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Design, synthesis and preliminary pharmacological evaluation of new analogues of DM232 (unifiram) and DM235 (sunifiram) as cognition modulators

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ABSTRACT

A series of amides, structurally related to DM232 (unifiram) and DM235 (sunifiram), characterized by a 1,2,3,4-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one, 1,4-diamino-cyclohexane or 1,4-diaminobenzene ring, have been synthesized and tested for cognition-enhancing activity in the mouse passive-avoidance test. Some of the compounds display good antiamnesic and procognitive activity, with higher potency than piracetam, while some cyclohexane derivatives are endowed with amnesia inducing properties.

1. Introduction

Cognition is a complex physiological process involving several areas of the central nervous system. It has been shown that various neurotransmitters can modulate, positively or negatively, learning and memory; thus, their receptors may represent suitable targets for developing cognition-enhancing drugs.[1–5] Substances able to increase learning and memory may be useful in several kinds of cognitive dysfunctions, such as age-related memory deficits, neurodegenerative disorders such as Alzheimer's or Parkinson's diseases or multiple sclerosis, other neuropsychiatric conditions such as schizophrenia and attention-deficit hyperactivity disorders.[6–10] Despite the efforts, at present the only drugs that have been approved to treat cognition deficits in Alzheimer's disease and other forms of dementia are modulators of the cholinergic and glutamatergic transmission; other substances targeting these systems (i.e., other cholinesterase inhibitors, nicotinic agonists, or AMPA receptor positive allosteric modulators) are now in clinical trials.

The pyrrolidin-2-one family of cognition enhancers, exemplified by piracetam (Chart 1), has been the subject of studies for almost four decades and a few members of the family are in use in several countries as drugs to control cognition impairment, to afford neuroprotection after stroke and to treat epilepsy.[11] The use of this class of substances is controversial, due to the lack of a common mechanism of action at the molecular level, although some members of this series (for instance, aniracetam and nefiracetam)

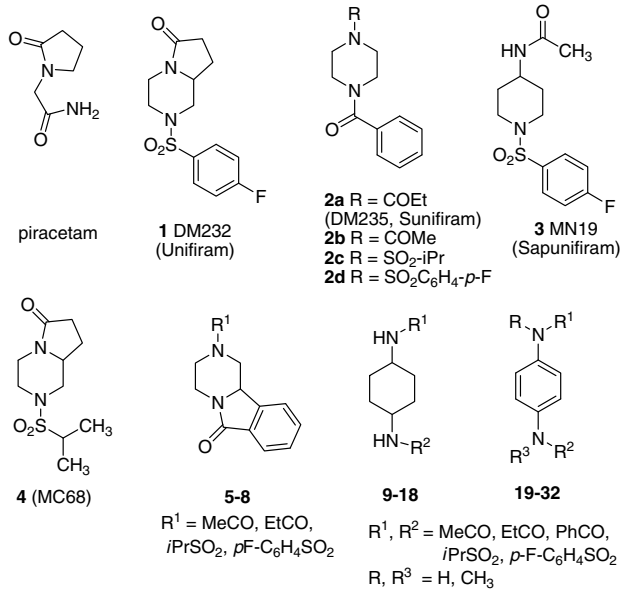

Chart 1.

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have been shown to modulate receptor systems such as the cholinergic and/or glutamatergic ones.[12,13]

It has previously been reported that DM232 (unifiram, **1**) and DM235 (sunifiram, **2a**) show cognition-enhancing properties with a potency four orders of magnitude greater than piracetam.[14,15] These compounds are well tolerated in rodents, but their development has been impaired because their mechanism of action has not been clarified.[16] In fact, unifiram and sunifiram did not show any affinity towards the most important central receptors or transporters.[15] These compounds are able to increase acetylcholine release from rat brain,[15] and nitric oxide production in rat adipocytes, the latter effect being antagonized by nicotinic antagonists such as mecamylamine and methyllycaconitine[17]; there is evidence that AMPA receptors are involved in the cognition-enhancing effect of these compounds.[18] However, a direct interaction of unifiram and sunifiram with nicotinic or AMPA receptors in vitro has not been proven yet.

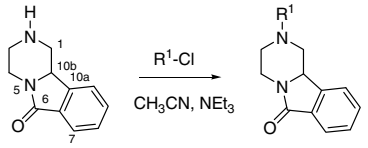
In order to improve the potency of our compounds, and possibly to elucidate the mechanism of action, several structural modifications were performed on the lead compounds **1** and **2a**, giving interesting results. For instance, the extrusion of one of the nitrogen atoms of the piperazine ring to give 4-aminopiperidine derivatives, exemplified by MN19 (**3**, sapunifiram), afforded compounds with cognition-enhancing properties similar to those of the parent compound sunifiram.[19] Moreover, the replacement of the 4-fluorophenyl moiety of **1** with an isopropyl group gave compound **4** (MC68), endowed with amnesia inducing properties.[20]

As a continuation of this research, we decided to modify the structure of our lead compounds following two different approaches: (i) the flexibility of the benzoylpiperazine moiety of **2** has been reduced by incorporating it into a 1,2,3,4-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one ring, obtaining compounds **5**–**8** and (ii) both amide functions have been extruded from the six-membered ring, providing the cyclohexane derivatives **9–18** and their aromatic analogues, the 1-4-diamidobenzenes **19–32**. The acyl and sulfonyl groups which decorate the structures were chosen among those giving, in the previous series, the most interesting compounds.[14,15,19] All the designed compounds maintain a diamidic structure, a feature which seems important for high nootropic activity.[16]

2. Chemistry

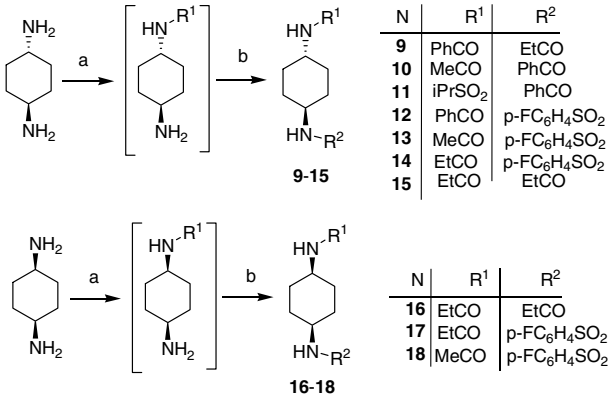
Compounds **5**–**8** were obtained by reaction of 1,2,3,4-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one, prepared according to Welch,[21] with the suitable acyl or sulfonyl chloride (Scheme 1).

Derivatives **9**–**15** were synthesized according to the method of Sueess (Scheme 2).[22] The commercially-available *trans*-1,4-cyclohexanediamine was sequentially treated with the suitable anhydrides or acyl or sulfonyl chlorides without isolation of the intermediate monoamide. The same pathway was applied to *cis*-1,4-cyclohexanediamine, prepared according to Johnstone,[23] providing compounds **16–18**. Compounds **15** and **16** derive from the double attack of propionic anhydride on both amine groups of, respectively, *trans*- and *cis*-1,4-cyclohexanediamine.



5: $R^1 = CH_3CO$
6: $R^1 = C_2H_5CO$
7: $R^1 = p\text{-}F\text{-}C_6H_4\text{-}SO_2$
8: $R^1 = (CH_3)_2CHSO_2$

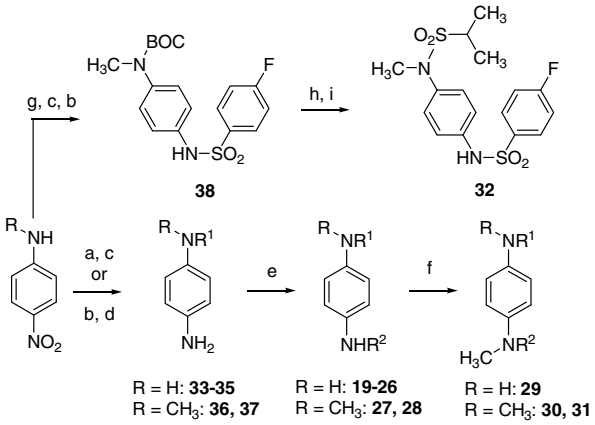
Scheme 1.



N	R^1	R^2
9	PhCO	EtCO
10	MeCO	PhCO
11	$iPrSO_2$	PhCO
12	PhCO	$p\text{-}FC_6H_4SO_2$
13	MeCO	$p\text{-}FC_6H_4SO_2$
14	EtCO	$p\text{-}FC_6H_4SO_2$
15	EtCO	EtCO

N	R^1	R^2
16	EtCO	EtCO
17	EtCO	$p\text{-}FC_6H_4SO_2$
18	MeCO	$p\text{-}FC_6H_4SO_2$

Scheme 2. Reagents: (a) $(R^1)_2O$ or R^1Cl, AcONa, H_2O, dioxane; (b) R^2Cl, Na_2CO_3, H_2O, dioxane.



