), 4.85 (td, *J* = 8.8/4.3 Hz, 0.5H, CH_2CH_2F), 6.60 (s, 1H, 8-$H_{isoquinoline}$), 6.66 (s, 1H, 5-$H_{isoquinoline}$), 7.04 (d, *J* = 6.6 Hz, 1H, 5-*H*), 7.07 – 7.17 (m, 3H, 6-*H*, 7-*H*, 8-*H*). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 24.4 (1C, *C*-3'), 24.6 (1C, *C*-5'), 29.4 (1C, *C*-$4_{isoquinoline}$), 29.6 (1C, *C*-6'), 34.1 (1C, *C*-2'), 35.9 (1C, *C*-4), 37.1 (d, *J* = 19.3 Hz, 1C, *C*H_2CH_2F), 47.5 (1C, *C*-$3_{isoquinoline}$), 53.5 (1C, *C*-$1_{isoquinoline}$), 56.1 (2C, 6-OCH_3, 7-OCH_3), 57.2 (1C, *C*-4'), 63.9 (d, *J* = 4.7 Hz, 1C, *C*-3), 76.3 (1C, *C*-1), 81.1 (d, *J* = 163.7 Hz, 1C, CH_2*C*H_2F), 109.9 (1C, *C*-$8_{isoquinoline}$), 111.3 (1C, *C*-$5_{isoquinoline}$), 125.8 (1C, *C*-6 or *C*-8), 126.0 (1C, *C*-6 or *C*-8), 126.3 (1C, *C*-7), 127.0 (1C, *C*-$8a_{isoquinoline}$), 127.7 (1C, *C*-$4a_{isoquinoline}$), 128.6 (1C, *C*-5), 133.3 (1C, *C*-

4a), 143.2 (1C, *C*-8a), 147.4 (1C, *C*-$7_{isoquinoline}$), 147.5 (1C, *C*-$6_{isoquinoline}$). FT-IR (neat): ν [cm^{-1}] = 2951, 2932, 2781 (C-H_{alkyl}), 1520, 1462, 1447 (C=C_{arom}). Purity (HPLC, method 1): 93.2 %, t_R = 19.7 min.

7.2.27. *cis*-6,7-Dimethoxy-2-[3-(2-fluoroethyl)-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-yl]-1,2,3,4-tetrahydroisoquinoline (13f)

A solution of alcohol **12f** (67 mg, 0.15 mmol) in CH_2Cl_2 (8 mL) was added dropwise to a solution of DAST (0.06 mL, 0.45 mmol, 3.0 eq) in CH_2Cl_2 (6 mL) under N_2 atmosphere at -78 °C. After 1 h, the mixture was warmed to rt and stirred for 20 h. 1 M NaOH (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (4 x 6 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified twice by fc (d = 1.5 cm, l = 23 cm, V = 5 mL, cyclohexane/ethyl acetate 66:33 + 1 % *N*,*N*-dimethylethanamine; d = 1.5 cm, l = 23 cm, V = 5 mL, cyclohexane/ethyl acetate 80:20 + 2 % *N*,*N*-dimethylethanamine). Colorless solid, mp 136 °C, yield 18 mg (27 %). $C_{27}H_{34}FNO_3$ (439.6 g/mol). R_f = 0.31 (cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 440.2613 (calcd. 440.2595 for $C_{27}H_{35}FNO_3$ [MH^+]). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.56 – 1.68 (m, 1H, 2'-*H*), 1.74 – 2.15 (m, 8H, 3'-*H*, 5'-*H*, 6'-*H*, CH_2CH_2F), 2.22 – 2.29 (m, 1H, 2'-*H*), 2.63 – 2.82 (m, 3H, 4-*H*, 4'-H_{ax}), 2.82 – 2.99 (m, 4H, 3-$H_{isoquinoline}$, 4-$H_{isoquinoline}$), 3.82 (s, 2H, 1-$H_{isoquinoline}$), 3.85 (s, 6H, 6-OCH_3, 7-OCH_3), 3.91 – 4.04 (m, 1H, 3-*H*), 4.69 (dddd, *J* = 46.7/9.2/5.3/4.4 Hz, 1H, CH_2CH_2F), 4.82 (dtd, *J* = 47.4/9.1/4.3 Hz, 1H, CH_2CH_2F), 6.55 (s, 1H, 8-$H_{isoquinoline}$), 6.60 (s, 1H, 5-$H_{isoquinoline}$), 7.06 – 7.10 (m, 1H, 5-*H*), 7.10 – 7.22 (m, 3H, 6-*H*, 7-*H*, 8-*H*). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 23.8 (2C, *C*-3', *C*-5'), 29.1 (1C, C-$4_{isoquinoline}$), 34.8 (1C,

C-2'), 35.7 (1C, *C*-4), 37.1 (d, *J* = 19.3 Hz, 1C, *C*$H_2$$CH_2$F), 39.1 (1C, *C*-6'), 47.0 (1C, C-$3_{isoquinoline}$), 51.5 (1C, C-$1_{isoquinoline}$), 56.07 (1C, 6-O*C*H_3 or 7-O*C*H_3), 56.12 (1C, 6-O*C*H_3 or 7-O*C*H_3), 62.7 (1C, *C*-4'), 64.0 (d, *J* = 4.7 Hz, 1C, *C*-3), 75.2 (1C, *C*-1), 81.2 (d, *J* = 164.0 Hz, 1C, CH_2*C*H_2F), 109.8 (1C, C-$8_{isoquinoline}$), 111.6 (1C, C-$5_{isoquinoline}$), 125.1 (1C, *C*-8), 126.29 (1C, *C*-6 or *C*-7), 126.32 (1C, *C*-6 or *C*-7), 126.5 (1C, C-$4a_{isoquinoline}$), 126.8 (1C, C-$8a_{isoquinoline}$), 128.9 (1C, *C*-5), 133.6 (1C, *C*-4a), 142.2 (1C, *C*-8a), 147.4 (1C, C-$7_{isoquinoline}$), 147.7 (1C, C-$6_{isoquinoline}$). FT-IR (neat): ν [cm^{-1}] = 2978, 2920 (C-H_{alkyl}), 1512, 1462, 1443 (C=C_{arom}). Purity (HPLC): 97.8 %, t_R = 19.7 min.

7.2.28. 3-[1-(4-Fluorophenyl)-indol-3-yl]propanoic acid (15)

A solution of 4-bromofluorobenzene (0.26 mL, 2.38 mmol), 3-(indol-3-yl)propionic acid (**14**, 500 mg, 2.64 mmol, 1.1 eq), CuI (320 mg, 1.68 mmol, 0.7 eq) and Cs_2CO_3 (2.58 g, 7.93 mmol, 3.3 eq) in DMF (20 mL) was heated to reflux for 2 d under N_2 atmosphere. After cooling to rt, ethyl acetate (100 mL) was added and the mixture was washed with 0.1 M HCl (2 x 80 mL). The aqueous layer was extracted with ethyl acetate (3 x 60 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 4 cm, l = 18 cm, V = 30 mL, cyclohexane/ethyl acetate 80:20 + 1 % HCOOH). Brownish solid, mp 140 °C, yield 586 mg (78 %). $C_{17}H_{14}FNO_2$ (283.3 g/mol). R_f = 0.69 (cyclohexane/ethyl acetate 50:50 + 1 % HCOOH). HR-MS (APCI): *m/z* = 283.1077 (calcd. 283.1081 for $C_{17}H_{15}FNO_2$ [MH^+]). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 2.83 (t, *J* = 7.6 Hz, 2H, CH_2CH_2CO), 3.17 (t, *J* = 7.6 Hz, 2H, C$H_2$$CH_2$CO), 7.13 (s, 1H, 2-*H*), 7.17 – 7.22 (m, 3H, 5-*H*, 3-H_{phenyl}, 5-H_{phenyl}), 7.22 – 7.25 (m, 1H, 6-*H*), 7.41 – 7.44 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.44 – 7.47 (m, 1H, 7-*H*), 7.64 – 7.66 (m, 1H, 4-*H*). A signal for the COOH

proton is not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 20.4 (1C, *C*H_2CH_2CO), 34.5 (1C, CH$_2$*C*H$_2$CO), 110.4 (1C, *C*-7), 115.8 (1C, *C*-3), 116.6 (d, *J* = 22.8 Hz, 2C, *C*-3$_{phenyl}$, *C*-5$_{phenyl}$), 119.2 (1C, *C*-4), 120.2 (1C, *C*-5), 122.9 (1C, *C*-6), 125.5 (1C, *C*-2), 126.1 (d, *J* = 8.1 Hz, 2C, *C*-2$_{phenyl}$, *C*-6$_{phenyl}$), 128.5 (1C, *C*-3a), 135.9 (d, *J* = 3.0 Hz, 1C, *C*-1$_{phenyl}$), 136.5 (1C, *C*-7a), 161.1 (d, *J* = 246.2 Hz, 1C, *C*-4$_{phenyl}$) , 178.8 (1C, *C*=O). FT-IR (neat): ν [cm^{-1}] = 3051 (COOH), 2978, 2909 (C-H$_{alkyl}$), 1717 (C=O), 1512, 1458, 1450 (C=C$_{arom}$). Purity (HPLC): 99.4 %, t_R = 21.2 min.

7.2.29. 3-[1-(4-Fluorophenyl)-indol-3-yl]propanamide (16)

Et_3N (1.0 mL, 7.2 mmol, 3.7 eq) and ethyl chloroformate (0.28 mL, 2.94 mmol, 1.5 eq) were added to a solution of **15** (548 mg, 1.93 mmol) in THF (10 mL) at 0 °C under N_2 atmosphere. After 1 h, NH_3 (0.5 M in THF, 20.0 mL, 10.0 mmol, 5.2 eq) was added and the mixture was stirred for 2 h. The precipitate was filtered off and the filtrate was concentrated in vacuo. H_2O (50 mL) was added and the aqueous phase was extracted with EtOAc (4 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Brownish solid, mp 123 °C, yield 532 mg (97 %). $C_{17}H_{15}FN_2O$ (282.3 g/mol). R_f = 0.22 (cyclohexane/ethyl acetate 50:50 + 1 % HCOOH). HR-MS (APCI): *m/z* = 189.1012 (calcd. 189.1022 for $C_{17}H_{16}FN_2O$ [MH$^+$]). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.68 (t, *J* = 7.4 Hz, 2H, CH$_2$C*H*$_2$CO), 3.17 (t, *J* = 7.2 Hz, 2H, C*H*$_2$CH$_2$CO), 5.49 (s, 1H, CON*H*$_2$), 5.66 (s, 1H, CON*H*$_2$), 7.14 (s, 1H, 2-*H*), 7.15 – 7.21 (m, 3H, 5-*H*, 3-*H*$_{phenyl}$, 5-*H*$_{phenyl}$), 7.21 – 7.26 (m, 1H, 6-*H*), 7.39 – 7.44 (m, 2H, 2-*H*$_{phenyl}$, 6-*H*$_{phenyl}$), 7.44 – 7.48 (m, 1H, 7-*H*), 7.63 – 7.68 (m, 1H, 4-*H*). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 21.0 (1C, *C*H$_2$CH$_2$CO), 36.4 (1C, CH$_2$*C*H$_2$CO), 110.5 (1C, *C*-7), 116.0 (1C, *C*-3), 116.6 (d, *J* = 22.9 Hz, 2C,

C-3_{phenyl}, *C*-5_{phenyl}), 119.2 (1C, *C*-4), 120.2 (1C, *C*-5), 122.8 (1C, *C*-6), 125.7 (1C, *C*-2), 126.0 (d, *J* = 8.4 Hz, 2C, *C*-2_{phenyl}, *C*-6_{phenyl}), 128.5 (1C, *C*-3a), 135.9 (d, *J* = 3.0 Hz, 1C, *C*-1_{phenyl}), 136.5 (1C, *C*-7a), 161.1 (d, *J* = 246.1 Hz, 1C, *C*-4_{phenyl}), 175.3 (1C, *C*=O). FT-IR (neat): ν [cm^{-1}] = 3395, 3206 (N-H), 2963, 2920 (C-H_{alkyl}), 1654 (C=O), 1508, 1454 (C=C_{arom}). Purity (HPLC): 93.2 %, t_R = 19.8 min.

7.2.30. 3-[1-(4-Fluorophenyl)-indol-3-yl]propan-1-amine (17)

$LiAlH_4$ (150 mg, 3.94 mmol, 3.4 eq) was added to a solution of amide **16** (329 mg, 1.17 mmol) in THF (25 mL) at 0 °C under N_2 atmosphere. The mixture was heated to reflux for 2 h. After cooling to rt, H_2O (15 mL) was added, the precipitate was filtered off.and the aqueous phase was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 4 cm, l = 18 cm, V = 30 mL, CH_2Cl_2: CH_3OH 95:5 + 3 % NH_3 (25 %)). Yellow oil, yield 200 mg (64 %). $C_{17}H_{17}FN_2$ (268.3 g/mol). R_f = 0.13 (CH_2Cl_2/CH_3OH 95:5 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 269.1464 (calcd. 269.1449 for $C_{17}H_{18}FN_2$ [MH^+]). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.93 (quint, *J* = 7.5 Hz, 2H, $CH_2CH_2CH_2NH_2$), 2.80 – 2.90 (m, 4H, $CH_2CH_2CH_2NH_2$), 7.09 (s, 1H, 2-*H*), 7.14 – 7.25 (m, 4H, 5-*H*, 6-*H*, 3-H_{phenyl}, 5-H_{phenyl}), 7.39 – 7.47 (m, 3H, 7-*H*, 2-H_{phenyl}, 6-H_{phenyl}), 7.64 – 7.67 (m, 1H, 4-*H*). A signal for the NH_2 protons is not observed in the spectrum. ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 22.5 (1C, $CH_2CH_2CH_2NH_2$), 33.9 (1C, $CH_2CH_2CH_2NH_2$), 42.1 (1C, $CH_2CH_2CH_2NH_2$), 110.3 (1C, *C*-7), 116.5 (d, *J* = 22.8 Hz, 2C, *C*-3_{phenyl}, *C*-5_{phenyl}), 117.5 (1C, *C*-3), 119.4 (1C, *C*-4), 120.0 (1C, *C*-5), 122.7 (1C, *C*-6), 125.2 (1C, *C*-2), 126.0 (d, *J* = 8.4 Hz, 2C, *C*-2_{phenyl}, *C*-6_{phenyl}), 129.0 (1C, *C*-3a), 136.1 (d, *J* = 3.0 Hz, 1C, *C*-1_{phenyl}), 136.5 (1C, *C*-7a), 161.0 (d, *J* = 246.0 Hz, 1C, *C*-4_{phenyl}). FT-IR (neat): ν [cm^{-1}] = 3051 (N-H),

2924, 2851 (C-H_{alkyl}), 1508, 1458 (C=C_{arom}). Purity (HPLC): 94.7 %, t_R = 17.9 min.

