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Design, synthesis and nootropic activity of new analogues of sunifiram and sapunifiram, two potent cognition-enhancers

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ABSTRACT

A series of amides and sulfonamides, structurally related to DM235 (sunifiram) and MN19 (sapunifiram), derived by ring expansion or contraction, or by inversion of the exocyclic amide function, 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, and with a potency similar to the parent compounds.

1. Introduction

Nootropics, or cognition-enhancers, are compounds able to stimulate cognitive processes acting through several different mechanisms, such as the modulation of signal transduction cascade (receptors or secondary messengers) or neurogenesis.[1] These compounds can 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.[2–6]

Piracetam (Chart 1) is a well-known nootropic drug. Piracetam and piracetam-like compounds have been studied 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.[7] 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) have been shown to modulate receptor systems such as the cholinergic and/or glutamatergic ones.[8,9] Recently, the neurogenic activity of piracetam and other nootropics on human stem cells has been claimed.[10]

It has previously been reported that DM232 (Chart 1, Unifiram, **1**) and DM235 (Chart 1, sunifiram, **2a**) show potent cognition-enhancing properties. DM232 shares some structural similarity with piracetam (the 2-oxopyrrolidine ring) but Unifiram, as well as its analog sunifiram, are four orders of magnitude more potent than piracetam.[11,12] Sapunifiram (Chart 1, MN19, **3**) is a close analog of DM235, which shows a potency similar to that of the parent compounds in several behavioural tests.[13,14] These compounds are well tolerated in rodents, but their development has been impaired because their mechanism of action has not been clarified.[14] In fact, unifiram and sunifiram did not show any affinity towards the most important central receptors or transporters.[12] These compounds are able to increase acetylcholine release from rat brain,[12] and nitric oxide production in rat adipocytes, the latter effect being antagonized by nicotinic antagonists such as mecamylamine and methyllycaconitine;[15] there is evidence that AMPA receptors are involved in the cognition-enhancing effect of these compounds.[16] However, a direct interaction of unifiram and sunifiram with nicotinic or AMPA receptors in vitro has not been proven yet.

In a continuing effort to find new potent analogues of unifiram and sunifiram, and to collect information to clarify the mechanism

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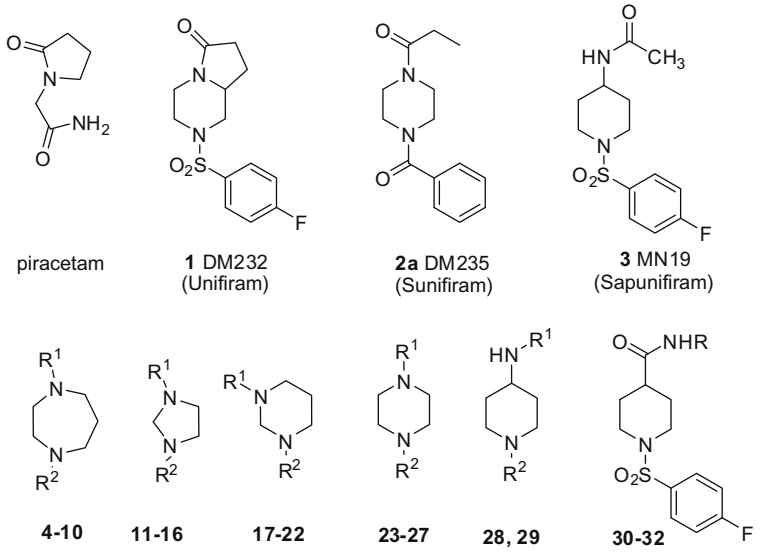


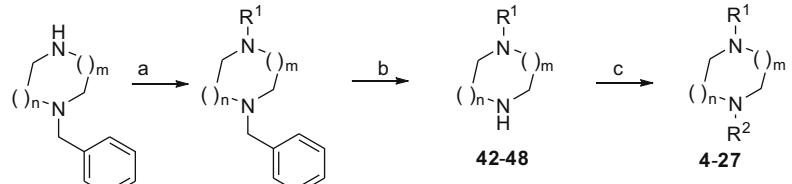
Chart 1.

of action of these substances, we made further structural modifications on the lead molecules DM235 and MN19. Therefore, compounds **4–22** (Chart 1) were designed, in which (a) the piperazine cycle of DM235 has been expanded into a seven-membered ring (homopiperazines **4–10**) or contracted into a five-membered ring (imidazolidines **11–16**); or (b) the amidic nitrogen atoms have been shifted from 1–4 into 1–3 position (hexahydropyrimidines **17–22**). To verify the importance of the presence and position of an aromatic ring, compounds **23–29** were designed, where the aromatic ring has been spaced from the carbonyl amide of DM235 by an oxygen (**23**) or a nitrogen (**24**) atom or by a methylene group (**25**), or where the aromatic benzoyl or *p*-fluorobenzenesulfonyl moieties have been replaced by a small acyl (acetyl or propionyl) group; the latter modification has been performed on both DM235, giving compounds **26** and **27**, and on MN19, obtaining **28** and **29**. Finally, compounds **30–32** have been prepared in order to verify the effect of the inversion of the amide moiety of MN19.

2. Chemistry

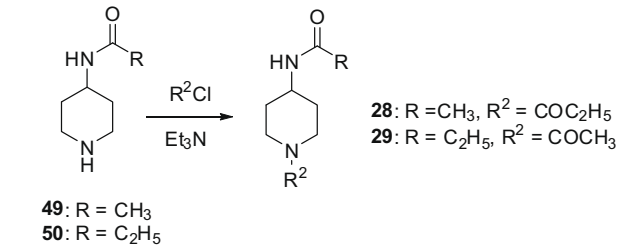
Compounds **4–27** were prepared according to Scheme 1. Commercially-available *N*-benzyl-homopiperazine **33** was treated with acetyl or propionyl chloride to give compound **36** and **37**, which were hydrogenated to **42** and **43**, and reacted with phenylacetyl, 4-fluorobenzenesulfonyl, benzoyl or isopropylsulfonyl chloride to give compounds **4–10**. The same sequence of reactions was performed on *N*-benzyl-imidazolidine **34** and *N*-benzyl-hexahydropyrimidines **35** (prepared according to literature methods[17,18]) and gave compounds **11–16** and **17–22**, respectively. Treatment of *N*-propionylpiperazine **48**[12] with phenyl chloroformiate, phenyl isocyanate or phenylacetyl chloride gave, respectively, the carbamate **23**, urea **24** or amide **25**. Reaction of commercially-available *N*-acetylpiperazine and **48** with propionyl chloride gave, respectively, compounds **26** and **27**.

The piperidine derivatives **28** and **29** (scheme 2) were prepared by treatment of *N*-(piperidin-4-yl)acetamide **49**[13] with propionyl

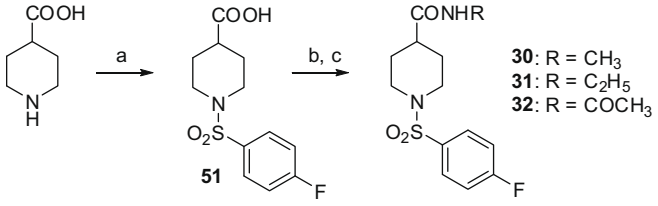


N	n	m	R1
36,42	2	1	CH_3CO
37, 43	2	1	C_2H_5CO
38, 44	1	0	CH_3CO
39, 45	1	0	C_2H_5CO
40, 46	2	0	CH_3CO
41, 47	2	0	C_2H_5CO
48	1	1	C_2H_5CO

Scheme 1. Reagents: (a) CH_3COCl or C_2H_5COCl, Et_3N; (b) H_2/Pd/C; (c) R_2Cl, Et_3N (PhNCO for compound **24**).



Scheme 2.



Scheme 3. Reagents: (a) 4-F-$C_6H_4SO_2Cl$, Et_3N; (b) $SOCl_2$; (c) $MeNH_2$ or $EtNH_2$, or MeCONHNa.

chloride or by acetylation of *N*-(piperidin-4-yl)propionamide **50**.[13] Reaction of commercially-available piperidine-4-carboxylic acid (Scheme 3) with 4-fluorobenzenesulfonyl chloride gave compound **51**,[19] which was reacted with thionyl chloride and then treated with methylamine, ethylamine or with sodium acetylamide, obtaining, respectively, amides **30** and **31**, and imide **32**.

