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# Synthesis, σ Receptor Affinity, and Pharmacological Evaluation of 5-Phenylsulfanyl- and 5-Benzyl-Substituted Tetrahydro-2-benzazepines

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In accordance with a novel strategy for generating the 2-benzazepine scaffold by connecting C6–C1 and C3–*N* building blocks, a set of 5-phenylsulfanyl- and 5-benzyl-substituted tetrahydro-2-benzazepines was synthesized and pharmacologically evaluated. Key steps of the synthesis were the Heck reaction, the Stetter reaction, a reductive cyclization, and the introduction of diverse N substituents at the end of the synthesis. High  $\sigma_1$  affinity was achieved for 2-benzazepines with linear or branched alk(en)yl residues containing at least an *n*-butyl substructure. The butyl- and 4-fluorobenzyl-substituted deriva-

### Introduction

Tetrahydro-2-benzazepines **2** can be regarded as regioisomers of tetrahydro-3-benzazepines **1** (Figure 1) and homologues of tetrahydroisoquinolines. Compounds with the 3-benzazepine



**Figure 1.** Development of novel tetrahydro-2-benzazepines **3** with a spacer X between the 2-benzazepine scaffold and the aryl moiety of the lead compounds **1** and **2**.

scaffold show promising neuropharmacological properties. For example, the introduction of a small methyl moiety in the 1-position of the 3-benzazepine ring of  $1 (R^2: CH_3)$  leads to lorcaserin, a potent 5-HT<sub>2C</sub> agonist, which can be used for the treatment of obesity.<sup>[1]</sup> 1-Phenyl-substituted tetrahydro-3-benzaze

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cmdc.201402110: physical, spectroscopic, and purity data for all compounds, synthetic methods, and descriptions of receptor binding assays; Figures SI1–SI5 show results of animal assays. tives,  $(\pm)$ -5-benzyl-2-butyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (**19b**) and  $(\pm)$ -5-benzyl-2-(4-fluorobenzyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine (**19m**), show high selectivity over more than 50 other relevant targets, including the  $\sigma_2$  subtype and various binding sites of the *N*-methyl-D-aspartate (NMDA) receptor. In the Irwin screen, **19b** and **19m** showed clean profiles without inducing considerable side effects. Compounds **19b** and **19m** did not reveal significant analgesic and cognition-enhancing activity. Compound **19m** did not have any antidepressant-like effects in mice.

pines 1 (R<sup>2</sup>: Ph) have been reported to interact with the dopamine D<sub>1</sub> and D<sub>2</sub> receptors, and the 3-benzazepine SCH-23390 represents a prototypical D<sub>1</sub> receptor antagonist.<sup>[2,3]</sup> The insertion of a methylene moiety or a bioisosteric equivalent between the 3-benzazepine ring and the phenyl moiety at the 1position of 1 (for example, R<sup>2</sup>: CH<sub>2</sub>Ph, SPh, or N(Ac)Ph) provided *N*-methyl-D-aspartate (NMDA) receptor antagonists, which block the NMDA-receptor-associated ion channel by interaction with the phencyclidine binding site.<sup>[4,5]</sup> Moreover, some promising  $\sigma_1$  receptor ligands based on the 3-benzazepine scaffold with various substituents have been identified.<sup>[6-8]</sup>

Very recently, we have reported on the synthesis and  $\sigma$  receptor affinity of regioisomeric tetrahydro-2-benzazepines **2** with a phenyl moiety in the 5-position. The 2-butyl-5-phenylte-trahydro-2-benzazepine, **2a** (R<sup>1</sup>: C<sub>4</sub>H<sub>9</sub>; R<sup>2</sup>: Ph), interacts with low nanomolar affinity (inhibition constant ( $K_0$  = 2.0 nM) and high selectivity with  $\sigma_1$  receptors.<sup>[9]</sup> It has been shown that the  $\sigma_1$  receptor can modulate the permeability of ion channels<sup>[10,11]</sup> and the activity of neurotransmitter systems.<sup>[12,13]</sup> In 2007, the role of the  $\sigma_1$  receptor as a ligand-operated chaperon was suggested.<sup>[14]</sup> Due to the various modulatory effects of  $\sigma_1$  receptors in the central nervous system, potent and selective  $\sigma_1$  receptor ligands represent potential drugs for the treatment of neurological and psychiatric diseases,<sup>[15–18]</sup> including neuropathic pain,<sup>[19,20]</sup> schizophrenia,<sup>[21,22]</sup> major depression,<sup>[12,23,24]</sup>

Neuropathic pain is defined as spontaneous hypersensitive pain response, which is recognized even when the origin of the pain has been cured.<sup>[26,27]</sup> Medical treatment is rather difficult, because of the diffuse origin of neuropathic pain conditions. With the help of  $\sigma_1$  receptor knockout mice, the positive effects of  $\sigma_1$  receptor antagonists on neuropathic pain condi-

tions was demonstrated.<sup>[28]</sup> As proof of principle, the potent and selective  $\sigma_1$  receptor antagonist S1RA has entered phase II clinical trials for the treatment of neuropathic pain.<sup>[20, 29, 30]</sup>

According to pharmacophore models, a basic N atom surrounded by two hydrophobic regions is required to achieve high  $\sigma_1$  receptor affinity.<sup>[31]</sup> When the structural elements of the pharmacophore models are transferred to the  $\sigma_1$  ligand **2a**, the N atom of the 2-benzazepine ring represents the basic N atom, as postulated by the pharmacophore model, and the hydrophobic regions are formed by the *n*-butyl residue on the N atom and the phenyl moiety in the 5-position of the 2-benzazepine system. However, in the pharmacophore models, the distance between the basic N atom and the primary hydrophobic region is longer (6–10 Å;  $^{[32,33]}$  6.3 and 9.8 Å $^{[34]}$ ) than the distance found in 2a (4.66-5.98 Å). Therefore, we planned to increase this distance by the introduction of a one-atom spacer, X, between the phenyl moiety in the 5-position and the 2-benzazepine scaffold (see compound 3 in Figure 1). The energetically most favored conformations of 3 (X: CH<sub>2</sub>) possess N-aryl distances of 6.03-6.45 Å, which exactly fit into the range postulated by the pharmacophore models. The envisaged structural modification could not only lead to ligands with high  $\sigma_1$  receptor affinity but could also result in promising NMDA receptor ligands with increased affinity toward the phencyclidine binding site, as already observed for the class of tetrahydro-3-benzazepines 1.<sup>[4]</sup>