7.2.31. *trans*-N-{3-[1-(4-Fluorophenyl)-(Indol-3-yl)]propyl}-3-methoxy-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-amine (18a) and *cis*-N-{3-[1-(4-Fluorophenyl)-(Indol-3-yl)]propyl}-3-methoxy-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-amine (18b)

A solution of ketone **5** (164 mg, 0.67 mmol), amine **17** (265 mg, 0.67 mmol, 1.5 eq) and acetic acid (45 µL, 0.79 mmol, 1.2 eq) in THF (20 mL) was stirred under N_2 atmosphere at rt. After 2.5 h, $NaBH(OAc)_3$ (252 mg, 1.19 mmol, 1.8 eq) was added and the mixture was stirred for 17 h at rt. 1 M NaOH (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 3 cm, l = 19 cm, V = 20 mL, CH_2Cl_2/CH_3OH 98:2 + 1 % *N*,*N*-dimethylethanamine). **18a** was eluted first and **18b** afterwards.

trans-**18a**: Yellow oil, yield 99 mg (30 %). $C_{32}H_{35}FN_2O_2$ (498.6 g/mol). R_f = 0.51 (CH_2Cl_2/CH_3OH 95:5 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): m/z = 499.2770 (calcd. 499.2755 for $C_{32}H_{36}FN_2O_2$ [MH^+]). ^{1}H NMR (600 MHz, CD_3OD): δ (ppm) = 1.55 (dq, *J* = 12.5/2.7 Hz, 1H, 2'-H_{equ}), 1.68 – 1.73 (m, 2H, 3'-*H*, 5'-*H*), 1.80 (ddt, *J* = 14.3/4.6/2.8 Hz, 1H, 6'-H_{equ}), 1.87 (td, *J* = 13.9/3.7 Hz, 1H, 6'-H_{ax}), 2.00 – 2.04 (m, 1H, 5'-*H*), 2.04 – 2.13 (m, 3H, 3'-*H*, $CH_2CH_2CH_2NH$), 2.13 – 2.19 (m, 1H, 2'-H_{ax}), 2.76 – 2.82 (m, 3H, 4-*H*, $CH_2CH_2CH_2NH$), 2.90 (dd, *J* = 15.7/2.9 Hz, 1H, 4-*H*), 2.91 – 2.96 (m, 3H, 4'-H_{equ}, $CH_2CH_2CH_2NH$), 3.53 (s, 3H, OCH_3), 4.88 (dd, *J* = 7.6/3.1 Hz, 1H, 3-*H*), 7.06 (d, *J* = 7.0 Hz, 1H, 5-*H*), 7.11 – 7.17 (m, 3H, 6-*H*, 7-*H*, 5-H_{indole}), 7.20 (ddd, *J* = 8.2/6.9/1.2 Hz, 1H, 6-H_{indole}), 7.26 – 7.30 (m, 3H, 2-H_{indole}, 3-H_{phenyl}, 5-H_{phenyl}), 7.32 (dd, *J* = 7.3/1.7 Hz, 1H, 8-*H*), 7.46 (d, *J* = 8.2 Hz, 1H,

7-H_{indole}), 7.50 – 7.54 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.69 (d, J = 7.7 Hz, 1H, 4-H_{indole}). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, CD_3OD): δ (ppm) = 24.0 (1C, $CH_2CH_2CH_2NH$), 26.1 (1C, *C*-3'), 26.3 (1C, *C*-5'), 30.7 (1C, $CH_2CH_2CH_2NH$), 31.5 (1C, *C*-6'), 34.1 (1C, *C*-2'), 36.2 (1C, *C*-4), 48.6 (1C, $CH_2CH_2CH_2NH$), 52.5 (1C, *C*-4'), 56.3 (1C, OCH_3), 78.0 (1C, *C*-1), 97.8 (1C, *C*-3), 111.1 (1C, *C*-7_{indole}), 117.4 (d, J = 23.1 Hz, 2C, *C*-3_{phenyl}, *C*-5_{phenyl}), 118.5 (1C, *C*-3_{indole}), 120.2 (1C, *C*-4_{indole}), 120.9 (1C, *C*-5_{indole}), 123.6 (1C, *C*-6_{indole}), 126.1 (1C, *C*-8), 126.4 (1C, *C*-2_{indole}), 127.0 (d, J = 8.3 Hz, 2C, *C*-2_{phenyl}, *C*-6_{phenyl}), 127.5 (1C, *C*-7), 127.6 (1C, *C*-6), 130.0 (1C, *C*-5), 130.3 (1C, *C*-$3a_{indole}$), 132.4 (1C, *C*-4a), 137.5 (d, J = 3.1 Hz, 1C, *C*-1_{phenyl}), 137.8 (1C, *C*-$7a_{indole}$), 143.4 (1C, *C*-8a), 162.2 (d, J = 244.0 Hz, 1C, *C*-4_{phenyl}). FT-IR (neat): ν [cm^{-1}] = 3318 (N-H), 2928, 2808 (C-H_{alkyl}), 1508, 1458 (C=C_{arom}). Purity (HPLC): 97.4 %, t_R = 23.0 min.

cis-**18b**: Yellow solid, mp 118 °C, yield 138 mg (42 %). $C_{32}H_{35}FN_2O_2$ (498.6 g/mol). R_f = 0.49 (CH_2Cl_2/CH_3OH 95:5 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): m/z = 499.2769 (calcd. 499.2755 for $C_{32}H_{36}FN_2O_2$ [MH^+]). ^{1}H NMR (600 MHz, CD_3OD): δ (ppm) = 1.62 – 1.72 (m, 2H, 2'-*H*, 3'-*H*), 1.72 – 1.86 (m, 4H, 3'-*H*, 5'-*H*, 6'-*H*), 1.94 (td, J = 13.7/4.1 Hz, 1H, 6'-*H*), 1.99 – 2.10 (m, 3H, 2'-*H*, $CH_2CH_2CH_2NH$), 2.71 (tt, J = 11.0/3.9 Hz, 1H, 4'-H_{ax}), 2.78 (dd, J = 15.6/7.5 Hz, 1H, 4-*H*), 2.81 – 2.85 (m, 2H, $CH_2CH_2CH_2NH$), 2.88 – 2.93 (m, 3H, 4-*H*, $CH_2CH_2CH_2NH$), 3.53 (s, 3H, OCH_3), 4.86 – 4.89 (m, 1H, 3-*H*), 7.05 – 7.08 (m, 1H, 5-*H*), 7.12 – 7.17 (m, 4H, 6-*H*, 7-*H*, 8-*H*, 5-H_{indole}), 7.17 – 7.21 (m, 1H, 6-H_{indole}), 7.25 – 7.30 (m, 3H, 2-H_{indole}, 3-H_{phenyl}, 5-H_{phenyl}), 7.46 (dt, J = 8.2/1.0 Hz, 1H, 7-H_{indole}), 7.49 – 7.55 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.67 (dt, J = 8.0/1.0 Hz, 1H, 4-H_{indole}). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, CD_3OD): δ (ppm) = 23.8 (1C, $CH_2CH_2CH_2NH$), 28.6 (1C, *C*-3' or *C*-5'), 28.7 (1C, *C*-3' or *C*-5'), 30.6 (1C,

$CH_2CH_2CH_2NH$), 36.1 (1C, *C*-4), 36.4 (1C, *C*-2'), 38.9 (1C, *C*-6'), 47.3 (1C, $CH_2CH_2CH_2NH$), 56.4 (1C, OCH_3), 57.3 (1C, *C*-4'), 77.3 (1C, *C*-1), 97.8 (1C, *C*-3), 111.1 (1C, *C*-7_{indole}), 117.4 (d, *J* = 23.0 Hz, 2C, *C*-3_{phenyl}, *C*-5_{phenyl}), 118.3 (1C, *C*-3_{indole}), 120.2 (1C, *C*-4_{indole}), 120.9 (1C, *C*-5_{indole}), 123.6 (1C, *C*-6_{indole}), 125.6 (1C, *C*-6 or *C*-8), 126.4 (1C, *C*-2_{indole}), 126.9 (d, *J* = 8.6 Hz, 2C, *C*-2_{phenyl}, *C*-6_{phenyl}), 127.5 (1C, *C*-7), 127.7 (1C, *C*-6 or *C*-8), 130.1 (1C, *C*-5), 130.3 (1C, *C*-$3a_{indole}$), 132.6 (1C, *C*-4a), 137.5 (d, *J* = 3.2 Hz, 1C, *C*-1_{phenyl}), 137.7 (1C, *C*-$7a_{indole}$), 142.5 (1C, *C*-8a), 162.2 (d, *J* = 244.4 Hz, 1C, *C*-4_{phenyl}). FT-IR (neat): ν [cm^{-1}] = 3318 (N-H), 2928, 2851 (C-H_{alkyl}), 1508, 1458 (C=C_{arom}). Purity (HPLC): 98.3 %, t_R = 23.0 min.

7.2.32. 3-Hydroxy-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-one (19)

A solution of acetal **5** (502 mg, 2.04 mmol) and 0.2 M HCl (50 mL, 10.0 mmol, 5 eq) in THF (50 mL) was stirred at rt for 3 d. 1 M NaOH (25 mL) was added and the aqueous layer was extracted with Et_2O (3 x 30 mL) and CH_2Cl_2 (1 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 3 cm, l = 18 cm, V = 20 mL, cyclohexane/ethyl acetate 67:33 → cyclohexane/ethyl acetate 1:1). Colorless solid, mp 169 °C, yield 448 mg (95 %). $C_{14}H_{16}O_3$ (232.3 g/mol). R_f = 0.14 (cyclohexane/ethyl acetate 67:33). HR-MS (APCI): m/z = 215.1067 (calcd. 215.1067 for $C_{14}H_{15}O_2$ [M-H_2O+H^+]). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.94 – 2.03 (m, 1H, 2'-*H*), 2.07 – 2.14 (m, 3H, 3'-*H*, 5'-*H*, 6'-*H*), 2.14 – 2.25 (m, 1H, 6'-*H*), 2.37 (td, *J* = 13.4/4.9 Hz, 1H, 2'-*H*), 2.69 – 2.82 (m, 3H, 4-*H*, 3'-*H*, 5'-*H*), 2.89 (dd, *J* = 15.8/3.0 Hz, 1H, 4-*H*), 5.24 (ddd, *J* = 7.3/5.3/3.0 Hz, 1H, 3-*H*), 6.56 (d, *J* = 5.3 Hz, 1H, 3-O*H*), 7.06 – 7.12 (m, 1H, 5-*H*), 7.12 – 7.18 (m, 2H, 6-*H*, 7-*H*), 7.22 – 7.28 (m, 1H, 8-*H*). ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm)

= 35.3 (1C, *C*-6'), 36.3 (1C, *C*-4), 36.9 (1C, *C*-3' or *C*-5'), 37.0 (1C, *C*-3' or *C*-5'), 37.9 (1C, *C*-2'), 74.7 (1C, *C*-1), 88.7 (1C, *C*-3), 124.4 (1C, *C*-8), 126.2 (1C, *C*-7), 126.6 (1C, *C*-6), 129.1 (1C; *C*-5), 132.1 (1C, *C*-4a), 140.4 (1C, *C*-8a), 210.3 (1C, *C*-4'). FT-IR (neat): ν [cm^{-1}] = 3283 (O-H), 2916, 2851 (C-H_{alkyl}), 1686 (C=O), 1450, 1439, 1412 (C=C_{arom}). Purity (HPLC): 96.4 %, t_R = 14.8 min.