N	R	R^1
33	H	$p\text{-}FC_6H_4SO_2$
34	H	PhCO
35	H	EtCO
36	CH_3	$p\text{-}FC_6H_4SO_2$
37	CH_3	PhCO

N	R	R^1	R^2
19	H	$p\text{-}FC_6H_4SO_2$	$iPrSO_2$
20	H	PhCO	$iPrSO_2$
21	H	PhCO	$p\text{-}FC_6H_4SO_2$
22	H	EtCO	$p\text{-}FC_6H_4SO_2$
23	H	EtCO	$iPrSO_2$
24	H	MeCO	PhCO
25	H	MeCO	$iPrSO_2$
26	H	MeCO	$p\text{-}FC_6H_4SO_2$
27	CH_3	$p\text{-}FC_6H_4SO_2$	$iPrSO_2$
28	CH_3	PhCO	$iPrSO_2$
29	H	PhCO	$iPrSO_2$
30	CH_3	PhCO	$iPrSO_2$
31	CH_3	$p\text{-}FC_6H_4SO_2$	$iPrSO_2$

Scheme 3. Reagents: (a) R_1C_l, K_2CO_3, THF; (b) p-F-$C_6H_4SO_2Cl$, DMAP, pyridine; (c) H_2/Pd/C, EtOAc; (d) Fe, AcOH; (e) R_2Cl, pyridine, THF; (f) MeI, tBuOK, THF; (g) $(BOC)_2O$; (h) HCl, EtOAc; (i) $iPrSO_2Cl$, pyridine, THF.

The synthesis of the 1,4-diaminobenzene analogues **19–32** is shown in Scheme 3. Commercially-available 4-nitroaniline was treated with the suitable acyl or sulfonyl chloride and reduced to the monoamides **33–35**, which were then reacted with the desired acyl or sulfonyl chlorides, to provide compounds **19–26**. The same pathway was applied to the synthesis of compounds **27** and **28**, starting from the commercially-available *N*-methyl-4-nitro-aniline, through the monoamides **36** and **37**. Treatment of compounds **27** and **28** with CH_3I under basic conditions gave the dimethyl derivatives **30** and **31**. When this reaction was performed on compound **20** only the more acid amide function was methylated, obtaining compound **29** as the only product. Catalytic hydrogenation of *N*-BOC-*N*-methyl-4-nitroaniline,[24] obtained under standard conditions, and subsequent treatment with *p*-fluorophenylsulfonyl chloride gave **38**, which was deprotected and treated with *i*-propylsulfonyl chloride to give compound **32** (Scheme 3).

3. Pharmacology

The compounds were tested for their ability to revert scopolamine-induced amnesia in the mouse passive-avoidance test of Jarvik and Kopp,[25] slightly modified by us (see Section 5). The compounds were tested in a 1:10 dilution sequence, up to the dose of 10 mg/kg; the results are expressed as minimal effective dose (MED, mg/kg) and are reported in Table 1. Compounds were considered inactive if they did not show activity up to the dose of 10 mg/kg, which is four orders of magnitude higher than the MED of the lead compounds **1** and **2a**. The passive-avoidance test was used to evaluate the amnesia inducing or procognitive properties of the compounds; for this reason the compounds were tested without addition of scopolamine. The results are reported in Table 2. All compounds were dissolved in saline, except compounds **27**–**31**, which were dissolved in a vehicle consisting of water/dimethylsulfoxide 4:1. Compound **32** proved to be unstable, and it was not tested.

4. Results and discussion

The ability of the compounds to revert scopolamine-induced amnesia is reported in Table 1, expressed as minimal effective dose (MED). Compounds **7**, **8**, **16**–**20**, **27**–**31** show some activity in this test; the other compounds (**5**, **6**, **9**–**12**, **15**, **21**–**26**) did not revert scopolamine-induced amnesia at doses up to 10 mg/kg ip, and therefore are not shown. On the contrary, compounds **13**, **14** were able to potentiate the effect of scopolamine. Compounds **13**, **14**, **16**–**20** and **27**–**31** were further tested in animals which had not been previously pre-treated with amnesia inducing drugs (Table 2): this test confirmed the amnesia inducing properties of compounds **13** and **14**, while compounds **16**–**20** and **27**, **28**, **30** and **31** show interesting procognitive activity. Under these conditions, where memory has not been pharmacologically impaired, some of the compounds show minimal effective doses one or two orders of magnitude greater than those recorded in scopolamine-treated mice. The procognitive activity of compounds **1** and **2a** was previously revealed by using the social learning test, performed according to Mondadori.[26] These two compounds exerted beneficial effects on cognitive performance in the social learning test by prolonging the time normally required by rats to delete mnemonic information.[15,27]

Reduction of the conformational flexibility of the benzoyl group of DM235 (sunifiram) by freezing it into a tricyclic moiety (see the structures reported in Scheme 1) gave compound **6**, and its lower homolog **5**, which are devoid of activity in the passive-avoidance test. On the contrary, the replacement of the acetyl or propionyl group with a sulfonyl moiety gave compounds (**7** and **8**) endowed with good nootropic activity. As a matter of fact, they are able to revert amnesia induced by scopolamine with MEDs of 0.1 and 1.0 mg/kg ip, respectively, both being much more active than piracetam, although their potency is not as high as that of the reference compounds **1**, **2a** and **3**. The rank order of potency in the tricyclic series does not correlate with that found in the piperazine series. In fact, both the *N*-acetyl and *N*-propionyl-benzoylpiperazine (**2b** and **2a**, respectively, see Chart 1) showed cognition-enhancing properties, although with quite different potency,[15] and both the sulfonyl analogues **2c** and **2d** were devoid of activity.[20] The difference between these two series can be explained by the fact that in in vivo studies the biological activity is the consequence of both the pharmacokinetic and pharmacodynamic properties, which may be differently affected by structural modifications. Unfortunately, the lack of knowledge about the mechanism of action makes it impossible to perform in vitro studies, where pharmacokinetic factors are largely reduced. Obviously other explanations cannot be ruled out, such as a different binding mode for the two series, or the interaction with a different biological target.

As far as the *trans*-1,4-diaminocyclohexane derivatives are concerned (compounds **9**–**15**, see structures in Scheme 2), none of them was able to revert scopolamine-induced amnesia. This lack of activity can be due to the presence of the cyclohexane spacer

Table 1
Minimal effective dose (MED) of the compounds against scopolamine-induced amnesia in the mouse passive-avoidance test, in comparison with reference compounds **1**, **2a** and **3**[a]

Treatment	Minimal effective dose (mg/kg)	*n*	Training session (s)	Retention session (s)	Δ
Saline	—	30	17.2 ± 2.3	99.5 ± 7.1	82.3
Saline/DMSO 4:1	—	19	21.3 ± 2.3	96.8 ± 6.1	75.5
Scopolamine (S)	1.5	31	16.5 ± 3.3	42.8 ± 8.3	26.3
S + piracetam	30	32	17.6 ± 3.6	108.8 ± 10.4*	91.2
S + **1**[b]	0.001	37	19.7 ± 5.8	104.4 ± 10.6*	93.8
S + **2a**[c]	0.001	29	20.5 ± 3.4	91.5 ± 8.0*	71.0
S + **2b**[c]	10	12	11.3 ± 5.3	119.0 ± 11.2*	107.7
S + **3**[d]	0.01	19	14.5 ± 3.8	90.6 ± 12.5*	76.1
S + **7**	0.1	13	15.6 ± 3.2	74.5 ± 10.3*	58.9
S + **8**	1.0	16	16.3 ± 4.1	85.5 ± 9.4*	69.2
S + **13**	10	18	17.0 ± 3.2	26.3 ± 8.9*	9.3
S + **14**	1.0	16	17.5 ± 3.1	16.4 ± 6.3*	−1.1
S + **16**	1.0	23	17.8 ± 3.7	106.2 ± 9.5*	88.4
S + **17**	0.1	12	16.8 ± 3.1	89.1 ± 7.9*	72.3
S + **18**	1.0	15	19.1 ± 3.5	104.5 ± 8.6*	85.4
S + **19**	1	14	19.1 ± 3.5	76.3 ± 7.9*	57.2
S + **20**	10	21	16.8 ± 3.8	88.1 ± 9.7*	61.3
S + **27**	0.1	13	20.2 ± 3.5	103.6 ± 8.5*	83.4
S + **28**	0.1	12	21.6 ± 3.7	75.9 ± 8.9*	54.3
S + **29**	0.01	14	20.6 ± 3.8	66.7 ± 7.1*	46.1
S + **30**	0.01	14	20.7 ± 4.3	91.8 ± 9.9*	70.6
S + **31**	0.01	18	18.8 ± 2.6	70.5 ± 8.3^	73.6

[a] All compounds were dissolved in saline, except **27**–**31**, which were dissolved in saline/dimethylsulfoxide 4:1, and injected ip 20 min before training session. Scopolamine (S) was injected immediately after punishment.
[b] From Ref. 14.
[c] From Ref. 15.
[d] From Ref. 19.
^ $P < 0.05$ in comparison with scopolamine-treated mice.
* $P < 0.01$ in comparison with scopolamine-treated mice.

