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Synthesis of σ Receptor Ligands with a Spirocyclic System Connected with a Tetrahydroisoquinoline Moiety via Different Linkers

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With the aim to develop new σ_2 receptor ligands, spirocyclic piperidines or cyclohexanamines with 2-benzopyran and 2-benzofuran scaffolds were connected to the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline moiety by variable linkers. In addition to flexible alkyl chains, linkers containing an amide as functional group were synthesized. The 2-benzopyran and 2-benzofuran scaffold of the spirocyclic compounds were synthesized from 2-bromobenzaldehyde. The amide linkers were constructed by acylation of amines with chloroacetyl chloride and subsequent nucleophilic substitution, the alkyl linkers were obtained by $LiAlH_4$ reduction of the corresponding amides. For the development of σ_2 receptor ligands, the spirocyclic 2-benzopyran scaffold is more favorable than the ring-contracted 2-benzofuran system. Compounds bearing an alkyl chain as linker generally show higher σ affinity than acyl linkers containing an amide as functional group. A higher σ_1 affinity for the *cis*-configured cyclohexanamines than for the *trans*-configured derivatives was found. The highest σ_2 affinity was observed for *cis*-configured spiro[[2]benzopyran-1,1′-cyclohexan]-4′-amine connected to the tetrahydroisoquinoline system by an ethylene spacer (*cis*-**31**, K_i (σ_2) = 200 nM; the highest σ_1 affinity was recorded for the corresponding 2-benzofuran derivative with a $CH_2C{=}O$ linker (*cis*-**29**, K_i (σ_1) = 129 nM).

1. Introduction

σ Receptors, initially classified as class of opioid receptors, are well established as unique class of receptors without any homology to opioid receptors or NMDA receptors.[1] Based on the results of comprehensive radioligand binding studies and biochemical analysis, the class of σ receptors was further divided into two distinct subtypes, which were termed σ_1 and σ_2 receptor.[2]

The σ_1 receptor has been cloned from different species, including human, rat, mouse, and guinea pig. The crystal structure of the human σ_1 receptor was recently reported by Kruse et al.[3,4] In contrast to the σ_1 receptor, details concerning the σ_2 receptor have been rather vague for many years. As a result from photoaffinity labeling studies a molecular weight of 21.5 kDa was postulated for the σ_2 receptor.[5] Xu and coworkers utilized a photoaffinity probe to label σ_2 receptors in rat liver and proposed that the σ_2 receptor binding site resides within the progesterone receptor membrane component 1 (PGRMC1) complex.[6] During the following years, the correlation between the σ_2 receptor and PGRMC1 protein complex was considered controversial.[7] In 2017, the σ_2 receptor was isolated from calf liver tissue and identified as the endoplasmic reticulum (ER)-resident membrane protein TMEM97, which is also described as MAC30 (meningioma-associated protein 30). Subsequent molecular cloning and binding experiments confirmed this result. Mutagenesis studies identified two aspartate residues as crucial for binding of [^{3}H]DTG, a radioligand frequently used in σ_2 receptor binding assays. Furthermore, it was demonstrated that the TMEM97 ligands elacridar (**1**; Figure 1) and Ro 48-8071 showed the same K_i values towards cell membranes from Sf9 cells overexpressing the TMEM97 protein and σ_2 receptor overexpressing MCF-7 cells.[8] According to these findings, the σ_2 receptor is now often termed σ_2 receptor/TMEM97. In 2018, Riad et al. demonstrated that the σ_2 receptor/TMEM97 protein, the PGRMC1 protein and the LDL receptor form a ternary complex, which is necessary for the rapid internalization of LDL.[9] In contrast to the σ_1 receptor, no crystal structure of the σ_2 receptor protein has been published so far.

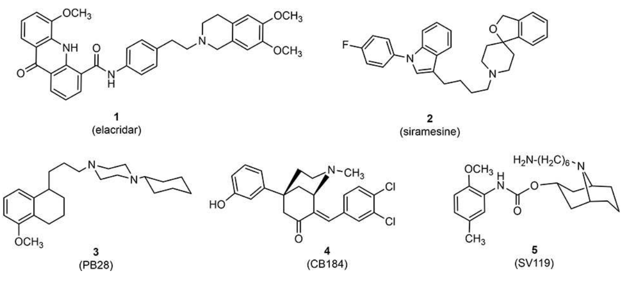

Figure 1. Elacridar and some prototypical σ_2 receptor ligands.

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For a variety of tumor cells an overexpression of σ_2 receptors was demonstrated, including breast cancer, lung cancer, colon cancer, leukemia and prostate cancer.[10–15] It was also shown that σ_2 receptor agonists are capable of killing tumor cells via apoptotic and non-apoptotic mechanisms. For example, several derivatives of the high affinity σ_2 receptor agonist PB28 (**3**; Figure 1) are able to inhibit the growth of pancreatic cancer cells and the neuroblastoma SK–N-SH cell line.[16,17] Very recently, it has been found that the potent and selective σ_2 receptor ligand PB221 inhibits the proliferation of brain tumor murine astrocytoma cells (ALTS1C1).[18] Haloperidol and its homopiperazine analog SYA013 exhibit high σ_2 affinity and, furthermore, antiproliferative effects on different tumor cell lines, including Panc-1.[19] Therefore, the development of σ_2 receptor ligands is a very promising goal. However, very recently it was reported that σ_2 receptor ligands could also induce cytotoxic effects in σ_2/TMEM97 knock out and σ_2/TMEM97 and PGRMC1 double knock out cell lines. It was concluded that the cytotoxic effects of these σ_2 ligands could not be mediated by the σ_2 receptor, but other mechanisms have to be responsible for these cytotoxic effects.[20]

In Figure 1, some prototypical σ_2 receptor ligands are shown. The spirocyclic benzofuran siramesine (**2**) displays a considerable selectivity for the σ_2 receptor ($K_i = 0.12$ nM) over the σ_1 receptor ($K_i = 17$ nM).[21] PB28 (**3**) with the 4-(cyclohexyl) piperazine substructure is also a potent σ_2 ligand ($K_i = 0.68$ nM), but exhibits even higher affinity towards the σ_1 subtype ($K_i = 0.38$ nM).[22] In the group of bicyclic compounds some morphans (e.g., CB184, **4**) and granatanes (e.g., SV119, **5**) display high σ_2 receptor affinity and high selectivity over the σ_1 receptor.[23,24]

The 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline residue is a pharmacophoric element present in several σ_2 receptor ligands.[25–33] (Figure 2) Mach and co-workers published a series of benzamides connected to the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline residue by linkers of different chain lengths. Among this series, **7** and **8** (ISO-1[32]) with an ethylene and tetramethylene linker, respectively, showed high σ_2 affinity and selectivity over the σ_1 receptor.[33] The same isoquinoline ring system is also a structural element of the σ_2 ligand **1** (Figure 1).

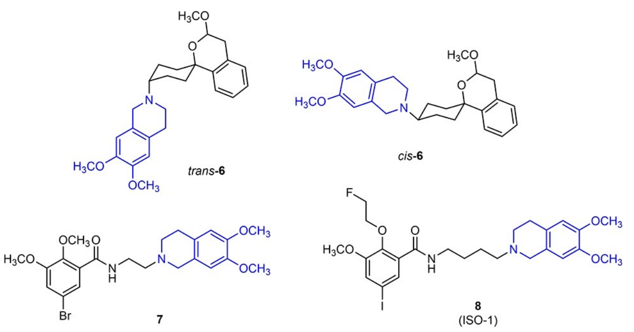
In a previous study, we have reported that the spirocyclic 2-benzopyran derivatives *trans*-**6** and *cis*-**6** bearing the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline residue without linker show medium to high affinity to the σ_2 receptor.[34] (Figure 2) However, the selectivity over the σ_1 subtype is moderate and has room for improvement. Therefore, it was envisaged to synthesize a new set of σ_2 selective ligands by introducing a linker between the spirocyclic 2-benzopyran scaffold and the isoquinoline ring system. To exploit further structure affinity relationships, not only alkyl chains were planned as linkers, but also amides with variable chain lengths and different positions of the carbonyl group were designed. Moreover, a ring contraction of the spirocyclic 2-benzopyran to the spirocyclic 2-benzofuran ring system was planned as this compound class is also known for its high σ affinity from previous studies. An overview of the structure modifications is presented in Figure 3.

2. Results and Discussion

2.1. Synthesis

For the synthesis of the designed σ ligands, spirocyclic 2-benzopyrans and 2-benzofurans **10**–**13** with endocyclic and exocyclic amino moiety were synthesized starting from 2-bromobenzaldehyde (Scheme 1).

The spirocyclic piperidines **10** and **12** were prepared by addition of an aryllithium intermediate at *N*-benzyl-protected piperidin-4-one as previously described.[35,36] The exocyclic primary amines *trans*-**11** and *cis*-**11** were obtained as reported in ref. [34]. Transfer hydrogenolysis using NH_4 HCO_2 in the presence of Pd/C converted *trans*- and *cis*-configured benzylamines *trans*-**9** and *cis*-**9**[37,38] into the diastereomeric primary



Compd.	$K_i(\sigma_1)$ [nM]	$K_i(\sigma_2)$ [nM]	σ_2/σ_1 selectivity
trans-**6**	639	58	11
cis-**6**	1200	105	11
7	2932	16.4	178
8	330	7.0	47

Figure 2. Lead compounds with a tetrahydroisoquinoline ring system showing a preference for σ_2 receptors over σ_1 receptors.

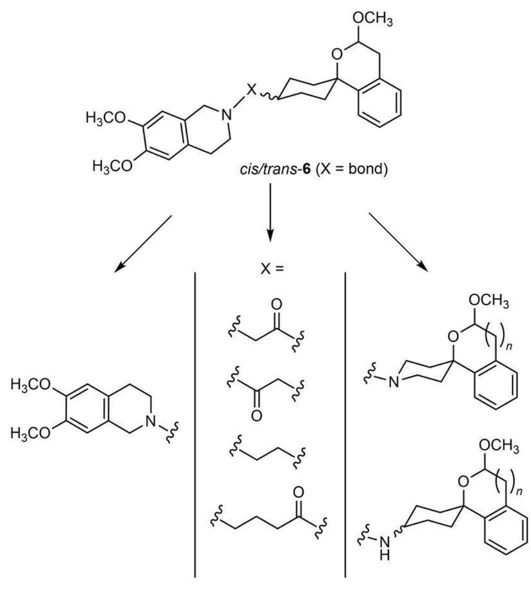
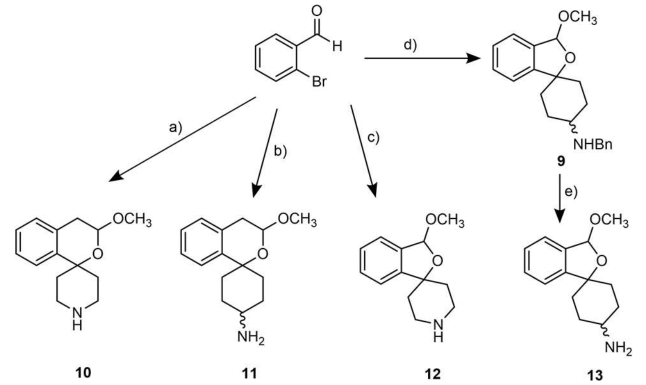


Figure 3. Overview of planned σ_2 receptor ligands with various linkers.



Scheme 1. Outline of the synthesis of spirocyclic piperidines **10**[35] and **12**.[36] and cyclohexanamines **11**[34] and **13** with 2-benzopyran and 2-benzofuran scaffold. a) 5 steps;[35] b) 7 steps;[34] c) 4 steps;[36] d) 4 steps;[37,38] e) NH_4 HCO_2, Pd/C, CH_3OH, 17–21 h, 65 °C; *trans*-**13**, 86 %, *cis*-**13**, 66 %.

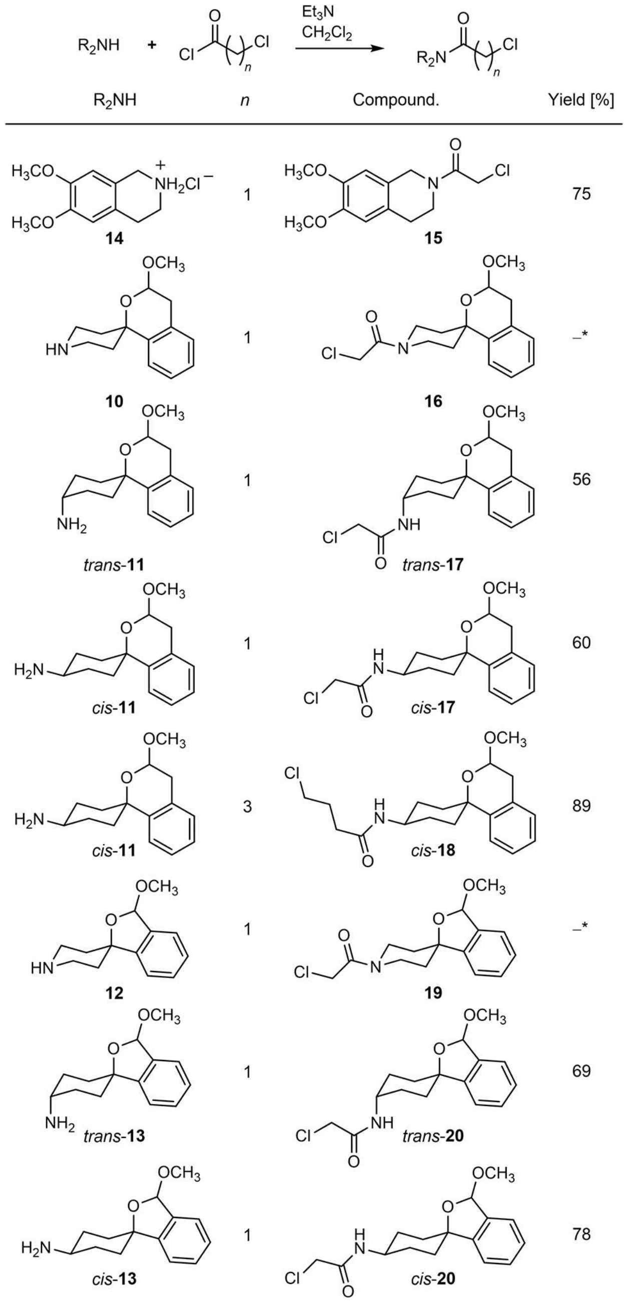
amines *trans*-**13** and *cis*-**13**. The secondary amine 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline HCl (**14** HCl) was commercially available (Scheme 1).

The amines **10**–**14** were acylated with α-chloroacetyl chloride affording chloroacetamides **15**[39]–**17** and **19**–**20**. The homologous 4-chlorobutyryl derivative *cis*-**18** was prepared by reaction of *cis*-**11** with 4-chlorobutyryl chloride. The amides **15**–**20** were obtained in yields of 56–89 % (Scheme 2). Acylation of tetrahydroisoquinoline **14** with 3-chloropropionyl chloride did not lead to the desired 3-chloropropinamide.

The final compounds were obtained by nucleophilic substitution of the terminal chloride in the side chain of the amides **15**–**20**. The acylated spirocyclic 2-benzopyrans **16**–**18** and 2-benzofurans **19** and **20** were reacted with the tetrahydroisoquinoline **14**, while the acylated isoquinoline **15** underwent a nucleophilic substitution with the spirocyclic amines **10**–**13**. In Table 1, the products and yields of these transformations are summarized.

The nucleophilic substitution of the 2-chloroacetylated isoquinoline derivative **15** with spirocyclic amines **10**–**13** in DMF with TBAI as catalyst resulted in the formation of the desired compounds **21**–**24** in satisfactory yields. Due to purification problems, the benzopyran-based spirocyclic compound *trans*-**22** could not be isolated in pure form for testing. S_N2 reaction of spirocyclic chloroacetamides **16**, **17** and **20** with the tetrahydroisoquinoline **14** provided the amides **25**, **26** and **29** in 62–86 % yields. The pure spirocyclic benzofuran **28** was obtained in only 44 % yield, due to purification problems. While the nucleophilic substitution of the 2-chloroacetylated compounds **16**, **17**, **19**, and **20** with tetrahydroisoquinoline **14** led to clean conversions, he corresponding 4-chlorobutyramide **18** reacted slower to produce *cis*-**27**, which was isolated in only 19 % yield (Table 1).