7.2.33. Ethyl 2-(4'-oxo-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-3-yl)acetate (20)

A solution of lactol **19** (100 mg, 0.43 mmol), (ethoxycarbonylmethylene)-triphenylphosphorane (211 mg, 0.60 mmol, 1.4 eq) and Cs_2CO_3 (141 mg ,0.43 mmol, 1.0 eq) in toluene (15 mL) was heated to reflux under N_2 atmosphere for 2 d. After cooling to rt, H_2O (10 mL) was added and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 2 cm, l = 20 cm, V = 10 mL, cyclohexane/ethyl acetate 90:10 → 80:20). Colorless solid, mp 83 °C, yield 81 mg (63 %). $C_{18}H_{22}O_4$ (302.4 g/mol). R_f = 0.50 (cyclohexane/ethyl acetate 67:33). HR-MS (APCI): *m/z* = 303.1563 (calcd. 303.1591 for $C_{18}H_{23}O_4$ [MH^+]). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.27 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 2.03 (td, *J* = 14.1/4.8 Hz, 1H, 2'-*H*), 2.06 – 2.12 (m, 1H, 6'-*H*), 2.22 – 2.36 (m, 3H, 3'-*H*, 5'-*H*, 6'-*H*), 2.48 – 2.54 (m, 1H, 2'-*H*), 2.63 – 2.73 (m, 2H, CH_2CO_2Et), 2.76 (dd, *J* = 15.8/3.0 Hz, 1H, 4-*H*), 2.79 – 2.93 (m, 3H, 4-*H*, 3'-*H*, 5'-*H*), 4.11 – 4.24 (m, 2H, OCH_2CH_3), 4.35 – 4.41 (m, 1H, 3-*H*), 7.07 (dd, *J* = 7.4/1.7 Hz, 1H, 8-*H*), 7.10 – 7.12 (m, 1H, 5-*H*), 7.16 – 7.22 (m, 2H, 6-*H*, 7-*H*). ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 14.4 (1C, OCH_2CH_3), 35.0 (1C, *C*-4), 35.3 (1C, *C*-2'), 37.3 (1C, *C*-3'), 37.4 (1C, *C*-5'), 39.3 (1C, *C*-6'), 41.4 (1C, CH_2CO_2Et), 60.9 (1C, OCH_2CH_3), 65.8 (1C, *C*-3), 75.0 (1C,

C-1), 124.8 (1C, *C*-8), 126.7 (1C, *C*-7), 126.8 (1C, *C*-6), 129.1 (1C, *C*-5), 133.0 (1C, *C*-4a), 140.2 (1C, *C*-8a), 171.5 (1C, *C*=O), 212.2 (1C, *C*-4'). FT-IR (neat): ν [cm^{-1}] = 2978, 2905 (C-H_{alkyl}), 1724 (C=O_{ester}), 1697 (C=O_{ketone}), 1435, 1408 (C=C_{arom}). Purity (HPLC): 96.0 %, t_R = 21.0 min.

7.2.34. Ethyl 2-(3,4-dihydrodispiro[[2]benzopyran-1,1'-cyclohexan-4',2''-[1,3]dioxolan]-3-yl)acetate (21)

A solution of ester **20** (1.37 g, 4.52 mmol), ethylene glycol (6 mL, 107 mmol, 24 eq), trimethyl orthoformate (3 mL, 27.4 mmol, 6 eq) and *p*-toluenesulfonic acid (174 mg, 0.91 mmol, 0.2 eq) in CH_2Cl_2 (100 mL) was stirred at rt for 24 h. The mixture was washed with saturated Na_2CO_3 solution (2 x 60 mL) and brine (1 x 60 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. Yellow oil, yield 1.55 g (99 %). $C_{20}H_{26}O_5$ (346.4 g/mol). R_f = 0.28 (CH_2Cl_2/CH_3OH 99:1). HR-MS (APCI): ***m/z*** = 347.1873 (calcd. 347.1853 for $C_{20}H_{27}O_5$ [MH^+]). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.30 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.55 – 1.64 (m, 2H, 3'-*H*, 5'-*H*), 1.71 – 1.76 (m, 1H, 6'-*H*), 1.86 (td, *J* = 13.9/3.7 Hz, 1H, 2'-*H*), 1.94 (td, *J* = 13.9/3.4 Hz, 1H, 3'-*H*), 2.04 – 2.12 (m, 1H, 5'-*H*), 2.14 – 2.21 (m, 2H, 2'-*H*, 6'-*H*), 2.58 (dd, *J* = 15.1/4.5 Hz, 1H, CH_2CO_2Et), 2.66 (dd, *J* = 14.8/8.3 Hz, 1H, CH_2CO_2Et), 2.71 – 2.80 (m, 2H, 4-*H*), 3.98 (s, 4H, OCH_2CH_2O), 4.13 – 4.27 (m, 3H, 3-*H*, OCH_2CH_3), 7.06 (d, *J* = 7.3 Hz, 1H, 5-*H*), 7.12 – 7.15 (m, 1H, 6-*H*), 7.16 – 7.20 (m, 2H, 7-*H*, 8-*H*). ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 14.4 (1C, OCH_2CH_3), 30.46 (1C, *C*-3'), 30.50 (1C, *C*-5'), 32.9 (1C, *C*-2'), 35.2 (1C, *C*-4), 37.2 (1C, *C*-6'), 41.6 (1C, CH_2CO_2Et), 60.8 (1C, OCH_2CH_3), 64.3 (1C, OCH_2CH_2O), 64.4 (1C, OCH_2CH_2O), 65.5 (1C, *C*-3), 75.4 (1C, *C*-1), 108.8 (1C, *C*-4'), 125.3 (1C, *C*-8), 126.3 (1C, *C*-6), 126.4 (1C, *C*-7), 128.8

(1C, *C*-5), 133.1 (1C, *C*-4a), 141.8 (1C, *C*-8a), 171.6 (1C, *C*=O). FT-IR (neat): ν [cm^{-1}] = 2978, 2928, 2889 (C-H_{alkyl}), 1728 (C=O), 1435, 1369 (C=C_{arom}). Purity (HPLC): 90.0 %, t_R = 22.4 min.

7.2.35. 2-(3,4-Dihydrodispiro[[2]benzopyran-1,1'-cyclohexan-4',2''-[1,3]dioxolan]-3-yl)ethanol (22)

$LiAlH_4$ (494 mg, 12.99 mmol, 2.9 eq) was added slowly to a solution of ester **21** (1.54 g, 4.46 mmol) in Et_2O (30 mL) at -20 °C under N_2 atmosphere. After stirring for 2 h, H_2O (50 mL) was added, the precipitate was filtered off and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 5 cm, l = 18 cm, V = 50 mL, cyclohexane/ethyl acetate 50:50). Colorless oil, yield 1.10 g (81 %). $C_{18}H_{24}O_4$ (304.4 g/mol). R_f = 0.19 (cyclohexane/ethyl acetate 50:50). HR-MS (APCI): *m/z* = 305.1736 (calcd. 305.1747 for $C_{18}H_{25}O_4$ [MH^+]). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.61 – 1.71 (m, 2H, 3'-*H*, 5'-*H*), 1.76 – 1.81 (m, 1H, 2'-*H*), 1.85 – 1.99 (m, 4H, 5'-*H*, 6'-*H*, C*H*$_2$CH$_2$OH), 2.00 – 2.06 (m, 1H, 3'-*H*), 2.14 – 2.19 (m, 1H, 6'-*H*), 2.22 (td, *J* = 13.8/4.3 Hz, 1H, 2'-*H*), 2.64 (dd, *J* = 15.9/2.7 Hz, 1H, 4-*H*), 2.82 (dd, *J* = 15.6/11.2 Hz, 1H, 4-*H*), 3.85 – 3.95 (m, 2H, CH$_2$C*H*$_2$OH), 4.00 (s, 4H, OC*H*$_2$C*H*$_2$O), 4.00 – 4.04 (m, 1H, 3-*H*), 7.06 (d, *J* = 7.6 Hz, 1H, 5-*H*), 7.10 – 7.16 (m, 1H, 6-*H*), 7.17 – 7.19 (m, 2H, 7-*H*, 8-*H*). A signal for the OH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 30.7 (1C, *C*-3' or *C*-5'), 30.8 (1C, *C*-3' or *C*-5'), 33.0 (1C,*C*-6'), 35.4 (1C, *C*-4), 37.1 (1C, *C*-2'), 38.2 (1C, *C*H$_2$CH$_2$OH), 60.6 (1C, CH$_2$*C*H$_2$OH), 64.4 (1C, O*C*H$_2$CH$_2$O), 64.5 (1C, OCH$_2$*C*H$_2$O), 67.3 (1C, *C*-3), 75.4 (1C, *C*-1), 108.5 (1C, *C*-4'), 125.3 (1C, *C*-8), 126.30 (1C, *C*-7),

126.33 (1C, *C*-6), 128.9 (1C, *C*-5), 133.5 (1C, *C*-4a), 141.7 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 3421 (O-H), 2928, 2886 (C-H_{alkyl}), 1508, 1435 (C=C_{arom}). Purity (HPLC): 95.4 %, t_R = 18.0 min.

7.2.36. 3-(2-Fluoroethyl)-3,4-dihydrodispiro[[2]benzopyran-1,1'-cyclohexan-4',2''-[1,3]dioxolan] (23)

A solution of alcohol **22** (55 mg, 0.18 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of DAST (0.05 mL, 0.38 mmol, 2.1 eq) in CH_2Cl_2 (10 mL) under N_2 atmosphere at -78 °C. After 1 h, the mixture was warmed to rt and stirred for 18 h. H_2O (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 1.5 cm, l = 19 cm, V = 5 mL, cyclohexane/ethyl acetate 90:10). Yellow oil, yield 27 mg (49 %). $C_{18}H_{23}FO_3$ (306.4 g/mol). R_f = 0.66 (cyclohexane/ethyl acetate 67:33). HR-MS (APCI): *m/z* = 307.1690 (calcd. 307.1704 for $C_{18}H_{24}FO_3$ [MH^+]). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.61 – 1.69 (m, 2H, 3'-*H*, 5'-*H*), 1.77 (ddt, *J* = 13.2/3.8/2.8 Hz, 1H, 2'-H_{equ}), 1.84 – 1.99 (m, 3H, 5'-*H*, 6'-*H*, CH_2CH_2F), 2.04 – 2.18 (m, 3H, 3'-*H*, 6'-*H*, CH_2CH_2F), 2.22 (td, *J* = 13.6/4.0 Hz, 1H, 2'-H_{ax}), 2.67 (dd, *J* = 15.8/2.8 Hz, 1H, 4-*H*), 2.76 (dd, *J* = 15.8/10.7 Hz, 1H, 4-*H*), 3.96 (ddt, *J* = 11.0/9.1/3.2 Hz, 1H, 3-*H*), 4.00 (s, 4H, OCH_2CH_2O), 4.63 (dddd, *J* = 46.8/9.5/5.5/4.3 Hz, 1H, CH_2CH_2F), 4.76 (dtd, *J* = 47.6/9.4/4.1 Hz, 1H, CH_2CH_2F), 7.05 – 7.09 (m, 1H, 5-*H*), 7.11 – 7.17 (m, 1H, 6-*H*), 7.17 – 7.22 (m, 2H, 7-*H*, 8-*H*). ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 30.6 (1C, *C*-3'), 30.7 (1C, *C*-5'), 32.9 (1C, *C*-6'), 35.7 (1C, *C*-4), 37.0 (d, *J* = 19.3 Hz, 1C, *C*H_2CH_2F), 37.3 (1C, *C*-2'), 64.0 (d, *J* = 4.7 Hz, 1C, *C*-3), 64.4 (1C, OCH_2CH_2O), 64.5 (1C,

OCH_2CH_2O), 75.1 (1C, *C*-1), 81.0 (d, *J* = 163.4 Hz, 1C, CH_2CH_2F), 108.7 (1C, *C*-4'), 125.3 (1C, *C*-8), 126.29 (1C, *C*-7), 126.32 (1C, *C*-6), 128.9 (1C, *C*-5), 133.5 ,(1C, *C*-4a) 142.0 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 2967, 2928, 2855 ($C\text{-}H_{alkyl}$), 1489, 1439 ($C{=}C_{arom}$). Purity (HPLC): 95.8 %, t_R = 22.4 min.

7.2.37. 3-(2-Fluoroethyl)-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-one (24)

A solution of ketal **23**(694 mg, 2.27 mmol) and 2 M HCl (20 mL, 40.0 mmol, 17.6 eq) in Et_2O (50 mL) was heated to reflux for 3 d. After cooling to rt, H_2O (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 4 cm, l = 18 cm, V = 30 mL, cyclohexane/ethyl acetate 90:10). Colorless solid, mp 105 °C, yield 566 mg (95 %). $C_{16}H_{19}FO_2$ (262.3 g/mol). R_f = 0.39 (cyclohexane/ethyl acetate 80:20). HR-MS (APCI): *m/z* = 263.1459 (calcd. 263.1442 for $C_{16}H_{20}FO_2$ [MH^+]). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.89 – 1.98 (m, 1H, CH_2CH_2F), 1.98 – 2.07 (m, 1H, 2'-*H*), 2.07 – 2.23 (m, 2H, 6'-*H*, CH_2CH_2F), 2.27 – 2.40 (m, 3H, 3'-*H*, 5'-*H*, 6'-*H*), 2.43 – 2.51 (m, 1H, 2'-*H*), 2.67 – 2.79 (m, 2H, 4-*H*, 3'-*H*), 2.83 (dd, *J* = 16.0/10.9 Hz, 1H, 4-*H*), 2.88 – 2.99 (m, 1H, 5'-*H*), 4.09 (ddt, *J* = 10.6/9.1/3.4 Hz, 1H, 3-*H*), 4.59 (ddd, *J* = 9.3/5.2/4.3 Hz, 0.5H, CH_2CH_2F), 4.70 (td, *J* = 9.6/4.4 Hz, 2 x 0.5H, CH_2CH_2F), 4.82 (td, *J* = 9.3/3.9 Hz, 0.5H, CH_2CH_2F), 7.05 – 7.10 (m, 1H, 8-*H*), 7.10 – 7.15 (m, 1H, 5-*H*), 7.15 – 7.23 (m, 2H, 6-*H*, 7-*H*). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 35.3 (1C, C-2'), 35.6 (1C, *C*-4), 36.9 (d, *J* = 19.2 Hz, 1C, CH_2CH_2F), 37.3 (1C, *C*-3'), 37.5 (1C, *C*-5'), 39.3 (1C, *C*-6'), 64.6 (d, *J* = 4.3 Hz, 1C, *C*-3), 74.7 (1C, *C*-1), 80.6 (d, *J* = 164.5 Hz, 1C, CH_2CH_2F), 124.7 (1C, *C*-8),

126.6 (1C, *C*-7), 126.8 (1C, *C*-6), 129.2 (1C, *C*-5), 133.4 (1C, *C*-4a), 140.4 (1C, *C*-8a), 211.9 (1C, *C*=O). FT-IR (neat): ν [cm^{-1}] = 2932, 2897 (C-H_{alkyl}), 1705 (C=O), 1493, 1439 (C=C_{arom}). Purity (HPLC): 97.0 %, t_R = 20.9 min.