Herein, we report on the synthesis,  $\sigma_1$  and  $\sigma_2$  receptor affinity, and NMDA receptor affinity of 5-phenylsulfanyl- and 5benzyl-substituted tetrahydro-2-benzazepines of type **3** (X: S, CH<sub>2</sub>) with various substituents at the N atom. The selectivity over further receptors, the in vitro absorption, distribution, metabolism, and excretion (ADME) parameters, and the cognitionenhancing and analgesic activity of the most promising ligands was investigated. For the introduction of a wide variety of substituents, the late-stage diversification strategy was followed, which makes use of the introduction of different substituents at the end of the synthesis into a central building block.<sup>[35]</sup>

### **Results and Discussion**

#### Synthesis

For the synthesis of the 2-benzazepine system, we planned to follow the recently reported strategy of connecting C6–C1 and C3–N building blocks.<sup>[9]</sup> The synthesis of the 5-phenylsulfanyl-substituted tetrahydro-2-benzazepine **10** started with the conjugate addition of thiophenol to the  $\alpha$ , $\beta$ -unsaturated nitrile **5**, which was prepared by the Heck reaction of 2-iodobenzalde-hyde acetal **4** with acrylonitrile<sup>[9]</sup> (Scheme 1). Different bases were investigated to enhance the activity of thiophenol for the conjugate addition. Whereas K<sub>2</sub>CO<sub>3</sub> and triethylamine gave very low yields (0–16%), *n*-butyllithium afforded the addition product **6** in 88% yield.

The reduction of nitrile **6** with LiAlH<sub>4</sub> in THF led to the primary amines **7** and **8**<sup>[9]</sup> which were isolated in 64 and 13% yields, respectively. The formation of the primary amine **7** is explained by  $\beta$  elimination of thiophenolate catalyzed by LiAlH<sub>4</sub>



**Scheme 1.** Synthesis of 5-phenylsulfanyl-substituted tetrahydro-2-benzazepine **10**. *Reagents and conditions*: a)  $CH_2$ =CHCN, Pd(OAc)<sub>2</sub>, Bu<sub>4</sub>NBr, NaHCO<sub>3</sub>, DMF, 140 °C, 24 h, 99%;<sup>[9]</sup> b) PhSH, *n*BuLi, THF, RT, 16 h, 88%; c) LiAlH<sub>4</sub>, THF, 0–4 °C, 16 h, 38%; d) *p*-TolSO<sub>3</sub>·H<sub>2</sub>O, THF, RT, 2 h; e) NaBH<sub>3</sub>CN, RT, 1 h, 30%. *p*-Tol: *para*-tolyl.

to result in cinnamonitrile **5**, which was reduced by LiAlH<sub>4</sub> to give the primary amine **7**. To inhibit the  $\beta$  elimination, a conjugate Suzuki reduction<sup>[36]</sup> of **6** with NaBH<sub>4</sub> and CoCl<sub>2</sub> in boiling methanol was performed. However, the reaction provided exclusively the primary amine **7** in 61% yield. A decreased reaction temperature of 0–4 °C during the LiAlH<sub>4</sub> reduction of **6** led to an increased amount of the desired phenylsulfanyl-substituted primary amine **8**, which was isolated in 38% yield.

Finally, the 2-benzazepine scaffold was prepared in a twostep process consisting of an acid-catalyzed hydrolysis of the dimethyl acetal of **8** and subsequent formation of imine **9**, which was reduced by NaBH<sub>3</sub>CN to afford the tetrahydro-2benzazepine **10** with a phenylsulfanyl substituent in the 5-position in 30% yield.

Due to the problems during the synthesis, we decided to focus on the corresponding benzyl derivatives, **19**. For this purpose, a benzyl nucleophile needed be added to the  $\alpha$ , $\beta$ -unsaturated nitrile **5**. However, all attempts to make cinnamonitrile **5** react with BnMgBr or corresponding cuprates (for example, Bn<sub>2</sub>CuMgBr) failed to give the 1,4 addition product.

Therefore, the benzyl substituent was introduced by a Stetter reaction.<sup>[37,38]</sup> The highest yield (49%) of ketonitrile **11** was obtained by the reaction of the  $\alpha$ , $\beta$ -unsaturated nitrile **5** with benzaldehyde and NaCN at 35 °C (Scheme 2). Lower (20 °C) or higher (40 °C) temperature, as well as the use of benzoin<sup>[38]</sup> instead of benzaldehyde, gave considerably lower yields. Replacement of NaCN with a thiazolium salt (3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide)<sup>[39,40]</sup> led predominantly to hydrolysis of the acetal moiety of **5**.

The reduction of ketonitrile **11** with NaBH<sub>4</sub> at 0 °C provided, diastereoselectively, the *like*-configured hydroxynitrile **12** in 82% yield. The relative configuration of the racemic mixture of **12** was confirmed by transformation of hydroxynitrile **12** into 2-benzopyran **13** upon treatment with BF<sub>3</sub>·OEt<sub>2</sub>. The *trans* configuration of the 3-phenyl and 4-cyanomethyl moieties was

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Scheme 2. Synthesis of 2-benzopyran 13. *Reagents and conditions*: a) PhCH=O, NaCN, DMF, 35 °C, 12 h, 49%; b) NaBH<sub>4</sub>, CH<sub>3</sub>OH, 0 °C, 16 h, 82%; c) BF<sub>3</sub>·OEt<sub>2</sub>, THF, RT, 16 h, 70%. Only one enantiomer of the racemic mixtures 12 and 13 is shown here.

proven by the large coupling constant of J = 10.2 Hz for the *trans* diaxially oriented protons in the 3- and 4-positions.

In the next step, the hydroxy moiety in the benzyl position of **12** needed to be removed by hydrogenolysis. However, treatment of hydroxynitrile **12** with H<sub>2</sub> in the presence of Pd/C afforded predominantly the 2-benzopyran **13**. This intramolecular transacetalization of **12** to form the 2-benzopyran **13** is catalyzed by traces of acid in the Pd/C catalyst, so K<sub>2</sub>CO<sub>3</sub> was added to remove the acid from the reaction mixture. In fact, the hydroxy moiety was cleaved off by hydrogenolysis after the addition of K<sub>2</sub>CO<sub>3</sub>, but instead of the expected butyronitrile, the primary amide **15** was isolated in 98% yield (Scheme 3). The formation of primary amide **15** is explained by base-catalyzed cyclization of the hydroxynitrile **12** to afford the imidolactone **14**, which was cleaved by hydrogenolysis to give the primary amide **15**.