3. Pharmacology

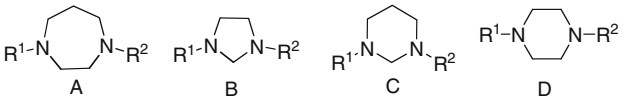
The compounds were tested for their ability to revert scopolamine-induced amnesia in the mouse passive-avoidance test of Jarvik and Kopp,[20] slightly modified by us (see Section 5). The compounds were dissolved in saline and tested in a 1:10 dilution sequence, up to the dose of 10 mg/kg; the results are expressed as the Minimal Effective Dose (MED, mg/kg) and are reported in Tables 1 and 2, in comparison with reference compounds **2a** and **3**, and with piperazines **2b**–**2f**, previously synthesized by us.[12,21] 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**. To further evaluate the procognitive properties of the most active nootropic compounds (**4–9** and **30**), these agents were tested in the passive-avoidance test without the addition of scopolamine.

The results are reported in Table 3.

4. Results and discussion

The ability of the compounds to revert scopolamine-induced amnesia is reported in Tables 1 and 2, expressed as the Minimal Effective Dose (MED). The most interesting compounds are

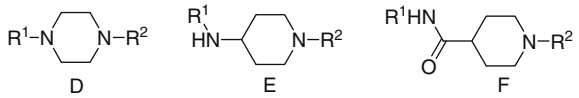
Table 1
Minimal effective dose (MED) of the compounds **4–22** against scopolamine-induced amnesia in the mouse passive-avoidance test, in comparison with reference compounds piracetam, **2a–f** and **3**



Treatment	Structure	R^1	R^2	MED (mg/kg)	Training session	Retention session	Δ
Saline					17.8 ± 2.3	96.6 ± 7.7	78.8
S					15.8 ± 3.0	44.3 ± 7.9^	28.5
Piracetam	—	—	—	30	17.6 ± 3.6	108.8 ± 10.4**	91.2
2a DM235 [a]	D	COC_2H_5	COPh	0.001	20.5 ± 3.4	91.5 ± 8.0**	71.0
2b[a]	D	COC_2H_5	$SO_2C_6H_4F$	0.01	15.9 ± 3.2	90.6 ± 8.2**	74.7
2c[b]	D	COC_2H_5	$SO_2C_3H_7$	1.0	13.7 ± 3.9	88.9 ± 10.3*	75.2
2d[a]	D	$COCH_3$	$SO_2C_6H_4F$	0.01	19.8 ± 4.1	89.0 ± 18.3*	69.2
2e[a]	D	$COCH_3$	COPh	10	11.3 ± 5.3	119.0 ± 11.2**	107.7
2f[b]	D	$COCH_3$	$SO_2C_3H_7$	0.1	13.8 ± 3.6	87.1 ± 9.6*	73.3
4	A	$COCH_3$	$COCH_2Ph$	0.01	15.7 ± 3.5	75.1 ± 7.3*	59.4
5	A	$COCH_3$	$SO_2C_6H_4F$	1.0	22.5 ± 3.6	109.7 ± 8.1**	87.2
6	A	$COCH_3$	COPh	0.01	17.3 ± 3.6	77.2 ± 8.4*	59.9
7	A	$COCH_3$	$SO_2C_3H_7$	n.a.	—	—	—
8	A	COC_2H_5	$SO_2C_6H_4F$	1.0	18.8 ± 3.5	99.4 ± 7.1**	80.6
9	A	COC_2H_5	COPh	0.1	16.2 ± 2.6	88.1 ± 7.3**	71.9
10	A	COC_2H_5	$SO_2C_3H_7$	n.a.	—	—	—
11	B	$COCH_3$	$SO_2C_6H_4F$	1.0	18.5 ± 3.5	105.4 ± 7.2**	86.9
12	B	$COCH_3$	COPh	1.0	16.4 ± 3.5	73.4 ± 8.2**	57.0
13	B	$COCH_3$	$SO_2C_3H_7$	10	15.3 ± 2.9	61.3 ± 6.7*	46.0
14	B	COC_2H_5	$SO_2C_6H_4F$	1.0	19.0 ± 3.2	81.6 ± 8.6**	62.6
15	B	COC_2H_5	COPh	1.0	19.0 ± 3.3	79.4 ± 8.5**	60.4
16	B	COC_2H_5	$SO_2C_3H_7$	n.a.	—	—	—
17	C	$COCH_3$	$SO_2C_6H_4F$	1.0	19.1 ± 4.4	92.9 ± 10.6**	73.8
18	C	$COCH_3$	COPh	1.0	18.1 ± 4.2	83.5 ± 9.8**	65.4
19	C	$COCH_3$	$SO_2C_3H_7$	1.0	15.5 ± 4.2	71.8 ± 9.4**	56.3
20	C	COC_2H_5	$SO_2C_6H_4F$	1.0	18.9 ± 4.8	77.5 ± 9.5**	58.6
21	C	COC_2H_5	COPh	1.0	16.2 ± 4.3	92.4 ± 9.0**	76.2
22	C	COC_2H_5	$SO_2C_3H_7$	n.a.	—	—	—

All drugs were administered ip 20 min before training session. Each value represents the mean of 12–22 mice. Scopolamine (S, 1.5 mg/kg ip) was injected immediately after punishment. *P <0.05, **P <0.01 in comparison with scopolamine-treated mice. ^P <0.01 in comparison with saline-treated mice.
n.a.: Not active.
[a] From Ref. 12.
[b] From Ref. 21.

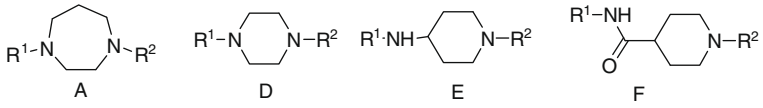
Table 2
Minimal effective dose (MED) of compounds **23–32** against scopolamine-induced amnesia in the mouse passive-avoidance test, in comparison with reference compounds piracetam, **2a** and **3**



N	Structure	R^1	R^2	MED (mg/kg)	Training session	Retention session	Δ
Saline					17.8 ± 2.3	96.6 ± 7.7	78.8
S					15.8 ± 3.0	44.3 ± 7.9^	28.5
Piracetam				30	17.6 ± 3.6	108.8 ± 10.4**	91.2
2a DM235[a]	D	COC_2H_5	COPh	0.001	20.5 ± 3.4	91.5 ± 8.0**	71.0
3 MN19[b]	E	$COCH_3$	$SO_2C_6H_4F$	0.01	14.5 ± 3.8	90.6 ± 12.5**	76.1
23	D	COC_2H_5	COOPh	10	15.0 ± 3.5	86.8 ± 7.6**	71.8
24	D	COC_2H_5	CONHPh	n.a.	—	—	—
25	D	COC_2H_5	$COCH_2Ph$	1	17.5 ± 3.3	81.2 ± 9.3**	63.7
26	D	$COCH_3$	COC_2H_5	10	12.8 ± 4.1	88.3 ± 9.2**	75.5
27	D	COC_2H_5	COC_2H_5	n.a.	—	—	—
28	E	$COCH_3$	COC_2H_5	n.a.	—	—	—
29	E	COC_2H_5	$COCH_3$	10	16.2 ± 2.7	85.7 ± 8.4**	69.5
30	F	CH_3	$SO_2C_6H_4F$	0.1	16.3 ± 2.6	89.4 ± 9.5**	73.1
31	F	C_2H_5	$SO_2C_6H_4F$	1	19.0 ± 3.7	91.3 ± 8.7**	72.3
32	F	$COCH_3$	$SO_2C_6H_4F$	1	15.3 ± 2.1	86.3 ± 6.9**	71.0

All compounds were dissolved in saline and injected ip 20 min before training session. Each value represent the mean of 10–19 mice. Scopolamine (S, 1.5 mg/kg ip) was injected immediately after punishment. *P <0.05, **P <0.01 in comparison with scopolamine-treated mice. ^P <0.01 in comparison with saline-treated mice.
n.a.: Not active.
[a] From Ref. 12.
[b] From Ref. 13.