During the reaction to obtain the secondary amines *trans*-**22**, *cis*-**22**, *trans*-**24** and *cis*-**24**, formation of tertiary amines as side-products was observed (double nucleophilic substitution). The R_f values of the tertiary amines was almost identical to the R_f value of the secondary amines, rendering the fc purification



Scheme 2. Acylation of amines with chloroacyl chlorides. *The spirocyclic piperidines **16** and **19** were not isolated, but directly used for subsequent nucleophilic substitution with **14**.

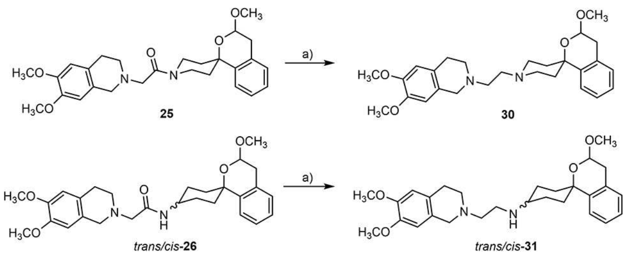
of the desired products very difficult. Although the isolation and purification of the secondary amines *cis*-**22**, *trans*-**24** and *cis*-**24** was successful, *trans*-**22** could not be isolated in sufficient purity.

As not only linkers bearing a carbonyl group were planned, derivatives **30**, *trans*-**31** and *cis*-**31** with an ethylene linker between the amino moiety of the spirocyclic benzopyran and the tetrahydroisoquinoline were synthesized. (Scheme 3) This type of compounds features two basic amino moieties instead of one and can therefore adopt different orientations within the

Table 1. Nucleophilic substitution at chloroamides **15–20**.[a]

Chloroamide	Amine	Product	Yield [%]
15	**10**	**21**	22
15	*trans*-**11**	*trans*-**22**	–*
15	*cis*-**11**	*cis*-**22**	60
15	**12**	**23**	36
15	*trans*-**13**	*trans*-**24**	54
15	*cis*-**13**	*cis*-**24**	43
16	**14**	**25**	75
trans-**17**	**14**	*trans*-**26**	83
cis-**17**	**14**	*cis*-**26**	62
cis-**18**	**14**	*cis*-**27**	19
19	**14**	**28**	44
trans-**20**	**14**	*trans*-**29**	66
cis-**20**	**14**	*cis*-**29**	86

[a] For structures, see Scheme 2 and Table 2. *The product could not be isolated.



Scheme 3. Synthesis of isoquinolines **30**, *trans*-**31** und *cis*-**31** with an ethylene linker. a) $LiAlH_4$, THF, 2–22 h, 70 °C, 63 % (**30**), 86 % (*trans*-**31**), 76 % (*cis*-**31**).

binding pocket of both σ receptor subtypes. Additionally, the effect of the carbonyl moiety on the binding affinity and selectivity can be studied.

At first, a direct alkylation of the tetrahydroisoquinoline **14** was envisaged. For this purpose, 2-bromoethanol was oxidized with Dess-Martin perioidinane to afford 2-bromoacetaldehyde. The aldehyde should be attached to the isoquinoline **14** in a reductive alkylation with $NaBH(OAc)_3$. Unfortunately, after 4 h reaction time the alkylated isoquinoline could not be isolated. Next, a nucleophilic substitution with 1,2-dibromoethane and K_2CO_3 in CH_3CN was performed. But even after a reaction time of 18 h the desired product could not be obtained. The reaction conditions which led to a successful acylation of the isoquinoline **14** (DMF, Et_3N and TBAI) also didn't lead to the formation of the alkylated product. Finally, the desired alkylated amines **30**, *trans*-**31** and *cis*-**31** were synthesized by reduction of the corresponding amides **25**, *trans*-**26** and *cis*-**26** with $LiAlH_4$. (Scheme 3) The piperidine derivative **30** was obtained in 63 % yield after 2 h heating to reflux. *trans*-**31** and *cis*-**31** were isolated after 22 h in 86 and 76 % yield, respectively.

2.2. σ_1 and σ_2 receptor affinity

Competitive binding assays with tritiated radioligands were utilized to determine the σ_1 and σ_2 receptor affinity of the synthesized compounds. In the σ_1 binding assay, [^{3}H]-(+)-pentazocine was used as radioligand and homogenates of guinea pig brains served as receptor material. The σ_2 assay was performed with the radioligand [^{3}H]-di(o-tolyl)guanidine ([^{3}H] DTG) and homogenates of rat liver were used as receptor material. The nonselective properties of DTG was compensated by masking σ_1 receptors with an excess of non-tritiated (+)-pentazocine.[40]

In Table 2, the receptor affinities of the synthesized compounds are summarized. In comparison to the lead compounds *trans*-**7** and *cis*-**7**, the 2-benzopyran derivatives with an acetyl linker generally show a lower σ_2 affinity. The highest σ_2 affinity was observed for *cis*-**26** with a K_i value of 371 nM. In this compound, the acyl group is located at the spirocyclic ring system. When the acyl moiety is located at the isoquinoline ring system (*cis*-**22**), the σ_2 affinity is reduced (11 % inhibition of radioligand binding). A similar trend was observed for the corresponding piperidine derivatives **25** and **21** with K_i values of 534 nM and 19 % inhibition of radioligand binding, respectively.

The σ_1 affinity of the piperidine derivative **21** is higher than that of the corresponding cyclohexanamine derivative *cis*-**22**. A general observation is that the σ_1 affinity is higher for the compounds bearing the acyl group at the isoquinoline ring. For the development of σ_1 ligands with the 2-benzoypran scaffold, it can therefore be concluded that the basic center at the spirocyclic ring system should be retained.

For the derivatives with the 2-benzofuran scaffold similar observations were made in terms of σ_2 affinity. The introduction of an acetyl spacer led to loss of σ_2 affinity, independent of the position of the acyl moiety (e.g., *trans*-**24**, *cis*-**24**, **28**). In contrast to the 2-benzopyrans, the σ_1 affinity of the piperidine derivatives of the spirocyclic 2-benzofurans was not higher than the respective cyclohexanamines. A notable exception is *cis*-**29** with a K_i value of 129 nM at the σ_1 receptor. This compound even represents a σ_1 receptor selective ligand despite the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline structural element.

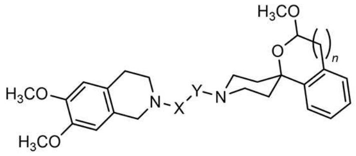
The elongation of the acyl linker also led to a decrease in σ_2 affinity, while the σ_1 affinity was slightly increased. For the butyramide *cis*-**27** a K_i value of 2100 nM at the σ_2 receptor and 712 nM at the σ_1 receptor was observed.

For the derivatives **30**, *cis*-**31** and *trans*-**31** with an ethylene linker an increased σ_2 affinity in comparison to the corresponding amides (e.g., **21**, *cis*-**22**) was found. The σ_1 receptor affinity of the cyclohexanamines *cis*-**31** and *trans*-**31** was also increased, resulting in a loss of σ_2 preference of *cis*-**31**. The piperidine **30** shows a slight preference for the σ_2 receptor (K_i values of 348 nM and 608 nM, respectively).

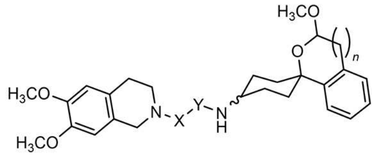
3. Conclusion

The introduction of a spacer between the spirocyclic 2-benzopyran and 2-benzofuran scaffold and the tetrahydroisoquinoline system was envisaged to study structure affinity relationships and evaluate possibilities to optimize selectivity of the lead compounds *trans*-**7** and *cis*-**7**. A set of compounds with amide and alkyl spacers was synthesized and pharmacologically

Table 2. σ1 and σ2 receptor affinities of synthesized compounds.



21, **23**, **25**, **28**, **30**



*cis-/trans-***22**, **24**, **26**, **27**, **29**, **31**

Compound	X	Y	n	K_i [nM] ± SEM[a] σ1	σ2
trans-**6**	–	–	1	639	58 ± 27
cis-**6**	–	–	1	1200	105 ± 8
21	C=O	CH_2	1	319	19%
cis-**22**	C=O	CH_2	1	740	11%
23	C=O	CH_2	0	0%	0%
trans-**24**	C=O	CH_2	0	15%	0%
cis-**24**	C=O	CH_2	0	1600	9%
25	CH_2	C=O	1	518	534
trans-**26**	CH_2	C=O	1	7%	4%
cis-**26**	CH_2	C=O	1	1000	371
cis-**27**	$(CH_2)_3$	C=O	1	712	2100
28	CH_2	C=O	0	19%	3400
trans-**29**	CH_2	C=O	0	1300	1900
cis-**29**	CH_2	C=O	0	129	0%
30	CH_2	CH_2	1	608	348
trans-**31**	CH_2	CH_2	1	1400	499
cis-**31**	CH_2	CH_2	1	251	200

[a] K_i values are given as means of 3 different experiments; percentage values indicate inhibition of the radioligand at a concentration of 1 μM of the test compound.

evaluated in competitive binding assays. Although the introduction of the linker generally resulted in a loss of σ affinity in comparison to the lead compounds **7** without linker, some interesting observations could be made. Compounds containing the 2-benzopyran scaffold showed a higher affinity than the corresponding 2-benzofurans. Compounds **30**, *trans*-**31** and *cis*-**31** with an ethylene linker displayed higher affinity than compounds with an amide in the side chain. The introduction of the linker in compounds **21** and *cis*-**29** resulted in an unexpected selectivity for the σ_1 receptor. In conclusion, the combination of wo promising σ_2 pharmacophoric elements, that is, the connection of an O-containing spirocyclic system with the tetrahydroisoquinoline moiety by different spacers, did not provide high-affinity σ_2 selective ligands. However, the synthesized σ ligands allow an interesting insight into the limitations of acyl chains as linker between the two pharmacophoric elements. *cis*-**31** and *trans*-**31** could serve as a starting point for further structural modifications resulting in higher σ_2 affinity and selectivity.

Experimental Section

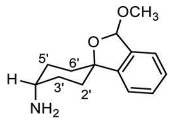
Chemistry, General

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. 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; microTof mass spectrometer (Bruker Daltonics); ESI, electrospray ionization. IR: FTIR 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 $CHCl_3$ ($\delta = 7.26$ ppm (^{1}H NMR) and $\delta = 77.2$ ppm (^{13}C NMR)) and CHD_2OD ($\delta = 3.31$ ppm (^{1}H NMR) and $\delta = 49.0$ 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 (data not shown); multiplicities of the signals are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet; dd = doublet of doublets, m = multiplet. 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 $\lambda = 210$ nm; solvents: A: water with 0.05% (*v/v*) trifluoroacetic acid; B: acetonitrile with 0.05% (*v/v*) trifluoroacetic acid: gradient elution: (A%): 0–4 min: 90%, 4–29 min: 90→0%, 29–31 min: 0%, 31–31.5 min: 0→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%.

Synthetic procedures

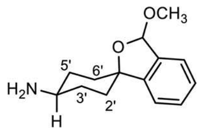
The synthesis of the spirocyclic piperidines **10** and **12** has been reported in the literature.[35,36] The synthesis of exocyclic primary amines *trans*-**11** and *cis*-**11** was described in ref. [34]. The synthesis of *trans*- and *cis*-configured benzylamines *trans*-**9** and *cis*-**9** was reported in ref. [37] and [38].

trans-3-Methoxy-3H-spiro[[2] benzofuran-1,1′-cyclohexan]-4′-amine (*trans*-13)



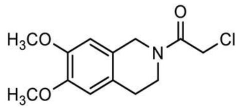
A solution of benzylamine *trans*-**9** (248 mg, 0.76 mmol), ammonium formate (255 mg, 4.05 mmol, 5.3 equiv) and 10% Pd/C (35 mg, 0.03 mmol, 4 mol-%) in CH_3OH (15 mL) was heated to reflux for 17 h. The mixture was filtered through Celite, washed with CH_2Cl_2 (150 mL) and concentrated in vacuo. 1 M NaOH (15 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Yellow oil, yield 153 mg (86%). $C_{14}H_{19}NO_2$ (233.3 g/mol). TLC: R_f=0.03 (cyclohexane/ethyl acetate 67:33+1% *N*,*N*-dimethylethanamine). HRMS (APCI, method 1): *m/z* 234.1477 (calcd. 234.1489 for $C_{14}H_{20}NO_2$ [*M*H$^+$]). ^{1}H NMR (600 MHz, CD_3OD): δ= 1.58–1.64 (m, 1H, 2′-*H*), 1.65–1.76 (m, 3H, 3′-*H*, 5′-*H*, 6′-*H*), 2.01–2.09 (m, 4H, 2′-*H*, 3′-*H*, 5′-*H*, 6′-*H*), 3.11–3.15 (m, 1H, 4′-H_{equ}), 3.47 (s, 3H, OCH_3), 6.04 (s, 1H, 3-*H*), 7.34–7.38 (m, 2H, 4-*H*, 5-*H*), 7.38–7.42 (m, 1H, 6-*H*), 7.49 ppm (d, *J*=7.7 Hz, 1H, 7-*H*). A signal for the NH_2 protons is not observed in the spectrum. ^{13}C NMR (151 MHz, CD_3OD): δ=30.5 (1 C, *C*-3′ or *C*-5′), 30.7 (1 C, *C*-3′ or *C*-5′), 34.0 (1 C, *C*-2′), 35.2 (1 C, *C*-6′), 47.2 (1 C, *C*-4′), 54.8 (1 C, OCH_3), 88.0 (1 C, *C*-1), 106.9 (1 C, *C*-3), 122.6 (1 C, *C*-7), 124.2 (1 C, *C*-4), 128.9 (1 C, *C*-5), 130.3 (1 C, *C*-6), 138.8 (1 C, *C*-3a), 148.8 ppm (1 C, *C*-7a). FTIR (neat): ν [cm^{-1}]=3364 (N–H), 2924, 2855 (C–H_{alkyl}), 1435, 1366 (C=C_{arom}). Purity (HPLC): 93.9%, t_R=8.7 min.

cis-3-Methoxy-3*H*-spiro[[2] benzofuran-1,1′-cyclohexan]-4′-amine (*cis*-13)



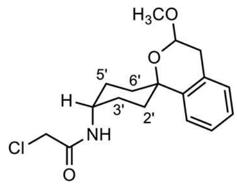
A solution of benzylamine *cis*-**9** (414 mg, 1.28 mmol), ammonium formate (406 mg, 6.44 mmol, 5.0 equiv) and 10% Pd/C (55 mg, 0.05 mmol, 4 mol-%) in CH_3OH (25 mL) was heated to reflux for 21 h. The mixture was filtered through Celite, washed with CH_2Cl_2 (200 mL) and concentrated in vacuo. 1 M NaOH (15 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Yellow oil, yield 198 mg (66%). $C_{14}H_{19}NO_2$ (233.3 g/mol). TLC: R_f=0.02 (cyclohexane/ethyl acetate 67:33+1% *N*,*N*-dimethylethanamine). HRMS (APCI, method 1): *m/z* 234.1479 (calcd. 234.1489 for $C_{14}H_{20}NO_2$ [*M*H$^+$]). ^{1}H NMR (600 MHz, CD_3OD): δ= 1.63–1.68 (m, 1H, 2′-*H*), 1.68–1.76 (m, 2H, 3′-*H*, 5′-*H*), 1.82–1.89 (m, 4H, 3′-*H*, 5′-*H*, 6′-*H*), 1.93 (td, *J*=13.5/4.1 Hz, 1H, 2′-*H*), 2.82 (tt, *J*= 11.5/3.8 Hz, 1H, 4′-H_{ax}), 3.49 (s, 3H, OCH_3), 6.05 (s, 1H, 3-*H*), 7.23 (d, *J*=7.4 Hz, 1H, 7-*H*), 7.32–7.41 ppm (m, 3H, 4-*H*, 5-*H*, 6-*H*). A signal for the NH_2 protons is not observed in the spectrum. ^{13}C NMR (151 MHz, CD_3OD): δ=32.5 (1 C, *C*-3′ or *C*-5′), 32.9 (1 C, *C*-3′ or *C*-5′), 37.6 (1 C, *C*-2′), 38.9 (1 C, *C*-6′), 50.5 (1 C, *C*-4′), 54.9 (1 C, OCH_3), 87.1 (1 C, *C*-1), 107.1 (1 C, *C*-3), 121.7 (1 C, *C*-7), 124.2 (1 C, *C*-4), 128.9 (1 C, *C*-5), 130.4 (1 C, *C*-6), 138.7 (1 C, *C*-3a), 148.6 ppm (1 C, *C*-7a). FTIR (neat): ν [cm^{-1}]=3356 (N–H), 2928, 2859 (C–H_{alkyl}), 1458, 1439 (C=C_{arom}). Purity (HPLC): 99.3%, t_R=10.5 min.