Scheme 3. Synthesis of 5-benzyl-substituted 2-benzazepines 19a–n. *Reagents and conditions*: a) H<sub>2</sub> (1 bar), Pd/C, CH<sub>3</sub>OH, K<sub>2</sub>CO<sub>3</sub>, RT, 16 h, 98%; b) LiAlH<sub>4</sub>, THF, 4 °C, 4 h, then RT, 12 h, 76%; c) *p*-ToISO<sub>3</sub>H·H<sub>2</sub>O, RT, 2 h; d) NaBH<sub>3</sub>CN, RT, 1 h 48%; e) alkyl halide, CH<sub>3</sub>CN, K<sub>2</sub>CO<sub>3</sub>, reflux, 16 h, 14–55%; f) R<sup>1</sup>CH=O, NaBH(OAc)<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, RT, 16 h, 44–76%.

Reduction of the primary amide **15** with LiAlH<sub>4</sub> provided the primary amine **16** in 76% yield. For the cyclization of primary amine **16**, the same two-step procedure as for the cyclization of the phenylsulfanyl-substituted amine **8** was used; this comprised an acid-catalyzed acetal hydrolysis followed by the formation of imine **17**, which was reduced with NaBH<sub>3</sub>CN. The resulting 5-benzyltetrahydro-2-benzazepine **18** represents the central building block for the introduction of various substituents at the N atom. The diversification at the last stage of the synthesis<sup>[35]</sup> was performed by alkylation with the appropriate alde-

hyde and NaBH(OAc)<sub>3</sub>. In general, the reductive alkylation gave higher yields of the tertiary amines **19**. Various alkyl and alkenyl substituents, derived from the dimethylallyl moiety of the prototypical  $\sigma_1$  agonist (+)-pentazocine, and substituted and unsubstituted (hetero)arylalkyl substituents, derived from benzylated spirocyclic  $\sigma_1$  receptor antagonists, were selected.<sup>[4142]</sup>

#### Pharmacological evaluation

#### Affinity toward $\sigma$ receptors

The affinities of the 5-substituted tetrahydro-2-benzyzepines **10**, **18**, and **19** toward  $\sigma_1$  and  $\sigma_2$  receptors were determined in radioligand receptor binding studies. In this type of assay, the test compound competes with a potent and selective radioligand for the respective binding sites. The radioligands [<sup>3</sup>H]-(+)-pentazocine ( $\sigma_1$  assay).<sup>[43,44]</sup> and [<sup>3</sup>H]-1,3-di(*ortho*-tolyl)guanidine ( $\sigma_2$  assay).<sup>[43,44]</sup> were employed. In the  $\sigma_2$  assay, an excess of nonlabeled (+)-pentazocine was added in order to mask the  $\sigma_1$  receptors. Membrane preparations from guinea pig brains and rat liver served as receptor materials in the  $\sigma_1$  and  $\sigma_2$ assays, respectively.

In Table 1, the  $\sigma$  receptor affinities of the 5-phenylsulfanyland 5-benzyl-substituted 2-benzazepines **10**, **18**, and **19** are summarized and compared with the  $\sigma$  receptor affinities of the

corresponding 5-phenyl-substituted analogues 2 and selected reference compounds. A proton or a small methyl moiety at the N atom (10, 18, and 19a) led to low  $\sigma_{\! 1}$  affinity. However, an increase in the size of the N-alkyl substituent to an n-butyl or even n-pentyl group resulted in the high affinity  $\sigma_1$  receptor ligands 19b and 19c. Whereas short branched and small cyclic N substituents, like isobutyl (19d) and cyclopropylmethyl (19 f) groups, are less tolerated by the  $\sigma_1$  receptor, larger branched and cyclic N substituents, like dimethylallyl (19e) and cyclohexylmethyl (19g) groups, are well accepted. A similar tendency was found in the corresponding class of 5-phenylsubstituted 2-benzazepines 2; the n-butyl-substituted derivative  $\mathbf{2a}$  shows the highest  $\sigma_1$  receptor affinity for this type of compounds.

Replacement of the cyclohexylmethyl moiety (in **19g**) by the aromatic benzyl group (in **19h**) resulted in eightfold decreased  $\sigma_1$  affinity. However, the  $\sigma_1$  affinity of the 5-benzyl derivative **19h** is about three times higher than the  $\sigma_1$  affinity of the corresponding 5-phenyl-substituted 2benzazepine **2b**, which proved the favorable effect of the methylene spacer between the aryl moiety and the 2-benzazepine scaffold. The 2-benzazepine **19i** with a 2-phenylethyl substituent shows a similar  $\sigma_1$  affinity to the benzyl derivative **19h**, but the 4-phenylbutyl derivative **19j** reveals considerably lower  $\sigma_1$  affinity. The furan (**19k**) and thiophene (**19l**) bioisosteres of **19h** are less tolerated by the  $\sigma_1$  receptor than the parent benzyl derivative **19h**. Whereas an electron-donating

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Compd	х	R <sup>1</sup>	, [nм] <sup>[a]</sup>		Selectivity
			$\sigma_1$	σ <sub>2</sub>	$\sigma_1/\sigma_2$
2 a <sup>[9]</sup>	-	n-C₄H <sub>9</sub>	2.0±0.10	178	88
2 b <sup>[9]</sup>	-	$CH_2C_6H_5$	$61\pm8$	$>$ 1 $\mu$ M <sup>[b]</sup>	>16
10	S	Н	1850	$>$ 1 $\mu$ M <sup>[b]</sup>	-
18	$CH_2$	Н	1910	$>$ 1 $\mu$ M <sup>[b]</sup>	-
19a	$CH_2$	CH₃	$282\pm40$	$>$ 1 $\mu$ M <sup>[b]</sup>	>4
19b	$CH_2$	n-C₄H <sub>9</sub>	$8.5\pm0.37$	345	41
19c	$CH_2$	<i>n</i> -C₅H <sub>11</sub>	$4.9\pm1.1$	$54\pm7$	13
19 d	$CH_2$	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	$45\pm 6.9$	339	8
19e	$CH_2$	$CH_2CH=C(CH_3)_2$	$3.6\pm1.2$	256	71
19 f	$CH_2$	CH <sub>2</sub> -cyclopropyl	$53\pm7.5$	149	3
19g	$CH_2$	CH <sub>2</sub> -cyclohexyl	$2.4\pm0.9$	125	52
19h	$CH_2$	$CH_2C_6H_5$	$19\!\pm\!0.9$	$>$ 1 $\mu$ M <sup>[b]</sup>	-
19i	$CH_2$	$(CH_2)_2C_6H_5$	$16\pm0.9$	476	30
19j	$CH_2$	$(CH_2)_4C_6H_5$	$118\pm13$	201	2
19 k	$CH_2$	CH <sub>2</sub> -2-furyl	$60\pm4.7$	1670	28
191	$CH_2$	CH <sub>2</sub> -2-thienyl	$70\pm20$	$>$ 1 $\mu$ M <sup>[b]</sup>	-
19 m	$CH_2$	$CH_2C_6H_4$ -4-F	$7.1\pm3.2$	889	125
19 n	$CH_2$	CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -4-OMe	$24\pm3.5$	$>$ 1 $\mu$ M <sup>[b]</sup>	-
(+)-pentazocine		$5.7\pm2.2$	-	-	
haloperidol			$6.3\pm1.6$	$78\pm2.3$	13
di-o-tolylgua	anidine		$89\pm29$	$58\pm18$	0.6