Table 3
Procognitive effect of the compounds in the mouse passive-avoidance test, in comparison with reference substances **2a** and **3**



N	Structure	R^1	R^2	MED (mg/kg)	Training session	Retention session	Δ
Saline					23.8 ± 2.6	97.8 ± 8.2	74.0
2a DM235[a]	D	COC_2H_5	COPh	0.01	18.1 ± 2.7	126.7 ± 7.7^	108.6
3 MN19[a]	E	$COCH_3$	$SO_2C_6H_4F$	0.1	19.1 ± 2.9	126.8 ± 6.4*	107.7
4	A	$COCH_3$	$COCH_2Ph$	1.0	19.3 ± 7.7	141.5 ± 24.7^	122.2
5	A	$COCH_3$	$SO_2C_6H_4F$	10	27.6 ± 4.7	159.3 ± 14.0^	131.7
6	A	$COCH_3$	COPh	1.0	18.9 ± 3.8	135.6 ± 13.6^	116.7
8	A	COC_2H_5	$SO_2C_6H_4F$	10	31.3 ± 6.4	157.0 ± 14.8^	125.7
9	A	COC_2H_5	COPh	1.0	32.2 ± 3.7	139.5 ± 12.1*	107.3
30	F	CH_3	$SO_2C_6H_4F$	1.0	18.6 ± 3.7	159.2 ± 9.7*	140.6

All compounds were dissolved in saline and injected ip 20 min before training session. Each value represent the mean of 7–10 mice. ^P <0.05; *P <0.01 in comparison with mice treated with saline.
[a] From Ref. 23.

homopiperazines (Table 1): they show cognition-enhancing activity with a MED between 0.01 and 1.0 mg/kg, apart from the isopropylsolfonyl derivatives **7** and **10** which are not active up to a dose of 10 mg/kg. Compound **6** is only one order of magnitude less active than the lead analog **2a**. A comparison between homopiperazines **4–10** and piperazines **2a**–**2f**[12,21] shows that the same combination of substituents give different results on the two series: for instance, the 4-fluorobenzenesolfonyl group gives compounds (**2b** and **2d**) active at MED of 0.01 mg/kg in the piperazine series, but its introduction on the homopiperazine nucleus give compounds **5** and **8** which are active at doses 2 orders of magnitude higher (MED 1.0 mg/kg). On the contrary, the presence of the acetyl and benzoyl groups on the piperazine scaffold give compound **2e** which is 1000-fold less potent than its homopiperazine analogue **6**. This lack of correlation between analogous substitutions on different scaffolds, which has been already noticed on other compounds of this class,[22,23] can have several explanations. Ring enlargement increases the conformational flexibility of the heterocyclic scaffold, thus allowing different modes of interaction with the biological target. In addition, biological tests are performed in vivo, a situation where potency results from a combination of pharmacokinetic and pharmacodynamic properties, which may be differently affected by structural modification. The hypothesis that different biological targets are involved seems less probable since the two classes of substances are structurally very close, but it cannot be ruled out, as long as the mechanism of action has not been elucidated.

Imidazolidines **11–16** and hexahydropyrimidines **17–22** are generally less potent that the corresponding homopiperazines and piperazines: they show MED 2–3 orders of magnitude higher than their analogues **4–10** and **2a**–**2f**, although they are 30 times more potent than piracetam.[14] As for the homopiperazines, the introduction of an isopropyl-sulfonyl group generally gives compounds which are not active (**16**, **22**) or less active (**13**); only compound **19** has a potency comparable to the other derivatives. This finding suggests that the two amidic functions must be spaced by 2–3 carbon atoms, as in piperazines, homopiperazines and

4-aminopiperidine derivatives, to have high potency. In the imidazolidines and hexahydropyrimidines series, this distance (1 carbon atom) may be too short to allow an optimal interaction with the target. A similar drop in potency has already been noticed in the 3-aminopiperidine series,[22] whose activity in the passive-avoidance test was 2–3 orders of magnitude lower than the lead compounds **1** and **2a**.

The data reported in Table 2 show that the presence of an aromatic moiety is important for high potency on both piperazine and 4-aminopiperidine derivatives. In fact, compounds **26–29**, carrying only acetyl and propionyl groups are inactive (**27**, **28**) or much less active (**26**, **29**) than compounds **2a** and **3**. In addition, the spacing of the aryl group from the amidic function by an oxygen, amino or methylene units gives compounds **23–25**, which are much less active than **2a**, suggesting that the aromatic moiety must be directly linked to the amidic function to achieve optimal potency. The inversion of the exocyclic amidic function of MN19 gives compound **30**, which is one order of magnitude less potent than the parent compound. However, homologation of the *N*-alkyl group to give **31** or introduction of a second carbonyl group to give **32** further reduces activity.

The most active compounds in reverting scopolamine-induced amnesia were retested for their procognitive properties in the mouse passive-avoidance test but without the addition of scopolamine (Table 3). Under conditions where memory has not been pharmacologically impaired, the compounds show minimal effective doses one or two orders of magnitude greater than those recorded in scopolamine-treated mice. Such behavior has been already noticed for other analogs of **1** and **2a**.[23]

In conclusion, we have synthesized a series of analogs of DM235 showing different sizes of the heterocyclic scaffold, among which the homopiperazine derivatives maintain good nootropic activity, thus representing a promising new class of cognition-enhancers. In addition, we have shown that the presence of an aromatic ring, directly linked to the carbonyl group, is important for high potency, and that the inversion of the exocyclic amidic function on **3** gives only a small decrease of potency. We hope that these compounds may give useful information for structure–activity relationships in the class of nootropic drugs, and possibly be useful 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 column chromatography (Kieselgel 40, 0.063–0.200 mm; Merck) or flash chromatography (Kieselgel 40, 0.040–0.063 mm; 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 introduction of an acyl or sulfonyl moiety

To a solution of the amine (1.5 mmol) and anhydrous Et_3N (1.5 equiv) in $CHCl_3$ or CH_3CN (10 mL), cooled at 0 °C, the suitable acyl or sulfonyl chloride (1.2 equiv), or PhNCO for compound **24**, was added. The mixture was left stirring at rt (unless otherwise stated), then it was treated with saturated $NaHCO_3$ and extracted with $CHCl_3$. Dehydration (Na_2SO_4) and removal of the solvent gave

Table 4
Experimental details for the synthesis of compounds **35–40**, **4–29**

N	Amine	Reactant (solvent)	Time (h)	Yields (%)	Purification eluent
36	33	CH_3COCl ($CHCl_3$)	24	99	—
37	33	C_2H_5COCl ($CHCl_3$)	24	81	—
38	34[17]	CH_3COCl ($CHCl_3$)	12	29	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/Pet. ether 45:2.5:180:180:450
39	34[17]	C_2H_5COCl ($CHCl_3$)	12	29	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/Pet. ether 45:2.5:180:180:450
40	35[18]	CH_3COCl ($CHCl_3$)	12	50	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/Pet. Ether 45:2.5:180:180:450
41	35[18]	C_2H_5COCl ($CHCl_3$)	12	50	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/Pet. Ether 45:2.5:180:180:450
4	42	$PhCH_2COCl$ ($CHCl_3$)	2	91	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/Pet. ether 180: 9.9: 360: 360: 900
5	42	4-F-$C_6H_4SO_2Cl$ ($CHCl_3$)	1.5	76	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/Pet. ether 180: 9.9: 360: 360: 900
6	42	C_6H_5COCl ($CHCl_3$)	24	99	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/Pet. ether 180: 9.9: 360: 360: 900
7	42	*i*-$C_3H_7SO_2Cl$ ($CHCl_3$)	3 (60 °C)	46	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/Pet. ether 180: 9.9: 360: 360: 900
8	43	4-F-$C_6H_4SO_2Cl$ ($CHCl_3$)	1	66	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/Pet. ether 180: 9.9: 360: 360: 900
9	43	C_6H_5COCl ($CHCl_3$)	1	64	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/Pet. ether 180: 9.9: 360: 360: 900
10	43	*i*-$C_3H_7SO_2Cl$ ($CHCl_3$)	4 (60 °C)	25	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/Pet. ether 180: 9.9: 360: 360: 900
11	44	4-F-$C_6H_4SO_2Cl$ ($CHCl_3$)	3 (60 °C)	12	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/Pet. ether 180: 9.9: 360: 360: 900
12	44	C_6H_5COCl ($CHCl_3$)	1.5	14	$CHCl_3$/CH_3OH 96: 4
13	44	*i*-$C_3H_7SO_2Cl$ ($CHCl_3$)	1 (60 °C)	10	$CHCl_3$/CH_3OH 95: 5
14	45	4-F-$C_6H_4SO_2Cl$ ($CHCl_3$)	1 (60 °C)	20	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/Pet. ether 180: 9.9: 360: 360: 900
15	45	C_6H_5COCl ($CHCl_3$)	1	18	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/Pet. ether 180: 9.9: 360: 360: 900
16	45	*i*-$C_3H_7SO_2Cl$ ($CHCl_3$)	1 (60 °C)	28	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/Pet. ether 180: 9.9: 360: 360: 900
17	46	4-F-$C_6H_4SO_2Cl$ ($CHCl_3$)	12	39	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/Pet. ether 180: 9.9: 360: 360: 900
18	46	C_6H_5COCl ($CHCl_3$)	12	48	$CHCl_3$/CH_3OH 96: 4
19	46	*i*-$C_3H_7SO_2Cl$ ($CHCl_3$)	1.5 (60 °C)	9	$CHCl_3$/CH_3OH 96: 4
20	47	4-F-$C_6H_4SO_2Cl$ ($CHCl_3$)	12	99	$CHCl_3$/CH_3OH 95: 5
21	47	C_6H_5COCl ($CHCl_3$)	12	44	CH_2Cl_2/CH_3OH 97: 3
22	47	*i*-$C_3H_7SO_2Cl$ ($CHCl_3$)	12 (60 °C)	12	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/Pet. ether 180: 9.9: 360: 360: 900
23	48[12]	PhOCOCl ($CHCl_3$)	12	90	AcOEt
24	48[12]	PhNCO ($CHCl_3$)	12	95	—
25	48[12]	$PhCH_2COCl$ ($CHCl_3$)	12 (0 °C)	47	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/Pet. ether 180: 9.9: 360: 360: 900
26	*N*-Acetyl-piperazine	C_2H_5COCl (CH_3CN)	4	81	—
27	48[12]	C_2H_5COCl (CH_3CN)	24	76	—
28	49[13]	C_2H_5COCl (CH_3CN)	18	68	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O 65: 8: 340: 60
29	50[13]	CH_3COCl (CH_3CN)	18	62	abs EtOH/NH_4OH/CH_2Cl_2/Et_2O 65: 8: 340: 60