Table 2
Effect of the compounds in the mouse passive-avoidance test, in comparison with reference compounds **1**, **2a**–**4**[a]

Treatment	Minimal effective dose (mg/kg)	*n*	Training session (s)	Retention session (s)	Δ
Saline	—	27	19.3 ± 4.1	97.2 ± 7.5	77.9
Saline/DMSO 4:1	—	19	21.3 ± 2.3	96.8 ± 6.1	75.5
1	0.01	18	15.4 ± 3.6	131.6 ± 9.2*	116.2
2a	0.01	16	18.1 ± 2.7	126.7 ± 7.7^	108.6
3	0.1	13	19.1 ± 2.9	126.8 ± 6.4*	107.7
4[b]	10	18	13.6 ± 3.9	61.5 ± 10.4*	47.9
13	0.01	14	19.2 ± 2.5	52.8 ± 6.3*	33.6
14	0.1	13	16.9 ± 2.2	56.3 ± 7.1*	39.4
16	10	13	34.8 ± 4.3	165.2 ± 6.1*	130.4
17	10	13	25.3 ± 4.5	162.9 ± 7.3*	137.6
18	10	10	32.0 ± 3.2	156.6 ± 14.5*	121.6
19	10	10	21.1 ± 3.8	125.2 ± 6.7*	104.1
20	1.0	10	22.1 ± 3.3	116.7 ± 8.3^	94.6
27	1.0	16	26.2 ± 2.8	149.8 ± 12.1*	123.6
28	0.1	20	17.3 ± 4.5	121.0 ± 9.0*	113.7
30	1.0	12	19.6 ± 5.7	123.6 ± 18.9*	107.0
31	1.0	14	30.0 ± 4.1	158.6 ± 10.3*	128.6

[a] All compounds were dissolved in saline, except compounds **27**, **28**, **30** and **31**, which were dissolved in saline/dimethylsulfoxide 4:1, and injected ip 20 min before training session.
[b] From Ref. 20.
^ $P < 0.05$ in comparison with mice treated with saline or saline/DMSO.
* $P < 0.01$ in comparison with mice treated with saline or saline/DMSO.

which increases the distance between the amide functions with respect to piperazine or 4-aminopiperidine derivatives, or to the introduction of more hydrophilic characteristics. In fact, all compounds have two secondary amide or sulfonamide functions, which can inhibit the crossing of the blood–brain barrier. However, the latter hypothesis can be ruled out, since compounds **13** and **14**, carrying also two secondary amide or sulfonamide groups, at doses of 10 and 1 mg/kg, respectively, were able to increase the amnesic effect of scopolamine (Table 1). When tested alone (Table 2), they showed amnesic properties at doses of 0.01 and 0.1 mg/kg, respectively; they were able to reduce the entry latency in the retention session, at doses one or two orders of magnitude lower than scopolamine. This effect, which indicates that the compounds can enter the CNS, was unexpected. However, as stated in the introduction, we had already experienced a similar behavior in some of our molecules, such as the 1,4-diazabicyclo[4.3.0]nonan-9-one derivatives, where the replacement of the *p*-fluorophenyl moiety with an *i*-propyl group switched the activity of the molecules from cognition-enhancing (**1**) to amnesic (**4**).[20] Here we found a similar result: the extrusion of the amide function of compound **3** from the 6-membered ring gave compound **13** endowed with amnesic properties. These findings prompted us to synthesize the *cis* analogues of compounds **13** and **14**. Compounds **17** and **18**, as well as **16**, were initially tested without addition of scopolamine, in order to unveil a possible amnesic activity, but on the contrary, this test highlighted their procognitive effect at the dose of 10 mg/kg (Table 2). Moreover, at lower doses, compounds **16**–**18** were able to revert scopolamine-induced amnesia (Table 1), while compound **15** (the *trans* isomer of **16**) was completely devoid of activity. The marked influence on activity of structural modifications such as isomerization suggests that we are modulating a specific, but still unknown, biological target.

In the 1,4-diaminobenzene series, among the amide-sulfonamides **19**–**26**, only compounds **19** and **20** were able to revert scopolamine-induced amnesia with MED of 1 mg/kg and 10 mg/kg, respectively (Table 1). Their potency is in the same range as that of piracetam, but they are three to four orders of magnitude less potent than the lead compounds **1**, **2a** and **3**. This drop in potency can be due to the different physico-chemical characteristics of the compounds, which may affect their ability to cross the blood–brain barrier. In fact, in **19** and **20** the functional groups are amides or sulfonamides with H-bond donor properties and a more hydrophilic character with respect to the endocyclic amide-sulfonamide functions of compounds **1**–**3**; moreover, compounds **19** and **20** are weak acids while **1**–**3** are neutral compounds. To test this hypothesis, the mono and dimethyl analogues of compounds **19** (compounds **27**, **31** and **32**) and **20** (compounds **28**–**30**) were prepared. It was found that the removal of the hydrophilic function(s) increases the potency of compounds: indeed, the addition of one or two methyl groups on the amide moieties of **19** decreases the minimal effective dose (1.0 mg/kg) by one or two orders of magnitude (compounds **27** and **31**, respectively). A similar, even more evident shift can be seen by comparing the MED of compound **20** (10 mg/kg) with the *N*-methyl-derivatives (compounds **28** and **29**) or the *N*,*N*′-dimethyl analogue **30**. The increase of Clog*P* values in the series of compounds **19**, **27**, **31** and **20**, **28**–**30** (see Tables 3 and 5) is, as expected, associated to an increase of nootropic potency (Table 1); the absence of a more general correlation between the cognition-enhancing activity and the calculated lipophilicity values can be due, as previously suggested, to the different contribution of pharmacokinetic and pharmacodinamic factors in determining the potency of the compounds. These results seem to indicate that the benzene ring is a suitable spacer to maintain potent nootropic activity in this class of substances, since some the compounds (**29**–**31**) have MED values in the same range as that of **3** and only one order of magnitude greater than the reference compounds **1** and **2a**.

In conclusion, we have synthesized a series of diastereomeric 1,4-diamidocyclohexanes which show opposing activities in the mouse passive-avoidance test, suggesting that they are able to modulate in an opposite way the function of a specific biological target. In addition, a new class of compounds (1,4-diamidobenzenes) has been discovered, which maintain high nootropic activity. These compounds may give useful information for structure-activity relationships in the class of nootropic drugs, and possibly to elucidate their mechanism of action at the molecular level.

5. Experimental

5.1. Chemistry

All melting points were taken on a Büchi apparatus and are uncorrected. NMR spectra were recorded on a Brucker Avance 400 spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C). Chromatographic separations were performed on a silica gel column by gravity chromatography (Kieselgel 40, 0.063–0.200 mm; Merck) or flash chromatography (Kieselgel 40, 0.040–0.063 mm; Merck). When necessary, chromatographic separations were performed on an Al_2O_3 column by gravity chromatography (aluminium oxide

Table 3
Experimental details for the synthesis of compounds **5**–**18** (see general structures in Chart 1) and Clog*P* values

N	R^1	R^2	Eluent[a]	Yield (%)	Mp (°C)	Clog*P* [d]	Anal.
5	$COCH_3$	—	EtOAc[b]	71	130–131	1.48	$C_{13}H_{14}N_2O_2$
6	COC_2H_5	—	EtOAc[b]	38	132–134	1.92	$C_{14}H_{16}N_2O_2$
7	$SO_2C_6H_4F$	—	A	50	169–171[c]	2.02	$C_{17}H_{15}FN_2O_3S$
8	$SO_2CH(CH_3)_2$	—	B	43	136–138[c]	1.20	$C_{14}H_{18}N_2O_3S$
9	$COCH_2CH_3$	COC_6H_5	C	22	286–287	2.72	$C_{16}H_{22}N_2O_2$
10	$COCH_3$	COC_6H_5	C	17	304–305	2.26	$C_{15}H_{20}N_2O_2$
11	$SO_2CH(CH_3)_2$	COC_6H_5	C	20	262–263	2.34	$C_{16}H_{24}N_2O_3S$
12	COC_6H_5	$SO_2C_6H_4F$	C	6	224–225	3.17	$C_{19}H_{21}FN_2O_3S$
13	$COCH_3$	$SO_2C_6H_4F$	C	40	233–234	1.69	$C_{14}H_{19}FN_2O_3S$
14	$COCH_2CH_3$	$SO_2C_6H_4F$	C	23	218–219	2.16	$C_{15}H_{21}FN_2O_3S$
15	$COCH_2CH_3$	$COCH_2CH_3$	C	15	219–220	1.71	$C_{12}H_{22}N_2O_2$
16	$COCH_2CH_3$	$COCH_2CH_3$	—	21	Waxy solid	1.71	$C_{12}H_{22}N_2O_2$
17	$COCH_2CH_3$	$SO_2C_6H_4F$	C	9	Waxy solid	2.16	$C_{15}H_{21}FN_2O_3S$
18	$COCH_3$	$SO_2C_6H_4F$	C	12	Waxy solid	1.69	$C_{14}H_{19}FN_2O_3S$

[a] A: CH_2Cl_2/MeOH 98:2; B: CH_2Cl_2/MeOH/NH_4OH 95:5:0.5; C: CH_2Cl_2/abs.EtOH/NH_4OH/petroleum ether 340:65:8:60.
[b] Al_2O_3 was used as stationary phase.
[c] The compound melts with decomposition.
[d] The Clog*P* value of the tested compounds has been calculated using the program 'OSIRIS Property Explorer' (http://www.organic-chemistry.org/prog/peo/).