**Table 1.**  $\sigma_1$  and  $\sigma_2$  receptor affinities of 5-phenylsulfanyl- and 5-benyzl-substituted tet-

[a] All values were determined in triplicate (n=3), and data represent the mean  $\pm$  SEM; for compounds showing very low affinity in the first experiment, repetitions were not performed (n=1). [b] At a test compound concentration of 1  $\mu$ M, the decrease in radioligand binding was <30%.

substituent on the benzyl moiety, such as a methoxy group (in **19n**), decreased the  $\sigma_1$  affinity, an electron-accepting substituent like a fluoro group (in **19m**) increased the  $\sigma_1$  affinity.

Altogether, the butyl (**19b**:  $K_i$ =8.5 nM), pentyl (**19c**:  $K_i$ = 4.9 nM), dimethylallyl (**19e**:  $K_i$ =3.6 nM), cyclohexylmethyl (**19g**:  $K_i$ =2.4 nM), and 4-fluorobenzyl (**19m**:  $K_i$ =7.1 nM) derivatives represent the most potent  $\sigma_1$  ligands within this series of compounds.

The  $\sigma_2$  affinity of the 5-benzyl-substituted 2-benzazepines **18** and **19** is considerably lower than the  $\sigma_1$  affinity, which showed their preference for the  $\sigma_1$  subtype. The pentyl derivative **19c** is the only ligand with a  $\sigma_2$  affinity below 100 nm. As a general tendency, the  $\sigma_2$  affinity of the (hetero)arylmethyl derivatives is lower than the  $\sigma_2$  affinity of the alkyl-substituted 2-benzazepines. Thus, the 4-fluorobenzyl derivative **19m** shows the highest  $\sigma_1/\sigma_2$  selectivity (factor of 125) for this series of compounds. However, the  $\sigma_1/\sigma_2$  selectivity of the cyclohexylmethyl derivative **19g** (factor of 52) is also very high.

#### Affinity toward various binding sites of the NMDA receptor

It has been reported that compounds with a small substituent at the N atom (such as H or  $CH_3$ ) interact preferentially with the phencyclidine binding site of the NMDA receptor, whereas

the corresponding analogues with larger N substituents (for example, benzyl or dimethylallyl) interact with the  $\sigma_1$  receptors.<sup>[45-47]</sup> Moreover, in the class of 3-benzazepines 1, PhX substituents in the 1-position led to potent NMDA receptor antagonists, as detailed in the Introduction. Therefore, the interactions of the tetrahydro-2-bnzazepines 10, 18, and 19 with various binding sites of the NMDA receptor were recorded. However, at a test compound concentration of 10 µм, the 2-benzazepines did not compete considerably with the radioligands [3H]-MDL-105519 (glycine binding site), [<sup>3</sup>H]-(+)-MK-801<sup>[47,48]</sup> and [<sup>3</sup>H]- 1-[1-(2-thienyl)cyclohexyl])piperidine (phencyclidine binding site), [<sup>3</sup>H]-ifenprodil (ifenprodil binding site), and [<sup>3</sup>H]-CGP-39653 (glutamate binding site). The low affinity toward the different binding sites of the NMDA receptor indicates very high selectivity, at least for the most potent  $\sigma_1$  ligands.

#### Affinity of 19b and 19m toward other receptors

On the basis of the  $\sigma_1$  affinity and  $\sigma_1/\sigma_2$  selectivity, the butyl- and 4-fluorobenzyl-substituted 2-benzazepines **19b** and **19m** were selected for further evaluation. Both compounds were tested in 53 assays for relevant receptors (for example, noradrenaline, dopamine, histamine, serotonin, glutamate, GABA, opioid, and progesterone receptors), transporters (such as noradrenaline, dopamine, and serotonin transporters), ion channels (for example, Na<sup>+</sup>, Ca<sup>2+</sup>, and Cl<sup>-</sup> channels), and enzymes (like the monoaminoxidases). At a test compound concentration of 1.0  $\mu$ M, both compounds showed a rather good selectivity against

these molecular targets. The butyl derivative **19b** revealed only interactions with the  $\alpha_{1A}$  receptor (63% inhibition of radioligand binding) and the dopamine transporter (66% inhibition of radioligand binding). Competition between radioligands and the 4-fluorobenzyl-substituted derivative **19m** was found in the D<sub>4</sub> (91% inhibition) and H<sub>2</sub> (59%) receptor assays and in the noradrenaline (71%) and dopamine (85%) transporter assays.

#### Animal experiments performed with 19b and 19m

To get an idea about the tolerability of the 2-benzazepines **19b** and **19m**, the Irwin test<sup>[49]</sup> was performed. In this assay, increasing doses of **19b** and **19m** (1–100 mg kg<sup>-1</sup> body weight) were injected intraperitoneally and the behavior of the mice was observed for 24 h. The mice did not show unusual reactions after intraperitoneal application of either **19b** or **19m**. Only at the highest dose of 100 mg kg<sup>-1</sup> body weight, was a decreased abdominal tone observed with both test compounds during the first 1–2 h. This result indicates that 2-benzazepines **19b** and **19m** are well tolerated by the mice.