2-Chloro-1-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl) ethan-1-one (15)



The compound was synthesized according to the literature.[39] 2-Chloroacetyl chloride (0.12 mL, 1.51 mmol, 1.2 equiv) was slowly added to a solution of isoquinoline **14**·HCl (281 mg, 1.22 mmol) and Et_3N (0.42 mL, 3.03 mmol, 2.5 equiv) in CH_2Cl_2 (30 mL) under N_2 at 0°C. After stirring for 4.5 h at RT, H_2O (50 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×50 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 67:33). Pale yellow solid, m.p. 109°C, yield 247 mg (75%). $C_{13}H_{16}ClNO_3$ (269.7 g/mol). R_f=0.26 (cyclohexane/ethyl acetate 50:50). HRMS (APCI): *m/z* 270.0864 (calcd. 270.0891 for $C_{13}H_{17}{}^{35}ClNO_3$ [*M*H$^+$]). ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.80 (t, *J*=6.0 Hz, 0.8H, 4-*H*), 2.89 (t, *J*=5.9 Hz, 1.2H, 4-*H*), 3.73 (t, *J*=5.9 Hz, 1.2H, 3-*H*), 3.81–3.88 (m, 6.8H, 3-*H*, 6-OCH_3, 7-OCH_3), 4.15 (s, 1.2H, COCH_2Cl), 4.16 (s, 0.8H, COCH_2Cl), 4.62 (s, 0.8H, 1-*H*), 4.67 (s, 1.2H, 1-*H*), 6.59–6.65 ppm (m, 2H, 5-*H*, 8-*H*). ^{13}C NMR (101 MHz, $CDCl_3$): δ=27.9 (0.4 C, *C*-4), 29.1 (0.6 C, *C*-4), 40.7 (0.4 C, *C*-3), 41.3 (0.6 C, COCH_2Cl), 41.6 (0.4 C, COCH_2Cl), 44.1 (0.6 C, *C*-3), 44.6 (0.6 C, *C*-1), 47.7 (0.4 C, *C*-1), 56.13 (1.2 C, 6-OCH_3, 7-OCH_3), 56.18 (0.8 C, 6-OCH_3, 7-OCH_3), 109.0 (0.4 C, *C*-8), 109.5 (0.6 C, *C*-8), 111.4 (0.6 C, *C*-5), 111.7 (0.4 C, *C*-5), 123.7 (0.4 C, *C*-8a), 124.6 (0.6 C, *C*-8a), 125.6 (0.6 C, *C*-4a), 126.7 (0.4 C, *C*-4a), 148.0 (1.2 C, *C*-6, *C*-7), 148.2 (0.8 C, *C*-6, *C*-7), 165.5 (0.4 C, *C*=O), 165.6 ppm (0.4 C, *C*=O). FTIR (neat): ν [cm^{-1}]=2974, 2932 (C–H_{alkyl}), 1651 (C=O), 1520, 1443 (C=C_{arom}). Purity (HPLC): 99.7%, t_R=15.9 min.

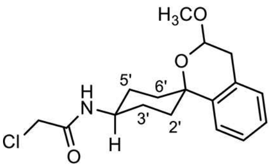
trans-2-Chloro-*N*-(3-methoxy-3,4-dihydrospiro[[2] benzopyran-1,1′-cyclohexan]-4′-yl)acetamide (*trans*-17)



2-Chloroacetyl chloride (19 µL, 0.24 mmol, 1.2 equiv) was slowly added to a solution of amine *trans*-**11** (50 mg, 0.20 mmol) and Et_3N (0.07 mL, 0.50 mmol, 2.5 equiv) in CH_2Cl_2 (5 mL) under N_2 at 0°C. After stirring for 6.5 h at RT, H_2O (30 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×30 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*=16 cm, *V*=5 mL, cyclohexane/ethyl acetate 50:50). Pale yellow solid, m.p. 144°C, yield 36 mg (56%). $C_{17}H_{22}ClNO_3$ (323.8 g/mol). R_f=0.22 (cyclohexane/ethyl acetate 67:33). HRMS (APCI): *m/z* 292.1080 (calcd. 292.1099 for $C_{16}H_{19}{}^{35}ClNO_2$ [*M*-CH_3OH+H$^+$]). ^{1}H NMR (600 MHz, CD_3OD): δ=1.68–1.72 (m, 1H, 2′-*H*), 1.76–1.81 (m, 2H, 3′-*H*, 5′-*H*), 1.88 (td, *J*=14.1/3.8 Hz, 1H, 6′-*H*), 1.92–1.97 (m, 1H, 6′-*H*), 2.10–2.25 (m, 3H, 2′-*H*, 3′-*H*, 5′-*H*), 2.81 (dd, *J*=15.6/7.4 Hz, 1H, 4-*H*), 2.94 (dd, *J*=15.6/3.1 Hz, 1H, 4-*H*), 3.55 (s, 3H, OCH_3), 4.12–4.16 (m, 1H, 4′-H_{equ}), 4.13 (s, 2H, COCH_2Cl), 4.92 (dd, *J*=7.4/3.1 Hz, 1H, 3-*H*), 7.10 (dd, *J*=7.6/1.3 Hz, 1H, 5-*H*), 7.17 (td, *J*=7.4/1.3 Hz, 1H, 6-*H*), 7.20–7.23 (m, 1H, 7-*H*), 7.29 ppm (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=26.2 (1 C, *C*-3′), 26.3 (1 C, *C*-5′), 32.0 (1 C, *C*-6′), 34.4 (1 C, *C*-2′), 36.1 (1 C, *C*-4), 43.4 (1 C, COCH_2Cl), 45.8 (1 C, *C*-

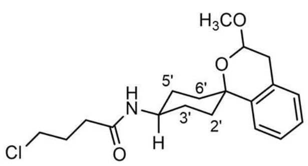
4′), 56.4 (1 C, OCH_3), 77.4 (1 C, *C*-1), 97.9 (1 C, *C*-3), 125.7 (1 C, *C*-8), 127.5 (1 C, *C*-7), 127.7 (1 C, *C*-6), 130.1 (1 C, *C*-5), 132.5 (1 C, *C*-4a), 143.0 (1 C, *C*-8a), 169.2 ppm (1 C, *C*=O). FTIR (neat): ν [cm^{-1}] = 3321 (N–H), 2928, 2851 ($C–H_{alkyl}$), 1636 (C=O), 1547, 1447 ($C=C_{arom}$). Purity (HPLC): 94.8 %, t_R = 18.9 min.

cis-2-Chloro-*N*-(3-methoxy-3,4-dihydrospiro[[2]benzopyran-1,1′-cyclohexan]-4′-yl)acetamide (*cis*-17)



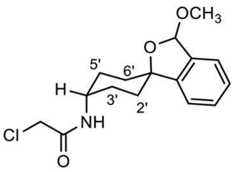
2-Chloroacetyl chloride (19 μL, 0.24 mmol, 1.2 equiv) was slowly added to a solution of amine *cis*-**11** (50 mg, 0.20 mmol) and Et_3N (0.07 mL, 0.50 mmol, 2.5 equiv) in CH_2Cl_2 (5 mL) under N_2 at 0 °C. After stirring for 6 h at RT, H_2O (30 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×30 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 67 : 33). Colorless solid, m.p. 148 °C, yield 40 mg (60 %). $C_{17}H_{22}ClNO_3$ (323.8 g/mol). R_f = 0.44 (cyclohexane/ethyl acetate 50 : 50). HRMS (APCI): *m/z* 292.1072 (calcd. 292.1099 for $C_{16}H_{19}{}^{35}ClNO_2$ [*M*-CH_3OH + H^+]). ^1H NMR (600 MHz, CD_3OD): δ = 1.77–1.91 (m, 5H, 2′-H_{ax}, 3′-*H*, 5′-*H*, 6′-H_{equ}), 1.92–1.97 (m, 1H, 5′-*H*), 2.08 (td, *J* = 13.2/3.9 Hz, 1H, 6′-H_{ax}), 2.13 (dq, *J* = 14.0/2.9 Hz, 1H, 2′-H_{equ}), 2.81 (dd, *J* = 15.6/7.5 Hz, 1H, 4-*H*), 2.94 (dd, *J* = 15.8/2.9 Hz, 1H, 4-*H*), 3.58 (s, 3H, OCH_3), 3.88 (tt, *J* = 11.3/4.7 Hz, 1H, 4′-H_{ax}), 4.03 (s, 2H, COCH_2Cl), 4.92 (dd, *J* = 7.5/3.1 Hz, 1H, 3-*H*), 7.09 (d, *J* = 7.3 Hz, 1H, 5-*H*), 7.16 (td, *J* = 7.2/1.9 Hz, 1H, 6-*H*), 7.18–7.24 ppm (m, 2H, 7-*H*, 8-*H*). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, CD_3OD): δ = 28.7 (1 C, *C*-5′), 28.8 (1 C, *C*-3′), 36.1 (1 C, *C*-4), 36.5 (1 C, *C*-2′), 39.1 (1 C, *C*-6′), 43.3 (1 C, COCH_2Cl), 49.7 (1 C, *C*-4′), 56.4 (1 C, OCH_3), 76.9 (1 C, *C*-1), 97.9 (1 C, *C*-3), 125.7 (1 C, *C*-8), 127.6 (1 C, *C*-7), 127.7 (1 C, *C*-6), 130.1 (1 C, *C*-5), 132.6 (1 C, *C*-4a), 142.5 (1 C, *C*-8a), 168.6 ppm (1 C, *C*=O). FTIR (neat): ν [cm^{-1}] = 3302 (N–H), 2932, 2862 ($C–H_{alkyl}$), 1643 (C=O), 1447 ($C=C_{arom}$). Purity (HPLC): 97.1 %, t_R = 18.6 min.

cis-4-Chloro-*N*-(3-methoxy-3,4-dihydrospiro[[2]benzopyran-1,1′-cyclohexan]-4′-yl)butanamide (*cis*-18)



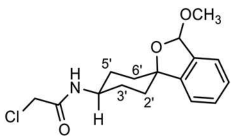
4-Chlorobutyryl chloride (27.4 μL, 0.24 mmol, 1.1 equiv) was slowly added to a solution of amine *cis*.**11** (54 mg, 0.22 mmol) and Et_3N (0.07 mL, 0.50 mmol, 2.3 equiv.) in CH_2Cl_2 (15 mL) under N_2 at 0 °C. After stirring for 4 h at RT, H_2O (30 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Colorless solid, m.p. 126 °C, yield 69 mg (89 %). $C_{19}H_{26}ClNO_3$ (351.9 g/mol). R_f = 0.37 (cyclohexane/ethyl acetate 50 : 50). HRMS (ESI): *m/z* 374.1504 (calcd. 374.1493 for $C_{19}H_{26}{}^{35}ClNO_3Na$ [*M*Na^+]). ^1H NMR (400 MHz, CD_3OD): δ = 1.78–1.94 (m, 6H, 2′-*H*, 3′-*H*, 5′-*H*, 6′-*H*), 2.02–2.17 (m, 4H, 2′-H, 6′-H, $COCH_2CH_2CH_2Cl$), 2.39 (t, *J* = 7.3 Hz, 2H, $COCH_2CH_2CH_2Cl$), 2.82 (dd, *J* = 15.7/7.5 Hz, 1H, 4-*H*), 2.94 (dd, *J* = 15.7/3.2 Hz, 1H, 4-*H*), 3.60 (s, 3H, OCH_3), 3.63 (t, *J* = 6.5 Hz, 2H, $COCH_2CH_2CH_2Cl$), 3.81–3.91 (m, 1H, 4′-H_{ax}), 4.93 (dd, *J* = 7.4/3.2 Hz, 1H, 3-*H*), 7.10 (d, *J* = 7.0 Hz, 1H, 5-*H*), 7.14–7.26 ppm (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 = 28.9 (1 C, *C*-3′ or *C*-5′), 29.1 (1 C, *C*-3′ or *C*-5′), 30.0 (1 C, $COCH_2CH_2CH_2Cl$), 34.2 (1 C, $COCH_2CH_2CH_2Cl$), 36.1 (1 C, *C*-4), 36.5 (1 C, *C*-2′), 39.1 (1 C, *C*-6′), 45.1 (1 C, $COCH_2CH_2CH_2Cl$), 49.1 (1 C, *C*-4′), 56.4 (1 C, OCH_3), 77.0 (1 C, *C*-1), 97.8 (1 C, *C*-3), 125.7 (1 C, *C*-8), 127.5 (1 C, *C*-6 or *C*-7), 127.7 (1 C, *C*-6 or *C*-7), 130.1 (1 C, *C*-5), 132.6 (1 C, *C*-4a), 142.5 (1 C, *C*-8a), 174.1 ppm (1 C, *C*=O). FTIR (neat): ν [cm^{-1}] = 3306 (N–H), 2928, 2862 ($C–H_{alkyl}$), 1636 (C=O), 1543, 1443 ($C=C_{arom}$). Purity (HPLC): 72.3 %, t_R = 19.6 min.

trans-2-Chloro-*N*-(3-methoxy-3*H*-spiro[[2]benzopyran-1,1′-cyclohexan]-4′-yl)acetamide (*trans*-20)



2-Chloroacetyl chloride (20 μL, 0.25 mmol, 1.2 equiv) was slowly added to a solution of amine *trans*-**13** (49 mg, 0.21 mmol) and Et_3N (0.07 mL, 0.50 mmol, 2.4 equiv) in CH_2Cl_2 (10 mL) under N_2 at 0 °C. After stirring for 6 h at RT, H_2O (30 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×30 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* = 5 mL, cyclohexane/ethyl acetate 67 : 33). Colorless solid, m.p. 123 °C, yield 45 mg (69 %). $C_{16}H_{20}ClNO_3$ (309.8 g/mol). R_f = 0.50 (cyclohexane/ethyl acetate 50 : 50). HRMS (ESI): *m/z* 332.1037 (calcd. 332.1024 for $C_{16}H_{20}{}^{35}ClNO_3Na$ [*M*Na^+]). ^1H NMR (600 MHz, CD_3OD): δ = 1.61–1.66 (m, 1H, 2′-*H*), 1.78 (dddd, *J* = 13.6/5.7/4.1/1.9 Hz, 1H, 6′-H_{equ}), 1.83–1.92 (m, 2H, 3′-*H*, 5′-*H*), 1.97–2.15 (m, 4H, 2′-*H*, 3′-*H*, 5′-*H*, 6′-H_{ax}), 3.48 (s, 3H, OCH_3), 4.07–4.14 (m, 1H, 4′-H_{equ}), 4.11 (s, 2H, COCH_2Cl), 6.05 (s, 1H, 3-*H*), 7.35–7.38 (m, 2H, 4-*H*, 5-*H*), 7.38–7.43 ppm (m, 2H, 6-*H*, 7-*H*). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, CD_3OD): δ = 27.4 (1 C, *C*-3′ or *C*-5′), 27.6 (1 C, *C*-3′ or *C*-5′), 34.0 (1 C, *C*-2′), 35.3 (1 C, *C*-6′), 43.4 (1 C, COCH_2Cl), 46.6 (1 C, *C*-4′), 55.0 (1 C, OCH_3), 87.3 (1 C, *C*-1), 107.0 (1 C, *C*-3), 122.1 (1 C, *C*-7), 124.3 (1 C, *C*-4), 129.0 (1 C, *C*-5), 130.4 (1 C, *C*-6), 138.9 (1 C, *C*-3a), 148.5 (1 C, *C*-7a), 169.0 ppm (1 C, *C*=O). FTIR (neat): ν [cm^{-1}] = 3302 (N–H), 2932 ($C–H_{alkyl}$), 1643 (C=O), 1543, 1443 ($C=C_{arom}$). Purity (HPLC): 97.6 %, t_R = 14.6 min.