a residue which was used as such for the following step, or purified by column chromatography if necessary. Other experimental details are reported in Table 4. By this way compounds **36–41** and **4–29** were prepared; their NMR spectra show the presence of rotamers.

5.1.1.1. 1-(3-Benzyl-[1,4]diazepan-1-yl)ethanone 36. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.76–1.81 (m, 2H, $CH_2CH_2CH_2$); 2.00 (s, 42%) and 2.02 (s, 58%) (3H, $COCH_3$); 2.53–2.60 (m, 4H, CH_2N); 3.38–3.52 (m, 2H, CH_2N); 3.35–3.57 (m, 4H, NCH_2Ph and CH_2N); 7.14–7.25 (m, 5H, aromatic protons) ppm.

5.1.1.2. 1-(3-Benzyl-[1,4]diazepan-1-yl)propan-1-one 37. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.09–1.16 (m, 3H, CH_2CH_3); 1.77–1.86 (m, 2H, $CH_2CH_2CH_2$); 2.25–2.33 (m, 2H, CH_2CH_3); 2.56–2.64 (m, 4H, CH_2N); 3.43–3.49 (m, 2H, CH_2N); 3.58–3.62 (m, 4H, CH_2Ph and CH_2N); 7.20–7.28 (m, 5H, aromatic protons) ppm.

5.1.1.3. 1-(3-Benzylimidazolidin-1-yl)ethanone 38. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.99 (s, 43%) and 2.07 (s, 57%) (3H, $COCH_3$); 2.91 (t, J = 6.4 Hz, 57%) and 2.97 (t, J = 6.4 Hz, 43%) (2H, CH_2N); 3.54–3.59 (m, 2H, CH_2N); 3.69 (s, 43%) and 3.70 (s, 57%) (2H, CH_2Ph); 4.05 (s, 43%) and 4.14 (s, 57%) (2H, NCH_2N); 7.27–7.36 (m, 5H, aromatic protons) ppm.

5.1.1.4. 1-(3-Benzylimidazolidin-1-yl)propan-1-one 39. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.01–1.09 (m, 3H, CH_2CH_3); 2.03 (q, J = 7.6 Hz, 45%) and 2.12 (q, J = 7.6 Hz, 55%) (2H, CH_2CH_3); 2.71 (t, J = 6.4 Hz, 45%) and 2.78 (t, J = 6.4 Hz, 55%) (2H, CH_2N); 3.36 (t, J = 6.4 Hz, 55%) and 3.43 (t, J = 6.4 Hz, 45%) (2H, CH_2N); 3.52 (s, 55%) and 3.54 (s, 45%) (2H, CH_2Ph); 3.89 (s, 45%) and 4.00 (s, 55%) (2H, NCH_2N); 7.12–7.20 (m, 5H, aromatic protons) ppm.

5.1.1.5. 1-(3-Benzyltetrahydropyrimidin-1-yl)ethanone 40. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.67–1.73 (m, 2H, $-CH_2CH_2CH_2$); 1.92 (s, 65%) and 2.14 (s, 35%) (3H, $COCH_3$); 2.71 (t, J = 5.6 Hz, 35%) and 2.80 (t, J = 5.6 Hz, 65%) (2H, CH_2N); 3.52 (t, J = 5.6 Hz, 35% of 2H, CH_2N); 3.61–3.65 (m, 65% of 2H, CH_2N, + 2H, CH_2Ph); 4.00 (s, 65%) and 4.32 (s, 35%) (2H, NCH_2N); 7.28–7.37 (m, 5H, aromatic protons) ppm.

5.1.1.6. 1-(3-Benzyltetrahydropyrimidin-1-yl)propan-1-one 41. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.05 (t, J = 7.6 Hz, 60%) and 1.16 (t, J = 7.6 Hz, 40%) (3H, CH_2CH_3); 1.64–1.68 (m, 2H, $CH_2CH_2CH_2$); 2.14 (q, J = 7.6 Hz, 60%) and 2.34–2.40 (m, J = 7.6 Hz, 40%) (2H, CH_2CH_3); 2.67–2.76 (m, 2H, NCH_2); 3.45–3.64 (m, 4H, $CH_2N + CH_2Ph$); 3.99 (s, 60%) and 4.30 (s, 40%) (2H, NCH_2N); 7.26–7.34 (m, 5H, aromatic protons) ppm.

5.1.1.7. 1-(4-Acetyl-[1,4]diazepan-1-yl)-2-phenylethanone 4. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.55–1.68 (m, 1H) and 1.81–1.90 (m, 1H) ($CH_2CH_2CH_2$); 2.01–2.04 (m, 3H, $COCH_3$); 3.33–3.40 (m, 2H, CH_2N); 3.43–3.55 (m, 4H, CH_2N); 3.62–3.71 (m, 4H, CH_2N and $COCH_2Ph$); 7.18–7.30 (m, 5H, aromatic protons) ppm. ^{13}C NMR ($CDCl_3$) δ: 20.91, 21.11, 21.64, 25.21, 26.71, 27.19, 28.05, 40.58, 40.97, 41.18, 41.65, 43.81, 44.62, 45.20, 45.34, 46.05, 46.82, 47.07, 47.37, 47.72, 48.06, 48.81, 48.91, 50.06, 50.34, 126.87, 126.98, 127.15, 128.39, 128.60, 128.64, 128.74, 128.80, 129.04, 134.77, 134.98, 170.24, 170.41, 170.92 ppm. Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 68.90; H, 7.68; N, 10.92.

5.1.1.8. 1-[4-(4-Fluorobenzenesulfonyl)-[1,4]diazepan-1-yl]ethanone 5. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.89–1.92 (m, 2H, $CH_2CH_2CH_2$); 2.00 (s, 3H, $COCH_3$); 3.18–3.33 (m, 4H, CH_2N); 3.50–3.57 (m, 3H, CH_2N); 3.63–3.65 (m, 1H, CH_2N); 7.12–7.17 (m, 2H) and 7.73–7.76 (m, 2H) (aromatic protons) ppm. ^{13}C NMR ($CDCl_3$) δ: 21.07, 21.51, 27.61, 28.72, 44.34, 47.12, 47.51, 48.42, 49.38, 50.08, 50.50, 116.47 (d, J = 25 Hz), 129.53 (d, J = 9.0 Hz), 135.28, 168.25 (d, J = 250.0 Hz), 170.06, 170.22 ppm. Anal. Calcd for $C_{13}H_{17}FN_2O_3S$: C, 51.99; H, 5.71; N, 9.33. Found: C, 52.23; H, 5.87; N, 9.43.