It has been reported that  $\sigma_1$  modulators are able to improve neuronal deficits,  $^{[17]}$  so a cognition test  $^{[50]}$  was performed. In this test, the recognition of an object after scopolamine-in-

duced amnesia was recorded. Doses of 1, 3, 10, and 30 mg kg<sup>-1</sup> body weight of the 2-benzazepines **19b** and **19m** were injected intraperitoneally into mice 40 min before the first and 110 min before the second trial. Scopolamine (0.3 mg kg<sup>-1</sup> body weight) was injected to induce amnesia 10 min after injection of the test compound. (For the setup of the experiment, see figure SI1 in the Supporting Information). The butyl derivative 19b did not improve object recognition, even at the highest dose of 30 mg kg<sup>-1</sup> body weight (Figure SI2 in the Supporting Information). However, the 4-fluorobenzyl derivative 19m showed a weak but not significant improvement in object recognition. At doses of 10 and 30 mg kg<sup>-1</sup> body weight, the object exploration during the second trial was similar to the object exploration with the reference compound thioperamide (Figure SI3 in the Supporting Information). It can be concluded that the 4-fluorobenzyl derivative 19m represents a weak cognition-enhancing drug.

 $\sigma_1$  Receptor antagonists represent a promising class of new drugs for the treatment of neuropathic pain.<sup>[20]</sup> Therefore, the potential of the 2-benzazepines 19b and 19m in the formalin assay<sup>[51]</sup> as a model for neuropathic pain was investigated. In this assay, doses of 1, 3, and 10  $mg\,kg^{-1}$  body weight of the  $\sigma_{1}$ ligands 19b and 19m were injected intraperitoneally into mice. After 15 min, an inflammatory process was induced upon injection of formalin into the hind paw. During the acute pain phase (0-5 min), the number of licking activities per second was regarded as a correlate for pain intensity. After 5 min, the acute pain phase decreased and a phase of neuropathic pain developed. In this situation, pain stimuli were set by pushing a von Frey filament on the inflamed paw of the mice and the reactions of the mice were recorded for 10-35 min after formalin injection. During the late phase of neuropathic pain, the butyl derivative 19b did not decrease the pain reactions of the mice, which indicates low analgesic activity. However, after administration of the 4-fluorobenzyl derivative 19m, weak analgesic activity was observed at the highest recorded dose of 10 mg kg<sup>-1</sup> body weight. However, the weak analgesic activity is not statistically significant.

Additionally, the antidepressive effect of the  $\sigma_1$  ligand **19m** was evaluated in the forced swim test, the open field test, and the home cage activity test after oral administration of 50 and 100 mg kg<sup>-1</sup> body weight in mice. Compound **19m** did not produce any significant behavioral changes in the forced swim test, did not have any effect on anxiety-related behavior or on locomotor activity in the open field test, and did not produce any behavioral changes during long-term home cage monitoring. It can be concluded that the 4-fluorobenzyl derivative **19m** does not have any antidepressant-like effect in mice.

## Conclusions

The novel synthetic strategy of connecting a C6–C1 building block with a C3–N fragment by a Heck reaction, a Stetter reaction, and reductive cyclization led to the tetrahydro-2-benzaze-pine building block **18**, which allowed the introduction of diverse substituents at the N atom during the last step of the synthesis. High  $\sigma_1$  affinity was observed for 2-benzazepines

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with N substituents larger than a linear propyl group. The butyl, dimethylallyl, cyclohexylmethyl, and 4-fluorobenzyl derivatives **19b**, **19e**, **20g**, and **19m** represent potent  $\sigma_1$  ligands with  $K_i$  values below 10 nm and  $\sigma_1/\sigma_2$  selectivity greater than 40. The butyl and 4-fluorobenzyl derivatives **19b** and **19m** show high selectivity over more than 50 further relevant targets. The clean profile in the Irwin screen indicates a low side effect potential for both **19b** and **19m**. Whereas the butyl derivative **19b** did not show analgesic activity or improved object recognition, the 4-fluorobenzyl derivative **19m** revealed weak but not significant activity in the formalin assay of neuropathic pain and the object recognition assay. Thus, the 4-fluorobenzyl derivative **19m** represents a promising starting point for the development of  $\sigma_1$  ligands with cognition-enhancing and analgesic activity.

### **Experimental Section**

#### Chemistry

**General:** <sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) spectroscopy: Mercury-400BB spectrometer (Varian); chemical shift ( $\delta$ ) in ppm related to tetramethylsilane; coupling constants are given with 0.5 Hz resolution. HPLC: Merck Hitachi equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614. Unless otherwise stated, the purity of all of the test compounds was greater than 95% according to two different HPLC methods.

 $(\pm)$ -3-[2-(Dimethoxymethyl)phenyl]-4-oxo-4-phenylbutyronitrile (11): Under N<sub>2</sub>, a solution of benzaldehyde (1.33 mL, 13.2 mmol) in DMF (6.6 mL) was added slowly (1 h) to a suspension of NaCN (323 mg, 6.58 mmol) in DMF (6.6 mL) at 35  $^\circ\text{C}.$  The mixture was stirred at 35 °C for 2 h. A solution of 5 (2.00 g, 9.86 mmol) in DMF (13.2 mL) was then added within 4 h, and the suspension was stirred for 12 h at 35 °C. H<sub>2</sub>O (600 mL) was added, and the mixture was extracted with  $Et_2O$  (4×100 mL). The combined organic layers were washed with H<sub>2</sub>O (3×100 mL), dried (K<sub>2</sub>CO<sub>3</sub>), and concentrated in vacuo, and the residue was purified by flash chromatography  $(6 \times 18 \text{ cm}, \text{ petroleum ether/EtOAc} (9/1), 65 \text{ mL}, R_f = 0.17)$ . The product was recrystallized with petroleum ether/EtOAc (8/2). Colorless crystals; yield: 1.48 g (49%); mp: 100 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta =$ 2.86 (dd, J=16.4, 4.5 Hz, 1 H; CH<sub>2</sub>CN), 3.07 (dd, J=16.4, 8.5 Hz, 1 H; CH<sub>2</sub>CN), 3.48 (s, 3H; OCH<sub>3</sub>), 3.51 (s, 3H; OCH<sub>3</sub>), 5.41 (s, 1H; CH(OCH<sub>3</sub>)<sub>2</sub>), 5.54 (dd, J=8.5, 4.4 Hz, 1 H; CHCH<sub>2</sub>CN), 7.02-7.06 (m, 1H; H<sub>arom</sub>), 7.19–7.28 (m, 2H; H<sub>arom</sub>), 7.31–7.37 (m, 2H; H<sub>arom</sub>), 7.41– 7.49 (m, 2H; H<sub>arom</sub>), 8.02–8.05 ppm (m, 2H; H<sub>arom</sub>).