Table of elemental analysis of the new compounds

		Calculated %			Found %		
N	formula	C	H	N	C	H	N
5	$C_{13}H_{14}N_2O_2$	67.81	6.13	12.17	68.11	6.34	12.33
6	$C_{14}H_{16}N_2O_2$	68.83	6.60	11.47	68.91	6.76	11.65
7	$C_{17}H_{15}FN_2O_3S$	58.95	4.36	8.09	59.16	4.50	8.32
8	$C_{14}H_{18}N_2O_3S$	57.12	6.16	9.52	57.31	6.28	9.73
9	$C_{16}H_{22}N_2O_2$	70.04	8.08	10.21	70.30	8.40	10.07
10	$C_{15}H_{20}N_2O_2$	69.20	7.74	10.76	69.41	7.58	10.62
11	$C_{16}H_{24}N_2O_3S$	59.23	7.46	8.63	59.42	7.32	8.51
12	$C_{19}H_{21}FN_2O_3S$	60.62	5.62	7.44	60.45	5.44	7.19
13	$C_{14}H_{19}FN_2O_3S$	53.49	6.09	8.91	53.21	6.34	8.74
14	$C_{15}H_{21}FN_2O_3S$	54.86	6.45	8.53	54.99	6.22	8.24
15	$C_{12}H_{22}N_2O_2$	63.68	9.80	12.38	63.57	9.58	12.15
16	$C_{12}H_{22}N_2O_2$	63.68	9.80	12.38	63.42	9.96	12.53
17	$C_{15}H_{21}FN_2O_3S$	54.86	6.45	8.53	54.98	6.58	8.69
18	$C_{14}H_{19}FN_2O_3S$	53.49	6.09	8.91	53.25	6.25	8.75
19	$C_{15}H_{17}FN_2O_4S_2$	48.37	4.60	7.52	48.52	4.35	7.31
20	$C_{16}H_{18}N_2O_3S$	60.36	5.70	8.80	60.15	5.48	9.07
21	$C_{19}H_{15}FN_2O_3S$	61.61	4.08	7.56	61.42	4.36	7.41
22	$C_{15}H_{15}FN_2O_3S$	55.89	4.69	8.69	55.58	4.42	8.65
23	$C_{12}H_{18}N_2O_3S$	53.31	6.71	10.36	53.24	6.87	10.19
24	$C_{15}H_{14}N_2O_2$	70.85	5.55	11.02	70.96	5.62	11.35
25	$C_{11}H_{16}N_2O_3S$	51.54	6.29	10.93	51.69	6.56	10.69
26	$C_{14}H_{13}FN_2O_3S$	54.54	4.25	9.09	54.63	4.46	9.35
27	$C_{16}H_{19}FN_2O_4S_2$	49.73	4.96	7.25	49.55	5.04	7.54
28	$C_{17}H_{20}N_2O_3S$	61.42	6.06	8.43	61.26	6.42	8.24
29	$C_{17}H_{20}N_2O_3S$	61.42	6.06	8.43	61.65	6.36	8.32
30	$C_{18}H_{22}N_2O_3S$	62.40	6.40	8.09	62.56	6.21	8.41
31	$C_{17}H_{21}FN_2O_4S_2$	50.98	5.29	6.99	50.68	5.63	7.32
32	$C_{16}H_{19}FN_2O_4S_2$	49.73	4.96	7.25	49.36	4.59	6.98
33	$C_{12}H_{11}FN_2O_2S$	54.12	4.16	10.52	54.36	4.25	10.24
34	$C_{13}H_{12}N_2O$	73.56	5.70	13.20	73.72	5.85	13.32
35	$C_9H_{12}N_2O$	65.83	7.37	17.06	65.99	7.54	17.21
36	$C_{13}H_{13}FN_2O_2S$	55.70	4.67	9.99	55.42	4.85	10.08
37	$C_{14}H_{14}N_2O$	74.31	6.24	12.38	74.62	6.42	12.55
38	$C_{18}H_{21}FN_2O_4S$	56.83	5.56	7.36	57.06	5.71	7.52

90 standardized, Merck). Yields are given after purification, unless stated otherwise. Where analyses are indicated by symbols, the analytical results are within 0.4% of the theoretical values. When reactions were performed under anhydrous conditions, the mixtures were maintained under nitrogen.

5.1.1. General procedure for the synthesis of compounds 5–8

To a solution of 1,2,3,4-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one[21] (1.5 mmol) and anhydrous Et_3N (2 eq) in CH_3CN (10 mL), cooled at 0 °C, the suitable acyl or sulfonyl chloride (1 eq) was added. After 1 h stirring at room T, the mixture was treated with saturated $NaHCO_3$ and extracted with $CHCl_3$. Dehydration (Na_2SO_4) and removal of the solvent gave a residue which was purified by column chromatography. Other experimental details are reported in Table 3; ^1H and ^{13}C NMR spectra are reported in Table 4. Compounds **5** and **6** are mixtures of A + B rotamers.

5.1.2. General procedure for the synthesis of cyclohexane derivatives 9–18[22]

To a solution of *trans*-1,4-cyclohexanediamine (2.5 mmol) and sodium acetate (2.19 eq) in water (15 mL), the suitable anhydride (acetic or propionic), benzoyl or sulfonyl chloride (1.2 eq) in dioxane (10 mL) was added, and the mixture was heated at 70 °C until appearance of the intermediate monoamide (t.l.c.). Solid Na_2CO_3 (4 eq) and benzoyl chloride or *p*-fluorobenzenesulfonyl chloride (1.1 eq) were then added, and the mixture heated at 70 °C for 0.5–3 h. After cooling, the mixture was acidified (HCl 1 N) and extracted with ethyl acetate; the organic phase was washed with saturated Na_2CO_3 and dehydrated (Na_2SO_4), the solvent was removed under low pressure to yield a residue which was purified by flash chromatography. The synthesis of the *cis* derivatives **16**–**18** was carried out with the same procedure, except that the first step was run at RT. Compounds **15** and **16** derive from the double attack of propionic anhydride on both amine groups. Other experimental details are reported in Table 3; ^1H and ^{13}C NMR spectra are reported in Table 4.

5.1.3. *N*-(4-aminophenyl)-4-fluorobenzenesulfonamide (33)

A mixture of 4-nitroaniline (1 g, 7.24 mmol, 1 eq), dimethylaminopyridine (DMAP, 0.1 eq) and *p*-F-benzenesulfonyl chloride (1 eq) in anhydrous pyridine (70 mL) was heated at 80 °C for 5 h. After cooling, the mixture was treated with ether, washed twice with a saturated solution of $CuSO_4$ and then with brine; dehydration (Na_2SO_4) and removal of the solvent gave a yellow solid (mp 142 °C, 90% yield). ^1H NMR (DMSO d_6, δ): 7.32 (d, 2H, J = 9.2 Hz); 7.41–7.47 (m, 2H); 7.91–7.96 (m, 2H); 8.14 (d, 2H, J = 9.2 Hz)