5.1.1.9. 1-(4-Benzoyl-[1,4]diazepan-1-yl)ethanone 6. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.66–1.68 (m, 1H) and 2.01–2.04 (m, 1H) ($CH_2CH_2CH_2$); 2.13 (s, 70%) and 2.16 (s, 30%) (3H, $COCH_3$); 3.33–3.56 (m, 4H, CH_2N); 3.60–3.86 (m, 4H, CH_2N); 7.34–7.40 (m, 5H, aromatic protons) ppm. ^{13}C NMR ($CDCl_3$) δ: 21.03, 21.73, 27.10, 27.66, 43.84, 44.72, 47.06, 47.46, 47.52, 48.91, 49.51, 50.23, 126.20, 126.54, 128.57, 129.59, 129.61, 136.04, 170.21, 170.42 ppm. Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.23; H, 7.64; N, 11.71.

5.1.1.10. 1-[4-(Propane-2-sulfonyl)-[1,4]diazepan-1-yl]ethanone 7. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.33–1.35 (m, 6H, $CH(CH_3)_2$); 1.96–2.01 (m, 2H, $CH_2CH_2CH_2$); 2.11 (s, 37%) and 2.13 (s, 63%) (3H, $COCH_3$); 3.22 (sept., 1H, J = 6.8 Hz, $CHMe_2$); 3.37–3.48 (m, 4H, CH_2N); 3.58–3.70 (m, 4H, CH_2N) ppm. ^{13}C NMR ($CDCl_3$) δ: 16.69, 21.04, 21.59, 28.31, 29.43, 44.51, 47.49, 47.80, 49.05, 49.07, 49.14, 50.35, 50.94, 51.51, 53.17, 53.28, 169.2 ppm. Anal. Calcd for $C_{10}H_{20}N_2O_3S$: C, 48.36, H, 8.12, N, 11.28. Found: C, 48.66; H, 8.35; N, 11.53.

5.1.1.11. 1-[4-(4-Fluorobenzenesulfonyl)-[1,4]diazepan-1-yl]propan-1-one 8. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.09 (t, 3H, J = 7.6 Hz, CH_2CH_3); 1.92–1.95 (m, 2H, $CH_2CH_2CH_2$); 2.26 (q, 2H, J = 7.6 Hz, CH_2CH_3); 3.20–3.33 (m, 4H, CH_2N); 3.53–3.62 (m, 3H, CH_2N); 3.64–3.67 (m, 1H, CH_2N); 7.14–7.19 (m, 2H) and 7.74–7.78 (m, 2H) (aromatic protons) ppm. ^{13}C NMR ($CDCl_3$) δ: 9.36, 26.02, 26.41, 27.65. 28.85, 44.55, 46.58, 47.13, 47.79, 48.44, 49.46, 49.56, 50.24, 116.45 (d, J = 22 Hz), 129.53 (d, J = 9.0 Hz), 135.27, 162.44 (d, J = 266 Hz), 173.50 ppm. Anal. Calcd for $C_{14}H_{19}FN_2O_3S$: C, 53.49; H, 6.09; N, 8.91. Found: C, 53.64; H, 6.34; N, 9.21.

5.1.1.12. 1-(4-Benzoyl-[1,4]diazepan-1-yl)propan-1-one 9. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.11–1.17 (m, 3H, CH_2CH_3); 1.60–1.72 (m, 1H) and 2.01–2.09 (m, 1H) ($CH_2CH_2CH_2$); 2.35–2.50 (m, 2H, CH_2CH_3); 3.35–3.84 (m, 8H, CH_2N); 7.30–7.43 (m, 5H, aromatic protons) ppm. ^{13}C NMR ($CDCl_3$) δ: 9.47, 9.54, 26.04, 26.68, 27.20, 27.81, 43.91, 44.70, 45.39, 46.25, 46.50, 47.14, 47.69, 47.98, 49.61, 50.25, 51.19, 126.17, 126.56, 127.52, 128.56, 129.56, 136.11, 171.85, 173.41, 173.83 ppm. Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.50; H, 7.56; N, 10.64.

5.1.1.13. 1-[4-(Propane-2-sulfonyl)-[1,4]diazepan-1-yl]propan-1-one 10. Mp 92 °C. ^{1}H NMR ($CDCl_3$) δ: 1.16–1.19 (m, 3H, CH_2CH_3); 1.33–1.36 (m, 6H, $C(CH_3)_2$); 1.94–2.02 (m, 2H, $CH_2CH_2CH_2$); 2.32–2.40 (m, 2H,-CH_2CH_3); 3.23 (sept., 1H, J = 6.8 Hz, $CHMe_2$); 3.34–3.48 (m, 4H, CH_2N); 3.58–3.72 (m, 4H, CH_2N) ppm. ^{13}C NMR ($CDCl_3$) δ: 9.36, 9.49, 16.69, 16.71, 26.00, 26.49, 28.36, 29.58, 44.68, 46.59, 47.78, 49.10, 49.25, 50.35, 50.53, 51.09, 53.15, 53.25, 171.00 ppm. Anal. Calcd for $C_{11}H_{22}N_2O_3S$: C, 50.36; H, 8.45; N, 10.68. Found: C, 50.43; H, 8.75; N, 10.31.

5.1.1.14. 1-[3-(4-Fluoro-benzenesulfonyl)-imidazolidin-1-yl]-ethanone 11. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.19 (s, 66%) and 2.02 (s, 34%) (3H, $COCH_3$); 3.38 (t, J = 6.4 Hz, 66%) and 3.45 (t, J = 6.4 Hz, 34%) (2H, CH_2N); 3.52 (t, J = 6.4 Hz, 34%) and 3.64 (t, J = 6.4 Hz, 66%) (2H,CH_2N); 4.71 (s, 34%) and 4.75 (s, 66%) (2H, NCH_2N); 7.23–7.29 (m, 2H) and 7.87–7.89 (m, 2H) (aromatic protons) ppm. ^{13}C NMR ($CDCl_3$) δ: 21.90, 22.30, 43.90, 44.96, 46.14, 47.38, 61.93, 62.24, 117.05 (d, J = 25 Hz), 130.42 (d, J = 9.0 Hz), 132.21, 165.68 (d, J = 240 Hz), 172.43 ppm. Anal. Calcd for $C_{11}H_{13}FN_2O_3S$: C, 48.52; H, 4.81; N, 10.29. Found: C, 48.39; H, 5.12; N, 10.32.

5.1.1.15. 1-(3-Benzoyl-imidazolidin-1-yl)ethanone 12[24]. Oil. (^{1}H) NMR ($CDCl_3$) δ: 2.09 (s, 3H, $COCH_3$); 3.69–3.75 (m, 3H) and 4.08 (br s, 1H) (CH_2N); 4.92 (br s, 1H) and 5.16 (br s, 1H) (NCH_2N); 7.40–7.50 (m, 5H, aromatic protons) ppm. (^{13}C) NMR ($CDCl_3$) δ: 21.99, 22.33, 37.40, 44.50, 63.15, 127.21, 128.64, 130.93, 135.14, 168.40 ppm.

5.1.1.16. 1-[3-(Propane-2-sulfonyl)imidazolidin-1-yl]ethanone 13. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.39–1.42 (m, 6H, $CH(CH_3)_2$); 2.09–2.10 (m, 3H, $COCH_3$); 3.25 (sept., 1H, J = 6.8 Hz, $CHMe_2$); 3.62 (t, 2H, J = 6.8 Hz, CH_2N); 3.79 (t, 2H, J = 6.8 Hz, CH_2N); 4.84 (s, 38%) and 4.87 (s, 62%) (2H, NCH_2N) ppm. ^{13}C NMR ($CDCl_3$) δ: 16.51, 44.34, 45.95, 46.85, 47.95, 54.70, 62.18, 62.42, 167.49, 168.30 ppm. Anal. Calcd for $C_8H_{16}N_2O_3S$: C, 43.62; H, 7.32; N, 12.72. Found: C, 43.32; H, 7.62; N, 12.37.