7.2.38. *trans*-3-Methoxy-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-amine (25a)

A solution of amine **4a** (274 mg, 0.81 mmol) and 10 % Pd/C (36 mg, 0.03 mmol, 4 mol-%) in CH_3OH (20 mL) was stirred at rt for 20 h under H_2 atmosphere. The mixture was filtered through Celite, washed with CH_2Cl_2 (150 mL), concentrated in vacuo and the residue was purified by fc (d = 2 cm, l = 20 cm, V = 10 mL, CH_2Cl_2/CH_3OH 95:5 + 1 % *N*,*N*-dimethylethanamine). Pale yellow solid, mp 94 °C, yield 143 mg (72 %). $C_{15}H_{21}NO_2$ (247.3 g/mol). R_f = 0.09 (cyclohexane/ethyl acetate 67:33 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 248.1648 (calcd. 248.1645 for $C_{15}H_{22}NO_2$ [MH^+]). ^{1}H NMR (600 MHz, CD_3OD): δ (ppm) = 1.58 – 1.63 (m, 3H, 3'-*H*, 5'-*H*, 6'-*H*), 1.84 – 1.89 (m, 1H, 2'-*H*), 1.98 (td, *J* = 14.1/3.8 Hz, 1H, 2'-*H*), 2.11 – 2.20 (m, 1H, 3'-*H*), 2.20 – 2.30 (m, 2H, 5'-*H*, 6'-*H*), 2.80 (dd, *J* = 15.6/7.6 Hz, 1H, 4-*H*), 2.92 (dd, *J* = 15.6/3.1 Hz, 1H, 4-*H*), 3.26 (quint, *J* = 3.2 Hz, 1H, 4'-H_{equ}), 3.55 (s, 3H, OCH_3), 4.91 (dd, *J* = 7.6/3.1 Hz, 1H, 3-*H*), 7.08 (d, *J* = 7.5 Hz, 1H, 5-*H*), 7.15 (td, *J* = 7.4/1.3 Hz, 1H, 6-*H*), 7.18 – 7.22 (m, 1H, 7-*H*), 7.38 (dd, *J* = 7.7/1.3 Hz, 1H, 8-*H*). A signal for the NH_2 protons is not observed in the spectrum. ^{13}C NMR (151 MHz, CD_3OD): δ (ppm) = 28.8 (1C, *C*-5'), 29.0 (1C, *C*-3'), 31.0 (1C, *C*-2'), 33.6 (1C, *C*-6'), 36.2 (1C, *C*-4), 45.6 (1C, *C*-4'), 56.3 (1C, O*C*H_3), 78.0 (1C, *C*-1), 97.8 (1C, *C*-3), 126.1 (1C, *C*-8), 127.5 (1C, *C*-7), 127.6 (1C, *C*-6), 130.0 ,(1C, *C*-5) 132.4 (1C, *C*-4a), 143.4 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 3360 (N-H), 2947, 2870 (C-H_{alkyl}), 1562, 1447, 1431 (C=C_{arom}). Purity (HPLC): 96.4 %, t_R = 13.3 min.

7.2.39. *cis*-3-Methoxy-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-amine (25b)

A solution of amine **4b** (326 mg, 0.97 mmol) and 10 % Pd/C (41 mg, 0.04 mmol, 4 mol-%) in CH_3OH (20 mL) was stirred at rt for 19 h under H_2 atmosphere. The mixture was filtered through Celite, washed with CH_2Cl_2 (150 mL), concentrated in vacuo and the residue was purified by fc (d = 2 cm, l = 20 cm, V = 10 mL, CH_2Cl_2/CH_3OH 97:3 + 1 % *N*,*N*-dimethylethanamine). Pale yellow solid, mp 114 °C, yield 202 mg (89 %). $C_{15}H_{21}NO_2$ (247.3 g/mol). R_f = 0.17 (CH_2Cl_2/CH_3OH 95:5 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 248.1626 (calcd. 248.1645 for $C_{15}H_{22}NO_2$ [MH^+]). ^{1}H NMR (600 MHz, CD_3OD): δ (ppm) = 1.72 – 1.94 (m, 6H, 2'-H_{ax}, 3'-*H*, 5'-*H*, 6'-*H*), 1.99 – 2.07 (m, 1H, 6'-*H*), 2.11 (dq, *J* = 14.0/3.0 Hz, 1H, 2'-H_{equ}), 2.80 (dd, *J* = 15.7/7.3 Hz, 1H, 4-*H*), 2.92 (dd, *J* = 15.8/3.1 Hz, 1H, 4-*H*), 3.01 – 3.08 (m, 1H, 4'-H_{ax}), 3.56 (s, 3H, OCH_3), 4.91 (dd, *J* = 7.4/3.1 Hz, 1H, 3-*H*), 7.08 (d, *J* = 7.6 Hz, 1H, 5-*H*), 7.13 – 7.20 (m, 3H, 6-*H*, 7-*H*, 8-*H*). A signal for the NH_2 protons is not observed in the spectrum. ^{13}C NMR (151 MHz, CD_3OD): δ (ppm) = 29.9 (1C, *C*-3' or *C*-5'), 30.0 (1C, *C*-3' or *C*-5'), 36.1 (1C, *C*-4), 36.3 (1C, *C*-2'), 38.7 (1C, *C*-6'), 50.7 (1C, *C*-4'), 56.4 (1C, O*C*H_3), 76.7 (1C, *C*-1), 97.9 (1C, *C*-3), 125.6 (1C, *C*-8), 127.6 (1C, *C*-7), 127.8 (1C, *C*-6), 130.2 (1C, *C*-5), 132.6 (1C, *C*-4a), 142.2 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 3445, 3352 (N-H), 2928, 2859 (C-H_{alkyl}), 1574, 1443, 1385 (C=C_{arom}). Purity (HPLC, method 1): 98.6 %, t_R = 13.4 min.

7.2.40. *trans*-3-Methoxy-N-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-7-yl)-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-amine (27a)

A solution of ketone **26** (52 mg, 0.32 mmol), amine **25a** (77 mg, 0.31 mmol, 1.0 eq) and acetic acid (18 µL, 0.32 mmol, 1.0 eq) in CH_2Cl_2 (5 mL) was stirred under N_2 atmosphere at rt. After 30 min, $NaBH(OAc)_3$ (119 mg, 0.56 mmol, 1.8 eq) was added and the mixture was stirred for 3 h at rt. 1 M NaOH (15 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 2.5 cm, l = 20 cm, V = 10 mL, cyclohexane/ethyl acetate 80:20 + 1 % *N*,*N*-dimethylethanamine). Colorless oil, yield 58 mg (48 %). $C_{26}H_{33}NO_2$ (391.6 g/mol). R_f = 0.32 (cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 392.2599 (calcd. 392.2584 for $C_{26}H_{34}NO_2$ [MH^+]). ^{1}H NMR (400 MHz, CD_3OD): δ (ppm) = 1.25 – 1.37 (m, 2H, 6-$H_{benzannulene}$, 8-$H_{benzannulene}$), 1.64 (dt, *J* = 12.6/3.0 Hz, 1H, 2'-*H*), 1.71 – 1.78 (m, 2H, 3'-*H*, 5'-*H*), 1.85 – 1.92 (m, 1H, 6'-*H*), 1.96 (td, *J* = 13.5/3.6 Hz, 1H, 6'-*H*), 2.06 – 2.29 (m, 5H, 2'-*H*, 3'-*H*, 5'-*H*, 6-$H_{benzannulene}$, 8-$H_{benzannulene}$), 2.78 – 2.87 (m, 5H, 4-H, 5-$H_{benzannulene}$, 9-$H_{benzannulene}$), 2.89 – 2.98 (m, 2H, 4-*H*, 7-$H_{benzannulene}$), 3.18 (quint, *J* = 3.1 Hz, 1H, 4'-H_{equ}), 3.58 (s, 3H, O*C*H_3), 4.93 (dd, *J* = 7.5/3.2 Hz, 1H, 3-*H*), 7.08 – 7.14 (m, 5H, 5-*H*, 1-$H_{benzannulene}$, 2-$H_{benzannulene}$, 3-$H_{benzannulene}$, 4-$H_{benzannulene}$), 7.17 (td, *J* = 7.4/1.4 Hz, 1H, 6-*H*), 7.22 (td, *J* = 7.5/1.6 Hz, 1H, 7-*H*), 7.35 (dd, *J* = 7.7/1.4 Hz, 1H, 8-*H*). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (101 MHz, CD_3OD): δ (ppm) = 26.6 (1C, *C*-3'), 26.8 (1C, *C*-5'), 31.6 (1C, *C*-6'), 33.5 (2C, *C*-$5_{benzannulene}$, *C*-$9_{benzannulene}$), 34.2 (1C, *C*-2'), 35.7 (2C, *C*-$6_{benzannulene}$, *C*-$8_{benzannulene}$), 36.2 (1C, *C*-4), 48.5 (1C, *C*-4'), 56.3 (1C, O*C*H_3), 60.0 (1C, C-$7_{benzannulene}$), 78.0 (1C, *C*-1), 97.8 (1C, *C*-3), 126.0 (1C, *C*-8), 127.3 (2C, *C*-$2_{benzannulene}$, *C*-$3_{benzannulene}$), 127.5 (1C, *C*-7), 127.6 (1C, *C*-6), 129.8 (2C, *C*-$1_{benzannulene}$, *C*-$4_{benzannulene}$), 130.0 (1C, *C*-5), 132.4 (1C, *C*-4a), 143.4 (1C, *C*-8a), 143.7 (2C, *C*-$4a_{benzannulene}$, *C*-$9a_{benzannulene}$). FT-IR (neat): ν [cm^{-1}] = 3314 (N-H), 2924,

2843 (C-H_{alkyl}), 1489, 1443 (C=C_{arom}). Purity (HPLC, method 1): 99.1 %, t_R = 20.0 min.

7.2.41. *cis*-3-Methoxy-*N*-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-7-yl)-3,4-dihydrospiro([2]benzopyran-1,1'-cyclohexan)-4'-amine (27b)

A solution of ketone **26** (50.0 mg, 0.31 mmol, 1.0 eq), amine **25b** (77.0 mg, 0.31 mmol, 1.0 eq) and $NaBH(OAc)_3$ (132 mg, 0.62 mmol, 2.0 eq) in CH_2Cl_2 (4 mL) was stirred for 12 h at rt. A saturated solution of $NaHCO_3$ (10 mL) and CH_2Cl_2 (5 mL) were added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 2 cm, l = 25 cm, V = 7 mL, cyclohexane:ethyl acetate = 20:80 + 1 % *N*,*N*-dimethylethanamine). Colorless solid, mp 132 °C, yield 34 mg (28 %). $C_{26}H_{33}NO_2$ (391.6). R_f = 0.36 (cyclohexane:ethyl acetate = 1:9 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): m/z = 392.2572 (calcd. 392.2584 for $C_{26}H_{34}NO_2$ $[M+H]^+$). ^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 1.18 - 1.26 (m, 2H, 6-$H_{benzannulene}$, 8-$H_{benzannulene}$), 1.66 - 1.80 (m, 3H, 3'-*H*, 5'-*H*, 6'-*H*), 1.82 - 1.89 (m, 3H, 2'-*H*, 3'-*H*, 5'-*H*), 2.01 (dt, *J* = 13.6/4.2 Hz, 1H, 2'-*H*), 2.10 (dt, *J* = 10.5/3.0 Hz, 1H, 6'-*H*), 2.16 - 2.23 (m, 2H, 6-$H_{benzannulene}$, 8-$H_{benzannulene}$), 2.77 - 2.89 (m, 6H, 5-$H_{benzannulene}$, 9-$H_{benzannulene}$, 4'-H_{ax}, 4-*H*), 2.91 (dd, *J* = 15.6/3.0 Hz, 1H, 4-*H*), 3.01 (tt, *J* = 10.6/3.5 Hz, 1H, 7-$H_{benzannulene}$), 3.57 (s, 3H, OCH_3), 4.90 (dd, *J* = 7.5/3.1 Hz, 1H, 3-*H*), 7.05 - 7.10 (m, 5H, 5-*H*, 1-$H_{benzannulene}$, 2-$H_{benzannulene}$, 3-$H_{benzannulene}$, 4-$H_{benzannulene}$), 7.13 - 7.20 (m, 3H, 6-*H*, 7-*H*, 8-*H*). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 29.5 (1C, *C*-3'), 29.7 (1C, *C*-5'), 33.4 (2C, *C*-5$_{benzannulene}$, *C*-9$_{benzannulene}$), 35.51 (1C, *C*-6$_{benzannulene}$ or *C*-8$_{benzannulene}$), 35.53 (1C, *C*-6$_{benzannulene}$ or *C*-8$_{benzannulene}$), 36.2 (1C, *C*-4), 36.8 (1C,

C-6‘), 39.3 (1C, *C*-2’), 53.5 (1C, *C*-4’). 56.5 (1C, O*C*H$_3$), 59.0 (1C, *C*-7$_{benzannulene}$), 77.6 (1C, *C*-1), 97.8 (1C, *C*-3), 125.7 (1C, *C*-8), 127.3 (2C, *C*-2$_{benzannulene}$, *C*-3$_{benzannulene}$), 127.5 (1C, *C*-6), 127.6 (1C, *C*-7), 129.8 (2C, *C*-1$_{benzannulene}$, *C*-4$_{benzannulene}$), 130.1 (1C, *C*-5), 132.6 (1C, *C*-4a), 142.8 (1C, *C*-8a), 143.6 (2C, *C*-4a$_{benzannulene}$, *C*-9a$_{benzannulene}$). FT-IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3024, 2924 (C-H), 1489, 1443 (C=C). Purity (HPLC): 95.3 %, t_R = 19.9 min.