Table 4
NMR spectra of compounds **5**–**18**

N	^{1}H NMR (δ)	^{13}C NMR[a] (δ)
5[b,c]	2.19–2.30 (m, 4H, CH_3 + 1H, H-1ax$_B$); 2.55–2.62 (m, 1H, H-3ax$_A$); 2.76–2.82 (m, 1H, H-1ax$_A$); 3.09–3.25 (m, 3H, H-3ax$_B$ + H-4ax$_A$ + H-4ax$_B$); 3.88–3.95 (m, 1H, H-3eq$_B$); 4.33–4.36 (m, 1H, H-1eq$_A$); 4.43–4.51 (m, 4H, H-10b$_{A,B}$ + H-4eq$_{A,B}$,); 4.79–4.83 (m, 1H, H-3eq$_A$); 5.29 (dd, 1H, J = 12.8 Hz, 2.9 Hz, H-1eq$_B$); 7.50–7.57 (m, 3H) and 7.89–7.91 (m, 1H) (A+B aromatic protons) ppm	21.78 (CH_3); 39.17 (C-4$_A$); 39.63 (C-4$_B$); 41.37 (C-3$_A$); 46.09 (C-3$_B$); 46.58 (C-1$_B$); 51.44 (C-1$_A$); 57.13 (C-10b$_B$); 57.57 (C-10b$_A$); 122.03 (CH_A); 122.42 (CH_B); 124.01 (CH_B); 124.25 (CH_A); 128.93 (CH_B); 129.19 (CH_A); 131.78 (CH_B); 132.44 (CH_A); 132.84 (C-10a$_B$); 134.09 (C-10a$_A$); 141.23 (C-6a$_A$); 141.98 (C-6a$_B$); 166.15 (C-11$_A$); 166.42 (C-11$_B$); 169.03 (C-6$_A$); 169.35 (C-6$_B$) ppm
6[b,c]	1.03–1.18 (m, 4H, CH_3 + 1H, H-1ax$_B$); 2.38–2.50 (m, 3H, CH_2CH3 + H-3ax$_A$); 2.64 (t, 1H, J = 11.2 Hz, H-1ax$_A$); 2.94–3.13 (m, 3H, H-3ax$_B$ + H-4ax$_{A,B}$); 3.90 (d, 1H, J = 12.8 Hz, H-3eq$_B$); 4.32–4.38 (m, 5H, H-1eq$_A$ + H-10b$_{A,B}$ + H-4eq$_{A,B}$); 4.70 (d, 1H, J = 12.2 Hz, H-3eq$_A$); 5.18 (d, 1H, J = 12.5 Hz, H-1eq$_B$); 7.41–7.43 (m, 2H), 7.48–7.50 (m, 1H) and 7.77 (s, 1H) (aromatic protons) ppm	9.38 (CH_3); 26.65 (CH_2CH_{3A}); 26.83 (CH_2CH_{3B}); 39.19 (C-4$_A$); 39.64 (C-4$_B$); 41.46 (C-3$_A$); 45.08 (C-3$_B$); 46.68 (C-1$_B$); 50.42 (C-1$_A$); 57.19 (C-10b$_B$); 57.60 (C-10b$_A$); 122.38, 123.85, 128.81 and 131.69 (aromatic CH); 132.36 (C-10a$_B$); 132.72 (C-10a$_A$); 141.34 (C-6a$_A$); 142.02 (C-6a$_B$); 166.13 (C-11$_A$); 166.34 (C-11$_B$); 172.40 (C-6$_A$); 172.72 (C-6$_B$) ppm
7[b]	1.89–1.94 (m, 1H, H-1ax); 2.28 (td, 1H, J = 11.8 Hz, 3.7 Hz, H-3ax); 3.37 (td, 1H, J = 12.7 Hz, 4.0 Hz, H-4ax); 3.89 (td, 1H, J = 11.6 Hz, 3.8 Hz, H-3eq); 4.36–4.40 (m, 1H, H-1eq); 4.46 (dd, 1H, J = 13.4 Hz, 3.3 Hz, H-4eq); 4.64 (dd, 1H, J = 10.8 Hz, 4.1 Hz, H-10b); 7.19 (t, J = 8.4 Hz, 2H), 7.50 (t, J = 7.2 Hz, 2H), 7.55.7.59 (m, 1H), 7.75–7.78 (m, 2H) and 7.83 (d, J = 7.2 Hz, 1H) (aromatic protons) ppm	38.66 (C-4); 45.73 (C-3); 50.80 (C-1); 56.88 (C-10b); 116.69 (CH, J_{C-F} = 22.6 Hz); 122.32 (CH); 124.15 (CH); 129.20 (CH); 130.23 (CH, J_{C-F} = 9.0 Hz); 131.80, 132.47 and 141.37 (quat. C); 165.41 (CF, J_{C-F} = 256.1 Hz); 165.99 (C-6) ppm
8[b]	1.37 (d, 6H, J = 6.8 Hz, 2CH_3);2.55 (dd, 1H, J = 12.4 Hz, 10.8 Hz, H-1ax); 2.91 (td, 1H, J = 24.8 Hz, 3.5 Hz, H-3ax); 3.21–3.36 (m, 2H, CH + H-4ax); 3.92 (dd, 1H, J = 12.8 Hz, 3.8 Hz, H-3eq); 4.38–4.47 (m, 2H, H-4eq + H-1eq); 4.59 (dd, 1H, J = 10.7 Hz, 4.2 Hz, H-10b); 7.47–7.60 (m, 3H) and 7.88 (d, J = 7.4 Hz, 1H) (aromatic protons) ppm	16.70 (CH_3); 39.96 (C-4); 46.08 (C-3); 51.31 (C-1); 54.08 ($CHSO_2$); 57.81 (C-10b); 122.31, 124.12, 129.11 and 131.74 (aromatic CH); 132.57 (quat. C); 141.43 (quat. C); 166.24 (C-6) ppm
9[d]	0.98 (t, 3H, CH_3CH_2, J = 7.2 Hz); 1.20–1.44 (m, 4H, cyclohexane); 1.80–1.89 (m, 4H, cyclohexane); 2.04 (q, 2H, CH_2CH_3, J = 7.2 Hz); 3.46–3.52 (m, 1H, cyclohexane); 3.67- 3.79 (m, 1H, cyclohexane); 7.42–7.50 (m, 3H); 7.65 (d, 1H, NH, J = 7.2 Hz); 7.81–7.83 (m, 2H); 8.21 (d, 1H, NH, J = 7.2 Hz) ppm	10.47 (CH_3); 29.01 (CH_2); 31.48 and 31.80 (cyclohexane CH_2); 47.45 and 48.23 (CH); 127.69, 128.60 and 131.44 (aromatic CH); 135.23 (quat. C); 165.95 and 172.45 (CO) ppm
10[d]	1.22–1.25 (m, 2H, cyclohexane); 1.38–1.44 (m, 2H, cyclohexane); 1.77–1.82 (m, 7H, CH_3 + 4H cyclohexane); 3.39–3.53 (m, 1H, cyclohexane); 3.68–3.81 (m, 1H, cyclohexane); 7.44–7.50 (m, 3H); 7.75–7.83 (m, 3H, 2H aromatics + NH); 8.22 (d, 1H, NH, J = 6.4 Hz) ppm	23.22 (CH_3); 31.46 and 31.78 (cyclohexane CH_2); 47.55 and 48.21 (CH); 127.70, 128.60 and 131.44 (aromatic CH); 135.21 (quat. C); 165.95 and 168.69 (CO) ppm
11[d]	1.22 (d, 6H, 2CH_3, J = 6.8 Hz); 1.38–1.50 (m, 4H, cyclohexane); 1.83–1.92 (m, 4H, cyclohexane); 3.05–3.10 (m, 1H, cyclohexane); 3.14 (sept, 1H, J = 6.8 Hz); 3.60–3.70 (m, 1H, cyclohexane); 6.99 (d, 1H, NH, J = 8.0 Hz); 7.42–7.52 (m, 3H); 7.81–7.85 (m, 2H); 8.20 (d, 1H, NH, J = 8.0 Hz) ppm	16.91 (CH_3); 31.49 and 33.41 (CH_2); 48.01 and 52.51 (aliphatic CH); 127.71, 128.61 and 131.46 (aromatic CH), 135.21 (quat. C), 165.93 (CO) ppm
12[d]	1.15–1.32 (m, 4H, cyclohexane); 1.67–1.76 (m, 4H, cyclohexane); 2.89–2.91 (m, 1H, cyclohexane); 3.63–3.65 (m, 1H, cyclohexane); 7.41–7.51 (m, 5H); 7.66–7.79 (m, 3H, 2H aromatics + NH); 7.83–7.88 (m, 2H); 8.13 (d, 1H, NH, J = 7.8 Hz) ppm	31.19 and 32.50 (CH_2); 47.81 and 52.28 (CH); 116.89 (CH, J_{C-F} = 22 Hz); 127.67, 128.60 and 131.44 (benzoyl CH); 129.68 (CH, J_{C-F} = 10 Hz); 135.18 (quat. C); 155.57 (CF, J_{C-F} = 253 Hz); 165.99 (CO) ppm
13[d]	1.05–1.23 (m, 4H, cyclohexane); 1.49–1.68 (m, 4H, cyclohexane); 1.72 (s, 3H, CH_3); 2.55–2.93 (m, 1H, cyclohexane); 3.27–3.43 (m, 1H, cyclohexane); 7.38–7.45 (m, 2H); 7.62–7.78 (m, 2H, 1H aromatic + NH); 7.81–7.92 (m, 2H, 1H aromatic + NH) ppm	23.15 (CH_3); 31.27 and 32.32 (cyclohexane CH_2); 47.05 and 52.09 (cyclohexane CH); 116.76 (CH, J_{C-F} = 22 Hz); 129.64 (CH, J_{C-F} = 9 Hz); 139.03 (CSO_2); 164.37 (CF, J_{C-F} = 248 Hz); 168.66 (CO) ppm
14[d]	0.93 (t, 3H, CH_3CH_2, J = 7.6 Hz); 1.01–1.23 (m, 4H, cyclohexane); 1.58–1.68 (m, 4H, cyclohexane); 1.98 (q, 2H, CH_2CH_3, J = 7.6 Hz); 2.83–2.95 (m, 1H, cyclohexane); 3.29–3.41 (m,1H, cyclohexane); 7.43 (t, 2H,, J = 8.8 Hz); 7.55 (d, 1H, NH, J = 4.0 Hz); 7.73(d, 1H, NH, J = 4.0 Hz); 7.85–7.88 (m, 2H) ppm	10.40 (CH_3); 28.92 (CH_2); 31.29 and 32.34 (cyclohexane CH_2); 46.94 and 52.13 (CH); 116.76 (CH, J_{C-F} = 23 Hz); 129.65 (CH, J_{C-F} = 10 Hz); 139.04 (CSO_2); 164.37 (CF, J_{C-F} = 249 Hz); 172.41 (CO) ppm
15[d]	0.96 (t, 6H, J = 7.6 Hz, 2CH_3CH_2); 1.15–1.21 (m, 4H, cyclohexane); 1.74–1.76 (m, 4H, cyclohexane); 2.02 (q, 4H, 2CH_2CH_3, J = 7.6 Hz); 3.39–3.47 (m, 2H, cyclohexane); 7.61 (d, 2H, NH, J = 7.6 Hz) ppm	10.46 (CH_3); 29.00 (CH_2); 31.64 (cyclohexane CH_2); 47.37 (CH); 172.42 (CO) ppm
16[b]	1.16 (t, 6H, 2CH_3CH_2, J = 8.0 Hz); 1.51–1.61 (m, 4H, cyclohexane); 1.73–1.82 (m, 4H, cyclohexane); 2.20 (q, 4H, 2CH_2CH_3, J = 8.0 Hz); 3.86–3.99 (m, 2H, cyclohexane); 5.42–5.51 (m, 2H, NH) ppm	
17[e]	1.09 (t, 3H, CH_3CH_2, J = 7.6 Hz); 1.50–1.64 (m, 8H, cyclohexane); 2.17 (q, 2H, CH_2CH_3, J = 7.6 Hz); 3.14–3.20 (m, 1H, cyclohexane); 3.61–3.69 (m, 1H, cyclohexane); 7.26–7.32 (m, 2H); 7.89–7.94 (m, 2H) ppm	9.23 (CH_3); 26.99, 27.03, 28.77, 28.84 and 28.87 (CH_2); 46.15 and 49.45 (CH_2); 115.76 (CH, J_{C-F} = 23 Hz); 129.49 (CH, J_{C-F} = 10 Hz); 137.53 (C-SO_2), 164.9 (C–F, J_{C-F} = 251 Hz), 174.99 (CO) ppm
18[e]	1.50–1.63 (m, 8H, cyclohexane); 1.91 (s, 3H, CH_3); 3.12–3.20 (m, 1H, cyclohexane); 3.61–3.70 (m, 1H, cyclohexane); 7.29 (t, 2H, J = 6.8 Hz); 7.90–7.94 (m, 2H) ppm	21.23 (CH_3); 26.99 and 28.82 (CH_2); 46.29 and 49.48 (CH); 115.75 (CH, J_{C-F} = 22 Hz), 129.39 (CH, J_{C-F} = 10 Hz), 137.58, 164.92 (C–F, J_{C-F} = 251 Hz); 171.17 (CO) ppm