5.1.1.17. 1-[3-(4-Fluorobenzenesulfonyl)imidazolidin-1-yl]propan-1-one 14. Mp 96 °C. ^{1}H NMR ($CDCl_3$) δ: 1.05 (t, J = 7.6 Hz, 66%) and 1.12 (t, J = 7.6 Hz, 34%) (3H, CH_2CH_3); 2.07 (q, J = 7.6 Hz, 66%) and 2.20 (q, J = 7.6 Hz, 34%) (2H, CH_2CH_3); 3.43–3.50 (m, 34%) and 3.62 (t, J = 6.4 Hz, 66%) (4H, CH_2N); 4.69 (s, 34%) and 4.75 (s, 66%) (2H, NCH_2N); 7.21–7.28 (m, 2H) and 7.81–7.86 (m, 2H) (aromatic protons) ppm. ^{13}C NMR ($CDCl_3$) δ: 8.46, 8.68, 27.38, 27.90, 43.54, 44.07, 45.96, 47.43, 61.61, 61.69, 116.70 (d, J = 23.0 Hz), 130.35 (d, J = 9 Hz), 132.26, 165.64 (d, J = 255.0 Hz), 171.46 ppm. Anal. Calcd for $C_{12}H_{15}FN_2O_3S$: C, 50.34; H, 5.28; N, 9.78. Found: C, 50.40; H, 5.49; N, 9.63.

5.1.1.18. 1-(3-Benzoylimidazolidin-1-yl)propan-1-one 15[24]. Mp 78 °C. ^{1}H NMR ($CDCl_3$) δ: 1.14–1.24 (m, 3H, CH_2CH_3); 2.29–2.35 (m, 2H, CH_2CH_3); 3.50–3.76 (m, 4H, CH_2N); 4.93–5.15 (m, 2H, NCH_2N); 7.41–7.55 (m, 5H, aromatic protons) ppm. ^{13}C NMR ($CDCl_3$) δ: 8.68, 8.79, 27.47, 27.89, 42.15, 42.28, 47.50, 47.80, 126.94, 127.05, 127.21, 127.44, 128.48, 128.61, 130.88, 131.49, 135.18, 168.20, 171.68 ppm.

5.1.1.19. 1-[3-(Propane-2-sulfonyl)imidazolidin-1-yl]propan-1-one 16. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.08–1.11 (m, 3H, CH_2CH_3); 1.31–1.33 (m, 6H, $CH(CH_3)_2$); 2.21–2.26 (m, 2H, CH_2CH_3); 3.17–3.22 (m, 1H, $-CHMe_2$); 3.55 (t, J = 6.4 Hz, 2H, CH_2N); 3.72 (t, J = 6.4 Hz, 2H, CH_2N); 4.77 (s, 39%) and 4.80 (s, 61%) (2H, NCH_2N) ppm. ^{13}C NMR ($CDCl_3$) δ: 8.58, 8.72, 16.45, 16.94, 27.71, 27.94, 44.09, 45.04, 46.56, 47.87, 54.50, 54.56, 61.61, 61.72, 170.86, 171.54 ppm. Anal. Calcd for $C_9H_{18}N_2O_3S$: C, 46.13; H, 7.74; N, 11.96. Found: C, 46.37; H, 7.90; N, 11.72.

5.1.1.20. 1-[3-(4-Fluorobenzenesulfonyl)tetrahydropyrimidin-1-yl]ethanone 17. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.46–1.51 (m, 42%) and 1.63–1.69 (m, 58%) (2H, $CH_2CH_2CH_2$); 1.95 (s, 42%) and 2.24 (s, 58%) (3H, $COCH_3$); 3.31 (t, J = 5.6 Hz, 58%) and 3.42 (t, J = 5.6 Hz, 42%) (2H, CH_2N); 3.52–3.60 (m, 2H, CH_2N); 4.74 (s, 58%) and 5.00 (s, 42%) (2H, NCH_2N); 7.17–7.28 (m, 2H, aromatic protons); 7.80–7.82 (m, 58%) and 7.84–7.87 (m, 42%) (2H, aromatic protons) ppm. ^{13}C NMR ($CDCl_3$) δ: 20.99, 21.19, 23.87, 24.01, 41.11, 45.18, 45.25, 45.75, 55.96, 61.45, 116.26 (d, J = 23.0 Hz), 116.72 (d, J = 23.0 Hz), 130.00 (d, J = 9 Hz), 130.30 (d, J = 9 Hz), 168.03 (d, J = 290.2 Hz), 168.20 (d, J = 290 Hz) 169.51 ppm. Anal. Calcd for $C_{12}H_{15}FN_2O_3S$: C, 50.34; H, 5.28; N, 9.78. Found: C, 50.43; H, 5.57; N, 9.41.

5.1.1.21. 1-(3-Benzoyltetrahydropyrimidin-1-yl)ethanone 18. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.63–1.82 (m, 3H, $COCH_3$); 2.33–2.36 (m, 2H, $CH_2CH_2CH_2$); 3.61–3.78 (m, 4H, CH_2N); 5.07–5.21 (m, 2H, NCH_2N); 7.43–7.46 (m, 5H, aromatic protons) ppm. ^{13}C NMR ($CDCl_3$) δ: 21.34, 25.28, 25.42, 41.43, 45.90, 127.12, 127.48, 128.27, 128.68, 128.78, 130.40, 134.69, 170.37 ppm. Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.98; H, 7.12; N, 12.39.

5.1.1.22. 1-[3-(Propane-2-sulfonyl)tetrahydropyrimidin-1-yl]-ethanone 19. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.32–1.36 (m, 6H, $CH(CH_3)_2$); 1.72–1.78 (m, 2H, $CH_2CH_2CH_2$); 2.10 (s, 38%) and 2.24 (s, 62%) (3H, $-COCH_3$); 3.13–3.20 (m, 62%) and 3.29–3.34 (m, 38%) (1H, $CHMe_2$); 3.55–3.74 (m, 4H, CH_2N); 4.89 (s, 62%) and 4.95 (s, 38%) (2H, NCH_2N) ppm. ^{13}C NMR ($CDCl_3$) δ: 16.58, 20.67, 41.08, 46.40, 54.20, 61.14, 168.45 ppm. Anal. Calcd for $C_9H_{18}N_2O_3S$: C, 46.13; H, 7.74; N, 11.96. Found: C, 46.54; H, 7.65; N, 11.76.

5.1.1.23. 1-[3-(4-Fluoro-benzenesulfonyl)tetrahydropyrimidin-1-yl]propan-1-one 20. Mp 87 °C. ^{1}H NMR ($CDCl_3$) δ: 1.06 (t, J = 7.2 Hz, 45%) and 1.19 (t, J = 7.2 Hz, 55%) (3H, CH_2CH_3); 1.45–1.47 (m, 45%) and 1.66–1.68 (m, 55%) (2H, $CH_2CH_2CH_2$); 2.16 (q, J = 7.2 Hz, 45%) and 2.51 (q, J = 7.2 Hz, 55%) (2H, CH_2CH_3); 3.29 (t, J = 5.2 Hz, 55%) and 3.42 (t, J = 5.2 Hz, 45%) (2H, CH_2N); 3.54–3.59 (m, 2H, CH_2N); 4.73 (s, 55%) and 5.04 (s, 45%) (2H, NCH_2N); 7.15–7.28 (m, 2H) and 7.79–7.90 (m, 2H) (aromatic protons) ppm. ^{13}C NMR ($CDCl_3$) δ: 9.06, 9.16, 23.93, 24.07, 26.20, 41.26, 44.31, 45.35, 45.88, 56.14, 60.65, 116.19 (d, J = 22.0 Hz), 116.70 (d, J = 22.0 Hz), 130.01 (d, J = 9.0 Hz), 130.30 (d, J = 9.0 Hz), 132.20, 161.20 (d, J = 250.0 Hz), 162.40 (d, J = 250 Hz), 170.8 ppm. Anal. Calcd for $C_{13}H_{17}FN_2O_3S$: C, 51.99; H, 5.71; N, 9.33. Found: C, 51.86; H, 5.49; N, 9.54.

5.1.1.24. 1-(3-Benzoyl-tetrahydropyrimidin-1-yl)propan-1-one 21. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.08–1.26 (m, 3H, CH_2CH_3); 1.64–1.81 (m, 2H, $CH_2CH_2CH_2$); 2.31–2.34 (m, 1H, CH_2CH_3); 2.64–2.66 (m, 1H, CH_2CH_3); 3.62–3.78 (m, 4H, CH_2N); 5.09–5.23 (m, 2H, NCH_2N); 7.42–7.44 (m, 5H, aromatic protons) ppm. ^{13}C NMR ($CDCl_3$) δ: 9.27, 25.32, 26.45, 32.20, 41.57, 44.98, 127.09, 127.49, 128.28, 128.43, 128.63, 129.94, 130.33, 134.77, 170.27 ppm. Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.41; H, 7.53; N, 11.60.