7.2.42. *trans*-N-Benzyl-3-(2-fluoroethyl)-3,4-dihydrospiro[[2]benzopyran-1,1’-cyclohexan]-4’-amine (28a) and *cis*-N-Benzyl-3-(2-fluoroethyl)-3,4-dihydrospiro[[2]benzopyran-1,1’-cyclohexan]-4’-amine (28b)

A solution of ketone **24** (248 mg, 0.94 mmol), benzylamine (distilled, 0.16 mL, 1.47 mmol, 1.6 eq), acetic acid (59 µL, 1.04 mmol, 1.1 eq) and NaBH(OAc)$_3$ (366 mg, 1.73 mmol, 1.8 eq) in THF (20 mL) was stirred under N_2 atmosphere at rt. After 3 h, 1 M NaOH (15 mL) was added and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 4 cm, l = 16 cm, V = 20 mL, cyclohexane/ethyl acetate 80:20 + 1 % *N*,*N*-dimethylethanamine → 67:33 + 1 % *N*,*N*-dimethylethanamine). **28a** was eluted first and **28b** afterwards.

trans-**28a**: Colorless oil, yield 148 mg (45 %). $C_{23}H_{28}FNO$ (353.8 g/mol). R_f = 0.57 (cyclohexane/ethyl acetate 67:33 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 354.2224 (calcd. 354.2228 for $C_{23}H_{29}FNO$ [MH$^+$]). ^{1}H NMR (600 MHz, CD_3OD): δ (ppm) = 1.45 (dq, *J* = 13.6/3.2 Hz, 1H, 2’-*H*$_{equ}$), 1.64 – 1.73 (m, 2H, 3’-*H*, 5’-*H*), 1.82 – 1.96 (m, 4H, 5’-*H*, 6’-*H*, C*H*$_2$CH$_2$F), 2.00 – 2.11 (m, 2H, 3’-*H*, C*H*$_2$CH$_2$F), 2.29 (td, *J* = 13.7/4.0 Hz, 1H, 2’-*H*$_{ax}$), 2.65 – 2.69 (m, 2H, 4-*H*), 2.92 (quint, *J* = 3.2 Hz, 1H, 4’-*H*$_{equ}$), 3.82 (s, 2H, ArC*H*$_2$NH), 3.94 (tdd, *J* = 8.8/5.3/3.5 Hz, 1H, 3-*H*), 4.61 (dddd, *J* =

47.0/9.2/5.5/4.8 Hz, 1H, CH_2CH_2F), 4.72 (dtd, *J* = 47.7/9.0/4.4 Hz, 1H CH_2CH_2F), 7.05 (d, *J* = 7.5 Hz, 1H, 5-*H*), 7.10 (td, *J* = 7.4/1.3 Hz, 1H, 6-*H*), 7.16 (t, *J* = 7.7 Hz, 1H, 7-*H*), 7.24 – 7.29 (m, 1H, 4-H_{benzyl}), 7.33 – 7.38 (m, 3H, 8-*H*, 3-H_{benzyl}, 5-H_{benzyl}), 7.39 – 7.43 (m, 2H, 2-H_{benzyl}, 6-H_{benzyl}). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, CD_3OD): δ (ppm) = 26.1 (1C, *C*-3'), 26.2 (1C, *C*-5'), 30.0 (1C, *C*-6'), 34.4 (1C, *C*-2'), 36.6 (1C, *C*-4), 38.1 (d, *J* = 19.6 Hz, 1C, CH_2CH_2F), 51.3 (1C, *C*-4'), 52.3 (1C, $ArCH_2NH$), 65.1 (d, *J* = 5.0 Hz, 1C, *C*-3), 76.9 (1C, *C*-1), 81.7 (d, *J* = 163.2 Hz, 1C, CH_2CH_2F), 126.5 (1C, *C*-8), 127.0 (1C, *C*-6), 127.2 (1C, *C*-7), 128.0 (1C, *C*-4_{benzyl}), 129.4 (2C, *C*-3_{benzyl}, *C*-5_{benzyl}), 129.6 (3C, *C*-5, *C*-2_{benzyl}, *C*-6_{benzyl}), 134.3 (1C, *C*-4a), 141.3 (1C, *C*-1_{benzyl}), 144.2 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 3317 (N-H), 2978, 2924, 2893 (C-H_{alkyl}), 1489, 1450 (C=C_{arom}). Purity (HPLC, method 1): 98.8 %, t_R = 19.2 min.

cis-**28b**: Colorless oil, yield 150 mg (45 %). $C_{23}H_{28}FNO$ (353.8 g/mol). R_f = 0.22 (cyclohexane/ethyl acetate 67:33 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 354.2221 (calcd. 354.2228 for $C_{23}H_{29}FNO$ [MH^+]). ^{1}H NMR (400 MHz, CD_3OD): δ (ppm) = 1.56 – 1.69 (m, 2H, 2'-*H*, 3'-*H*), 1.70 – 1.79 (m, 1H, 6'-*H*), 1.80 – 2.02 (m, 5H, 3'-*H*, 5'-*H*, 6'-*H*, CH_2CH_2F), 2.03 – 2.13 (m, 1H, CH_2CH_2F), 2.13 – 2.20 (m, 1H, 2'-*H*), 2.64 – 2.77 (m, 3H, 4-*H*, 4'-H_{ax}), 3.86 (s, 2H, $ArCH_2NH$), 3.96 (tdd, *J* = 8.9/5.6/3.5 Hz, 1H, 3-*H*), 4.67 (dddd, *J* = 46.9/10.1/6.0/4.5 Hz, 1H, CH_2CH_2F), 4.83 (dtd, *J* = 47.8/9.2/4.7 Hz, 1H, CH_2CH_2F), 7.06 – 7.10 (m, 1H, 5-*H*), 7.10 – 7.19 (m, 3H, 6-*H*, 7-*H*, 8-*H*), 7.26 – 7.32 (m, 1H, 4-H_{benzyl}), 7.34 – 7.43 (m, 4H, 2-H_{benzyl}, 3-H_{benzyl}, 5-H_{benzyl}, 6-H_{benzyl}). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (101 MHz, CD_3OD): δ (ppm) = 28.7 (1C, *C*-5'), 28.8 (1C, *C*-3'), 34.8 (1C, *C*-2'), 36.6 (1C, *C*-4), 38.1 (d, *J* = 19.5 Hz, 1C, CH_2CH_2F), 39.3 (1C, *C*-6'), 51.5 (1C, $ArCH_2NH$), 56.4 (1C, *C*-4'), 65.2 (d, *J* = 5.3 Hz, 1C, *C*-3), 76.4 (1C, *C*-1), 81.8 (d, *J* =

162.6 Hz, 1C, CH_2CH_2F), 126.1 (1C, *C*-8), 127.1 (1C, *C*-6 or *C*-7), 127.2 (1C, *C*-6 or *C*-7), 128.1 (1C, $C\text{-}4_{benzyl}$), 129.52 (2C, $C\text{-}2_{benzyl}$ and $C\text{-}6_{benzyl}$ or $C\text{-}3_{benzyl}$ and $C\text{-}5_{benzyl}$), 129.53 (2C, $C\text{-}2_{benzyl}$ and $C\text{-}6_{benzyl}$ or $C\text{-}3_{benzyl}$ and $C\text{-}5_{benzyl}$), 129.7 (1C, *C*-5), 134.7 (1C, *C*-4a), 140.9 (1C, $C\text{-}1_{benzyl}$), 143.4 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 3059 (N-H), 2924, 2855 ($C\text{-}H_{alkyl}$), 1489, 1450 ($C{=}C_{arom}$). Purity (HPLC): 98.2 %, t_R = 19.2 min.

7.2.43. *trans*-3-(2-Fluoroethyl)-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-amine (29a)

A solution of amine **28a** (118 mg, 0.33 mmol), ammonium formate (102 mg, 1.61 mmol, 4.9 eq) and 10 % Pd/C (15 mg, 0.01 mmol, 4 mol-%) in CH_3OH (15 mL) was heated to reflux for 2 h under N_2 atmosphere. After cooling to rt, the mixture was filtered through Celite, washed with CH_2Cl_2 (100 mL) and concentrated in vacuo. 0.1 M NaOH (60 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Yellow oil, yield 83 mg (96 %). $C_{16}H_{22}FNO$ (263.4 g/mol). R_f = 0.06 (cyclohexane/ethyl acetate 67:33 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 264.1753 (calcd. 264.1758 for $C_{16}H_{23}FNO$ [MH^+]). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.43 – 1.57 (m, 3H, 2'-*H*, 3'-*H*, 5'-*H*), 1.83 – 2.01 (m, 4H, 5'-*H*, 6'-*H*, CH_2CH_2F), 2.02 – 2.16 (m, 2H, 3'-H, CH_2CH_2F), 2.31 (td, *J* = 13.5/4.2 Hz, 1H, 2'-*H*), 2.66 (dd, *J* = 15.8/3.2 Hz, 1H, 4-*H*), 2.74 (dd, *J* = 15.9/10.6 Hz, 1H, 4-*H*), 3.32 – 3.37 (m, 1H, $4'\text{-}H_{equ}$), 3.95 (ddt, *J* = 10.6/9.3/3.4 Hz, 1H, 3-*H*), 4.58 (ddd, *J* = 9.1/5.7/4.3 Hz, 0.5H, CH_2CH_2F), 4.67 – 4.73 (m, 2 x 0.5H, CH_2CH_2F), 4.82 (td, *J* = 9.1/4.4 Hz, 0.5H, CH_2CH_2F), 7.04 – 7.08 (m, 1H, 5-*H*), 7.13 (td, *J* = 7.3/1.6 Hz, 1H, 6-*H*), 7.16 – 7.21 (m, 1H, 7-*H*), 7.23 (dd, *J* = 7.7/1.7 Hz, 1H, 8-*H*). A signal for the NH_2

protons is not observed in the spectrum. ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 28.4 (1C, *C*-3'), 28.5 (1C, *C*-5'), 28.6 (1C, *C*-6'), 32.8 (1C, *C*-2'), 35.8 (1C, *C*-4), 37.1 (d, *J* = 19.4 Hz, 1C, *C*H_2CH_2F), 44.5 (1C, *C*-4'), 63.8 (d, *J* = 5.0 Hz, 1C, *C*-3), 75.8 (1C, *C*-1), 81.0 (d, *J* = 163.7 Hz, 1C, CH_2*C*H_2F), 125.5 (1C, *C*-8), 126.2 (1C, *C*-6), 126.3 (1C, *C*-7), 128.8 (1C, *C*-5), 133.3 (1C, *C*-4a), 143.1 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 3372 (N-H), 2920, 2851 (C-H_{alkyl}), 1489, 1439 (C=C_{arom}). Purity (HPLC): 94.4 %, t_R = 15.6 min.

7.2.44. *cis*-3-(2-Fluoroethyl)-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-amine (29b)

A solution of amine **28b** (137 mg, 0.39 mmol), ammonium formate (125 mg, 1.99 mmol, 5.1 eq) and 10 % Pd/C (17 mg, 0.02 mmol, 4 mol-%) in CH_3OH (15 mL) was heated to reflux for 4.5 h under N_2 atmosphere. After cooling to rt, the mixture was filtered through Celite, washed with CH_2Cl_2 (100 mL) and concentrated in vacuo. 0.1 M NaOH (60 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Yellow oil, yield 90 mg (88 %). $C_{16}H_{22}FNO$ (263.4 g/mol). R_f = 0.06 (cyclohexane/ethyl acetate 67:33 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 264.1748 (calcd. 264.1758 for $C_{16}H_{23}FNO$ [MH^+]). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.45 – 1.60 (m, 2H, 2'-*H*, 3'-*H*), 1.60 – 1.81 (m, 4H, 3'-*H*, 5'-*H*, 6'-*H*), 1.85 – 2.12 (m, 3H, 6'-H, CH_2CH_2F), 2.12 – 2.19 (m, 1H, 2'-*H*), 2.66 (dd, *J* = 15.8/3.1 Hz, 1H, 4-*H*), 2.75 (dd, *J* = 15.8/10.7 Hz, 1H, 4-*H*), 2.82 (tt, *J* = 11.3/10.6/4.6 Hz, 1H, 4'-H_{ax}), 3.94 (ddt, *J* = 10.6/9.1/3.4 Hz, 1H, 3-*H*), 4.59 (ddd, *J* = 9.0/5.6/4.4 Hz, 0.5H, CH_2CH_2F), 4.68 – 4.76 (m, 2 x 0.5H, CH_2CH_2F), 4.84 (td, *J* = 9.0/4.4 Hz, 0.5H, CH_2CH_2F), 7.04 – 7.12 (m, 2H, 5-*H*, 8-*H*), 7.12 – 7.20 (m, 2H, 6-*H*, 7-*H*). A signal for

the NH_2 protons is not observed in the spectrum. ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 32.1 (1C, *C*-5'), 32.2 (1C, *C*-3'), 34.4 (1C, *C*-2'), 35.7 (1C, *C*-4), 37.1 (d, *J* = 19.4 Hz, 1C, CH_2CH_2F), 38.7 (1C, *C*-6'), 50.4 (1C, *C*-4'), 64.0 (d, *J* = 4.9 Hz, 1C, *C*-3), 74.9 (1C, *C*-1), 81.1 (d, *J* = 163.7 Hz, 1C, CH_2CH_2F), 125.1 (1C, *C*-8), 126.2 (1C, *C*-6 or *C*-7), 126.3 (1C, *C*-6 or *C*-7), 128.9 (1C, *C*-5), 133.6 (1C, *C*-4a), 142.4 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 3356 (N-H), 2924, 2855 (C-H_{alkyl}), 1516, 1447 (C=C_{arom}). Purity (HPLC): 96.0 %, t_R = 15.2 min.