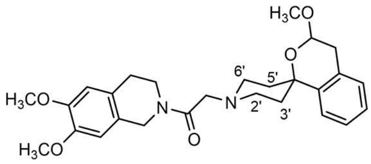
cis-2-Chloro-*N*-(3-methoxy-3*H*-spiro[[2]benzopyran-1,1′-cyclohexan]-4′-yl)acetamide (*cis*-20)



2-Chloroacetyl chloride (20 μL, 0.25 mmol, 1.2 equiv) was slowly added to a solution of amine *cis*-**13** (50 mg, 0.21 mmol) and Et_3N (0.07 mL, 0.50 mmol, 2.4 equiv) in CH_2Cl_2 (8 mL) under N_2 at 0 °C. After stirring for 6 h at RT, H_2O (30 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×30 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* = 18 cm, *V* = 10 mL, cyclohexane/ethyl acetate 33 : 67). Colorless solid, m.p. 165 °C, yield 51 mg (78 %). $C_{16}H_{20}ClNO_3$ (309.8 g/mol). R_f = 0.48 (cyclohexane/ethyl acetate 50 : 50). HRMS (ESI): *m/z* 332.1014 (calcd. 332.1024 for

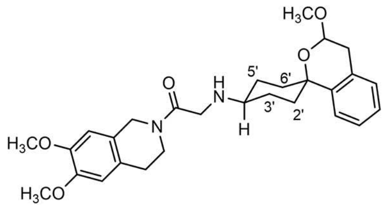
$C_{16}H_{20}{}^{35}ClNO_3Na$ [MNa$^+$]). ^{1}H NMR (600 MHz, CD_3OD): $\delta = 1.69$ (dq, $J = 13.6/3.0$ Hz, 1H, 2′-H_{equ}), 1.82–1.94 (m, 6H, 3′-*H*, 5′-*H*, 6′-*H*), 2.00 (td, $J = 13.5/4.1$ Hz, 1H, 2′-H_{ax}), 3.49 (s, 3H, OCH_3), 3.87 (tt, $J = 11.1/3.9$ Hz, 1H, 4′-H_{ax}), 4.03 (s, 2H, $COCH_2Cl$), 6.07 (s, 1H, 3-*H*), 7.26 (d, $J = 7.5$ Hz, 1H, 7-*H*), 7.33–7.38 (m, 2H, 4-*H*, 5-*H*), 7.39–7.42 ppm (m, 1H, 6-*H*). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, CD_3OD): $\delta = 29.3$ (1 C, *C*-3′), 29.7 (1 C, *C*-5′), 37.5 (1 C, *C*-2′), 38.7 (1 C, *C*-6′), 43.3 (1 C, $COCH_2Cl$), 49.5 (1 C, *C*-4′), 54.9 (1 C, OCH_3), 86.8 (1 C, *C*-1), 107.2 (1 C, *C*-3), 121.8 (1 C, *C*-7), 124.2 (1 C, *C*-4), 129.0 (1 C, *C*-5), 130.5 (1 C, *C*-6), 138.6 (1 C, *C*-3a), 148.3 (1 C, *C*-7a), 168.6 ppm (1 C, *C*=O). FTIR (neat): ν [cm^{-1}] = 3271 (N–H), 2978, 2940, 2866 (C–H_{alkyl}), 1651 (C=O), 1555, 1462, 1431 (C=C_{arom}). Purity (HPLC): 98.1 %, $t_R = 15.1$ min.

1-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-{3-methoxy-3,4-dihydrospiro[[2]benzopyran-1,4′-piperidin]-1′-yl}ethan-1-one (21)



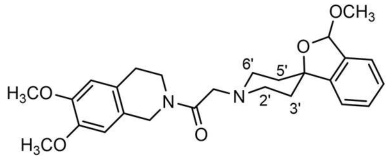
A solution of piperidine **10** (43 mg, 0.18 mmol), chloroacetamide **15** (58 mg, 0.22 mmol, 1.2 equiv), Et_3N (0.09 mL, 0.65 mmol, 3.6 equiv) and TBAI (9 mg, 0.02 mmol, 0.1 equiv) in DMF (4 mL) was stirred at RT for 18 h. H_2O (70 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×60 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, $l = 25$ cm, $V = 10$ mL, CH_2Cl_2/CH_3OH 99:1 + 1 % *N*,*N*-dimethylethanamine; $d = 1$ cm, $l = 20$ cm, $V = 3$ mL, cyclohexane/ethyl acetate 67:33 + 1 % *N*,*N*-dimethylethanamine→1:1 + 1 % *N*,*N*-dimethylethanamine). Pale yellow oil, yield 31 mg (22 %). $C_{27}H_{34}N_2O_5$ (466.6 g/mol). $R_f = 0.46$ (CH_2Cl_2/CH_3OH 99:1 + 1 % *N*,*N*-dimethylethanamine). HRMS (APCI): *m/z* 467.2531 (calcd. 467.2540 for $C_{27}H_{35}N_2O_5$ [MH$^+$]). ^{1}H NMR (400 MHz, CD_3OD): $\delta = 1.70$ (dq, $J = 13.5/2.8$ Hz, 0.5H, 3′-H_{equ}), 1.75–1.85 (m, 1H, 3′-*H*, 5′-*H*), 1.95 (dq, $J = 13.9/2.6$ Hz, 0.5H, 5′-H_{equ}), 2.00–2.09 (m, 1.5H, 3′-*H*, 5′-*H*), 2.29 (td, $J = 13.1/4.5$ Hz, 0.5H, 3′-H_{ax}), 2.57–2.73 (m, 2H, 2′-*H*, 6′-*H*), 2.73–3.00 (m, 6H, 4-*H*, 2′-*H*, 6′-*H*, 4-$H_{isoquinoline}$), 3.38–3.52 (m, 2H, $COCH_2N$), 3.54 (s, 1.5H, 3-OCH_3), 3.57 (s, 1.5H, 3-OCH_3), 3.81–3.90 (m, 8H, 3-$H_{isoquinoline}$, 6-OCH_3, 7-OCH_3), 4.66 (s, 1H, 1-$H_{isoquinoline}$), 4.80 (s, 1H, 1-$H_{isoquinoline}$), 4.90 (dd, $J = 7.2/3.2$ Hz, 0.5H, 3-*H*), 4.95 (dd, $J = 7.2/3.2$ Hz, 0.5H, 3-*H*), 6.76–6.83 (m, 1.5H, 5-$H_{isoquinoline}$, 8-$H_{isoquinoline}$), 6.86 (s, 0.5H, 8-$H_{isoquinoline}$), 7.01–7.05 (m, 0.5H, 8-*H*), 7.06–7.14 (m, 1H, 5-*H*) 7.14–7.26 ppm (m, 2.5H, 6-*H*, 7-*H*, 8-*H*). ^{13}C NMR (101 MHz, CD_3OD): $\delta = 28.6$ (0.5 C, *C*-4$_{isoquinoline}$), 29.7 (0.5 C, *C*-4$_{isoquinoline}$), 35.86 (0.5 C, *C*-4), 35.89 (0.5 C, *C*-4), 37.18 (0.5 C, *C*-5′), 37.20 (0.5 C, *C*-5′), 39.6 (0.5 C, *C*-3′), 39.7 (0.5 C, *C*-3′), 41.7 (0.5 C, *C*-3$_{isoquinoline}$), 44.4 (0.5 C, *C*-3$_{isoquinoline}$), 44.9 (0.5 C, *C*-1$_{isoquinoline}$), 48.2 (0.5 C, *C*-1$_{isoquinoline}$), 50.2–50.7 (m, 2 C, *C*-2′, *C*-6′), 56.2–56.4 (m, 3 C, 3-OCH_3, 6-OCH_3, 7-OCH_3), 61.68 (0.5 C, $COCH_2N$), 61.74 (0.5 C, $COCH_2N$), 75.2 (0.5 C, *C*-1), 75.4 (0.5 C, *C*-1), 97.55 (0.5 C, *C*-3), 97.59 (0.5 C, *C*-3), 110.6 (0.5 C, *C*-8$_{isoquinoline}$), 110.9 (0.5 C, *C*-8$_{isoquinoline}$), 112.9 (0.5 C, *C*-5$_{isoquinoline}$), 113.1 (0.5 C, *C*-5$_{isoquinoline}$), 125.6 (1 C, *C*-8), 126.1 (1 C, *C*-8a$_{isoquinoline}$), 126.9 (1 C, *C*-4a$_{isoquinoline}$), 127.37 (0.5 C, *C*-7), 127.39 (0.5 C, *C*-7), 127.56 (0.5 C, *C*-6), 127.62 (0.5 C, *C*-6), 129.9 (0.5 C, *C*-5), 130.0 (0.5 C, *C*-5), 132.4 (0.5 C, *C*-4a), 132.5 (0.5 C, *C*-4a), 141.89 (0.5 C, *C*-8a), 141.92 (0.5 C, *C*-8a), 149.0–149.3 (m, 2 C, *C*-6$_{isoquinoline}$, *C*-7$_{isoquinoline}$), 170.7 (0.5 C, *C*=O), 170.8 ppm (0.5 C, *C*=O). FTIR (neat): ν [cm^{-1}] = 2978, 2835 (C–H_{alkyl}), 1624 (C=O), 1516, 1454 (C=C_{arom}). Purity (HPLC): 92.1 %, $t_R = 17.4$ min.

cis-1-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-[*N*-(3-methoxy-3,4-dihydrospiro[[2]benzopyran-1,1′-cyclohexan]-4′-yl)amino]ethan-1-one (*cis*-22)



A solution of chloroacetamide **15** (32 mg, 0.12 mmol), amine *cis*-**11** (36 mg, 0.15 mmol, 1.2 equiv), Et_3N (0.06 mL, 0.43 mmol, 2.9 equiv) and TBAI (5 mg, 0.01 mmol, 0.1 equiv) in DMF (4 mL) was stirred at RT for 7 d. H_2O (80 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×60 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc ($d = 2$ cm, $l = 29$ cm, $V = 10$ mL, CH_2Cl_2/CH_3OH 99:1 + 1 % *N*,*N*-dimethylethanamine). Pale yellow oil, yield 35 mg (60 %). $C_{28}H_{36}N_2O_5$ (480.6 g/mol). $R_f = 0.29$ (CH_2Cl_2/CH_3OH 95:5 + 1 % *N*,*N*-dimethylethanamine). HRMS (ESI): *m/z* 481.2700 (calcd. 481.2697 for $C_{28}H_{37}N_2O_5$ [MH$^+$]). ^{1}H NMR (600 MHz, CD_3OD): δ = 1.64–1.78 (m, 2H, 2′-*H*, 3′-*H*), 1.78–1.92 (m, 4H, 3′-*H*, 5′-*H*, 6′-*H*), 1.92–2.02 (m, 1H, 6′-*H*), 2.07–2.13 (m, 1H, 2′-*H*), 2.63–2.72 (m, 1H, 4′-H_{ax}), 2.77–2.82 (m, 2H, 4-*H*, 4-$H_{isoquinoline}$), 2.87 (t, $J = 6.0$ Hz, 1H, 4-$H_{isoquinoline}$), 2.89–2.95 (m, 1H, 4-*H*), 3.56 (s, 1.5H, OCH_3), 3.57 (s, 1.5H, 3-OCH_3), 3.65 (s, 2H, $COCH_2NH$), 3.70 (t, $J = 5.9$ Hz, 1H, 3-$H_{isoquinoline}$), 3.80–3.83 (m, 1H, 3-$H_{isoquinoline}$), 3.82 (s, 6H, 6-OCH_3, 7-OCH_3), 4.61 (s, 1H, 1-$H_{isoquinoline}$), 4.66 (s, 1H, 1-$H_{isoquinoline}$), 4.89–4.92 (m, 1H, 3-*H*), 6.76–6.79 (m, 1.5H, 5-$H_{isoquinoline}$, 8-$H_{isoquinoline}$), 6.80 (s, 0.5H, 8-$H_{isoquinoline}$), 7.06–7.09 (m, 1H, 5-*H*), 7.12–7.20 ppm (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): $\delta = 28.8$ (0.5 C, *C*-4$_{isoquinoline}$), 29.1 (1 C, *C*-3′ or *C*-5′), 29.3 (1 C, *C*-3′ or *C*-5′), 29.6 (0.5 C, *C*-4$_{isoquinoline}$), 36.2 (1 C, *C*-4), 36.4 (1 C, *C*-2′), 38.9 (1 C, *C*-6′), 41.6 (0.5 C, *C*-3$_{isoquinoline}$), 43.6 (0.5 C, *C*-3$_{isoquinoline}$), 45.2 (0.5 C, *C*-1$_{isoquinoline}$), 46.9 (0.5 C, *C*-1$_{isoquinoline}$), 48.1 (0.5 C, $COCH_2NH$), 48.3 (0.5 C, $COCH_2NH$), 56.4–56.6 (m, 3 C, 3-OCH_3, 6-OCH_3, 7-OCH_3), 57.47 (0.5 C, *C*-4′), 57.49 (0.5 C, *C*-4′), 77.37 (0.5 C, *C*-1), 77.39 (0.5 C, *C*-1), 97.8 (1 C, *C*-3), 110.9 (0.5 C, *C*-8$_{isoquinoline}$), 111.0 (0.5 C, *C*-8$_{isoquinoline}$), 113.0 (0.5 C, *C*-5$_{isoquinoline}$), 113.1 (0.5 C, *C*-5$_{isoquinoline}$), 125.6 (0.5 C, *C*-8), 125.7 (0.5 C, *C*-8), 125.8 (0.5 C, *C*-8a$_{isoquinoline}$), 126.3 (0.5 C, *C*-8a$_{isoquinoline}$), 127.5 (1 C, *C*-7), 127.67 (1 C, *C*-6), 127.74 (0.5 C, *C*-4a$_{isoquinoline}$), 128.2 (0.5 C, *C*-4a$_{isoquinoline}$), 130.1 (1 C, *C*-5), 132.6 (1 C, *C*-4a), 142.61 (0.5 C, *C*-8a), 142.62 (0.5 C, *C*-8a), 149.2–149.6 (m, 2 C, *C*-6$_{isoquinoline}$, *C*-7$_{isoquinoline}$), 171.4 (0.5 C, *C*=O), 171.5 ppm (0.5 C, *C*=O). FTIR (neat): ν [cm^{-1}] = 3375 (N–H), 2978, 2936, 2909 (C–H_{alkyl}), 1640 (C=O), 1516, 1435 (C=C_{arom}). Purity (HPLC): 98.0 %, $t_R = 17.7$ min.

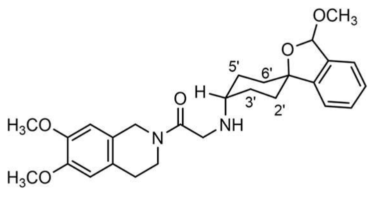
1-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-{3-methoxy-3H-spiro[[2]benzofuran-1,4′-piperidin]-1′-yl}ethan-1-one (23)



A solution of piperidine **12** (40 mg, 0.18 mmol), chloroacetamide **15** (50 mg, 0.19 mmol, 1.0 equiv), Et_3N (0.09 mL, 0.65 mmol, 3.6 equiv) and TBAI (7 mg, 0.02 mmol, 0.1 equiv) in DMF (5 mL) was stirred at