5.1.1.25. 1-[3-(Propane-2-sulfonyl)tetrahydropyrimidin-1-yl]-propan-1-one 22. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.13–1.17 (m, 3H, CH_2CH_3); 1.31–1.36 (m, 6H, $C(CH_3)_2$); 1.74–1.76 (m, 2H, $CH_2CH_2CH_2$); 2.35–2.52 (m, 2H, CH_2CH_3); 3.13–3.28 (m, 1H, $CHMe_2$); 3.45–3.73 (m, 4H, CH_2N); 4.89 (s, 61%) and 4.94 (s, 39%) (2H, NCH_2N) ppm. ^{13}C NMR ($CDCl_3$) δ: 9.15, 9.68, 16.56, 25.33, 25.92, 41.21, 42.46, 44.66, 46.39, 50.69, 54.08, 56.54, 60.22, 172.11 ppm. Anal. Calcd for $C_{10}H_{20}N_2O_3S$: C, 48.36; H, 8.12; N, 11.28. Found: C, 48.64; H, 8.46; N, 11.39.

5.1.1.26. 4-Propionylpiperazine-1-carboxylic acid phenyl ester 23. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.20 (t, J = 7.2 Hz, 3H, CH_2CH_3); 2.40 (q, J = 7.2 Hz, 2H, CH_2CH_3); 3.52–3.77 (m, 8H, CH_2N); 7.12–7.15 (m, 2H), 7.21–7.26 (m, 1H) and 7.36–7.41 (m, 2H) (aromatic protons) ppm. ^{13}C NMR ($CDCl_3$) δ: 9.40, 26.55, 41.28, 43.94, 44.41, 45.10, 121.63, 125.54, 129.36, 151.13, 153.90, 172.51 ppm. Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.54; H, 6.78; N, 10.89.

5.1.1.27. 4-Propionylpiperazine-1-carboxylic acid phenylamide 24. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.19 (t, J = 7.2 Hz, 3H, CH_2CH_3); 2.40 (q, J = 7.2 Hz, 2H, CH_2CH_3); 3.46–3.77 (m, 8H, CH_2N); 6.44 (br s, 1H, NH); 7.06–7.10 (m, 1H) and 7.28–7.38 (m, 4H) (aromatic protons) ppm. ^{13}C NMR ($CDCl_3$) δ: 9.41, 26.51, 41.11, 43.53, 44.12, 45.08, 120.60, 123.31, 128.77, 139.08, 155.37, 172.64 ppm. Anal. Calcd for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.54; H, 7.61; N, 16.41.

5.1.1.28. 1-(4-Phenylacetylpiperazin-1-yl)propan-1-one 25. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.09 (t, J = 7.6 Hz, 3H, CH_2CH_3); 2.27 (br s, 2H, CH_2CH_3); 3.19 (br s, 1H) and 3.37–3.70 (m, 7H) (CH_2N); 3.87 (s, 2H, $COCH_2Ph$); 7.17–7.23 (m, 3H) and 7.25–7.31 (m, 2H) (aromatic protons) ppm. ^{13}C NMR ($CDCl_3$) δ: 9.31, 26.39, 41.01, 41.69, 44.94, 45.84, 126.97, 128.50, 128.83, 134.66, 169.73, 172.44 ppm. Anal.

Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.56; H, 7.52; N, 10.90.

5.1.1.29. 1-(4-Acetylpiperazin-1-yl)propan-1-one 26. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.12 (t, J = 8.0 Hz, 3H, CH_2CH_3); 2.10 (s, 3H, $COCH_3$); 2.34 (q, J = 8.0 Hz, 2H, CH_2CH_3); 3.39–3.49 (m, 4H, CH_2N); 3.57–3.67 (m, 4H, CH_2N) ppm. ^{13}C NMR ($CDCl_3$) δ: 9.29, 21.30, 26.40, 41.17, 41.31, 41.42, 44.97, 45.24, 45.95, 46.17, 169.25, 172.56 ppm. Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.76; H, 8.51; N, 15.43.

5.1.1.30. 1-(4-Propionylpiperazin-1-yl)propan-1-one 27[25]. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.19 (t, J = 7.2 Hz, 6H, CH_2CH_3); 2.38 (q, J = 7.2 Hz, 4H, CH_2CH_3); 3.42–3.72 (m, 8H, CH_2N) ppm. ^{13}C NMR ($CDCl_3$) δ: 9.35, 26.49, 41.52, 45.17, 172.53 ppm.

5.1.1.31. *N*-(1-Propionylpiperidin-4-yl)acetamide 28. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.15 (t, J = 8.0 Hz, 3H, CH_2CH_3); 1.26–1.33 (m, 2H,CH_2CH_2CH); 1.99 (s, 3H, $COCH_3$); 2.04 (br s, 2H, CH_2CH_2CH); 2.36 (q, J = 8 Hz, 2H, CH_2CH_3); 2.73 (br s, 1H, CH_2N); 3.13 (br s, 1H, CH_2N); 3.83 (br s, 1H, CH_2N); 3.98–4.02 (m, 1H, $(CH_2)_2CHNH$); 4.57 (br s, 1H, CH_2N); 5.87 (br s, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$) δ: 9.55, 23.34, 26.50, 34.00, 36.97, 41.55, 46.02, 169.61, 172.26 ppm. Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.78; H, 9.47; N, 14.52.

5.1.1.32. *N*-(1-Acetyl-piperidin-4-yl)propionamide 29. Oil. ^{1}H NMR ($CDCl_3$) δ: 1.18 (t, J = 8.0 Hz, 3H, CH_2CH_3); 1.27–1.35 (m, 2H, CH_2CH_2CH); 1.93 (d, J = 12 Hz, 1H, CH_2CH_2CH); 2.05 (d, J = 12 Hz, 1H, CH_2CH_2CH); 2.10 (s, 3H, $COCH_3$); 2.20 (q, J = 8 Hz, 2H, CH_2CH_3); 2.73 (t, J = 11.6 Hz, 1H, CH_2N); 3.17 (t, J = 11.6 Hz, 1H, CH_2N); 3.80 (d, J = 13.6 Hz, 1H, CH_2N); 3.97–4.05 (m, 1H, $(CH_2)_2CHNH$); 4.56 (d, J = 13.6 Hz, 1H, CH_2N); 5.54 (br s, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$) δ: 9.83, 21.42, 29.77, 31.75, 32.81, 40.56, 45.30, 46.48, 48.25, 168.90, 173.21 ppm. Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.86; H, 8.87; N, 13.93.

5.1.2. General procedure for the synthesis of compounds 42–47

The *N*-benzyl derivative (1 mmol) is dissolved in abs. ethanol (10 mL), Pd/C (0.3 equiv) is added, and the mixture is hydrogenated in a Parr apparatus at 55 psi overnight. After filtration, the solvent is removed under vacuum, leaving a residue which was used as such for the following step. By this way the following compounds were prepared.

5.1.2.1. 1-[1,4]Diazepan-1-ylethanone 42. Oil, 89% yield from **36**. ^{1}H NMR ($CDCl_3$) δ (mixture of rotamers): 1.53–1.60 (m, 2H, $CH_2CH_2CH_2$); 1.85 (s, 38%) and 1.87 (s, 62%) (3H, $COCH_3$); 2.41 (br s, 1H, NH); 2.60–2.74 (m, 4H, CH_2N); 3.24–3.41 (m, 4H, CH_2N) ppm.

5.1.2.2. 1-[1,4]Diazepan-1-ylpropan-1-one 43. Oil, 92% yield from **36**. ^{1}H NMR ($CDCl_3$) δ (mixture of rotamers): 1.04–1.08 (m, 3H, CH_2CH_3); 1.70–1.81 (m, 2H, $CH_2CH_2CH_2$); 2.22–2.30 (m, 2H, CH_2CH_3); 2.77–2.90 (m, 4H, CH_2N); 3.41–3.47 (m, 2H, CH_2N); 3.54–3.56 (m, 2H, CH_2N); 3.69 (br s, 1H, NH) ppm.

5.1.2.3. 1-Imidazolidin-1-ylethanone 44[26]. Prepared from **38**. This compound was not characterized by NMR due to its instability.