7.2.45. *trans*-3-(2-Fluoroethyl)-N-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-7-yl)-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-amine (30a)

A solution of ketone **26** (25 mg, 0.16 mmol), amine **29a** (42 mg, 0.16 mmol, 1.0 eq), acetic acid (10 µL, 0.18 mmol, 1.1 eq) and $NaBH(OAc)_3$ (62 mg, 0.29 mmol, 1.8 eq) in CH_2Cl_2 (3 mL) was stirred under N_2 atmosphere at rt. After 21 h, 1 M NaOH (3 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 2 cm, l = 19 cm, V = 10 mL, cyclohexane/ethyl acetate 90:10 + 1 % *N*,*N*-dimethylethanamine). Colorless oil, yield 50 mg (76 %). $C_{27}H_{34}FNO$ (407.6 g/mol). R_f = 0.34 (cyclohexane/ethyl acetate 67:33 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI): *m/z* = 408.2668 (calcd. 408.2697 for $C_{27}H_{35}FNO$ [MH^+]). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.22 – 1.39 (m, 2H, 6-$H_{benzannulene}$, 8-$H_{benzannulene}$), 1.46 – 1.53 (m, 1H, 2'-*H*), 1.53 – 1.65 (m, 2H, 3'-*H*, 5'-*H*), 1.81 – 2.14 (m, 6H, 3'-*H*, 5'-*H*, 6'-*H*, CH_2CH_2F), 2.14 – 2.24 (m, 2H, 6-$H_{benzannulene}$, 8-$H_{benzannulene}$), 2.30 (td, *J* = 13.3/3.6 Hz, 1H, 2'-*H*), 2.65 (dd, *J* = 16.2/3.1 Hz, 1H, 4-*H*), 2.69 – 2.80 (m, 3H, 4-*H*, 5-$H_{benzannulene}$, 9-$H_{benzannulene}$), 2.80 – 2.89 (m, 3H, 5-$H_{benzannulene}$, 7-$H_{benzannulene}$, 9-$H_{benzannulene}$), 3.13 – 3.19 (m, 1H, 4'-H_{equ}), 3.96 (ddt, *J* =

10.6/9.2/3.3 Hz, 1H, 3-*H*), 4.60 (dddd, *J* = 49.9/9.0/5.7/4.3 Hz, 1H, CH_2CH_2F), 4.78 (dtd, *J* = 47.4/9.1/4.4 Hz, 1H, CH_2CH_2F), 7.06 (d, *J* = 7.3 Hz, 1H, 5-*H*), 7.09 – 7.16 (m, 5H, 6-*H*, 1-$H_{benzannulene}$, 2-$H_{benzannulene}$, 3-$H_{benzannulene}$, 4-$H_{benzannulene}$), 7.16 – 7.22 (m, 2H, 7-*H*, 8-*H*). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 26.4 (1C, *C*-3'), 26.6 (1C, *C*-5'), 29.2 (1C, *C*-6'), 32.7 (2C, *C*-$5_{benzannulene}$, *C*-$9_{benzannulene}$), 33.5 (1C, *C*-2'), 35.4 (2C, *C*-$6_{benzannulene}$, *C*-$8_{benzannulene}$), 35.8 (1C, *C*-4), 37.1 (d, *J* = 19.3 Hz, 1C, CH_2CH_2F), 47.4 (1C, *C*-4'), 58.2 (1C, *C*-$7_{benzannulene}$), 63.8 (d, *J* = 5.1 Hz, 1C, *C*-3), 76.0 (1C, *C*-1), 81.1 (d, *J* = 163.7 Hz, 1C, CH_2CH_2F), 125.5 (1C, *C*-8), 126.1 (1C, *C*-6), 126.3 (3C, *C*-7, *C*-$2_{benzannulene}$, *C*-$3_{benzannulene}$), 128.7 (1C, *C*-5), 129.0 (2C, *C*-$1_{benzannulene}$, *C*-$4_{benzannulene}$), 133.3 (1C, *C*-4a), 142.8 (2C, *C*-$4a_{benzannulene}$, *C*-$9a_{benzannulene}$), 143.3 (1C, *C*-8a). FT-IR (neat): ν [cm^{-1}] = 3318 (N-H), 2924, 2843 (C-H_{alkyl}), 1489, 1450 (C=C_{arom}). Purity (HPLC): 96.8 %, t_R = 21.3 min.

7.2.46. *trans*-3-(2-Fluoroethyl)-N-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-7-yl)-3,4-dihydrospiro[[2]benzopyran-1,1'-cyclohexan]-4'-amine (30b)

A solution of ketone **26** (25 mg, 0.15 mmol), amine **29b** (43 mg, 0.16 mmol, 1.1 eq), acetic acid (10 µL, 0.18 mmol, 1.1 eq) and $NaBH(OAc)_3$ (59 mg, 0.28 mmol, 1.9 eq) in CH_2Cl_2 (3 mL) was stirred under N_2 atmosphere at rt. After 22 h, 1 M NaOH (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (d = 2 cm, l = 20 cm, V = 10 mL, cyclohexane/ethyl acetate 80:20 + 1 % *N*,*N*-dimethylethanamine → 67:33 + 1 % *N*,*N*-dimethylethanamine). Colorless oil, yield 49 mg (81 %). $C_{27}H_{34}FNO$ (407.6 g/mol). R_f = 0.47 (cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine). HR-MS (APCI):

m/z = 408.2656 (calcd. 408.2697 for $C_{27}H_{35}FNO$ [MH^+]). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.28 – 1.39 (m, 2H, 6-*H*$_{benzannulene}$, 8-*H*$_{benzannulene}$), 1.44 – 1.55 (m, 1H, 3'-*H*), 1.60 (td, *J* = 13.7/3.2 Hz, 1H, 2'-*H*), 1.65 – 1.75 (m, 1H, 5'-*H*), 1.75 – 1.85 (m, 3H, 3'-*H*, 5'-*H*, 6'-*H*), 1.85 – 2.10 (m, 3H, 6'-H, C*H*$_2$CH$_2$F), 2.10 – 2.23 (m, 3H, 2'-*H*, 6-*H*$_{benzannulene}$, 8-*H*$_{benzannulene}$), 2.66 (dd, *J* = 15.8/3.0 Hz, 1H, 4-*H*), 2.70 – 2.88 (m, 6H, 4-*H*, 4'-*H*$_{ax}$, 5-*H*$_{benzannulene}$, 9-*H*$_{benzannulene}$), 2.92 – 3.02 (m, 1H, 7-*H*$_{benzannulene}$), 3.95 (ddt, *J* = 11.7/8.8/3.4 Hz, 1H, 3-*H*), 4.65 (ddt, *J* = 46.7/9.0/5.5/4.5 Hz, 1H, CH$_2$C*H*$_2$F), 4.85 (dtd, *J* = 47.5/9.0/4.4 Hz, 1H, CH$_2$C*H*$_2$F), 7.07 (d, *J* = 7.3 Hz, 1H, 5-*H*), 7.09 – 7.16 (m, 6H, 6-*H*, 8-*H*, 1-*H*$_{benzannulene}$, 2-*H*$_{benzannulene}$, 3-*H*$_{benzannulene}$, 4-*H*$_{benzannulene}$), 7.16 – 7.22 (m, 1H, 7-*H*). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 29.6 (1C, *C*-3' or *C*-5'), 29.7 (1C, *C*-3' or *C*-5'), 32.6 (2C, *C*-5$_{benzannulen}$, *C*-9$_{benzannulen}$), 34.5 (1C, *C*-2'), 35.2 (2C, *C*-6$_{benzannulen}$, *C*-8$_{benzannulen}$), 35.7 (1C, *C*-4), 37.0 (d, *J* = 19.3 Hz, 1C, *C*H$_2$CH$_2$F), 38.9 (1C, *C*-6'), 53.3 (1C, *C*-4'), 58.0 (1C, *C*-7$_{benzannulen}$), 64.1 (d, *J* = 4.8 Hz, 1C, *C*-3), 75.4 (1C, *C*-1), 81.1 (d, *J* = 163.6 Hz, 1C, CH$_2$*C*H$_2$F), 125.1 (1C, *C*-8), 126.2 (1C, *C*-6 or *C*-7), 126.27 (1C, *C*-6 or *C*-7), 126.32 (2C, *C*-2$_{benzannulen}$, *C*-3$_{benzannulen}$), 128.9 (1C, *C*-5), 129.0 (2C, *C*-1$_{benzannulen}$, *C*-4$_{benzannulen}$), 133.7 (1C, *C*-4a), 142.5 (1C, *C*-8a), 142.7 (2C, *C*-4a$_{benzannulen}$, *C*-9a$_{benzannulen}$). FT-IR (neat): ν [cm^{-1}] = 3059 (N-H), 2924, 2847 (C-H$_{alkyl}$), 1489, 1447 (C=C$_{arom}$). Purity (HPLC): 98.8 %, t_R = 21.4 min.

7.3. X-Ray diffraction

For compound *trans*-**6e** data sets were collected with an APEX II CCD diffractometer. For compound *cis*-**6f** data sets were collected with a D8 Venture Dual Source 100

CMOS diffractometer. Programs used: data collection: *APEX3* V2016.1-0 (Bruker AXS Inc., **2016**);[58] cell refinement: *SAINT* V8.37A (Bruker AXS Inc., **2015**);[59] data reduction: *SAINT* V8.37A (Bruker AXS Inc., **2015**);[59] absorption correction, *SADABS* V2014/7 (Bruker AXS Inc., **2014**);[60] structure solution *SHELXT*-2015 (Sheldrick, **2015**);[61] structure refinement *SHELXL*-2015 (Sheldrick, **2015**)[61] and graphics, *XP* (Bruker AXS, **1998**).[62] *R*-values are given for observed reflections, and *w*R^2 values are given for all reflections.

7.3.1. X-ray crystal structure analysis of *trans*-6e (dan8992)

A colorless prism-like specimen of $C_{26}H_{33}NO_4$, approximate dimensions 0.200 mm x 0.200 mm x 0.230 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 1635 frames were collected. The total exposure time was 24.64 hours. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 34283 reflections to a maximum θ angle of 66.67° (0.84 Å resolution), of which 3931 were independent (average redundancy 8.721, completeness = 99.9%, R_{int} = 4.32%, R_{sig} = 2.24%) and 3521 (89.57%) were greater than $2\sigma(F^2)$. The final cell constants of a = 13.7232(4) Å, b = 6.5580(2) Å, c = 24.7015(7) Å, β = 93.5540(10)°, volume = 2218.78(11) $Å^3$, are based upon the refinement of the XYZ-centroids of 9967 reflections above 20 σ(I) with 7.186° < 2θ < 133.1°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.889. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.8600 and 0.8770. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P2_{1/n}$, with Z = 4 for the formula

unit, $C_{26}H_{33}NO_4$. The final anisotropic full-matrix least-squares refinement on F^2 with 283 variables converged at R1 = 3.88%, for the observed data and wR2 = 9.74% for all data. The goodness-of-fit was 1.043. The largest peak in the final difference electron density synthesis was 0.342 e-/Å^3 and the largest hole was -0.203 e-/Å^3 with an RMS deviation of 0.040 e-/Å^3. On the basis of the final model, the calculated density was 1.268 g/cm^3 and F(000), 912 e$^-$. CCDC number: 1855388.

7.3.2. X-ray crystal structure analysis of *cis*-6f (dan8995)

A colorless plate-like specimen of $C_{26}H_{33}NO_4$, approximate dimensions 0.094 mm x 0.279 mm x 0.327 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 1121 frames were collected. The total exposure time was 16.57 hours. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 24421 reflections to a maximum θ angle of 68.34° (0.83 Å resolution), of which 4026 were independent (average redundancy 6.066, completeness = 99.5%, R_{int} = 3.12%, R_{sig} = 2.26%) and 3798 (94.34%) were greater than 2σ(F^2). The final cell constants of a = 21.9660(9) Å, b = 6.2458(3) Å, c = 32.4538(13) Å, β = 99.1270(10)°, volume = 4396.1(3) Å^3, are based upon the refinement of the XYZ-centroids of 9316 reflections above 20 σ(I) with 5.516° < 2θ < 136.6°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.893. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.8080 and 0.9390. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group *C*2/*c*, with Z = 8 for the formula unit, $C_{26}H_{33}NO_4$. The final anisotropic full-matrix least-squares refinement on F^2 with

283 variables converged at R1 = 3.56%, for the observed data and wR2 = 8.99% for all data. The goodness-of-fit was 1.055. The largest peak in the final difference electron density synthesis was 0.267 $e^-/Å^3$ and the largest hole was -0.215 $e^-/Å^3$ with an RMS deviation of 0.046 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.280 g/cm^3 and F(000), 1824 e^-. CCDC number: 1855389.

7.4. *In Vitro* studies

7.4.1. Receptor binding studies

7.4.1.1. Materials

Guinea pig brains and rat livers were commercially available (Harlan-Winkelmann, Borchen, Germany). Homogenizers: Elvehjem Potter (B. Braun Biotech International, Melsungen, Germany) and Soniprep® 150, MSE, London, UK). Centrifuges: Cooling centrifuge Eppendorf 5424R (Eppendorf, Hamburg, Germany) and High-speed cooling centrifuge model Sorvall® RC-5C plus (Thermo Fisher Scientific, Langenselbold, Germany). Multiplates: standard 96 well multiplates (Diagonal, Muenster, Germany). Shaker: self-made device with adjustable temperature and tumbling speed (scientific workshop of the institute). Harvester: MicroBeta® FilterMate 96 Harvester. Filter: Printed Filtermat Typ A and B. Scintillator: Meltilex® (Typ A or B) solid state scintillator. Scintillation analyzer: MicroBeta® Trilux (all Perkin Elmer LAS, Rodgau-Jügesheim, Germany).