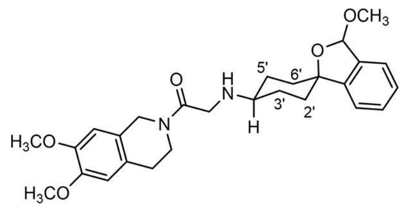
RT for 19 h. H_2O (70 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3×60 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo, and the residue was purified twice by fc (d = 2 cm, l = 25 cm, V = 10 mL, CH_2Cl_2/CH_3OH 95:5; d = 2 cm, l = 20 cm, V = 10 mL, cyclohexane/ethyl acetate 50:50 + 1% *N,N*-dimethylethanamine). Pale yellow solid, m.p. 103 °C, yield 30 mg (36%). $C_{26}H_{32}N_2O_5$ (452.6 g/mol). R_f = 0.30 (CH_2Cl_2/CH_3OH 95:5 + 1% *N,N*-dimethylethanamine). HRMS (APCI): *m/z* 453.2406 (calcd. 453.2384 for $C_{26}H_{33}N_2O_5$ [MH^+]). ^1H NMR (600 MHz, CD_3OD): δ = 1.52 (dq, J = 13.5/2.7 Hz, 0.5H, 3′-H_{equ}), 1.61 (dq, J = 13.6/2.8 Hz, 0.5H, 3′-H_{equ}), 1.70 (dq, J = 13.5/2.7 Hz, 0.5H, 5′-H_{equ}), 1.78 (dq, J = 13.6/2.8 Hz, 0.5H, 5′-H_{equ}), 1.88–2.00 (m, 1H, 3′-H_{ax}, 5′-H_{ax}), 2.09 (td, J = 13.1/4.5 Hz, 0.5H, 5′-H_{ax}), 2.17 (td, J = 13.2/4.5 Hz, 0.5H, 3′-H_{ax}), 2.55–2.66 (m, 2H, 2′-*H*, 6′-*H*), 2.81 (t, J = 6.1 Hz, 1H, 4-$H_{isoquinoline}$), 2.84–2.89 (m, 1H, 2′-*H* or 6′-*H*), 2.90–2.96 (m, 2H, 2′-*H* or 6′-*H*, 4-$H_{isoquinoline}$), 3.40–3.43 (m, 2H, $COCH_2N$), 3.47 (s, 1.5H, 3-OCH_3), 3.49 (s, 1.5H, 3-OCH_3), 3.79–3.87 (m, 8H, 3-$H_{isoquinoline}$, 6-OCH_3, 7-OCH_3), 4.65 (s, 1H, 1-$H_{isoquinoline}$), 4.76 (d, J = 15.9 Hz, 0.5H, 1-$H_{isoquinoline}$), 4.79 (d, J = 15.9 Hz, 0.5H, 1-$H_{isoquinoline}$), 6.04 (s, 0.5H, 3-*H*), 6.06 (s, 0.5H, 3-*H*), 6.77 (s, 1H, 5-$H_{isoquinoline}$, 8-$H_{isoquinoline}$), 6.79 (s, 0.5H, 5-$H_{isoquinoline}$), 6.83 (s, 0.5H, 8-$H_{isoquinoline}$), 7.15 (d, J = 7.6 Hz, 0.5H, 4-*H*), 7.29 (d, J = 7.6 Hz, 0.5H, 4-*H*), 7.32–7.43 ppm (m, 3H, 5-*H*, 6-*H*, 7-*H*). ^{13}C NMR (151 MHz, CD_3OD): δ = 28.8 (0.5 C, *C*-4$_{isoquinoline}$), 30.0 (0.5 C, *C*-4$_{isoquinoline}$), 38.07 (0.5 C, *C*-3′), 38.14 (0.5 C, *C*-3′), 39.60 (0.5 C, *C*-5′), 39.64 (0.5 C, *C*-5′), 41.8 (0.5 C, *C*-3$_{isoquinoline}$), 44.6 (0.5 C, *C*-3$_{isoquinoline}$), 45.2 (0.5 C, *C*-1$_{isoquinoline}$), 48.3 (0.5 C, *C*-1$_{isoquinoline}$), 50.9–51.7 (m, 2 C, *C*-2′, *C*-6′), 54.98 (0.5 C, 3-OCH_3), 55.01 (0.5 C, 3-OCH_3), 56.5–56.6 (m, 2 C, 6-OCH_3, 7-OCH_3), 61.89 (0.5 C, $COCH_2N$), 61.92 (0.5 C, $COCH_2N$), 85.5 (1 C, *C*-1), 107.1 (0.5 C, *C*-3), 107.2 (0.5 C, *C*-3), 110.9 (0.5 C, *C*-8$_{isoquinoline}$), 111.0 (0.5 C, *C*-8$_{isoquinoline}$), 113.1 (0.5 C, *C*-5$_{isoquinoline}$), 113.3 (0.5 C, *C*-5$_{isoquinoline}$), 121.7 (0.5 C, *C*-4), 121.8 (0.5 C, *C*-4), 124.21 (0.5 C, *C*-7), 124.25 (0.5 C, *C*-7), 126.3 (0.5 C, *C*-8a$_{isoquinoline}$), 126.9 (0.5 C, *C*-4a$_{isoquinoline}$), 127.8 (0.5 C, *C*-8a$_{isoquinoline}$), 128.0 (0.5 C, *C*-4a$_{isoquinoline}$), 129.08 (0.5 C, *C*-6), 129.12 (0.5 C, *C*-6), 130.49 (0.5 C, *C*-5), 130.51 (0.5 C, *C*-5), 138.86 (0.5 C, *C*-7a), 138.92 (0.5 C, *C*-7a), 148.01 (0.5 C, *C*-3a), 148.02 (0.5 C, *C*-3a), 149.2–149.5 (m, 2 C, *C*-6$_{isoquinoline}$, *C*-7$_{isoquinoline}$), 170.9 (0.5 C, *C*=O), 171.0 ppm (0.5 C, *C*=O). FTIR (neat): ν [cm^{-1}] = 2913, 2735 (C–H_{alkyl}), 1636 (C=O), 1516, 1447 (C=C_{arom}). Purity (HPLC): 99.7%, t_R = 14.9–17.0 min.

trans-1-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-[*N*-(3-methoxy-3*H*-spiro[[2]benzofuran-1,1′-cyclohexan]-4′-yl)amino]ethan-1-one (*trans*-24)



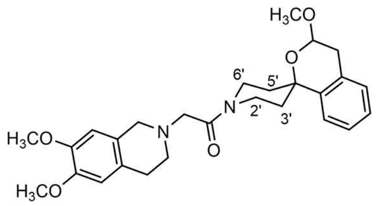
A solution of chloroacetamide **15** (30 mg, 0.11 mmol), amine *trans*-**13** (26 mg, 0.11 mmol, 1.0 equiv), Et_3N (0.05 mL, 0.36 mmol, 3.3 equiv.) and TBAI (5 mg, 0.01 mmol, 0.1 equiv) in DMF (4 mL) was stirred at RT for 3 d. H_2O (80 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×60 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 33:67 + 1% *N,N*-dimethylethanamine→20:80 + 1% *N,N*-dimethylethanamine; d = 2 cm, l = 31 cm, V = 10 mL, CH_2Cl_2/CH_3OH 95:5 + 1% *N,N*-dimethylethanamine). Colorless solid, m.p. 66 °C, yield 28 mg (54%). $C_{27}H_{34}N_2O_5$ (466.6 g/mol). R_f = 0.33 (CH_2Cl_2/CH_3OH 95:5 + 1% *N,N*-dimethylethanamine). HRMS (ESI): *m/z* 467.2533 (calcd. 467.2540 for $C_{27}H_{35}N_2O_5$ [MH^+]). ^1H NMR (600 MHz, CD_3OD): δ = 1.52–1.60 (m, 1H, 2′-*H*), 1.66–1.74 (m, 1H, 6′-*H*), 1.77–1.86 (m, 2H, 3′-*H*, 5′-*H*), 2.01–2.13 (m, 4H, 2′-*H*, 3′-*H*, 5′-*H*, 6′-*H*), 2.81 (t, J = 6.0 Hz, 1H, 4-$H_{isoquinoline}$), 2.81 (t, J = 6.0 Hz, 1H, 4-$H_{isoquinoline}$), 2.90–2.94 (m, 1H, 4′-H_{equ}), 3.46 (s, 1.5H, 3-OCH_3), 3.47 (s, 1.5H, 3-OCH_3), 3.65 (s, 2H, $COCH_2NH$), 3.73 (t, J = 5.9 Hz, 1H, 3-$H_{isoquinoline}$), 3.80–3.86 (m, 7H, 3-$H_{isoquinoline}$, 6-OCH_3, 7-OCH_3), 4.67 (s, 1H, 1-$H_{isoquinoline}$), 4.68 (s, 1H, 1-$H_{isoquinoline}$), 6.04 (s, 0.5H, 3-*H*), 6.05 (s, 0.5H, 3-*H*), 6.77 (s, 0.5H, 5-$H_{isoquinoline}$), 6.78 (s, 0.5H, 5-$H_{isoquinoline}$), 6.79 (s, 0.5H, 8-$H_{isoquinoline}$), 6.81 (s, 0.5H, 8-$H_{isoquinoline}$), 7.30–7.41 (m, 3.5H, 4-*H*, 5-*H*, 6-*H*, 7-*H*), 7.44 ppm (d, J = 7.5 Hz, 0.5H, 7-*H*). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, CD_3OD): δ = 27.9 (0.5 C, *C*-3′ or *C*-5′), 28.0 (0.5 C, *C*-3′ or *C*-5′), 28.11 (0.5 C, *C*-3′ or *C*-5′), 28.14 (0.5 C, *C*-3′ or *C*-5′), 28.8 (0.5 C, *C*-4$_{isoquinoline}$), 29.6 (0.5 C, *C*-4$_{isoquinoline}$), 34.0 (0.5 C, *C*-2′), 34.1 (0.5 C, *C*-2′), 35.2 (0.5 C, *C*-6′), 35.3 (0.5 C, *C*-6′), 41.5 (0.5 C, *C*-3$_{isoquinoline}$), 43.7 (0.5 C, *C*-3$_{isoquinoline}$), 45.2 (0.5 C, *C*-1$_{isoquinoline}$), 46.9 (0.5 C, *C*-1$_{isoquinoline}$), 49.7 (1 C, $COCH_2NH$), 54.2 (0.5 C, *C*-4′), 54.3 (0.5 C, *C*-4′), 54.8 (1 C, 3-OCH_3), 56.47 (0.5 C, 6-OCH_3 or 7-OCH_3), 56.50 (0.5 C, 6-OCH_3 or 7-OCH_3), 56.5 (0.5 C, 6-OCH_3 or 7-OCH_3), 56.6 (0.5 C, 6-OCH_3 or 7-OCH_3), 88.1 (1 C, *C*-1), 106.9 (1 C, *C*-3), 110.9 (0.5 C, *C*-8$_{isoquinoline}$), 111.0 (0.5 C, *C*-8$_{isoquinoline}$), 113.0 (0.5 C, *C*-5$_{isoquinoline}$), 113.1 (0.5 C, *C*-5$_{isoquinoline}$), 122.4 (0.5 C, *C*-7), 122.5 (0,5 C, *C*-7), 124.16 (0.5 C, *C*-6), 124.19 (0.5 C, *C*-6), 125.8 (0.5 C, *C*-8a$_{isoquinoline}$), 126.3 (0.5 C, *C*-8a$_{isoquinoline}$), 127.8 (0.5 C, *C*-4a$_{isoquinoline}$), 128.2 (0.5 C, *C*-4a$_{isoquinoline}$), 128.88 (0.5 C, *C*-5), 128.90 (0.5 C, *C*-5), 130.30 (0.5 C, *C*-4), 130.31 (0.5 C, *C*-4), 138.7 (0.5 C, *C*-3a), 138.8 (0.5 C, *C*-3a), 148.7 (1 C, *C*-7a), 149.3 (0.5 C, *C*-6$_{isoquinoline}$ or C-7$_{isoquinoline}$), 149.38 (0.5 C, *C*-6$_{isoquinoline}$ or C-7$_{isoquinoline}$), 149.41 (0.5 C, *C*-6$_{isoquinoline}$ or C-7$_{isoquinoline}$), 149.5 (0.5 C, *C*-6$_{isoquinoline}$ or C-7$_{isoquinoline}$), 171.7 (0.5 C, *C*=O), 171.8 ppm (0.5 C, *C*=O). FTIR (neat): ν [cm^{-1}] = 3321 (N–H), 2978, 2928 (C–H_{alkyl}), 1643 (C=O), 1516, 1435 (C=C_{arom}). Purity (HPLC): 95.3%, t_R = 14.5 min.

cis-1-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-[*N*-(3-methoxy-3H-spiro[[2]benzofuran-1,1′-cyclohexan]-4′-yl)amino]ethan-1-one (*cis*-24)



A solution of chloroacetamide **15** (47 mg, 0.17 mmol, 1.3 equiv), amine *cis*-**13** (32 mg, 0.14 mmol), Et_3N (0.06 mL, 0.43 mmol, 3.1 equiv.) and TBAI (6 mg, 0.02 mmol, 0.1 equiv) in DMF (4 mL) was stirred at RT for 6 d. H_2O (80 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×60 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 = 29 cm, V = 10 mL, CH_2Cl_2/CH_3OH 99:1 + 1% *N,N*-dimethylethanamine). Yellow oil, yield 28 mg (43%). $C_{27}H_{34}N_2O_5$ (466.6 g/mol). R_f = 0.23 (CH_2Cl_2/CH_3OH 95:5 + 1% *N,N*-dimethylethanamine). HRMS (ESI): *m/z* 467.2534 (calcd. 467.2540 for $C_{27}H_{35}N_2O_5$ [MH^+]). ^1H NMR (600 MHz, CD_3OD): δ = 1.64–1.70 (m, 1H, 2′-*H*), 1.72–1.83 (m, 3H, 3′-*H*, 5′-*H*, 6′-*H*), 1.83–1.93 (m, 2H, 2′-*H*, 6′-*H*), 1.93–2.00 (m, 2H, 3′-*H*, 5′-*H*), 2.64–2.72 (m, 1H, 4′-H_{ax}), 2.81 (t, J = 6.2 Hz, 1H, 4-$H_{isoquinoline}$), 2.87 (t, J = 6.0 Hz, 1H, 4-$H_{isoquinoline}$), 3.49 (s, 1.5H, 3-OCH_3), 3.49 (s, 1.5H, 3-OCH_3), 3.67 (s, 2H, $COCH_2N$), 3.70 (t, J = 6.0 Hz, 1H, 3-$H_{isoquinoline}$), 3.80–3.85 (m, 7H, 3-$H_{isoquinoline}$, 6-OCH_3, 7-OCH_3), 4.61 (s, 1H, 1-$H_{isoquinoline}$), 4.66 (s, 1H, 1-$H_{isoquinoline}$), 6.04 (s, 0.5H, 3-*H*), 6.05 (s, 0.5H, 3-*H*), 6.76–6.79 (m, 1.5H, 5-$H_{isoquinoline}$, 8-$H_{isoquinoline}$), 6.80 (s, 0.5H, 8-$H_{isoquinoline}$), 7.18–7.25 (m, 1H, 7-*H*), 7.31–7.40 ppm (m, 3H, 4-*H*, 5-*H*, 6-*H*). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, CD_3OD): δ = 28.8 (0.5 C, *C*-4$_{isoquinoline}$), 29.6 (0.5 C, *C*-4$_{isoquinoline}$), 29.7 (1 C, *C*-3′ or *C*-5′), 30.0 (1 C, *C*-3′ or *C*-5′), 37.3 (1 C, *C*-2′), 38.7 (1 C, *C*-6′), 41.6 (0.5 C, *C*-3$_{isoquinoline}$), 43.6 (0.5 C, *C*-3$_{isoquinoline}$), 45.2 (0.5 C, *C*-1$_{isoquinoline}$), 46.8 (0.5 C, *C*-1$_{isoquinoline}$), 48.0 (0.5 C, CO*C*H_2N), 48.2 (0.5 C, CO*C*H_2N), 55.0 (1 C, 3-O*C*H_3), 56.5–56.6 (m, 2 C, 6-O*C*H_3, 7-O*C*H_3), 57.2 (1 C, *C*-4′), 87.30 (0.5 C, *C*-1), 87.32 (0.5 C, *C*-1), 107.1 (1 C, *C*-3), 110.9 (0.5 C, *C*-8$_{isoquinoline}$), 111.0 (0.5 C, *C*-8$_{isoquinoline}$), 113.0 (0.5 C, *C*-5$_{isoquinoline}$), 113.1 (0.5 C, *C*-5$_{isoquinoline}$), 121.68 (0.5 C, *C*-7), 121.70 (0.5 C, *C*-7), 124.2 (1 C, *C*-4), 125.7 (0.5 C, *C*-8a$_{isoquinoline}$), 126.3 (0.5 C, *C*-8a$_{isoquinoline}$), 127.7 (0.5 C, *C*-4a$_{isoquinoline}$), 128.2 (0.5 C, *C*-4a$_{isoquinoline}$), 129.0 (1 C, *C*-5), 130.4 (1 C, *C*-6), 138.8 (1 C, *C*-3a), 148.5 (1 C, *C*-7a), 149.2–149.6 (m, 2 C, *C*-6$_{isoquinoline}$, *C*-7$_{isoquinoline}$), 171.2 (0.5 C, *C*=O), 171.3 ppm (0.5 C, *C*=O). FTIR (neat): ν [cm^{-1}] = 3402 (N–H), 2928, 2855 (C–H$_{alkyl}$), 1643 (C=O), 1516, 1435 (C=C$_{arom}$). Purity (HPLC): 98.1 %, t_R = 15.1 min.