(±)-3-[2-(Dimethoxymethyl)phenyl]-4-phenylbutyramide (15): Alcohol 12 (2.03 g, 6.5 mmol), K<sub>2</sub>CO<sub>3</sub> (3.59 g, 25.9 mmol), and Pd/C (10%, 1.20 g) were suspended in CH<sub>3</sub>OH (300 mL), and the mixture was stirred at room temperature under H<sub>2</sub> (1 bar) for 16 h. The mixture was filtered through Celite. A saturated solution of NaCl (100 mL) was added to the filtrate, and the mixture was extracted with  $CH_2Cl_2$  (4×60 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo, and the residue was purified by flash chromatography (6.5×24 cm, EtOAc, 65 mL,  $R_{\rm f}$ =0.34). Pale yellow oil; yield: 1.99 g (98%); <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 2.81–2.87 (m, 2H; CH<sub>2</sub>Ph), 2.98 (dd, J=13.2, 7.5 Hz, 1H; CH<sub>2</sub>CONH<sub>2</sub>), 3.13 (dd, J= 13.2, 7.1 Hz, 1 H; CH<sub>2</sub>CONH<sub>2</sub>), 3.40 (s, 3 H; OCH<sub>3</sub>), 3.53 (s, 3 H; OCH<sub>3</sub>), 3.92-4.06 (m, 1H; CHCH<sub>2</sub>CONH<sub>2</sub>), 5.31 (s, 1H; CH(OCH<sub>3</sub>)<sub>2</sub>), 7.25-7.31 (m, 2H; H<sub>arom</sub>), 7.35–7.48 (m, 4H; H<sub>arom</sub>), 7.56–7.63 ppm (m, 3H;  $H_{arom}$ ); the signal for the protons of the NH<sub>2</sub> group is not visible in the <sup>1</sup>H NMR spectrum.

(±)-2-(4-Amino-1-phenylbutan-2-yl)benzaldehyde dimethyl acetal (16): Under N<sub>2</sub>, the primary amide 15 (1.38 g, 4.41 mmol) was dissolved in THF (150 mL), and the solution was cooled to  $4\,^\circ\text{C}$ in an ice bath. LiAlH<sub>4</sub> (834 mg, 21.9 mmol) was added, and the mixture was stirred for 4 h at 4 °C and for 12 h at room temperature. The suspension was diluted with THF (50 mL), a small amount of water was added carefully, and the precipitate was removed by filtration. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography (6×20 cm, EtOAc/CH<sub>3</sub>OH/N,N-dimethylethanamine (8/2/0.01), 65 mL,  $R_f = 0.22$ ). Colorless oil; yield: 1.00 g (76%); <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.52$  (brs, 2H; NH<sub>2</sub>), 1.85–1.97 (m, 2H; CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>), 2.47–2.57 (m, 1H; CH<sub>2</sub>NH<sub>2</sub>), 2.58–2.66 (m, 1H; CH<sub>2</sub>NH<sub>2</sub>), 2.85–2.95 (m, 1H; CH<sub>2</sub>Ph), 2.96–3.04 (m, 1H; CH<sub>2</sub>Ph), 3.18 (s, 3H; OCH<sub>3</sub>), 3.35 (s, 3H; OCH<sub>3</sub>), 3.79 (quint, J=7.4 Hz, 1H; PhCHCH<sub>2</sub>), 5.47 (s, 1 H; CH(CH<sub>3</sub>)<sub>2</sub>), 7.17–7.36 (m, 6 H; H<sub>arom</sub>) 7.38–7.47 (m, 2H; *H*<sub>arom</sub>), 7.81 ppm (d, *J*=7.9 Hz, 1H; *H*<sub>arom</sub>).

(±)-5-Benzyl-2,3,4,5-tetrahydro-1H-2-benzazepine (18): Under N<sub>2</sub>, p-toluenesulfonic acid (1.04 g, 5.48 mmol) was added to a solution of primary amine 16 (1.09 g, 3.65 mmol) in THF (450 mL), and the mixture was stirred at room temperature for 2 h. NaBH<sub>3</sub>CN (459 mg, 7.30 mmol) was then added, and the mixture was stirred at room temperature for 1 h. A saturated solution of NaHCO<sub>3</sub> (100 mL) was added, and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>  $(4 \times 100 \text{ mL})$ . The combined organic layers were dried (K<sub>2</sub>CO<sub>3</sub>), filtered, and concentrated in vacuo, and the residue was purified by flash chromatography (3.5×20 cm, EtOAc/CH<sub>3</sub>OH/N,N-dimethylethanamine (8/2/0.01), 20 mL, R<sub>f</sub>=0.24). Colorless oil; yield: 417 mg (48%); <sup>1</sup>H NMR ([D<sub>8</sub>]toluene):  $\delta = 1.03$  (brs, 1H; NH), 1.62–1.75 (m, 1H; 4-CH<sub>2</sub>), 1.86-1.96 (m, 1H; 4-CH<sub>2</sub>), 2.99-3.08 (m, 1H; CH<sub>2</sub>Ph), 3.08-3.16 (m, 1H; CH<sub>2</sub>Ph), 3.18-3.39 (m, 2H; 3-CH<sub>2</sub>), 3.40-3.48 (m, 1H; 5-CH), 4.13 (d, J=14.9 Hz, 1H; 1-CH<sub>2</sub>), 4.22 (d, J=14.9 Hz, 1H; 1-CH<sub>2</sub>), 7.21–7.48 ppm (m, 9H; H<sub>aron</sub>);  $^{13}{\rm C}$  NMR ([D\_8]toluene):  $\delta =$ 35.2 (1C; 4-CH<sub>2</sub>), 40.3 (1C; CH<sub>2</sub>Ph), 50.3 (1C; 5-CH), 55.7 (1C; 1-CH<sub>2</sub>), 123.6, 125.2, 125.5, 125.7, 126.5, 127.4, 128.1, 128.3, 137.8, 141.6, 143.6, 145.5 ppm (12C;  $C_{\text{arom}}$ ); the signal for the C3 carbon atom is not observed in the <sup>13</sup>C NMR spectrum.