7.4.1.1.1. Preparation of membrane homogenates from guinea pig brain

5 guinea pig brains were homogenized with the potter (500-800 rpm, 10 up and down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at

1,200 x g for 10 min at 4 °C. The supernatant was separated and centrifuged at 23,500 x g for 20 min at 4 °C. The pellet was resuspended in 5-6 volumes of buffer (50 mM TRIS, pH 7.4) and centrifuged again at 23,500 x g (20 min, 4 °C). This procedure was repeated twice. The final pellet was resuspended in 5-6 volumes of buffer and frozen (-80 °C) in 1.5 mL portions containing about 1.5 mg protein/mL.

7.4.1.1.2. Preparation of membrane homogenates from rat liver

Two rat livers were cut into small pieces and homogenized with the potter (500-800 rpm, 10 up and down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1,200 x g for 10 min at 4 °C. The supernatant was separated and centrifuged at 31,000 x g for 20 min at 4 °C. The pellet was resuspended in 5-6 volumes of buffer (50 mM TRIS, pH 8.0) and incubated at rt for 30 min. After the incubation, the suspension was centrifuged again at 31,000 x g for 20 min at 4 °C. The final pellet was resuspended in 5-6 volumes of buffer and stored at -80 °C in 1.5 mL portions containing about 2 mg protein/mL.

7.4.1.2. Protein determination

The protein concentration was determined by the method of Bradford,[63] modified by Stoscheck.[64] The Bradford solution was prepared by dissolving 5 mg of Coomassie Brilliant Blue G 250 in 2.5 mL of EtOH (95 %, v/v). 10 mL deionized H_2O and 5 mL phosphoric acid (85 %, m/v) were added to this solution, the mixture was stirred and filled to a total volume of 50 mL with deionized water. The calibration was carried out using bovine serum albumin as a standard in 9 concentrations (0.1, 0.2, 0.4, 0.6, 0.8, 1.0, 1.5, 2.0 and 4.0 mg /mL). In a 96 well standard multiplate, 10 µL of the

calibration solution or 10 µL of the membrane receptor preparation were mixed with 190 µL of the Bradford solution, respectively. After 5 min, the UV absorption of the protein-dye complex at λ = 595 nm was measured with a plate reader (Tecan Genios®, Tecan, Crailsheim, Germany).

7.4.1.3. General procedures for binding assays

The test compound solutions were prepared by dissolving approximately 10 µmol (usually 2-4 mg) of test compound in DMSO so that a 10 mM stock solution was obtained. To obtain the required test solutions for the assay, the DMSO stock solution was diluted with the respective assay buffer. The filtermats were presoaked in 0.5 % aqueous polyethylenimine solution for 2 h at rt before use. All binding experiments were carried out in duplicates in the 96 well multiplates. The concentrations given are the final concentration in the assay. Generally, the assays were performed by addition of 50 µL of the respective assay buffer, 50 µL of test compound solution in various concentrations (10^{-5}, 10^{-6}, 10^{-7}, 10^{-8}, 10^{-9} and 10^{-10} mol/L), 50 µL of the corresponding radioligand solution and 50 µL of the respective receptor preparation into each well of the multiplate (total volume 200 µL). The receptor preparation was always added last. During the incubation, the multiplates were shaken at a speed of 500-600 rpm at the specified temperature. Unless otherwise noted, the assays were terminated after 120 min by rapid filtration using the harvester. During the filtration, each well was washed five times with 300 µL of water. Subsequently, the filtermats were dried at 95 °C. The solid scintillator was melted on the dried filtermats at a temperature of 95 °C for 5 min. After solidifying of the scintillator at rt, the trapped radioactivity in the filtermats was measured with the scintillation analyzer. Each position on the filtermat corresponding to one well of the

multiplate was measured for 5 min with the [^{3}H]-counting protocol. The overall counting efficiency was 20 %. The IC_{50} values were calculated with the program GraphPad Prism® 3.0 (GraphPad Software, San Diego, CA, USA) by non-linear regression analysis. Subsequently, the IC_{50} values were transformed into K_i values using the equation of Cheng and Prusoff.[65] The K_i values are given as mean value ± SEM from three independent experiments.

7.4.1.4. σ_1 receptor affinity

The assay was performed with the radioligand [^{3}H]-(+)-pentazocine (22.0 Ci/mmol; Perkin Elmer). The thawed membrane preparation of guinea pig brain cortex (about 100 µg of the protein) was incubated with various concentrations of test compounds, 2 nM [^{3}H]-(+)-pentazocine, and TRIS buffer (50 mM, pH 7.4) at 37 °C. The non-specific binding was determined with 10 µM unlabeled (+)-pentazocine. The K_d value of (+)-pentazocine is 2.9 nM.[66]

7.4.1.5. σ_2 receptor affinity

The assay was performed with the radioligand [^{3}H]di-*o*-tolylguanidine (specific activity 50 Ci/mmol; ARC, St. Louis, MO, USA). The thawed rat liver membrane preparation (about 100 µg protein) was incubated with various concentrations of the test compound, 3 nM [^{3}H]di-*o*-tolylguanidine and buffer containing (+)-pentazocine (500 nM (+)-pentazocine in TRIS buffer (50 mM TRIS, pH 8.0)) at rt. The non-specific binding was determined with 10 µM non-labeled di-*o*-tolylguanidine. The K_d value of di-*o*-tolylguanidine is 17.9 nM.[67]

7.5. Pain behavioral studies

To evaluate the effect of drugs on mechanical allodynia induced by capsaicin, a previously described experimental procedure was used.[34] The compound under study or its solvent (HPMC) was administered s.c. to female CD-1 mice (Charles River, Barcelona, Spain) 30 min before the intraplantar (i.pl.) administration of 20 µL capsaicin (1 µg in 1% DMSO). 15 min after the i.pl. administration of capsaicin, a mechanical punctate stimulation (0.5 g force) was applied with an electronic von Frey device (Dynamic Plantar Aesthesiometer, Ugo Basile, Comerio, Italy) at least 5 mm from the site of injection toward the toes (area of secondary mechanical hypersensitivity), and the paw withdrawal latency time was automatically recorded. Each mouse was tested in three trials at 30 s intervals and the mean of the 3 measurements was calculated. A cutoff time of 50 s was used in each trial.

In the experiments to elucidate the influence of σ_1 receptors on the antiallodynic effect of compound tested, the σ_1 receptor agonist PRE-084 (compound **35**) was administered s.c. 5 minutes before the s.c. administration of the compound tested and 30 min later (i.e.. 35 min after compound **35** administration) capsaicin was ipl injected and the above-mentioned procedures were performed to measure mechanical allodynia.

Animal care was provided in accordance with institutional (Research Ethics Committee of the University of Granada, Granada, Spain), regional (Junta de Andalucía, Spain), and international standards (European Communities Council Directive 2010/63). The protocol of the experiments was approved by Junta de Andalucia (Licence 04/09/2017/113). The degree of effect on capsaicin-induced mechanical allodynia was calculated as: % Antiallodynic effect = [(LTD-LTS)/(CT-

LTS)] x 100 where LTD is the latency time for paw withdrawal in drug-treated animals, LTS is the latency time in solvent-treated animals (mean value 12.03 s), and CT is the cutoff time (50 s).The statistical significance of differences between values obtained in the different experimental groups were analyzed with one-way analysis of variance (ANOVA) followed by the Bonferroni test. The differences between means were considered statistically significant when the value of P was below 0.05.

All animal experiments performed in the manuscript were conducted in compliance with institutional guidelines. Licence number: 04/09/2017/113.

Supporting Information

Supporting Information contains purity data of all compounds. Moreover, ^{1}H and ^{13}C NMR spectra and HPLC chromatograms (purity) are included. Experimental details of *in vitro* assays and Molecular Formula Strings are given.. This material is available free of charge via the Internet at http://pubs.acs.org.

Author Information

Corresponding author

*Tel: +49-251-8333311. Fax: +49-8332144. Email: wuensch@uni-muenster.de

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft (DFG) and the Cells-in-motion Cluster of Excellence (EXC, 1300-CiM), University of Münster, Germany.

Conflict of interests

The authors declare no conflict of interest.

Abbreviations Used

APCI	atmospheric pressure chemical ionization
d	diameter of the column
DAST	diethylaminosulfur trifluoride
DOR	δ opioid receptor
DTG	1,3-di(o-tolyl)guanidine
ER	endoplasmic reticulum
fc	flash column chromatography
HPMC	hydroxypropyl-methyl-cellulose
IP_3	Inositol trisphosphate
i. pl.	intraplantar
KOR	κ opioid receptor
l	length of the stationary phase
MAM	mitochondrion-associated endoplasmic reticulum membranes
MOR	μ opioid receptor
mTOR	mammalian target of Rapamycine
NET	norepinephrine transporter
NMDA	N-methyl-D-aspartate

PCP	phencyclidine
p-TsOH	*p*-toluenesulfonic acid
SEM	standard error of the mean
TRIS	tris(hydroxymethyl)aminomethane
V	fraction size

References

(1) Martin, W. R.; Eades, C. G.; Thompson, J. A.; Huppler, R. E.; Gilbert, P. E. The effects of morphine- and nalorphine- like drugs in the nondependent and morphine-dependent chronic spinal dog, *J. Pharmacol. Exp. Ther.* **1976,** *197*, 517–532.

(2) Tam, S. W.; Cook, L. Sigma opiates and certain antipsychotic drugs mutually inhibit (+)-[3H] SKF 10,047 and [3H]haloperidol binding in guinea pig brain membranes, *Proc. Natl. Acad. Sci. U.S.A.* **1984,** *81*, 5618–5621.

(3) Tam, S. W. Naloxone-inaccessible sigma receptor in rat central nervous system, *Proc. Natl. Acad. Sci. U.S.A.* **1983,** *80*, 6703–6707.

(4) Bowen, W. D.; Hellewell, S. B.; McGarry, K. A. Evidence for a multi-site model of the rat brain sigma receptor, *Eur. J. Pharmacol.* **1989,** *163*, 309–318.

(5) Quirion, R.; Bowen, W. D.; Itzhak, Y.; Junien, J. L.; Musacchio, J.; Rothman, R. B.; Tsung-Ping, S.; Tam, S.W.; Taylor, D. P. A proposal for the classification of sigma binding sites, *Trends Pharmacol. Sci.* **1992,** *13*, 85–86.

(6) Maurice, T.; Roman, F. J.; Privat, A. Modulation by neurosteroids of the in vivo (+)-[3H]SKF-10,047 binding to sigma 1 receptors in the mouse forebrain, *J. Neurosci. Res.* **1996,** *46*, 734–743.

(7) Maurice, T.; Junien, J. L.; Privat, A. Dehydroepiandrosterone sulfate attenuates dizocilpine-induced learning impairment in mice via sigma 1-receptors, *Behav. Brain Res.* **1997,** *83*, 159–164.

(8) Romieu, P.; Martin-Fardon, R.; Bowen, W. D.; Maurice, T. Sigma 1 receptor-related neuroactive steroids modulate cocaine-induced reward, *J. Neurosci.* **2003,** *23*, 3572–3576.

(9) Fontanilla, D.; Johannessen, M.; Hajipour, A. R.; Cozzi, N. V.; Jackson, M. B.; Ruoho, A. E. The hallucinogen N,N-dimethyltryptamine (DMT) is an endogenous sigma-1 receptor regulator, *Science* **2009,** *323*, 934–937.

(10) Ruoho, A. E.; Chu, U. B.; Ramachandran, S.; Fontanilla, D.; Mavlyutov, T.; Hajipour, A. R. The ligand binding region of the sigma-1 receptor: studies utilizing photoaffinity probes, sphingosine and N-alkylamines, *Curr. Pharm. Des.* **2012,** *18*, 920–929.

(11) Hanner, M.; Moebius, F. F.; Flandorfer, A.; Knaus, H. G.; Striessnig, J.; Kempner, E.; Glossmann, H. Purification, molecular cloning, and expression of the mammalian sigma1-binding site, *Proc. Natl. Acad. Sci. U.S.A.* **1996,** *93*, 8072–8077.

(12) Seth, P.; Leibach, F. H.; Ganapathy, V. Cloning and structural analysis of the cDNA and the gene encoding the murine type 1 sigma receptor, *Biochem. Biophys. Res. Commun.* **1997,** *241*, 535–540.

(13) Kekuda, R.; Prasad, P. D.; Fei, Y. J.; Leibach, F. H.; Ganapathy, V. Cloning and functional expression of the human type 1 sigma receptor (hSigmaR1), *Biochem. Biophys. Res. Com.* **1996,** *229*, 553–558.

(14) Hellewell, S. B.; Bruce, A.; Feinstein, G.; Orringer, J.; Williams, W.; Bowen, W. D. Rat liver and kidney contain high densities of σ1 and σ2 receptors: characterization by ligand binding and photoaffinity labeling, *Eur. J. Pharmacol. Mol. Pharmacol.* **1994,** *268*, 9–18.

(15) Schmidt, H. R.; Zheng, S.; Gurpinar, E.; Koehl, A.; Manglik, A.; Kruse, A. C. Crystal structure of the human σ1 receptor, *Nature* **2016,** *532*, 527–530.

(16) Hayashi, T.; Su, T.-P. Sigma-1 receptor chaperones at the ER-mitochondrion interface regulate Ca(2+) signaling and cell survival, *Cell* **2007,** *131*, 596–610.