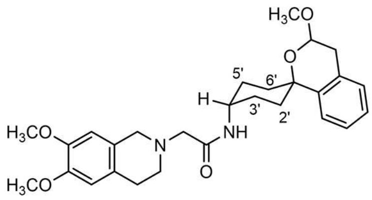
2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-1-(3-methoxy-3,4-dihydrospiro[[2]benzopyran-1,4′-piperidin]-1′-yl) ethan-1-one (25)



2-Chloroacetyl chloride (19 µL, 0.24 mmol, 1.2 equiv) was slowly added to a solution of piperidine **10** (46 mg, 0.20 mmol) and Et_3N (0.07 mL, 0.50 mmol, 2.5 equiv) in CH_2Cl_2 (4 mL) under N_2 at 0 °C. After 5 h of stirring at RT, H_2O (10 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo, and the residue was purified by fc (*d* = 2 cm, *l* = 18 cm, *V* = 10 mL, cyclohexane/ethyl acetate 67:33→50:50). Chloroacetamide **16**: Pale yellow oil, yield 25 mg (40 %). $C_{16}H_{20}ClNO_3$ (309.8 g/mol).

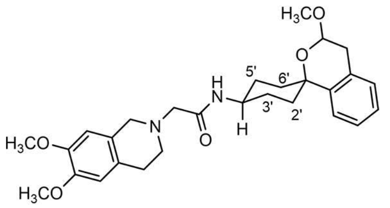
A solution of chloroacetamide **16** (25 mg, 0.08 mmol), isoquinoline **14**·HCl (20 mg, 0.09 mmol, 1.1 equiv), Et_3N (0.03 mL, 0.22 mmol, 2.8 equiv) and TBAI (5 mg, 0.01 mmol, 0.1 equiv) in DMF (4 mL) was stirred at RT for 63 h. H_2O (80 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×60 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 50:50 + 1 % *N*,*N*-dimethylethanamine). Pale yellow solid, m.p. 165 °C, yield 30 mg (75 %). $C_{27}H_{34}N_2O_5$ (466.6 g/mol). R_f = 0.26 (cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine). HRMS (APCI): *m/z* 467.2521 (calcd. 467.2540 for $C_{27}H_{35}N_2O_5$ [*M*H$^+$]). ^{1}H NMR (600 MHz, CD_3OD): δ = 1.76–1.86 (m, 1.5H, 3′-*H*, 5′-*H*), 1.90–1.96 (m, 0.5H, 5′-*H*), 1.99–2.10 (m, 1.5H, 3′-*H*, 5′-*H*), 2.17 (td, *J* = 13.3/4.6 Hz, 0.5H, 5′-*H*), 2.79–2.93 (m, 5H, 4-*H*, 3-*H*$_{isoquinoline}$, 4-*H*$_{isoquinoline}$), 2.93–2.98 (m, 1H, 4-*H*), 3.13–3.23 (m, 1H, 2′-*H*), 3.37 (d, *J* = 14.0 Hz, 1H, COC*H*$_2$N), 3.54 (s, 1.5H, 3-OC*H*$_3$), 3.55 (s, 1.5H, 3-OC*H*$_3$), 3.56–3.66 (m, 3H, 6′-*H*, COC*H*$_2$N, 1-*H*$_{isoquinoline}$), 3.67–3.72 (m, 1H, 1-*H*$_{isoquinoline}$), 3.79–3.82 (m, 6H, 6-OC*H*$_3$, 7-OC*H*$_3$), 4.09–4.14 (m, 1H, 6′-*H*), 4.50–4.57 (m, 1H, 2′-*H*), 4.96 (dd, *J* = 6.9/3.2 Hz, 0.5H, 3-*H*), 4.98 (dd, *J* = 7.0/3.2 Hz, 0.5H, 3-*H*), 6.69 (s, 0.5H, 8-*H*$_{isoquinoline}$), 6.69 (s, 0.5H, 8-*H*$_{isoquinoline}$), 6.70 (s, 0.5H, 5-*H*$_{isoquinoline}$), 6.72 (s, 0.5H, 5-*H*$_{isoquinoline}$), 6.94–6.97 (m, 0.5H, 8-*H*), 7.00 (dd, *J* = 7.5/1.6 Hz, 0.5H, 8-*H*), 7.08–7.17 ppm (m, 3H, 5-*H*, 6-*H*, 7-*H*). ^{13}C NMR (151 MHz, CD_3OD): δ = 29.5 (0.5 C, *C*-4$_{isoquinoline}$), 29.6 (0.5 C, *C*-4$_{isoquinoline}$), 36.0 (1 C, *C*-4), 37.6 (0.5 C, *C*-3′), 38.2 (0.5 C, *C*-5′), 39.6 (0.5 C, *C*-2′), 39.7 (0.5 C, *C*-2′), 39.8 (0.5 C, *C*-3′), 40.4 (0.5 C, *C*-5′), 43.48 (0.5 C, *C*-6′), 43.50 (0.5 C, *C*-6′), 52.2 (0.5 C, *C*-3$_{isoquinoline}$), 52.3 (0.5 C, *C*-3$_{isoquinoline}$), 56.4–56.6 (m, 4 C, *C*-1$_{isoquinoline}$, 3-O*C*H_3, 6-O*C*H_3, 7-O*C*H_3), 61.28 (0.5 C, CO*C*H_2N), 61.30 (0.5 C, CO*C*H_2N), 76.08 (0.5 C, *C*-1), 76.11 (0.5 C, *C*-1), 98.15 (0.5 C, *C*-3), 98.22 (0.5 C, *C*-3), 111.1 (1 C, *C*-8$_{isoquinoline}$), 113.1 (0.5 C, *C*-5$_{isoquinoline}$), 113.2 (0.5 C, *C*-5$_{isoquinoline}$), 125.7 (1 C, *C*-8), 127.40 (1 C, *C*-4a$_{sioquinoline}$ or *C*-8a$_{isoquinoline}$), 127.44 (1 C, *C*-4a$_{sioquinoline}$ or *C*-8a$_{isoquinoline}$), 127.6 (0.5 C, *C*-7), 127.7 (0.5 C, *C*-7), 128.0 (1 C, *C*-6), 130.2 (1 C, *C*-5), 132.6 (1 C, *C*-4a), 141.32 (0.5 C, *C*-8a), 141.34 (0.5 C, *C*-8a), 148.8 (1 C, *C*-6$_{sioquinoline}$ or *C*-7$_{isoquinoline}$), 149.2 (1 C, *C*-6$_{sioquinoline}$ or *C*-7$_{isoquinoline}$), 170.4 (0.5 C, *C*=O), 170.5 ppm (0.5 C, *C*=O). FTIR (neat): ν [cm^{-1}] = 2924, 2835 (C–H$_{alkyl}$), 1639 (C=O), 1516, 1443 (C=C$_{arom}$). Purity (HPLC): 99.4 %, t_R = 17.4 min.

***trans*-2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-(3-methoxy-3,4-dihydrospiro[[2]benzopyran-1,1′-cyclohexan]-4′-yl) acetamide (*trans*-26)**



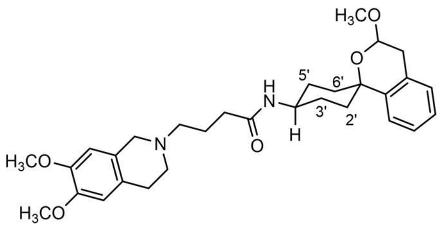
A solution of chloroacetamide *trans*-**17** (29 mg, 0.09 mmol), isoquinoline **14**·HCl (23 mg, 0.10 mmol, 1.1 equiv), Et_3N (0.04 mL, 0.29 mmol, 3.2 equiv) and TBAI (3 mg, 0.01 mmol, 0.1 equiv) in DMF (4 mL) was stirred at RT for 68 h. H_2O (80 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×60 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 50:50 + 1 % *N*,*N*-dimethylethanamine; *d* = 2 cm, *l* = 20 cm, *V* = 10 mL, cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine). Colorless oil, yield 36 mg (83 %). $C_{28}H_{36}N_2O_5$ (480.6 g/mol). R_f = 0.11 (cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine). HRMS (ESI): *m/z* 481.2695 (calcd. 481.2697 for $C_{28}H_{37}N_2O_5$ [*M*H$^+$]). ^{1}H NMR (600 MHz, CD_3OD): δ = 1.66–1.72 (m, 2H, 2′-*H*, 6′-*H*), 1.73–1.78 (m, 2H, 3′-*H*, 5′-*H*), 1.90–1.95 (m, 1H, 6′-*H*), 1.96–2.00 (m, 1H, 2′-*H*), 2.10–2.17 (m, 1H, 5′-*H*), 2.17–2.24 (m, 1H, 3′-*H*), 2.77 (dd, *J* = 15.7/7.3 Hz, 1H, 4-*H*), 2.90 (dd, *J* = 15.7/3.1 Hz, 1H, 4-*H*), 2.92–2.95 (m, 2H, 3-*H*$_{isoquinoline}$), 2.98 (t, *J* = 5.6 Hz, 2H, 4-*H*$_{isoquinoline}$), 3.30 (s, 2H, COC*H*$_2$N), 3.53 (s, 3H, 3-OC*H*$_3$), 3.72 (s, 5H, 1-*H*$_{isoquinoline}$, 7-OC*H*$_3$), 3.85 (s, 3H, 6-OC*H*$_3$,), 4.19 (quint, *J* = 3.3 Hz, 1H, 4′-*H*$_{equ}$), 4.88 (dd, *J* = 7.4/3.1 Hz, 1H, 3-*H*), 6.68 (s, 1H, 8-*H*$_{isoquinoline}$), 6.71 (dd, *J* = 7.9/1.2 Hz, 1H, 8-*H*), 6.80 (s, 1H, 5-*H*$_{isoquinoline}$), 6.89–6.92 (m, 1H, 7-*H*), 7.05 (dd, *J* = 7.6/1.3 Hz, 1H, 5-*H*), 7.10 ppm (td, *J* = 7.4/1.2 Hz, 1H, 6-*H*). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, CD_3OD): δ = 26.5 (1 C, *C*-3′), 26.6 (1 C, *C*-5′), 30.1 (1 C, *C*-4$_{isoquinoline}$), 32.2 (1 C, *C*-6′), 34.6 (1 C, *C*-2′), 36.1 (1 C, *C*-4), 44.6 (1 C, *C*-4′), 52.7 (1 C, *C*-3$_{isoquinoline}$), 56.35 (1 C, 3-O*C*H_3), 56.44 (1 C, 7-O*C*H_3), 56.5 (1 C, 6-O*C*H_3), 56.8 (1 C, *C*-1$_{isoquinoline}$), 62.3 (1 C, CO*C*H_2N), 77.1 (1 C, *C*-1), 97.9 (1 C, *C*-3), 111.1 (1 C, *C*-8$_{isoquinoline}$), 113.2 (1 C, *C*-5$_{isoquinoline}$), 125.4 (1 C, *C*-8), 127.1 (1 C, *C*-4a$_{isoquinoline}$), 127.4 (1 C, *C*-8a$_{isoquinoline}$), 127.5 (1 C, *C*-7), 127.7 (1 C, *C*-6), 130.1 (1 C, *C*-5), 132.4 (1 C, *C*-4a), 142.6 (1 C, *C*-8a), 148.9 (1 C, *C*-7$_{isoquinoline}$), 149.4 (1 C, *C*-6$_{isoquinoline}$), 172.1 ppm (1 C, *C*=O). FTIR (neat): ν [cm^{-1}] = 3341 (N–H), 2928, 2832 (C–H$_{alkyl}$), 1674 (C=O), 1516, 1447 (C=C$_{arom}$). Purity (HPLC): 90.6 %, t_R = 17.0 min.

cis-2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-(3-methoxy-3,4-dihydrospiro[[2]benzopyran-1,1′-cyclohexan]-4′-yl)acetamide (*cis*-26)



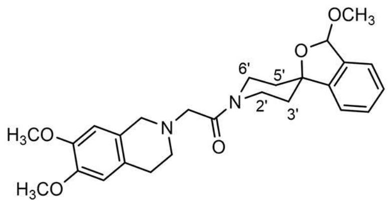
A solution of chloroacetamide *cis*-**17** (34 mg, 0.10 mmol), isoquinoline **14**·HCl (26 mg, 0.11 mmol, 1.1 equiv), Et_3N (0.04 mL, 0.29 mmol, 2.9 equiv) and TBAI (4 mg, 0.01 mmol, 0.1 equiv) in DMF (4 mL) was stirred at RT for 66 h. H_2O (80 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×60 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 50:50 + 1% *N*,*N*-dimethylethanamine). Colorless solid, m.p. 176 °C, yield 31 mg (62%). $C_{28}H_{36}N_2O_5$ (480.6 g/mol). R_f = 0.08 (cyclohexane/ethyl acetate 50:50 + 1% *N*,*N*-dimethylethanamine). HRMS (APCI): *m/z* 481.2720 (calcd. 481.2697 for $C_{28}H_{37}N_2O_5$ [*M*H$^+$]). ^{1}H NMR (600 MHz, CD_3OD): δ = 1.77–1.95 (m, 6H, 2′-*H*, 3′-*H*, 5′-*H*, 6′-*H*), 2.05–2.14 (m, 2H, 2′-*H*, 6′-*H*), 2.77–2.84 (m, 3H, 4-*H*, 3-$H_{isoquinoline}$), 2.86–2.90 (m, 2H, 4-$H_{isoquinoline}$), 2.93 (dd, *J* = 15.7/3.1 Hz, 1H, 4-*H*), 3.22 (s, 2H, COC*H*$_2$Cl), 3.54 (s, 3H, 3-OC*H*$_3$), 3.67 (s, 2H, 1-$H_{isoquinoline}$), 3.80 (s, 3H, 7-OC*H*$_3$), 3.81 (s, 3H, 6-OC*H*$_3$), 3.88–3.95 (m, 1H, 4′-H_{ax}), 4.91 (dd, *J* = 7.4/3.1 Hz, 1H, 3-*H*), 6.65 (s, 1H, 8-$H_{isoquinoline}$), 6.72 (s, 1H, 5-$H_{isoquinoline}$), 7.09 (d, *J* = 7.4 Hz, 1H, 5-*H*), 7.16 (td, *J* = 7.2/1.8 Hz, 1H, 6-*H*), 7.18–7.24 ppm (m, 2H, 7-*H*, 8-*H*). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, CD_3OD): δ = 29.0 (1 C, *C*-3′ or *C*-5′), 29.2 (1 C, *C*-3′ or *C*-5′), 29.4 (1 C, *C*-4$_{isoquinoline}$), 36.1 (1 C, *C*-4), 36.6 (1 C, *C*-2′), 39.1 (1 C, *C*-6′), 49.0 (1 C, *C*-4′), 52.3 (1 C, *C*-3$_{isoquinoline}$), 56.4 (2 C, *C*-1$_{isoquinoline}$, 3-O*C*H$_3$), 56.47 (1 C, 6-O*C*H$_3$), 56.51 (1 C, 7-O*C*H$_3$), 62.0 (1 C, CO*C*H$_2$N), 76.9 (1 C, *C*-1), 97.9 (1 C, *C*-3), 111.1 (1 C, *C*-8$_{isoquinoline}$), 113.1 (1 C, *C*-5$_{isoquinoline}$), 125.7 (1 C, *C*-8), 127.2 (1 C, *C*-4a$_{isoquinoline}$), 127.5 (1 C, *C*-8a$_{isoquinoline}$), 127.6 (1 C, *C*-7), 127.7 (1 C, *C*-6), 130.1 (1 C, *C*-5), 132.6 (1 C, *C*-4a), 142.5 (1 C, *C*-8a), 148.9 (1 C, *C*-7$_{isoquinoline}$), 149.2 (1 C, *C*-6$_{isoquinoline}$), 171.9 ppm (1 C, *C*=O). FTIR (neat): ν [cm^{-1}] = 3298 (N–H), 2978, 2924, 2835 (C–H$_{alkyl}$), 1639 (C=O), 1512, 1443 (C=C$_{arom}$). Purity (HPLC): 98.1%, t_R = 17.5 min.

cis-4-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-(3-methoxy-3,4-dihydrospiro[[2]benzopyran-1,1′-cyclohexan]-4′-yl)butanamide (*cis*-27)