 $(\pm)$ -5-Benzyl-2-butyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (19b): A mixture of secondary amine 18 (89 mg, 0.38 mmol), K<sub>2</sub>CO<sub>3</sub> (428 mg, 3.09 mmol), and 1-bromobutane (49 µL, 0.45 mmol) in CH<sub>3</sub>CN (10 mL) was heated at reflux for 16 h. A saturated solution of NaCl (10 mL) was added, and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4×10 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo, and the residue was purified by flash chromatography (2×28 cm, EtOAc/N,N-dimethylethanamine (1/0.01), 10 mL, R<sub>f</sub>=0.44). Pale yellow oil; yield: 52 mg (47%); C<sub>21</sub>H<sub>27</sub>N (293.2); purity (HPLC, method I): 99.6%; purity (HPLC, method II): 99.0%; <sup>1</sup>H NMR ([D<sub>8</sub>]toluene):  $\delta = 1.11$  (t, J = 7.2 Hz, 3H; CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.41–1.58 (m, 3H; CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and 4-CH<sub>2</sub>), 1.58– 1.71 (m, 2H; CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.86–2.04 (m, 1H; 4-CH<sub>2</sub>), 2.43–2.54 (m, 2H; CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.79-3.05 (m, 2H; CH<sub>2</sub>Ph), 3.15-3.37 (m, 3H; 3-CH<sub>2</sub> and 5-CH), 4.01 (d, J=14.7 Hz, 1H; 1-CH<sub>2</sub>), 4.07-4.22 (m, 1H; 1-CH<sub>2</sub>), 7.10–7.40 ppm (m, 9H; H<sub>arom</sub>); IR (ATR):  $\tilde{\nu}$  = 3026 (C- $H_{arom}$ ), 2925, 2857 (CH<sub>2</sub>), 754 (1,2-disubstituted arom), 698 cm<sup>-1</sup> (monosubstituted arom); MS (ESI): *m/z* (%): 294 [*M*+H<sup>+</sup>] (100).

(±)-5-Benzyl-2-(4-fluorobenzyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine (19m): A mixture of secondary amine 18 (100 mg, 0.42 mmol), K<sub>2</sub>CO<sub>3</sub> (470 mg, 3.40 mmol), 4-fluorobenzyl chloride (60  $\mu$ L, 0.50 mmol), and CH<sub>3</sub>CN (10 mL), was heated at reflux for 16 h. A saturated solution of NaCl (10 mL) was added, and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4×10 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo, and the residue was purified by flash chromatography (2×25 cm, cyclohexane/ EtOAc (7/3), 10 mL,  $R_f$ =0.35). Pale yellow oil; yield: 79 mg (55%);  $C_{24}H_{24}FN$  (345.2); purity (HPLC, method I): 97.9%; purity (HPLC, method II): 96.3%; <sup>1</sup>H NMR ([D<sub>8</sub>]toluene):  $\delta$ =1.58–1.69 (m, 1H; 4-CH<sub>2</sub>), 1.83–2.02 (m, 1H; 4-CH<sub>2</sub>), 2.75–2.87 (m, 1H; CH<sub>2</sub>Ph), 2.89–3.01 (m, 1H; CH<sub>2</sub>Ph), 3.10–3.27 (m, 2H; 3-CH<sub>2</sub>), 3.27–3.37 (m, 1H; 5-CH), 3.47 (s, 2H; CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>F), 3.92 (d, *J*=14.3 Hz, 1H; 1-CH<sub>2</sub>), 3.96–4.14 (m, 1H; 1-CH<sub>2</sub>), 6.97–7.04 (m, 2H; H<sub>arom</sub>), 7.14–7.36 ppm (m, 11H; H<sub>arom</sub>); <sup>13</sup>C NMR ([D<sub>8</sub>]toluene):  $\delta$ =29.5 (1C; 4-CH<sub>2</sub>), 40.3 (1C; CH<sub>2</sub>Ph), 58.1 (1C; CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>F), 59.5 (1C; 1-CH<sub>2</sub>), 115.4, 115.6, 125.5, 125.7, 126.5, 126.6, 127.8, 128.1, 128.3, 128.6, 129.8, 130.8, 130.9, 137.8, 139.3, 141.5, 161.6, 163.9 ppm (18C; C<sub>arom</sub>); the signals for the C3 and C5 carbon atoms are not visible in the <sup>13</sup>C NMR spectrum; IR (ATR):  $\hat{\nu}$ =3025 (C–H<sub>arom</sub>), 2922, 2850 (CH<sub>2</sub>), 756 (1,2-disubstituted arom), 698 cm<sup>-1</sup> (monosubstituted arom); MS (ESI): *m/z* (%): 346 [*M*+H<sup>+</sup>] (100).

#### Receptor binding studies

For details of the  $\sigma_1$  and  $\sigma_2$  assays, see references [43,44]. For details of the NMDA assay, see references [47,48].

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**Keywords:** antidepressant activity • benzazepines neuropathic pain • receptors • structure–activity relationships

- B. M. Smith, J. M. Smith, J. H. Tsai, J. A. Schultz, C. A. Gilson, S. A. Estrada, R. R. Chen, D. M. Park, E. B. Prieto, C. S. Gallardo, D. Sengupta, P. I. Dosa, J. A. Covel, A. Ren, R. R. Webb, N. R. A. Beeley, M. Marin, M. Morgan, S. Espitia, H. R. Saldana, C. Bjenning, K. T. Whelan, A. J. Grottick, F. Menzaghi, W. J. Thomsen, *J. Med. Chem.* **2008**, *51*, 305–313.
- [2] D. L. Ladd, J. Weinstock, M. Wise, G. W. Gessner, J. L. Sawyer, K. E. Flaim, J. Med. Chem. 1986, 29, 1904 – 1912.
- [3] J. B. Post IV, W. H. Frishman, J. Clin. Pharmacol. 1998, 38, 2-13.
- [4] O. Krull, B. Wünsch, Bioorg. Med. Chem. 2004, 12, 1439-1451.
- [5] U. Wirt, D. Schepmann, B. Wünsch, Eur. J. Org. Chem. 2007, 462-475.
- [6] S. M. Husain, R. Fröhlich, B. Wünsch, J. Org. Chem. 2009, 74, 2788-2793.
- [7] S. M. Husain, M. T. Heim, D. Schepman, B. Wünsch, *Tetrahedron: Asym*metry 2009, 20, 1383–1392.
- [8] S. Sarkar, D. Schepmann, J. Köhler, R. Fröhlich, B. Wünsch, Eur. J. Org. Chem. 2012, 5980–5990.
- [9] P. Hasebein, K. Aulinger, D. Schepmann, B. Wünsch, *Tetrahedron* 2013, 69, 4552–4562.
- [10] M. Martina, M. E. Turcotte, S. Halman, R. Bergeron, J. Physiol. 2007, 578, 143-157.
- [11] T. Hayashi, T. Maurice, T. P. Su, J. Pharmacol. Exp. Ther. 2000, 293, 788– 798.
- [12] R. Bergeron, G. Debonnel, C. De Montigny, Eur. J. Pharmacol. 1993, 240, 319-323.
- [13] J. E. Bermack, G. Debonnel, Br. J. Pharmacol. 2001, 134, 691-699.
- [14] T. Hayashi, T. Su, Cell 2007, 131, 596-610.
- [15] S. Collina, R. Gaggeri, A. Marra, A. Bassi, S. Negrinotti, F. Negri, D. Rossi, Expert Opin. Ther. Pat. 2013, 23, 597–613.
- [16] E. J. Cobos, J. M. Entrena, F. R. Nieto, C. M. Cendán, E. Del Pezo, Curr. Neuropharmacol. 2008, 6, 344–366.
- [17] T. Maurice, T. P. Su, Pharmacol. Ther. 2009, 124, 195-206.