[a] APT ^{13}C NMR.
[b] $CDCl_3$.
[c] Mixture of 30:70 A + B rotamers.
[d] DMSO d_6.
[e] MeOD d_4.

ppm. The compound was used as such in the next step: it was solubilized (1.2 g, 1 eq) in hot glacial acetic acid (10 mL) and treated with iron powder (16 eq). The mixture was heated at 90 °C for 2 h, and then filtered when still hot. Removal of the solvent under vacuum gave a residue which was purified by flash chromatography ($CHCl_3$/petroleum ether/abs. EtOH/NH_4OH 340:60:65:8 as eluent) obtaining the title compound as white solid. Mp 141 °C. Yield: 35%. ^{1}H NMR (DMSO d_6, δ): 4.99 (br s, 2H, NH_2); 6.39 (d, 2H, J = 6.8 Hz); 6.66 (d, 2H, J = 6.8 Hz); 7.34–7.38 (m, 2H); 7.66–7.69 (m, 2H) ppm. Anal. ($C_{12}H_{11}FN_2O_2S$) (C, H, N).

5.1.4. General procedure for the synthesis of compounds 34, 35, 37

A mixture of 4-nitroaniline or *N*-methyl-4-nitroaniline (7 mmol), the acyl or benzoyl chloride (1.05 eq) and potassium carbonate (2 eq) in anhydrous THF (20 mL) was kept stirring for 12 h at RT. The mixture was acidified with HCl 10% and extracted with CH_2Cl_2; anhydrification (Na_2SO_4) and removal of the solvent gave a residue, which was solubilized in ethyl acetate and hydrogenated at 50 psi over Pd 10%/C for 24 h, then the catalyst was filtered off, and the solvent was removed under vacuum giving the desired compounds.

Table 5
Experimental details for the synthesis of compounds **19–31** (see structures in Scheme 3) and *C*log*P* values

N	R	R^1	R^2	Eluent[a]	Yield%	Mp (°C)	*C*log*P*[b]	Anal.
19	H	$SO_2C_6H_4F$	$SO_2CH(CH_3)_2$	A	60	227–229	1.96	$C_{15}H_{17}FN_2O_4S_2$
20	H	COC_6H_5	$SO_2CH(CH_3)_2$	A	17	166	2.64	$C_{16}H_{18}N_2O_3S$
21	H	COC_6H_5	$SO_2C_6H_4F$	A	55	250–252	3.47	$C_{19}H_{15}FN_2O_3S$
22	H	$COCH_2CH_3$	$SO_2C_6H_4F$	A	28	174–175	2.45	$C_{19}H_{15}FN_2O_3S$
23	H	$COCH_2CH_3$	$SO_2CH(CH_3)_2$	A	34	168	1.63	$C_{12}H_{18}N_2O_3S$
24	H	$COCH_3$	COC_6H_5	A	29	175	2.67	$C_{15}H_{14}N_2O_2$
25	H	$COCH_3$	$SO_2CH(CH_3)_2$	A	60	200–202	1.17	$C_{11}H_{16}N_2O_3S$
26	H	$COCH_3$	$SO_2C_6H_4F$	A	65	180–182	1.99	$C_{14}H_{13}FN_2O_3S$
27	CH_3	$SO_2C_6H_4F$	$SO_2CH(CH_3)_2$	B	22	144–145	2.02	$C_{16}H_{19}FN_2O_4S_2$
28	CH_3	COC_6H_5	$SO_2CH(CH_3)_2$	A	24	149–150	3.07	$C_{17}H_{20}N_2O_3S$
29	H	COC_6H_5	$SO_2CH(CH_3)_2$	C	29	135–137	2.70	$C_{17}H_{20}N_2O_3S$
30	CH_3	COC_6H_5	$SO_2CH(CH_3)_2$	D	80	144	3.12	$C_{18}H_{22}N_2O_3S$
31	CH_3	$SO_2C_6H_4F$	$SO_2CH(CH_3)_2$	E	38	135–136	2.07	$C_{17}H_{21}FN_2O_4S_2$

[a] A: cyclohexane/ethyl acetate 50:50; B: $CH_2Cl_2/CH_3OH/NH_4OH$ 98:2:0.2; C: CH_2Cl_2/abs.EtOH/NH_4OH/petroleum ether/Et_2O/toluene 12:6:0.3:29.7:12:40 as eluent; D: cyclohexane/ethyl acetate 60:40; E: CH_2Cl_2/abs.EtOH/NH_4OH/petroleum ether 340:65:8:60 as eluent.
[b] The *C*log*P* value of the tested compounds has been calculated using the program 'OSIRIS Property Explorer' (http://www.organic-chemistry.org/prog/peo/).

34: oil, yields: 84% ^{1}H NMR (DMSO d_6, δ) 6.70 (d, 2H, J = 8.4 Hz); 7.41–7.56 (m, 5H); 7.75 (br s, 1H, NH); 7.86 (d, 2H, J = 8.4 Hz) ppm. Anal. ($C_{13}H_{12}N_2O$) C, H, N.

35: oil, yields: 90% ^{1}H NMR (DMSO d_6, δ) 1.18 (t, 3H, J = 7.6 Hz); 2.30 (q, 2H, J = 7.6 Hz); 6.58 (d, 2H, J = 8.8 Hz); 7.24 (d, 2H, J = 8.8 Hz); 7.7 (br s, 1H, NH) ppm. Anal. ($C_9H_{12}N_2O$) C, H, N.

37 Mp 122 °C. Yields: 90% after purification with flash chromatography (cyclohexane/ethyl acetate 6:4 as eluent) ^{1}H NMR (DMSO d_6, δ) 3.26 (s, 3H); 5.08 (br s, 2H, NH_2);6.38 (d, 2H, J = 8.4 Hz); 6.77 (d, 2H, J = 8.4 Hz);7.20–7.22 (m, 5H) ppm. Anal. ($C_{14}H_{14}N_2O$) C, H, N.

5.1.5. *N*-Methyl-*N*-(4-aminophenyl)-4-fluorobenzenesulfonamide (36)

N-Methyl-4-nitroaniline (2 g, 13.15 mmol, 1 eq) was dissolved in anhydrous THF (25 mL), then *p*-F-benzenesulfonyl chloride (1 eq) and anhydrous pyridine (2 eq) were added and the mixture heated at 60 °C for 24 h. After cooling, the mixture was acidified with HCl 10% and extracted with ethyl acetate; dehydration (Na_2SO_4) and removal of the solvent gave a residue, which was purified with flash chromatography (CH_2Cl_2/abs.EtOH/NH_4OH/petroleum ether/Et_2O/toluene 12.6:3.1:0.2:31.5:12.6:40 as eluent) leaving *N*-methyl-*N*-(4-nitrophenyl)-4-fluorobenzenesulfonamide (mp 144 °C, 65% yield). ^{1}H NMR ($CDCl_3$, δ): 3.25 (s, 3H); 7.15 (t, 2H, J = 8.8 Hz); 7.35 (d, 2H, J = 9.2 Hz); 7.55–7.60 (m, 2H); 8.21 (d, 2H, J = 9.2 Hz) ppm. This compound (2.65 g, 8.55 mol) was solubilized in methanol (35 mL), and iron powder (1.39 g) and glacial acetic acid (2.85 mL) were added. The mixture was left stirring at RT until completion (t.l.c.), then the solvent was removed under vacuum, the residue was partitioned between H_2O and ethyl acetate, the organic phase was collected and washed with satd $NaHCO_3$. Dehydration (Na_2SO_4) and removal of the solvent gave the title compound (FEB18) as white solid. Mp 180 °C. Yield: 71%. ^{1}H NMR ($CDCl_3$, δ): 3.13 (s, 3H); 6.57 (d, 2H, J = 8.4 Hz); 6.83 (d, 2H, J = 8.4 Hz); 7.11–7.18 (m, 2H); 7.57–7.61 (m, 2H) ppm. Anal. ($C_{13}H_{13}FN_2O_2S$) C, H, N.