A solution of isoquinoline **14**·HCl (27 mg, 0.12 mmol), chlorobutyramide *cis*-**18** (45 mg, 0.13 mmol, 1.1 equiv), Et_3N (0.05 mL, 0.36 mmol, 3.0 equiv) and TBAI (5 mg, 0.01 mmol, 0.1 equiv) in DMF (4 mL) was stirred at RT for 6 d. H_2O (80 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×60 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* = 32 cm, *V* = 10 mL, CH_2Cl_2/CH_3OH 99:1 + 1% *N*,*N*-dimethylethanamine; *d* = 1 cm, *l* = 25 cm, *V* = 3 mL, CH_2Cl_2/CH_3OH 95:5). Pale yellow oil, yield 11 mg (19%). $C_{30}H_{40}N_2O_5$ (508.7 g/mol). R_f = 0.19 (CH_2Cl_2/CH_3OH 95:5). HRMS (ESI): *m/z* 509.3024 (calcd. 509.3010 for $C_{30}H_{41}N_2O_5$ [*M*H$^+$]). ^{1}H NMR (400 MHz, CD_3OD): δ = 1.74–1.91 (m, 6H, 2′-*H*, 3′-*H*, 5′-*H*, 6′-*H*), 1.97 (quint, *J* = 7.5 Hz, 2H, COCH$_2$C*H*$_2$CH$_2$N), 2.02–2.09 (m, 1H, 6′-*H*), 2.09–2.15 (m, 1H, 2′-*H*), 2.31 (t, *J* = 7.3 Hz, 2H, COC*H*$_2$CH$_2$CH$_2$N), 2.65 (t, *J* = 7.8 Hz, 2H, COCH$_2$CH$_2$C*H*$_2$N), 2.78–2.88 (m, 3H, 4-*H*, 3-$H_{isoquinoline}$), 2.88–2.92 (m, 2H, 4-$H_{isoquinoline}$), 2.95 (dd, *J* = 15.7/3.2 Hz, 1H, 4-*H*), 3.58 (s, 3H, 3-OC*H*$_3$), 3.68 (s, 2H, 1-$H_{isoquinoline}$), 3.79–3.90 (m, 1H, 4′-H_{ax}), 3.817 (s, 3H, 6-OC*H*$_3$ or 7-OC*H*$_3$), 3.818 (s, 3H, 6-OC*H*$_3$ or 7-OC*H*$_3$), 4.93 (dd, *J* = 7.5/3.2 Hz, 1H, 3-*H*), 6.69 (s, 1H, 8-$H_{isoquinoline}$), 6.73 (s, 1H, 5-$H_{isoquinoline}$), 7.08–7.13 (m, 1H, 5-*H*), 7.15–7.20 (m, 1H, 6-*H*), 7.20–7.24 ppm (m, 2H, 7-*H*, 8-*H*). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (101 MHz, CD_3OD): δ = 23.8 (1 C, COCH$_2$*C*H$_2$CH$_2$N), 28.8 (1 C, *C*-4$_{isoquinoline}$), 29.0 (1 C, *C*-3′ or *C*-5′), 29.1 (1 C, *C*-3′ or *C*-5′), 35.0 (1 C, CO*C*H$_2$CH$_2$CH$_2$N), 36.2 (1 C, *C*-4), 36.6 (1 C, *C*-2′), 39.1 (1 C, *C*-6′), 49.1 (1 C, *C*-4′), 52.0 (1 C, *C*-3$_{isoquinoline}$), 56.4 (1 C, *C*-1$_{isoquinoline}$), 56.4 (1 C, 3-O*C*H$_3$), 56.47 (1 C, 6-O*C*H$_3$ or 7-O*C*H$_3$), 56.53 47 (1 C, 6-O*C*H$_3$ or 7-O*C*H$_3$), 58.4 (1 C, COCH$_2$CH$_2$*C*H$_2$N), 77.0 (1 C, *C*-1), 97.9 (1 C, *C*-3), 111.2 (1 C, *C*-8$_{isoquinoline}$), 113.0 (1 C, *C*-5$_{isoquinoline}$), 125.7 (1 C, *C*-8), 126.9 (1 C, *C*-8a$_{isoquinoline}$), 127.1 (1 C, *C*-4a$_{isoquinoline}$), 127.6 (1 C, *C*-7), 127.7 (1 C, *C*-6), 130.1 (1 C, *C*-5), 132.6 (1 C, *C*-4a), 142.5 (1 C, *C*-8a), 149.0 (1 C, *C*-7$_{isoquinoline}$), 149.4 (1 C, *C*-6$_{isoquinoline}$), 174.8 ppm (1 C, *C*=O). FTIR (neat): ν [cm^{-1}] = 3275 (N–H), 2924, 2855 (C–H$_{alkyl}$), 1639 (C=O), 1516, 1447 (C=C$_{arom}$). Purity (HPLC): 93.5%, t_R = 17.9 min.

2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-1-{3-methoxy-3*H*-spiro[[2]benzofuran-1,4′-piperidin]-1′-yl}ethan-1-one (28)

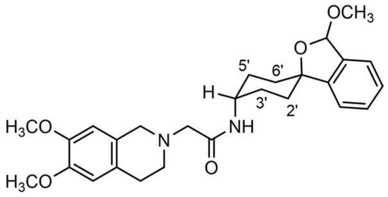


2-Chloroacetyl chloride (36 µL, 0.45 mmol, 1.2 equiv) was slowly added to a solution of piperidine **12** (83 mg, 0.38 mmol) and Et_3N (0.12 mL, 0.87 mmol, 2.3 equiv) in CH_2Cl_2 (10 mL) under N_2 at 0 °C. After stirring for 6 h at RT, H_2O (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×10 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 67:33). Chloroacetamide **19**: Pale yellow oil, yield 50 mg (44%). $C_{15}H_{18}ClNO_3$ (295.8 g/mol).

A solution of chloroacetamide **19** (50 mg, 0.17 mmol, 1.2 equiv), isoquinoline **14**·HCl (33 mg, 0.14 mmol), Et_3N (0.07 mL, 0.50 mmol, 3.6 equiv) and TBAI (6 mg, 0.02 mmol, 0.1 equiv) in DMF (6 mL) was stirred at RT for 5 d. H_2O (70 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (4×30 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* = 25 cm, *V* = 10 mL, CH_2Cl_2/CH_3OH 95:5; *d* = 2 cm, *l* = 20 cm, *V* = 10 mL, cyclohexane/ethyl acetate 50:50 + 1% *N*,*N*-dimethylethanamine). Pale yellow oil, yield 31 mg (49%). $C_{26}H_{32}N_2O_5$ (452.6 g/mol). R_f = 0.16 (cyclohexane/ethyl acetate 50:50 + 1% *N*,*N*-dimethylethanamine). HRMS (APCI): *m/z* 453.2403 (calcd. 453.2384 for $C_{26}H_{33}N_2O_5$ [*M*H$^+$]). ^{1}H NMR (600 MHz, CD_3OD): δ = 1.59–1.67 (m, 1H, 3′-*H*, 5′-*H*), 1.77–1.84 (m, 1H, 3′-*H*, 5′-*H*), 1.88–1.94 (m, 0.5H, 3′-*H*), 1.96–2.05 (m, 1H, 3′-*H*, 5′-*H*), 2.09 (td, *J* = 13.3/4.8 Hz, 0.5H, 5′-*H*), 2.82–2.85 (m, 2H, 3-$H_{isoquinoline}$), 2.86–2.90

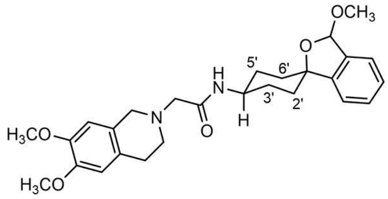
(m, 2H, 4-$H_{isoquinoline}$), 3.13–3.19 (m, 1H, 2′-*H*), 3.40 (d, *J* = 8.3 Hz, 0.5H, $COCH_2N$), 3.42 (d, *J* = 8.3 Hz, 0.5H, $COCH_2N$), 3.50 (s, 1.5H, 3-OCH_3), 3.51 (s, 1.5H, 3-OCH_3), 3.53–3.61 (m, 2H, 6′-*H*, $COCH_2N$), 3.66 (s, 1H, 1-$H_{isoquinoline}$), 3.67 (s, 1H, 1-$H_{isoquinoline}$), 3.79–3.82 (m, 6H, 6-OCH_3, 7-OCH_3), 4.16–4.21 (m, 1H, 6′-*H*), 4.56–4.62 (m, 1H, 2′-*H*), 6.09 (s, 0.5H, 3-*H*), 6.10 (s, 0.5H, 3-*H*), 6.67 (s, 0.5H, 8-$H_{isoquinoline}$), 6.68 (s, 0.5H, 8-$H_{isoquinoline}$), 6.71 (s, 0.5H, 5-$H_{isoquinoline}$), 6.72 (s, 0.5H, 5-$H_{isoquinoline}$), 7.11–7.13 (m, 0.5H, 4-*H*), 7.15–7.17 (m, 0.5H, 4-*H*), 7.34–7.40 ppm (m, 3H, 5-*H*, 6-*H*, 7-*H*). ^{13}C NMR (151 MHz, CD_3OD): δ = 29.47 (0.5 C, C-4$_{isoquinoline}$), 29.51 (0.5 C, C-4$_{isoquinoline}$), 38.0 (0.5 C, C-3′), 38.7 (0.5 C, C-5′), 39.5 (0.5 C, C-3′), 40.1 (1 C, C-2′, C-5′), 40.5 (0.5 C, C-2′), 43.9 (0.5 C, C-6′), 44.2 (0.5 C, C-6′), 52.2 (1 C, C-3$_{isoquinoline}$), 55.2 (1 C, 3-OCH_3), 56.4–56.6 (m, 3 C, C-1$_{isoquinoline}$, 6-OCH_3, 7-OCH_3), 61.1 (0.5 C, $COCH_2N$), 61.2 (0.5 C, $COCH_2N$), 85.9 (1 C, C-1), 107.4 (1 C, C-3), 111.1 (1 C, C-8$_{isoquinoline}$), 113.11 (0.5 C, C-5$_{isoquinoline}$), 113.13 (0.5 C, C-5$_{isoquinoline}$), 121.75 (0.5 C, C-4), 121.77 (0.5 C, C-4), 124.4 (1 C, C-7), 127.38 (0.5 C, C-4a$_{isoquinoline}$), 127.40 (0.5 C, C-4a$_{isoquinoline}$), 127.6 (0.5 C, C-8a$_{isoquinoline}$), 127.7 (0.5 C, C-8a$_{isoquinoline}$), 129.3 (1 C, C-6), 130.58 (0.5 C, C-5), 130.60 (0.5 C, C-5), 138.9 (1 C, C-7a), 147.3 (1 C, C-3a), 148.82 (0.5 C, C-7$_{isoquinoline}$), 148.83 (0.5 C, C-7$_{isoquinoline}$), 149.16 (0.5 C, C-6$_{isoquinoline}$), 149.17 (0.5 C, C-6$_{isoquinoline}$), 170.39 (0.5 C, C=O), 170.40 ppm (0.5 C, C=O). FTIR (neat): ν [cm^{-1}] = 2913, 2735 (C–H_{alkyl}), 1636 (C=O), 1516, 1447 (C=C_{arom}). Purity (HPLC): 98.7 %, t_R = 14.3–16.7 min.

trans-2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-(3-methoxy-3*H*-spiro[[2]benzofuran-1,1′-cyclohexan]-4′-yl)acetamide (*trans*-29)



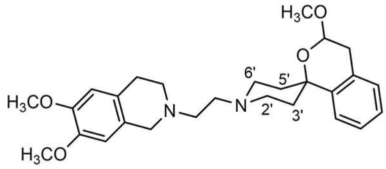
A solution of chloroacetamide *trans*-**20** (40 mg, 0.13 mmol), isoquinoline **14**·HCl (33 mg, 0.14 mmol, 1.1 equiv), Et_3N (0.05 mL, 0.36 mmol, 2.8 equiv.) and TBAI (48 mg, 0.13 mmol, 1.0 equiv) in DMF (4 mL) was stirred at RT for 66 h. H_2O (80 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 60 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* = 20 cm, *V* = 10 mL, cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine; *d* = 2 cm, *l* = 18 cm, *V* = 10 mL, cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine). Colorless solid, m.p. 107 °C, yield 40 mg (66 %). $C_{27}H_{34}N_2O_5$ (466.6 g/mol). R_f = 0.11 (cyclohexane/ethyl acetate 50:50 + 1 % *N*,*N*-dimethylethanamine). HRMS (ESI): *m/z* 467.2549 (calcd. 467.2540 for $C_{27}H_{35}N_2O_5$ [MH^+]). ^{1}H NMR (600 MHz, CD_3OD): δ = 1.55–1.61 (m, 1H, 2′-*H*), 1.71–1.77 (m, 1H, 6′-*H*), 1.79–1.90 (m, 4H, 2′-*H*, 3′-*H*, 5′-*H*, 6′-*H*), 2.06–2.16 (m, 2H, 3′-*H*, 5′-*H*), 2.92 (t, *J* = 5.9 Hz, 2H, 3-$H_{isoquinoline}$), 2.97 (t, *J* = 5.9 Hz, 2H, 4-$H_{isoquinoline}$), 3.29 (s, 2H, $COCH_2N$), 3.47 (s, 3H, 3-OCH_3), 3.70 (s, 2H, 1-$H_{isoquinoline}$), 3.74 (s, 3H, 7-OCH_3), 3.85 (s, 3H, 6-OCH_3), 4.17 (quint, *J* = 3.7 Hz, 1H, 4′-H_{equ}), 6.03 (s, 1H, 3-*H*), 6.68 (s, 1H, 8-$H_{isoquinoline}$), 6.75 (d, *J* = 7.5 Hz, 1H, 7-*H*), 6.80 (s, 1H, 5-$H_{isoquinoline}$), 7.24 (t, *J* = 7.4 Hz, 1H, 6-*H*), 7.29–7.36 ppm (m, 2H, 4-*H*, 5-*H*). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, CD_3OD): δ = 27.4 (1 C, C-3′ or C-5′), 27.7 (1 C, C-3′ or C-5′), 30.1 (1 C, C-4$_{isoquinoline}$), 33.8 (1 C, C-2′), 35.1 (1 C, C-6′), 45.1 (1 C, C-4′), 52.6 (1 C, C-3$_{isoquinoline}$), 55.0 (1 C, 3-OCH_3), 56.4 (1 C, 7-OCH_3), 56.5 (1 C, 6-OCH_3), 56.7 (1 C, C-1$_{isoquinoline}$), 62.1 (1 C, $COCH_2N$), 87.0 (1 C, C-1), 107.1 (1 C, C-3), 111.1 (1 C, C-8$_{isoquinoline}$), 113.1 (1 C, C-5$_{isoquinoline}$), 121.8 (1 C, C-7), 124.2 (1 C, C-4), 127.2 (1 C, C-4a$_{isoquinoline}$), 127.5 (1 C, C-8a$_{isoquinoline}$), 129.0 (1 C, C-5), 130.4 (1 C, C-6), 138.7 (1 C, C-3a), 148.2 (1 C, C-7a), 149.0 (1 C, C-7$_{isoquinoline}$), 149.4 (1 C, C-6$_{isoquinoline}$), 172.1 ppm (1 C, C=O). FTIR (neat): ν [cm^{-1}] = 3341 (N–H), 2932, 2832 (C–H_{alkyl}), 1674 (C=O), 1516, 1463, 1451 (C=C_{arom}). Purity (HPLC): 92.4 %, t_R = 14.0 min.

cis-2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-(3-methoxy-3*H*-spiro[[2]benzofuran-1,1′-cyclohexan]-4′-yl)acetamide (*cis*-29)