(17) Weissman, A. D.; Su, T. P.; Hedreen, J. C.; London, E. D. Sigma receptors in post-mortem human brains, *J. Pharmacol. Exp. Ther.* **1988,** *247*, 29–33.

(18) Samovilova, N. N.; Nagornaya, L. V.; Vinogradov, V. A. (+)-[3H]SKF 10,047 sites in rat liver, *Eur. J. Pharmacol.* **1988,** *147*, 259–264.

(19) Ela, C.; Barg, J.; Vogel, Z.; Hasin, Y.; Eilam, Y. Sigma receptor ligands modulate contractility, Ca++ influx and beating rate in cultured cardiac myocytes, *J. Pharmacol. Exp. Ther.* **1994,** *269*, 1300–1309.

(20) Morin-Surun, M. P.; Collin, T.; Denavit-Saubié, M.; Baulieu, E.-E.; Monnet, F. P. Intracellular σ1 receptor modulates phospholipase C and protein kinase C activities in the brainstem, *Proc. Natl. Acad. Sci. U.S.A.* **1999,** *96*, 8196–8199.

(21) Hayashi, T.; Su, T.-P. Intracellular dynamics of sigma-1 receptors (sigma(1) binding sites) in NG108-15 cells, *J. Pharmacol. Exp. Ther.* **2003,** *306*, 726–733.

(22) Tsai, S.-Y.; Hayashi, T.; Mori, T.; Su, T.-P. Sigma-1 Receptor Chaperones and Diseases, *Cent. Nerv. Syst Agents Med. Chem.* **2009,** *9*, 184–189.

(23) Zhang, H.; Cuevas, J. Sigma receptors inhibit high-voltage-activated calcium channels in rat sympathetic and parasympathetic neurons, *J. Neurophysiol.* **2002,** *87*, 2867–2879.

(24) Soriani, O.; Foll, F. L.; Roman, F.; Monnet, F. P.; Vaudry, H.; Cazin, L. A-Current down-modulated by sigma receptor in frog pituitary melanotrope cells through a G protein-dependent pathway, *J. Pharmacol. Exp. Ther.* **1999,** *289*, 321–328.

(25) Soriani, O.; Le Foll, F.; Galas, L.; Roman, F.; Vaudry, H.; Cazin, L. The sigma-ligand (+)-pentazocine depresses M current and enhances calcium conductances in frog melanotrophs, *Am. J. Physiol.* **1999,** *277*, E73-80.

(26) Cheng, Z.-X.; Lan, D.-M.; Wu, P.-Y.; Zhu, Y.-H.; Dong, Y.; Ma, L.; Zheng, P. Neurosteroid dehydroepiandrosterone sulphate inhibits persistent sodium currents in rat medial prefrontal cortex via activation of sigma-1 receptors, *Exp. Neurol.* **2008,** *210*, 128–136.

(27) Renaudo, A.; L'Hoste, S.; Guizouarn, H.; Borgèse, F.; Soriani, O. Cancer cell cycle modulated by a functional coupling between sigma-1 receptors and Cl- channels, *J. Biol. Chem.* **2007,** *282*, 2259–2267.

(28) Maurice, T.; Romieu, P. Involvement of the sigma1 receptor in the appetitive effects of cocaine, *Pharmacopsychiatry* **2004,** *37 Suppl 3*, S198-207.

(29) Jin, J.-L.; Fang, M.; Zhao, Y.-X.; Liu, X.-Y. Roles of sigma-1 receptors in Alzheimer's disease, *Int. J. Clin. Exp. Med.* **2015,** *8*, 4808–4820.

(30) Kulkarni, S. K.; Dhir, A. sigma-1 receptors in major depression and anxiety, *Expert Rev. Neurother.* **2009,** *9*, 1021–1034.

(31) Niitsu, T.; Iyo, M.; Hashimoto, K. Sigma-1 receptor agonists as therapeutic drugs for cognitive impairment in neuropsychiatric diseases, *Curr. Pharm. Des.* **2012,** *18*, 875–883.

(32) Zamanillo, D.; Romero, L.; Merlos, M.; Vela, J. M. Sigma 1 receptor: a new therapeutic target for pain, *Eur. J. Pharmacol.* **2013,** *716*, 78–93.

(33) Jensen, T. S.; Finnerup, N. B. Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms, *Lancet Neurol.* **2014,** *13*, 924–935.

(34) Entrena, J. M.; Cobos, E. J.; Nieto, F. R.; Cendán, C. M.; Gris, G.; del Pozo, E.; Zamanillo, D.; Baeyens, J. M. Sigma-1 receptors are essential for capsaicin-induced mechanical hypersensitivity: studies with selective sigma-1 ligands and sigma-1 knockout mice, *Pain* **2009,** *143*, 252–261.

(35) Díaz, J. L.; Cuberes, R.; Berrocal, J.; Contijoch, M.; Christmann, U.; Fernández, A.; Port, A.; Holenz, J.; Buschmann, H.; Laggner, C.; Serafini, M. T.; Burgueño, J.; Zamanillo, D.; Merlos, M.; Vela, J. M.; Almansa, C. Synthesis and biological evaluation of the 1-arylpyrazole class of σ(1) receptor antagonists: identification of 4-{2-5-methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxyethyl}morpholine (S1RA, E-52862), *J. Med. Chem.* **2012,** *55*, 8211–8224.

(36) Alon, A.; Schmidt, H. R.; Wood, M. D.; Sahn, J. J.; Martin, S. F.; Kruse, A. C. Identification of the gene that codes for the σ2 receptor, *Proc. Natl. Acad. Sci. U.S.A.* **2017,** *114*, 7160–7165.

(37) Walker, J. M.; Bowen, W. D.; Walker, F. O.; Matsumoto, R. R.; Costa, B. de; Rice, K. C. Sigma receptors: biology and function, *Pharmacol. Rev.* **1990,** *42*, 355–402.

(38) Bowen, W. D. Sigma receptors: recent advances and new clinical potentials, *Pharm. Acta. Helv.* **2000,** *74*, 211–218.

(39) Vilner, B. J.; Bowen, W. D. Modulation of cellular calcium by sigma-2 receptors: release from intracellular stores in human SK-N-SH neuroblastoma cells, *J. Pharmacol. Exp. Ther.* **2000,** *292*, 900–911.

(40) Wilke, R. A.; Mehta, R. P.; Lupardus, P. J.; Chen, Y.; Ruoho, A. E.; Jackson, M. B. Sigma receptor photolabeling and sigma receptor-mediated modulation of potassium channels in tumor cells, *J. Biol. Chem.* **1999,** *274*, 18387–18392.

(41) Huang, Y.-S.; Lu, H.-L.; Zhang, L.-J.; Wu, Z. Sigma-2 receptor ligands and their perspectives in cancer diagnosis and therapy, *Med. Res. Rev.* **2014,** *34*, 532–566.

(42) Guitart, X.; Codony, X.; Monroy, X. Sigma receptors: biology and therapeutic potential, *Psychopharmacology* **2004,** *174*, 301–319.

(43) van Waarde, A.; A. Rybczynska, A.; K. Ramakrishnan, N.; Ishiwata, K.; H. Elsinga, P.; A.J.O. Dierckx, R. Sigma receptors in oncology: therapeutic and diagnostic applications of sigma ligands, *Curr. Pharm. Des.* **2010,** *16*, 3519–3537.

(44) Berardi, F.; Abate, C.; Ferorelli, S.; Colabufo, N.; Perrone, R. 1-Cyclohexylpiperazine and 3,3-dimethylpiperidine derivatives as sigma-1 (σ1) and sigma-2 (σ2) receptor ligands: a review, *Cent. Nerv. Syst. Agents Med. Chem.* **2009,** *9*, 205–219.

(45) Perregaard, J.; Moltzen, E. K.; Meier, E.; Sanchez, C. sigma. Ligands with Subnanomolar Affinity and Preference for the .sigma.2 Binding Site. 1. 3-(.omega.-Aminoalkyl)-1H-indoles, *J. Med. Chem.* **1995,** *38*, 1998–2008.

(46) Mach, R. H.; Huang, Y.; Freeman, R. A.; Wu, L.; Vangveravong, S.; Luedtke, R. R. Conformationally-flexible benzamide analogues as dopamine D3 and σ2 receptor ligands, *Bioorg. Med. Chem. Lett.* **2004,** *14*, 195–202.

(47) Maier, C. A.; Wünsch, B. Novel spiropiperidines as highly potent and subtype selective σ-receptor ligands. Part 1., *J. Med. Chem.* **2002,** *45*, 438–448.

(48) Maier, C. A.; Wünsch, B. Novel σ receptor ligands. Part 2. SAR of spiro[[2]benzopyran-1,4‘-piperidines] and spiro[[2]benzofuran-1,4‘-piperidines] with carbon substituents in position 3, *J. Med. Chem.* **2002,** *45*, 4923–4930.

(49) Rack, E.; Fröhlich, R.; Schepmann, D.; Wünsch, B. Design, synthesis and pharmacological evaluation of spirocyclic σ(1) receptor ligands with exocyclic amino moiety (increased distance 1), *Bioorg. Med. Chem.* **2011,** *19*, 3141–3151.

(50) Grosse Maestrup, E.; Wiese, C.; Schepmann, D.; Hiller, A.; Fischer, S.; Scheunemann, M.; Brust, P.; Wünsch, B. Synthesis of spirocyclic sigma1 receptor ligands as potential PET radiotracers, structure-affinity relationships and in vitro metabolic stability, *Bioorg. Med. Chem.* **2009,** *17*, 3630–3641.

(51) Oberdorf, C.; Schepmann, D.; Vela, J. M.; Diaz, J. L.; Holenz, J.; Wünsch, B. Thiophene bioisosteres of spirocyclic sigma receptor ligands. 1. N-substituted spiro[piperidine-4,4'-thieno[3,2-c]pyrans], *J. Med. Chem.* **2008,** *51*, 6531–6537.

(52) Schläger, T.; Schepmann, D.; Würthwein, E.-U.; Wünsch, B. Synthesis and structure-affinity relationships of novel spirocyclic sigma receptor ligands with furopyrazole structure, *Bioorg. Med. Chem.* **2008,** *16*, 2992–3001.

(53) Bruckner, R.; Wender, P. A.; Beifuss, K.; Zettlmeier, W. *Organic mechanisms*; Springer-Verlag: Berlin, Heidelberg, **2010**.

(54) Rack, E. *Struktur-Affinitäts- und Selektivitätsuntersuchungen spirocyclischer Sigma-Rezeptorliganden mit exocyclischer Aminfunktion (doctoral dissertation):* Münster, **2010**.

(55) Søby, K. K.; Mikkelsen, J. D.; Meier, E.; Thomsen, C. Lu 28-179 labels a σ2-site in rat and human brain, *Neuropharmacology* **2002,** *43*, 95–100.

(56) Matsumoto, R. R.; McCracken, K. A.; Friedman, M. J.; Pouw, B.; Costa, B. R. de; Bowen, W. D. Conformationally restricted analogs of BD1008 and an antisense oligodeoxynucleotide targeting σ1 receptors produce anti-cocaine effects in mice, *Eur. J. Pharmacol.* **2001,** *419*, 163–174.

(57) Maurice, T.; Su, T.-P.; Parish, D. W.; Nabeshima, T.; Privat, A. PRE-084, a σ selective PCP derivative, attenuates MK-801-induced impairment of learning in mice, *Pharmacol. Biochem. Behav.* **1994,** *49*, 859–869.

(58) Bruker AXS Inc. APEX3, *Madison, Wisconsin, USA* **2016**.

(59) Bruker AXS Inc. SAINT, *Madison, Wisconsin, USA* **2015**.

(60) Bruker AXS Inc. SADABS, *Madison, Wisconsin, USA* **2014**.

(61) Sheldrick, G. M. SHELXT - integrated space-group and crystal-structure determination, *Acta Crystallogr. A Found. Adv.* **2015,** *71*, 3–8.

(62) Bruker AXS Inc. XP-Interactive molecular graphics, Version 5.1, *Madison, Wisconsin, USA* **1998**.

(63) Bradford, M. M. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding, *Anal. Biochem.* **1976,** *72*, 248–254.

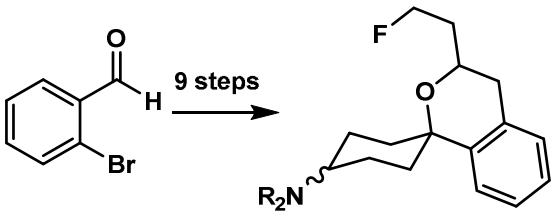
(64) Stoscheck, C. M. Quantitation of protein, *Methods Enzymol.* **1990,** *182*, 50–68.

(65) Yung-Chi, C.; Prusoff, W. H. Relationship between the inhibition constant (KI) and the concentration of inhibitor which causes 50 per cent inhibition (I50) of an enzymatic reaction, *Biochem. Pharmacol.* **1973,** *22*, 3099–3108.

(66) DeHaven-Hudkins, D. L.; Fleissner, L. C.; Ford-Rice, F. Y. Characterization of the binding of [3H](+)-pentazocine to σ recognition sites in guinea pig brain, *Eur. J. Pharmacol. Mol. Pharmacol.* **1992,** *227*, 371–378.

(67) Mach, R. H.; Smith, C. R.; Childers, S. R. Ibogaine possesses a selective affinity for σ2 receptors, *Life Sci.* **1995,** *57*, PL57-PL62.

Table of Contents Graphic



13c
NR_2 = 4-cyclohexylpiperazin-1-yl
$K_i(\sigma_1)$ = 12 nM; σ_1:σ_2= 4
σ_1 antagonist
antiallodynic activity