- [18] M. Ishikawa, K. Hashimoto, J. Recept. Ligand Channel Res. 2010, 3, 25-36.
- [19] B. de La Puente, X. Nadal, E. Portillo-Salido, R. Sanchez-Arroyos, S. Ovalle, G. Palacios, A. Muro, L. Romero, J. M. Entrena, J. M. Baeyens, J. A. Lopez-Garcia, R. Maldonado, D. Zamanillo, J. M. Vela, *Pain* **2009**, *145*, 294–303.
- [20] Viewpoint article: B. Wünsch, J. Med. Chem. 2012, 55, 8209-8210.
- [21] "Selective Loss of Cerebral Cortical Sigma, but Not PCP Binding Sites in Schizophrenia": A. D. Weissman, M. F. Casanova, J. E. Kleinman, E. D. London, E. B. De Souza, *Biol. Psychiatry* **1991**, *29*, 41–54.
- [22] T. Hayashi, T. Su, CNS Drugs 2004, 18, 269–284.
- [23] K. Matsuno, T. Kobayashi, M. K. Tanaka, S. Mita, Eur. J. Pharmacol. 1996, 312, 267–271.
- [24] J. E. Bermack, G. Debonnel, J. Pharmacol. Sci. 2005, 97, 317-336.
- [25] T. Maurice, T. P. Su, A. Privat, Neuroscience 1997, 83, 413-428.
- [26] J. A. Butera, J. Med. Chem. 2007, 50, 2543-2546.
- [27] J. D. Kennedy, J. Med. Chem. 2007, 50, 2547-2556.
- [28] J. M. Entrena, E. J. Cobos, F. R. Nieto, C. M. Cendan, G. Gris, E. Del Pozo, D. Zampanillo, J. M. Baeyens, *Pain* **2009**, *143*, 252–261.
- [29] J. L. Diaz, D. Zamanillo, J. Corbera, J. M. Baeyens, R. Maldonado, M. A. Pericàs, J. M. Vela, A. Torrens, *Cent. Nerv. Syst. Agents Med. Chem.* 2009, 9, 172-183.
- [30] J. L. Diaz, R. Cuberes, J. Berrocal, M. Contijoch, U. Christmann, A. Fernández, A. Port, J. Holenz, H. Buschmann, C. Laggner, M. T. Serafini, J. Burgeño, D. Zamanillo, M. Merlos, J. M. Vela, C. Almansa, *J. Med. Chem.* 2012, 55, 8211–8224.
- [31] B. Wünsch, Curr. Pharm. Des. 2012, 18, 930-937.
- [32] R. A. Glennon, S. Y. Ablordeppey, A. M. Ismaiel, M. B. El-Ashmawy, J. B. Fischer, K. B. Howie, J. Med. Chem. 1994, 37, 1214–1219.
- [33] R. A. Glennon, Mini-Rev. Med. Chem. 2005, 5, 927-940.
- [34] C. Laggner, C. Schieferer, B. Fiechtner, G. Poles, R. D. Hoffmann, H. Glossmann, T. Langer, F. F. Moebius, J. Med. Chem. 2005, 48, 4754.
- [35] J. Wencel-Delord, F. Glorius, Nat. Chem. 2013, 5, 369-375.

- [36] B. Classon, P. J. Garegg, B. Samuelsson, Acta Chem. Scand. Ser. B 1984, 38, 419-422.
- [37] H. Stetter, M. Schreckenberg, Chem. Ber. 1974, 107, 210-214.
- [38] H. Stetter, M. Schreckenberg, Angew. Chem. 1973, 85, 89.
- [39] H. Stetter, H. Kuhlmann, Angew. Chem. 1974, 86, 589; Angew. Chem. Int. Ed. Engl. 1974, 13, 539.
- [40] H. Stetter, H. Kuhlmann, Tetrahedron Lett. 1974, 4505-4508.
- [41] E. G. Maestrup, S. Fischer, C. Wiese, D. Schepmann, A. Hiller, W. Deuther-Conrad, J. Steinbach, B. Wünsch, P. Brust, J. Med. Chem. 2009, 52, 6062– 6072.
- [42] E. G. Maestrup, C. Wiese, D. Schepmann, P. Brust, B. Wünsch, *Bioorg. Med. Chem.* 2011, 19, 393-405.
- [43] C. A. Maier, B. Wünsch, J. Med. Chem. 2002, 45, 4923-4930.
- [44] C. Meyer, B. Neue, D. Schepmann, S. Yanagisawa, J. Yamaguchi, E.-U. Wuerthwein, K. Itami, B. Wünsch, *Bioorg. Med. Chem.* 2013, 21, 1844– 1856.
- [45] F. I. Carroll, P. Abraham, K. Parham, X. Bai, X. Zhang, G. A. Brine, S. W. Mascarella, B. R. Martin, F. L. May, C. Sauss, L. Di Paolo, P. Wallace, J. M. Walker, W. D. Bowen, J. Med. Chem. 1992, 35, 2812–2818.
- [46] E. L. May, M. D. Aceto, E. R. Bowman, C. Bentley, B. R. Martin, C. S. Harris, F. Medzihradsky, M. V. Mattson, A. E. Jacobson, J. Med. Chem. 1994, 37, 3408–3418.
- [47] J. Köhler, K. Bergander, J. Fabian, D. Schepmann, B. Wünsch, J. Med. Chem. 2012, 55, 8953–8957.
- [48] A. Banerjee, D. Schepmann, J. Köhler, E.-U. Würthwein, B. Wünsch, Bioorg. Med. Chem. 2010, 18, 7855-7867.
- [49] S. Irwin, Psychopharmacologia 1968, 13, 222-257.
- [50] Animal Models of Cognitive Impairment (Eds.: E. D. Levin, J. J. Buccafusco), CRC, Boca Raton, 2006.
- [51] M. Tsuda, S. Ueno, K. Inoue, Br. J. Pharmacol. 1999, 128, 1497-1504.

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