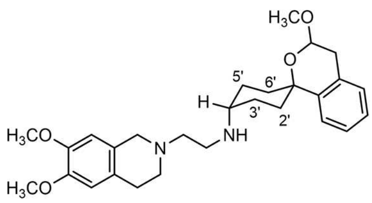
A solution of chloroacetamide *cis*-**20** (35 mg, 0.11 mmol), isoquinoline **14**·HCl (30 mg, 0.13 mmol, 1.2 equiv), Et_3N (0.05 mL, 0.36 mmol, 3.3 equiv) and TBAI (4 mg, 0.01 mmol, 0.1 equiv) in DMF (4 mL) was stirred at RT for 6 d. H_2O (80 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 60 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* = 29 cm, *V* = 10 mL, CH_2Cl_2/CH_3OH 99:1 + 1 % *N*,*N*-dimethylethanamine; *d* = 2 cm, *l* = 31 cm, *V* = 10 mL, CH_2Cl_2/CH_3OH 199:1 + 1 % *N*,*N*-dimethylethanamine). Yellow oil, yield 45 mg (86 %). $C_{27}H_{34}N_2O_5$ (466.6 g/mol). R_f = 0.31 (CH_2Cl_2/CH_3OH 95:5 + 1 % *N*,*N*-dimethylethanamine). HRMS (ESI): *m/z* 467.2531 (calcd. 467.2540 for $C_{27}H_{35}N_2O_5$ [MH^+]). ^{1}H NMR (400 MHz, CD_3OD): δ = 1.70 (dq, *J* = 13.3/2.9 Hz, 1H, 2′-H_{equ}), 1.78–1.97 (m, 6H, 3′-*H*, 5′-*H*, 6′-*H*), 2.01 (td, *J* = 13.4/4.1 Hz, 1H, 2′-H_{ax}), 2.81–2.86 (m, 2H, 3-$H_{isoquinoline}$), 2.87–2.92 (m, 2H, 4-$H_{isoquinoline}$), 3.24 (s, 2H, $COCH_2N$), 3.49 (s, 3H, 3-OCH_3), 3.69 (s, 2H, 1-$H_{isoquinoline}$), 3.81 (s, 3H, 7-OCH_3), 3.83 (s, 3H, 6-OCH_3), 3.92 (tt, *J* = 11.4/4.1 Hz, 1H, 4′-H_{ax}), 6.07 (s, 1H, 3-*H*), 6.67 (s, 1H, 8-$H_{isoquinoline}$), 6.74 (s, 1H, 5-$H_{isoquinoline}$), 7.28 (d, *J* = 7.5 Hz, 1H, 7-*H*), 7.32–7.45 ppm (m, 3H, 4-*H*, 5-*H*, 6-*H*). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (101 MHz, CD_3OD): δ = 29.4 (1 C, C-4$_{isoquinoline}$), 29.6 (1 C, C-3′), 30.0 (1 C, C-5′), 37.5 (1 C, C-2′), 38.8 (1 C, C-6′), 48.8 (1 C, C-4′), 52.3 (1 C, C-3$_{isoquinoline}$), 54.9 (1 C, 3-OCH_3), 56.4 (1 C, C-1$_{isoquinoline}$), 56.48 (1 C, 6-OCH_3 or 7-OCH_3), 56.52 (1 C, 6-OCH_3 or 7-OCH_3), 62.0 (1 C, $COCH_2N$), 86.9 (1 C, C-1), 107.2 (1 C, C-3), 111.1 (1 C, C-8$_{isoquinoline}$), 113.2 (1 C, C-5$_{isoquinoline}$), 121.8 (1 C, C-7), 124.2 (1 C, C-4), 127.2 (1 C, C-4a$_{isoquinoline}$), 127.5 (1 C, C-8a$_{isoquinoline}$), 129.0 (1 C, C-5), 130.5 (1 C, C-6), 138.6 (1 C, C-3a), 148.3 (1 C, C-7a), 148.9 (1 C, C-7$_{isoquinoline}$), 149.2 (1 C, C-6$_{isoquinoline}$), 172.0 ppm (1 C, C=O). FTIR (neat): ν [cm^{-1}] = 3333 (N–H), 2932, 2909, 2832 (C–H_{alkyl}), 1667 (C=O), 1516, 1439 (C=C_{arom}). Purity (HPLC): 88.0 %, t_R = 14.4 min.

1′-[2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl]-3-methoxy-3,4-dihydrospiro[[2]benzopyran-1,4′-piperidine] (30)



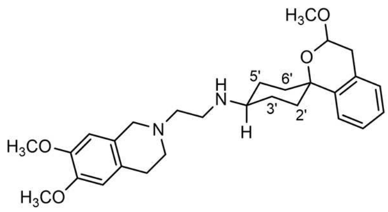
$LiAlH_4$ (7 mg, 0.19 mmol, 6.4 equiv) was added to a solution of amide **25** (16 mg, 0.03 mmol) in THF (3 mL) under N_2. The mixture was heated to reflux for 2 h. After cooling to RT, H_2O (10 mL) was added, the precipitate was filtered off, and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified twice by fc (d=1 cm, l=21 cm, V=3 mL, CH_2Cl_2/CH_3OH 97:3+1% *N,N*-dimethylethanamine; d=1 cm, l=21 cm, V=3 mL, CH_2Cl_2/CH_3OH 99:1+1% *N,N*-dimethylethanamine). Yellow oil, yield 10 mg (63%). $C_{27}H_{36}N_2O_4$ (452.6 g/mol). R_f=0.24 (CH_2Cl_2/CH_3OH 95:5+1% *N,N*-dimethylethanamine). HRMS (ESI): *m/z* 453.2754 (calcd. 453.2748 for $C_{27}H_{37}N_2O_4$ [MH^+]). ^{1}H NMR (600 MHz, CD_3OD): δ=1.82 (dq, J=13.8/2.6 Hz, 1H, 3′-H_{equ}), 2.00 (ddd, J=14.2/12.5/4.3 Hz, 1H, 5′-H_{ax}), 2.06 (dq, J=14.3/2.8 Hz, 1H, 5′-H_{equ}), 2.26 (td, J=13.4/4.3 Hz, 1H, 3′-H_{ax}), 2.64–2.74 (m, 2H, 2′-*H*, 6′-*H*), 2.75–2.86 (m, 7H, 4-*H*, 3-$H_{isoquinoline}$, NCH_2CH_2N), 2.88 (t, J=5.7 Hz, 2H, 4-$H_{isoquinoline}$), 2.91–2.97 (m, 3H, 4-*H*, 2′-*H*, 6′-*H*), 3.55 (s, 3H, 3-OC*H*$_3$), 3.67 (s, 2H, 1-$H_{isoquinoline}$), 3.80 (s, 3H, 7-OC*H*$_3$), 3.81 (s, 3H, 6-OC*H*$_3$), 4.94 (dd, J=7.2/3.2 Hz, 1H, 3-*H*), 6.68 (s, 1H, 8-$H_{isoquinoline}$), 6.71 (s, 1H, 5-$H_{isoquinoline}$), 7.10 (d, J=7.5 Hz, 1H, 5-*H*), 7.18 (ddd, J=7.6/6.2/2.4 Hz, 1H, 6-*H*), 7.19–7.24 ppm (m, 2H, 7-*H*, 8-*H*). ^{13}C NMR (151 MHz, CD_3OD): δ=29.1 (1 C, C-4$_{isoquinoline}$), 36.1 (1 C, C-4), 37.1 (1 C, C-5′), 39.5 (1 C, C-3′), 50.9 (1 C, C-2′), 51.0 (1 C, C-6′), 52.5 (1 C, C-3$_{isoquinoline}$), 56.1 (1 C, $N_{isoquinoline}CH_2CH_2N$), 56.46 (2 C, 3-OCH$_3$, 6-OCH$_3$ or 7-OCH$_3$), 56.51 (1 C, $N_{isoquinoline}CH_2CH_2N$), 56.7 (1 C, 6-OCH$_3$ or 7-OCH$_3$), 56.9 (1 C, C-1$_{isoquinoline}$), 75.6 (1 C, C-1), 97.9 (1 C, C-3), 111.2 (1 C, C-8$_{isoquinoline}$), 113.0 (1 C, C-5$_{isoquinoline}$), 125.7 (1 C, C-8), 127.3 (1 C, C-8a$_{isoquinoline}$), 127.4 (1 C, C-4a$_{isoquinoline}$), 127.6 (1 C, C-7), 127.9 (1 C, C-6), 130.2 (1 C, C-5), 132.7 (1 C, C-4a), 141.9 (1 C, C-8a), 148.9 (1 C, C-7$_{isoquinoline}$), 149.3 ppm (1 C, C-6$_{isoquinoline}$). FTIR (neat): ν [cm^{-1}]=2947, 2820, 2778 (C–H$_{alkyl}$), 1516, 1466, 1454 (C=C$_{arom}$). Purity (HPLC): 91.2%, t_R=14.0 min.

trans-N-[2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl) ethyl]-3-methoxy-3,4-dihydrospiro[[2] benzopyran-1,1′-cyclohexan]-4′-amine (*trans*-31)



$LiAlH_4$ (4 mg, 0.12 mmol, 5.3 equiv) was added to a solution of amide *trans*-**26** (11 mg, 0.02 mmol) in THF (3 mL) under N_2. The mixture was heated to reflux for 22 h. After cooling to RT, H_2O (10 mL) was added, the precipitate was filtered off, and the aqueous phase was extracted with CH_2Cl_2 (5×10 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified twice by fc (d=1 cm, l=25 cm, V=3 mL, CH_2Cl_2/CH_3OH 99:1+1% *N,N*-dimethylethanamine; d=1 cm, l=25 cm, V=3 mL, CH_2Cl_2/CH_3OH 99:1→97:3+1% *N,N*-dimethylethanamine). Yellow solid, m.p. 73 °C, yield 9 mg (86%). $C_{28}H_{38}N_2O_4$ (466.6 g/mol). R_f=0.33 (CH_2Cl_2/CH_3OH 90:10+1% *N,N*-dimethylethanamine). HRMS (APCI): *m/z* 467.2895 (calcd. 467.2904 for $C_{28}H_{39}N_2O_4$ [MH^+]). ^{1}H NMR (600 MHz, CD_3OD): δ=1.60 (dt, J=9.5/2.0 Hz, 1H, 2′-*H*), 1.78–1.83 (m, 2H, 3′-*H*, 5′-*H*), 1.84–1.89 (m, 2H, 6′-*H*), 2.06–2.13 (m, 1H, 5′-*H*), 2.13–2.17 (m, 2H, 2′-*H*, 3′-*H*), 2.73–2.85 (m, 5H, 4-*H*, $N_{isoquinoline}CH_2CH_2N$, 3-$H_{isoquinoline}$), 2.86–2.95 (m, 5H, 4-*H*, $N_{isoquinoline}CH_2CH_2N$, 4-$H_{isoquinoline}$), 3.02 (quint, J=3.0 Hz, 1H, 4′-H_{equ}), 3.55 (s, 3H, 3-OCH$_3$), 3.66 (s, 2H, 1-$H_{isoquinoline}$), 3.78 (s, 3H, 7-OC*H*$_3$), 3.82 (s, 3H, 6-OC*H*$_3$), 4.90 (dd, J=7.5/3.1 Hz, 1H, 3-*H*), 6.68 (s, 1H, 8-$H_{isoquinoline}$), 6.73 (s, 1H, 5-$H_{isoquinoline}$), 7.01–7.08 (m, 2H, 5-*H*, 7-*H*), 7.09–7.13 (m, 1H, 6-*H*), 7.17 ppm (d, J=7.8 Hz, 1H, 8-*H*). A signal for the NH proton is not observed in the spectrum. ^{13}C NMR (151 MHz, CD_3OD): δ=25.9 (1 C, C-3′), 26.2 (1 C, C-5′), 29.5 (1 C, C-4$_{isoquinoline}$), 31.5 (1 C, C-6′), 34.1 (1 C, C-2′), 36.2 (1 C, C-4), 44.7 (1 C, $N_{isoquinoline}CH_2CH_2N$), 52.5 (1 C, C-4′), 52.5 (1 C, C-3$_{isoquinoline}$ or $N_{isoquinoline}CH_2CH_2N$), 56.3 (1 C, 3-OCH$_3$), 56.4–56.5 (m, 2 C, 6-OCH$_3$, 7-OCH$_3$), 56.8 (1 C, C-1$_{isoquinoline}$), 58.0 (1 C, C-3$_{isoquinoline}$ or $N_{isoquinoline}CH_2CH_2N$), 77.8 (1 C, C-1), 97.9 (1 C, C-3), 111.3 (1 C, C-8$_{isoquinoline}$), 113.1 (1 C, C-5$_{isoquinoline}$), 125.9 (1 C, C-8), 127.4 (1 C, C-4a$_{isoquinoline}$), 127.5 (1 C, C-7), 127.55 (1 C, C-6), 127.62 (1 C, C-8a$_{isoquinoline}$), 130.0 (1 C, C-5), 132.4 (1 C, C-4a), 143.2 (1 C, C-8a), 148.9 (1 C, C-7$_{isoquinoline}$), 149.3 ppm (1 C, C-6$_{isoquinoline}$). FTIR (neat): ν [cm^{-1}]=3368 (N–H), 2924, 2832 (C–H$_{alkyl}$), 1516, 1447 (C=C$_{arom}$). Purity (HPLC): 61.5%, t_R=14.7 min.

cis-N-[2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl) ethyl]-3-methoxy-3,4-dihydrospiro[[2] benzopyran-1,1′-cyclohexan]-4′-amine (*cis*-31)



$LiAlH_4$ (8 mg, 0.22 mmol, 6.0 equiv.) was added to a solution of amide *cis*-**26** (17 mg, 0.04 mmol) in THF (3 mL) under N_2. The mixture was heated to reflux for 19 h. After cooling to RT, H_2O (10 mL) was added, the precipitate was filtered off, and the aqueous phase was extracted with CH_2Cl_2 (4×10 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=25 cm, V=3 mL, CH_2Cl_2/CH_3OH 98:2→98:2+1% *N,N*-dimethylethanamine). Yellow solid, m.p. 70 °C, yield 13 mg (76%). $C_{28}H_{38}N_2O_4$ (466.6 g/mol). R_f=0.26 (CH_2Cl_2/CH_3OH 90:10+1% *N,N*-dimethylethanamine). HRMS (APCI): *m/z* 467.2921 (calcd. 467.2904 for $C_{28}H_{39}N_2O_4$ [MH^+]). ^{1}H NMR (400 MHz, CD_3OD): δ=1.65–1.82 (m, 3H, 2′-*H*, 3′-*H*, 5′-*H*), 1.82–1.96 (m, 3H, 3′-*H*, 5′-*H*, 6′-*H*), 2.03 (td, J=13.5/4.2 Hz, 1H, 6′-*H*), 2.10–2.18 (m, 1H, 2′-*H*), 2.71–2.78 (m, 3H, 4′-H_{ax}, $N_{isoquinoline}CH_2CH_2N$), 2.78–2.85 (m, 3H, 4-*H*, 3-$H_{isoquinoline}$), 2.88 (t, J=5.9 Hz, 2H, 4-$H_{isoquinoline}$), 2.91–2.98 (m, 3H, 4-*H*, $N_{isoquinoline}CH_2CH_2N$), 3.58 (s, 3H, 3-OC*H*$_3$), 3.64 (s, 2H, 1-$H_{isoquinoline}$), 3.82 (s, 3H, 6-OC*H*$_3$ or 7-OC*H*$_3$), 3.82 (s, 3H, 6-OC*H*$_3$ or 7-OC*H*$_3$), 4.92 (dd, J=7.4/3.2 Hz, 1H, 3-*H*), 6.69 (s, 1H, 8-$H_{isoquinoline}$), 6.73 (s, 1H, 5-$H_{isoquinoline}$), 7.10 (d, J=7.2 Hz, 1H, 5-*H*), 7.14–7.22 ppm (m, 3H, 6-*H*, 7-*H*, 8-*H*). A signal for the NH proton was not observed. ^{13}C NMR (101 MHz, CD_3OD): δ=29.0 (1 C, C-3′ or C-5′), 29.1 (1 C, C-3′ or C-5′), 29.2 (1 C, C-4$_{isoquinoline}$), 36.2 (1 C, C-4), 36.5 (1 C, C-2′), 39.0 (1 C, C-6′), 44.3 (1 C, $N_{isoquinoline}CH_2CH_2N$), 52.4 (1 C, C-3$_{isoquinoline}$), 56.4 (1 C, 3-OCH$_3$), 56.47 (1 C, 6-OCH$_3$ or 7-OCH$_3$), 56.53 (1 C, 6-OCH$_3$ or 7-OCH$_3$), 56.8 (1 C, C-1$_{isoquinoline}$), 57.4 (1 C, C-4′), 58.2 (1 C, $N_{isoquinoline}CH_2CH_2N$), 77.4 (1 C, C-1), 97.8 (1 C, C-3), 111.2 (1 C, C-8$_{isoquinoline}$), 113.0 (1 C, C-5$_{isoquinoline}$), 125.7 (1 C, C-8), 127.4 (1 C, C-4a$_{isoquinoline}$), 127.50 (1 C, C-7), 127.53 (1 C, C-8a$_{isoquinoline}$), 127.7 (1 C, C-6), 130.1 (1 C, C-5), 132.6 (1 C, C-4a), 142.6 (1 C, C-8a), 148.9 (1 C, C-7$_{isoquinoline}$), 149.3 ppm (1 C, C-6$_{isoquinoline}$). FTIR (neat): ν [cm^{-1}]=3402 (N–H), 2928, 2832 (C–H$_{alkyl}$), 1516, 1447 (C=C$_{arom}$). Purity (HPLC): 69.2%, t_R=14.5 min.

Receptor binding studies

The σ_1 and σ_2 affinities were recorded as described in ref. [40]. Details of the assays are given in the Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: acyl linkers · alkyl linkers · sigma receptor affinity · spirocyclic sigma ligands · structure-affinity relationships · tetrahydroisoquinoline

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