5.1.6. General procedure for the synthesis of benzene derivatives 19–28

To a solution of the suitable aniline (**33–37** or commercially-available *N*-(4-aminophenyl)acetamide, 2.5 mmol) and anhydrous pyridine (2 eq) in anhydrous THF (15 mL), the suitable acyl or sulfonyl chloride (1 eq) was added at 0 °C. The mixture was allowed to warm to RT and heated under reflux for 8 h under stirring. After cooling, the mixture was treated with 10% HCl and extracted with ethyl acetate; the organic phase was washed with H_2O, dehydrated (Na_2SO_4) and then the solvent was removed under vacuum. Flash chromatography gave the desired compound. Other experimental details are reported in Table 5; ^{1}H and ^{13}C NMR spectra are reported in Table 6.

5.1.7. Synthesis of compounds 29–31

To a solution of the suitable secondary amide (0.25 mmol) (**27** or **28**) in anhydrous THF (5 mL), *t*-BuOK (1 eq) and CH_3I (10 eq) were added, and the mixture was stirred at RT under N_2 atmosphere. When the reaction was performed on compound 20, 0.8 eq of CH_3I was used, and the mixture was heated at 60 °C for 18 h. The mixture was then treated with 2 N HCl and extracted three times with ethyl acetate; dehydration (Na_2SO_4) and removal of the solvent under vacuum gave the desired compound. Other experimental details are reported in Table 5; [^{1}H] and [^{13}C] NMR are reported in Table 6.

5.1.8. *tert*-Butyl 4-(*p*-fluorophenylsulfonamido)phenyl-(methyl)carbamate (38)

A solution of $(BOC)_2O$ (3.2 g, 14.46 mmol, 1.1 eq) and DMAP (0.07 g, 0.04 eq) in anhydrous THF (12 mL) was added dropwise at 0 °C to a solution of *N*-methyl-4-nitro-aniline (2 g, 13.14 mmol, 1 eq) in anhydrous THF (12 mL). The mixture was allowed to warm to RT and then stirred for 48 h under N_2 atmosphere. After cooling, the mixture was treated with a 1 M aqueous solution of citric acid (20 mL) and extracted three times with ethyl acetate; the organic phase was washed with brine. Dehydration (Na_2SO_4) and removal of the solvent gave *tert*-butyl methyl-(4-nitrophenyl)carbamate[24] in 90% yield. ^{1}H NMR ($CDCl_3$) δ: 1.46 (s, 9H); 3.30 (s, 3H); 7.42 (d, 2H, J = 9.2 Hz); 8.13 (d, 2H, J = 9.2 Hz) ppm. This compound (3.3 g, 13.21 mmol) was dissolved in ethyl acetate (65 mL) and hydrogenated at 50 psi over Pd 10%/C (0.64 g) for 24 h. The mixture was filtered, the solvent was removed, and the residue was purified by flash chromatography (CH_2Cl_2/abs.EtOH/NH_4OH/petroleum ether 340:65:8:60 as eluent) giving *tert*-butyl 4-aminophenyl(methyl)carbamate in 77% yield. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9 H); 3.19 (s, 3H); 3.87 (br s, 2H); 6.67 (d, 2H, J = 8.4 Hz); 6.99 (d, 2H, J = 8.4 Hz) ppm. The compound (2.27 g, 10.22 mmol, 1 eq) was dissolved in the minimum amount of THF, anhydrous pyridine (1.65 mL, 2 eq) and *p*-fluoro-benzensulfonyl chloride (2.2 g, 1.1 eq) were added, and the mixture was stirred at RT for 12 h and at 60 °C for 3 h under N_2 atmosphere. The mixture was partitioned between H_2O and ethyl acetate; the organic phase was collected and dried (Na_2SO_4), Removal of the solvent gave the title compound in 94% yield. Mp 168 °C. ^{1}H NMR ($CDCl_3$) δ: 1.44 (s, 9H); 3.20 (s, 3H); 6.99–7.01 (m, 2H); 7.07–7.12 (m, 4H); 7.76–7.79 (m, 2H) ppm. Anal. ($C_{18}H_{21}FN_2O_4S$) C, H, N.

5.1.9. 4-Fluoro-*N*-(4-(*N*-methylpropan-2-ylsulfonamido)-phenyl)-benzenesulfonamide (32)

A mixture of compound **38** (3.65 g, 9.60 mmol, 1 eq), dissolved in ethyl acetate (15 mL), and 2 N HCl (10.48 mL, 1 eq) was left stirring at RT until disappearance of the starting material (t.l.c.). Water was added, the aqueous phase was washed with ethyl acetate, then

Table 6
NMR spectra of compounds **19**–**31**

N	^{1}H NMR (δ)	^{13}C NMR[a] (δ)
19[b]	1.18 (d, J = 8.0 Hz, 6H, 2CH_3); 3.13 (sept, 1H, J = 8.0 Hz, CH); 7.07 (d, 2H, J = 6.8 Hz); 7.10 (d, 2H, J = 6.8 Hz); 7.35–7.40 (m, 2H); 7.74–7.78 (m, 2H); 9.64 (br s, 1H, NH); 10.14 (br s, 1H, NH) ppm	16.58 (CH_3); 51.95 (CH); 116.8 (CH, J_{C-F} = 23 Hz); 121.11 (CH); 122.69 (CH); 130.20 (CH, J_{C-F} = 9 Hz); 133.59, 135.74 and 136.25 (quat. C); 164.73 (C–F, J_{C-F} = 250 Hz) ppm
20[b]	1.24 (d, J = 8.0 Hz, 6H, 2CH_3); 3.19 (sept, 1H, J = 8.0 Hz, CH); 7.21 (t, 2H, J = 8.0 Hz); 7.51–7.60 (m, 3H); 7.70–7.73 (m, 2H); 7.94 (d, J = 8.0 Hz, 2H) ppm	16.11 (CH_3); 52.14 (CH); 120.28, 121.35, 127.55, 128.32 and 131.47 (aromatic CH) 133.83, 134.07 and 135.23 quat. C); 165.32 (CO) ppm
21[b]	7.05 (d, J = 8.0 Hz, 2H); 7.39 (t, J = 8.8 Hz, 2H); 7.49–7.64 (m, 5H); 7.76–7.82 (m, 2H); 7.90 (d, J = 8.4 Hz, 2H) ppm	116.89 (CH, J_{C-F} = 22 Hz); 121.54 (CH); 121.64 (CH); 121.96 (CH); 128.03 (CH); 128.86 (CH); 130.25 (CH, J_{C-F} = 9 Hz); 133.17, 135.19, 135.24 and 136.45 (quat. C); 163.75 (CH, J_{C-F} = 250 Hz); 165.91 (CO) ppm
22[b]	1.10 (t, J = 8.0 Hz, 3H, *CH_3*CH_2); 2.26 (q, J = 8.0 Hz, 2H, *CH_2*CH_3); 6.98 (d, J = 8.0 Hz, 2H); 7.35–7.45 (m, 4H); 7.73–7.76 (m, 2H); 9.79 (br s, 1H, NH); 10.06 (br s, 1H, NH) ppm	10.1 (CH_3); 29.87 (CH_2); 116.80 (CH, J_{C-F} = 23 Hz), 120.17, 122.31, 130.18 and 132.50 (J_{C-F} = 9 Hz) (aromatic CH); 136.22, 136.25 and 136.83 (quat. C); 164.69 (CF, J_{C-F} = 250 Hz); 172.26 (CO) ppm
23[b]	1.07 (t, J = 7.6 Hz, 3H, *CH_3*CH_2); 1.22 (d, J = 6.8 Hz, 6H, 2CH_3); 2.28 (q, J = 7.6 Hz, 2H, *CH_2*CH_3); 3.15 (sept, J = 6.8 Hz, 1H, CH); 7.14 (d, J = 8.0 Hz, 2H); 7.51 (d, J = 8.0 Hz, 2H) 9.56 (br s, 1H, NH); 9.81 (br s, 1H, NH) ppm	10.15 (CH_3); 16.60 (CH_3); 29.87 (*CH_2*); 51.49 (CH); 120.42 and 121.11 (aromatic CH); 133.79 and 136.09 (quat. C) 172.21 (CO) ppm
24[b]	2.03 (s, 3H, CH_3); 7.50–7.58 (m, 5H); 7.68 (d, 2H, J = 8.0 Hz); 7.94 (d, 2H, J = 8.0 Hz); 9.91 (br s, 1H, NH); 10.18 (br s, 1H, NH) ppm	24.38 (CH_3); 119.65, 121.28, 128.03, 128.83 and 131.90 (aromatic CH); 134.79, 135.46 and 135.70 (quat. C); 165.69 and 168.46 (CO) ppm
25[b]	1.22 (d, 6H, 2CH_3, J = 6.8 Hz); 2.01 (s, 3H, CH_3); 3.15 (sept, 1H, CH, J = 6.8 Hz,); 7.11–7.16 (m, 2H); 7.48–7.51 (m, 2H); 9.55 (br s, 1H, NH); 9.89 (br s, 1H, NH) ppm	16.61 (CH_3); 24.31 (CH_3); 51.51 (CH); 120.4 and 121.12 (aromatic CH); 133.7 and 136.1 (quat. C); 168.5 (CO) ppm
26[b]	1.98 (s, 3H, CH_3); 6.97 (d, 2H, J = 8.0 Hz); 7.35–7.43 (m, 4H); 7.73–7.76 (m, 2H); 9.85 (br s, 1H, NH); 10.06 (br s, 1H, NH) ppm.	24.31 (CH_3); 116.80 (J_{C-F} = 22 Hz), 120.16, 122.36 and 130.17 (J_{C-F} = 9 Hz) (aromatic CH); 132.62, 136.25 and 136.75 (quat. C); 164.69 (CF, J_{C-F} = 250.0 Hz); 168.55 (CO) ppm.
27[c]	1.39 (d, 6H, 2CH_3, J = 6.8 Hz); 3.14 (s, 3H, CH_3); 3.31 (sept, 1H, CH, J = 6.8 Hz); 7.03 (d, 2H, J = 8.8 Hz); 7.12–7.21 (m, 4H); 7.38 (br s, 1H); 7.55–7.59 (m, 2H) ppm	16.50 (CH_3); 38.20 (CH_3); 53.02 (CH); 116.16 (J_{C-F} = 23 Hz), 120.14, 127.87 and 130.49 (J_{C-F} = 10 Hz) (aromatic CH); 132.45, 136.80 and 137.51 (quat. C); 165.27 (CF, J_{C-F} = 254 Hz) ppm
28[b]	1.18 (d, 6H, 2CH_3, J = 6.4 Hz); 3.16 (sept, 1H, CH, J = 6.4 Hz); 3.33 (s, 3H, CH_3); 7.09–7.12 (m, 4H); 7.18–7.30 (m, 5H); 9.75 (br s, 1H, NH) ppm	16.58 (CH_3); 35.45 (CH_3); 52.25 (CH); 120.14, 128.13, 128.52, 128.59 and 129.74 (aromatic CH) 136.77, 137.34 and 140.46 (quat. C); 169.96 (CO) ppm
29[d]	1.36 (d, 6H, J = 7.2 Hz); 3.38 (s, 3H); 3.42 (sept, 1H, J = 7.2 Hz); 7.44–7.49 (m, 2H); 7.52–7.55 (m, 2H); 7.59–7.63 (m, 1H); 7.76 (d, 2H, J = 8.8 Hz); 7.95 (d, 2H, J = 8.8 Hz) ppm	15.72, 43.61, 50.40, 121.31, 126.64, 126.96, 127.23, 128.25, 131.58, 152.05 ppm
30[b]	1.15 (d, 6H, J = 6.8 Hz); 3.23 (s, 3H), 3.33 (s, 3H); 3.37 (sept, 1H, J = 6.8 Hz); 7.17–7.34 (m, 9H) ppm	16.99, 38.22, 38.69, 52.56, 126.02, 127.95, 128.17, 128.64, 129.89, 136.62, 140.38, 140.76, 169.93 ppm
31[c]	1.36 (d, 6H, J = 6.8 Hz); 3.16 (s, 3H); 3.31 (sept, 1H, J = 6.8 Hz); 3.38 (s, 3H); 7.09–7.17 (m, 4H); 7.35 (d, 2H, J = 9.2 Hz); 7.56–7.58 (m, 2H) ppm	16.77, 38.04, 39.15, 53.02, 116.17 (d, J = 23.0 Hz), 126.96, 127.26, 130.46 (d, J = 10.0 Hz), 132.90, 139.38, 140.95, 165.28 (d, J = 256 Hz) ppm