5.1.2.4. 1-Imidazolidin-1-ylpropan-1-one 45. Oil, 95% yield from **39**. ^{1}H NMR ($CDCl_3$) δ (mixture of rotamers): 1.15–1.17 (m, 3H, CH_2CH_3); 2.12 (br s, 1H, NH); 2.23–2.33 (m, 2H, CH_2CH_3); 3.17 (t, J = 6.4 Hz, 42%) and 3.27 (t, J = 6.4 Hz, 58%) (2H, CH_2N); 3.37 (t, J = 6.4 Hz, 58%) and 3.41 (t, J = 6.4 Hz, 42%) (2H, CH_2N); 4.34 (s, 42%) and 4.41 (s, 58%) (2H, NCH_2N) ppm.

5.1.2.5. 1-(Tetrahydropyrimidin-1-yl)ethanone 46. Oil, 93% yield from **40**. ^{1}H NMR ($CDCl_3$) δ (mixture of rotamers): 1.55–1.59 (m, 2H, $CH_2CH_2CH_2$); 2.04–2.08 (m, 3H, $COCH_3$); 2.15 (br s, 1H, NH); 2.96–2.99 (m, 2H, CH_2N); 3.57 (t, J = 5.6 Hz, 57%) and 3.68 (t, J = 5.6 Hz, 43%) (2H, CH_2N); 4.34 (s, 43%) and 4.46 (s, 57%) (2H, NCH_2N) ppm.

5.1.2.6. 1-(Tetrahydropyrimidin-1-yl)propan-1-one 47. Oil, 92% yield from **41**. ^{1}H NMR ($CDCl_3$) δ (mixture of rotamers): 1.09–1.13 (m, 3H, CH_2CH_3); 1.60–1.62 (m, 2H, $CH_2CH_2CH_2$); 1.87 (br s, 1H, NH); 2.30–2.39 (m, 2H, CH_2CH_3); 2.97–3.01 (m, 2H, CH_2N); 3.63–3.70 (m, 2H, CH_2N); 4.36 (s, 47%) and 4.47 (s, 53%) (2H, NCH_2N) ppm.

5.1.3. Synthesis of compounds 30–32

Commercially-available 4-piperidinecarboxylic acid (1 g, 7.74 mmol) was dissolved in anhydrous CH_3CN (10 mL) and triethylamine (2.69 mL, 2.5 equiv) and 4-F-benzenesulfonyl chloride (1.8 g, 1.2 equiv) were added. The mixture was left stirring at rt until completion of the reaction (TLC), then it was treated with 2 N HCl and extracted with $CHCl_3$. After dehydration (Na_2SO_4) and removal of the solvent, the residue was purified by column chromatography (CH_2Cl_2/CH_3OH 85:15) obtaining 1-(4-fluoro-benzenesulfonyl)-piperidine-4-carboxylic acid **51**[19] in 21% yield. ^{1}H NMR δ ($CDCl_3$): 1.79–1.88 (m, 2H, CH_2CH_2CH); 1.99–2.03 (m, 2H, CH_2CH_2CH); 2.29–2.37 (m, 1H, $(CH_2)_2CHCOOH$); 2.48–2.55 (m, 2H, CH_2N); 3.62–3.66 (m, 2H,CH_2N); 7.19–7.25 (m, 2H) and 7.76–7.78 (m, 2H) (aromatic protons) ppm. Compound **51** (0.12 g, 0.41 mmol) was dissolved in ethanol-free $CHCl_3$, $SOCl_2$ (0.1 mL, 3 equiv) was added and the mixture was heated at 65 °C for 0.5 h. The solvent was removed, the residue was washed with cyclohexane and treated with the suitable nucleophile. After completion of the reaction, the mixture was treated with H_2O (2 N HCl for compound **32**) and extracted with $CHCl_3$. Dehydration (Na_2SO_4) and removal of the solvent gave a residue which, in some instances, was purified by flash chromatography. Compounds **30–32** were obtained.

5.1.3.1. 1-(4-Fluoro-benzenesulfonyl)piperidine-4-carboxylic acid methylamide 30. (prepared using 3 equiv of a 35% ethanolic solution of CH_3NH_2): mp 156 °C, 89% yield. ^{1}H NMR ($CDCl_3$) δ: 1.77–1.95 (m, 4H, CH_2CH_2CH); 2.05–2.12 (m, 1H, $(CH_2)_2CHCO$); 2.40–2.47 (m, 2H, CH_2N); 2.79–2.81 (m, 3H, $NHCH_3$); 3.73–3.78 (m, 2H, CH_2N); 5.59–5.69 (br s, 1H, NH); 7.21–7.28 (m, 2H) and 7.77–7.81 (m, 2H) (aromatic protons) ppm. ^{13}C NMR ($CDCl_3$) δ: 26.36, 27.91, 41.85, 45.47, 116.37 (d, J = 23 Hz), 130.26 (d, J = 9 Hz), 132.46, 165.22 (d, J = 254 Hz), 174.20 ppm. Anal. Calcd for $C_{13}H_{17}FN_2O_3S$: C, 51.99; H, 5.71; N, 9.33. Found: C, 52.32; H, 5.98; N, 9.12.

5.1.3.2. 1-(4-Fluoro-benzenesulfonyl)piperidine-4-carboxylic acid ethylamide 31. (prepared using 3 equiv of a 35% ethanolic solution of $C_2H_5NH_2$; purified by flash chromatography using CH_2Cl_2/CH_3OH/NH_4OH 9:1:0.5): mp 197 °C, 47% yield. ^{1}H NMR ($CDCl_3$) δ: 1.12 (t, 3H, J = 7.6 Hz, CH_2CH_3); 1.77–1.94 (m, 4H, CH_2CH_2CH); 2.02–2.08 (m, 1H, $(CH_2)_2CHCO$); 2.41–2.47 (m, 2H, CH_2N); 3.24–3.31 (m, 2H, CH_2CH_3); 3.75–3.79 (m, 2H, CH_2N); 5.45–5.52 (br s, 1H, NH); 7.21–7.25 (m, 2H) and 7.77–7.92 (m, 2H) (aromatic protons) ppm. ^{13}C NMR ($CDCl_3$) δ: 14.81, 28.15, 34.37, 41.97, 45.46, 116.35 (d, J = 23.0 Hz), 130.26 (d, J = 9.0 Hz), 135.5, 165.23 (d, J = 247.5 Hz), 173.30 ppm. Anal. Calcd for $C_{14}H_{19}FN_2O_3S$: C, 53.49; H, 6.09; N, 8.91. Found: C, 53.65; H, 6.27; N, 9.23.

5.1.3.3. 1-(4-Fluorobenzenesulfonyl)piperidine-4-carboxylic acid acetylamide 32. (Prepared using 1 equiv of sodium acetamide, prepared in THF from acetamide and sodium hydride. Purified by flash chromatography using CH_2Cl_2/CH_3OH 95:5): mp 188 °C,

15% yield. ^{1}H NMR ($CDCl_3$) δ: 1.79–1.88 (m, 2H, CH_2CH_2CH); 1.93–1.97 (m, 2H, CH_2CH_2CH); 2.33 (s, 3H,CH_3CO); 2.41–2.48 (m, 2H, CH_2N); 2.60–2.69 (br m, 1H, $(CH_2)_2CHCO$); 3.76–3.83 (m, 2H, CH_2N); 7.23–7.28 (m, 2H) and 7.78–7.82 (m, 2H) (aromatic protons); 8.80 (br s, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$) δ: 25.18, 27.36, 42.04, 45.34, 116.43 (d, J = 22.0 Hz), 130.29 (d, J = 9 Hz), 132.26, 165.27 (d, J = 254 Hz), 174.80 ppm. Anal. Calcd for $C_{14}H_{17}FN_2O_4S$: C, 51.21; H, 5.22; N, 8.53. Found: C, 51.56; H, 5.14; N, 8.74.

5.2. Pharmacology

5.2.1. Passive-avoidance test

The test was performed according to the step-through method described by Jarvik and Kopp.[20] 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 drug (scopolamine). All investigated drugs were dissolved in saline and injected ip, in a 1:10 dilution sequence, 20 min before the training session; the amnesic drug was injected immediately after termination of the training session. Saline 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 **2a** and **3** were used as the reference drugs.

All compounds elicited their effect without changing either gross behaviour or motor coordination, as revealed by the rota-rod test (performed as reported in Ref. 23, 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 (performed as reported in Ref. 23, data not shown).

5.2.2. Statistical analysis

All experimental results are given as the mean ± 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 analyzed with the StatView software for the Macintosh (1992). P values of less than 0.05 were considered significant.

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