[a] APT ^{13}C NMR.
[b] DMSO $d_{6,8}$.
[c] $CDCl_3$.
[d] CD_3OD.

it was made alkaline with 10% NaOH and extracted three times with ethyl acetate. Dehydration (Na_2SO_4) and removal of the solvent gave *p*-fluoro-*N*-(4-(methylamino)phenyl)benzenesulfonamide in 40% yield. ^{1}H NMR ($CDCl_3$) δ: 2.75 (s, 3H); 3.53–3.82 (m, 1 H); 6.43 (d, 2H, J = 8.8 Hz); 6.85 (d, 2H, J = 8.8 Hz); 7.05 (t, 3H, J = 8.4 Hz); 7.68–7.72 (m, 2H) ppm. This compound was used as such for the following step: it was dissolved (1.08 g, 3.86 mmol, 1 eq) in the minimum amount of anhydrous THF, treated with anydrous pyridine (0.63 mL, 2 eq) and *i*-propylsulfonyl chloride (1.5 eq, 0.64 mL), and the mixture was left stirring at RT for 12 h. The same work-up reported for compounds **19**–**28** gave a residue which was purified by flash chromatography (CH_2Cl_2/abs.EtOH/NH_4OH/petroleum ether/Et_2O 360:180:9.9:900:360 as eluent). The title compound was further crystallized from *i*-propanol, yielding a white solid mp 52–54 °C (19% yield). ^{1}H NMR ($CDCl_3$) δ: 1.35 (d, 6H, J = 7.2 Hz); 3.29 (sept, 1H, J = 7.2 Hz); 3.31 (s, 3H); 7.07–7.16 (m, 4H); 7.27–7.30 (m, 2H); 7.47 (br s, 1H); 7.81–7.85 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$) δ: 16.76, 39.35, 52.95, 116.44 (d, J = 23 Hz), 122.31, 127.01, 130.02 (d, J = 10 Hz), 155.05 (d, J = 251 Hz) ppm. Anal. ($C_{16}H_{19}FN_2O_4S_2$) C, H, N. This compound was unstable: after some time, the compound transformed into a tarry solid.

5.2. Pharmacology

5.2.1. Passive-avoidance test

The test was performed according to the step-through method described by Jarvik and Kopp.[25] The apparatus consists of a two-compartment acrylic box with a lighted compartment connected to a darkened one by a guillotine door. In the original method, mice received a punishing electrical shock as soon as they entered the dark compartment, while in our modified method, after entry into the dark compartment, mice receive a non-painful punishment consisting of a fall (from 40 cm) into a cold water bath (10 °C). For this purpose the dark chamber was constructed with a pitfall floor. Mice receive the punishment when entering the dark room in the training session and remember it in the session on the following day, unless their memory is impaired by the amnesic drug. Mice who did not enter after 60 s latency in the training session were excluded from the experiment; about 20–30% of mice was excluded from each group. For memory disruption, mice were injected with the amnesic drugs (scopolamine, **13** or **14**). All investigated drugs were injected ip, in a 1:10 dilution sequence, 20 min before the training session; amnesic drugs were injected immediately after termination of the training session. Saline and saline/DMSO treated mice received an additional injection of saline immediately after the training session as control of scopolamine injection. The maximum entry latency allowed in the retention session was 180 s. The degree of received punishment memory (fall into cold water) was expressed as the difference in seconds between training and retention latencies. Piracetam and compounds **1**, **2a** and **3** were used as the reference drugs.

All compounds were dissolved in saline, except compounds **27**–**31**, which were dissolved into a mixture of water/DMSO 4:1.

All compounds elicited their effect without changing either gross behavior or motor coordination, as revealed by the rota-rod test (data not shown). None of the drugs, at the active doses, increased the number of falls from the rotating rod in comparison with saline-treated mice. The number of falls in the rota-rod test

progressively decreased since mice learned how to balance on the rotating rod. The spontaneous motility and inspection activity of mice was unmodified by the administration of the studied compounds as revealed by the hole-board test in comparison with saline-treated mice (data not shown).

5.2.2. Rota-rod test

The apparatus consisted of a base platform and a rotating rod with a diameter of 3 cm and a non-slippery surface. The rod was placed at a height of 15 cm from the base. The rod, 30 cm in length, was divided into five equal sections by six disks. Thus, up to five mice were tested simultaneously on the apparatus, with a rod-rotating speed of 16 rpm. The integrity of motor coordination was assessed on the basis of the number of falls from the rod in 30 s according to Vaught et al.[28] Those mice scoring less than 3 and more than 6 falls in the pretest were rejected (20%). The performance time was measured before (pretest) and 15, 30 and 45 min after the beginning of the test.

5.2.3. Hole-board test

The hole-board test consisted of a 40 cm square plane with 16 flush mounted cylindrical holes (3 cm diameter) distributed 4 by 4 in an equidistant, grid-like manner. Mice were placed on the center of the board one by one and allowed to move about freely for a period of 10 min each. Two electric eyes, crossing the plane from mid-point to mid-point of opposite sides, thus dividing the plane into four equal quadrants, automatically signaled the movement of the animal (counts in 5 min) on the surface of the plane (spontaneous motility). Miniature photoelectric cells, in each of the 16 holes, recorded (counts in 5 min) the exploration of the holes (exploratory activity) by the mice.

5.2.4. Statistical analysis

All experimental results are given as means ± SEM. Analysis of variance (ANOVA), followed by Fisher's protected least significant difference (PLSD) procedure for post hoc comparison, was used to verify significance between two means. Data were analysed with the StatView software for the Macintosh (1992). *P* values of less than 0.05 were considered significant.

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