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Design, synthesis and preliminary pharmacological evaluation of new piperidine and piperazine derivatives as cognition-enhancers

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Abstract—A series of 2-oxopiperazine, 4-aminomethyl-, 3-amino- and 3-aminomethylpiperidine analogues of DM235 (sunifiram) and MN19 (sapunifiram), two previously reported potent cognition-enhancers, have been synthesized and tested in the mouse passive-avoidance test. The compounds display minimal effective doses in the range 0.3–10 mg/kg. Although the new substances do not show improved activity when compared to the parent compounds, some useful information has been obtained to understand structure–activity relationships. In addition, the 3-aminopiperidine moiety appears to be a promising scaffold to synthesize new drugs endowed with cognition-enhancing activity.

1. Introduction

Mild cognitive impairment (MCI) has been described as a condition occurring between normal ageing and Alzheimer's disease (AD) or other dementias.[1] MCI can be classified into four different subtypes of cognitive dysfunctions,[2,3] which may progress to Alzheimer's disease (AD). The aim of MCI treatment is to diminish memory loss and possibly to prevent further cognitive decline; several pharmacologic treatments for MCI have been studied or are under evaluation, including antioxidants, estrogen replacement therapy, cyclooxygenase2-selective inhibitors, nootropics and cholinesterase inhibitors.[3,4] A possible strategy to improve cognition is modulation of neurotransmission; among others, cholinergic and glutamatergic receptor systems continue to be explored as possible targets. Presently, four acetylcholinesterase inhibitors and a NMDA antagonist have been approved for the treatment of AD. Moreover, the positive allosteric modulators of AMPA receptors, called Ampakines, seem to be promising as neuroprotectors and cognition enhancing agents.[5]

The pyrrolidin-2-one family of cognition-enhancers, often referred to as nootropics and 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 to control cognition impairment, to afford neuroprotection after stroke and to treat epilepsy.[6] Although this class of substances lacks a common mechanism of action at the molecular level, some members of this series (for instance, aniracetam and nefiracetam) have been shown to modulate receptor systems such as cholinergic and/or glutamatergic.[7,8]

We have previously reported that DM232 (unifiram) and DM235 (sunifiram) show cognition-enhancing properties with a potency four orders of magnitude higher than piracetam (Chart 1).[9,10] These compounds are well tolerated in rodents, but their development slowed down because it was not possible to clarify their mechanism of action.[11] In fact, unifiram and sunifiram did not show any affinity towards the most important central receptors or transporters,[10] but they are able to increase ACh release from rat brain;[10] there is evidence that AMPA receptors are involved in their antiamnesic

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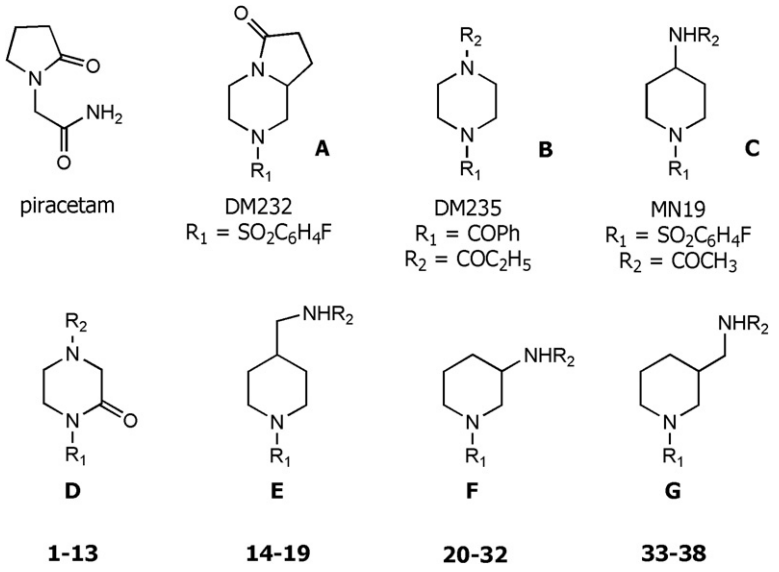


Chart 1.

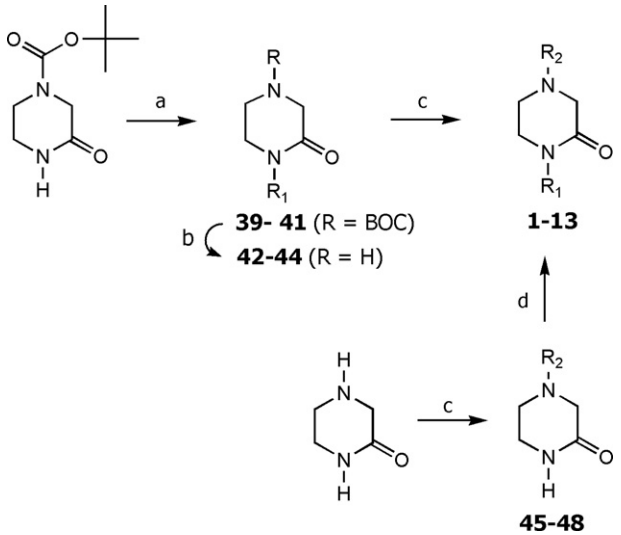
effect,[12] but a direct interaction of unifiram and sunifiram with AMPA receptors in vitro has not been proved yet.

The lack of knowledge regarding the mechanism of action precludes the possibility to test the compounds in vitro on a specific target, and in vivo tests do not provide precise information useful to derive sound structure–activity relationships. As a consequence, the structural modifications on the lead molecule DM232 have been performed, so far, mainly on the diamidic scaffold. For instance, molecular simplification of the diazabicyclo[4.3.0]nonanone moiety into the diacylpiperazine structure has given compounds, exemplified by DM235 (sunifiram), that maintain high nootropic activity. The extrusion of one of the nitrogen atoms of the piperazine ring to give 4-aminopiperidine derivatives, exemplified by MN19 (sapunifiram, Chart 1), afforded compounds with cognition enhancing properties similar to that of the parent compound unifiram.[13]

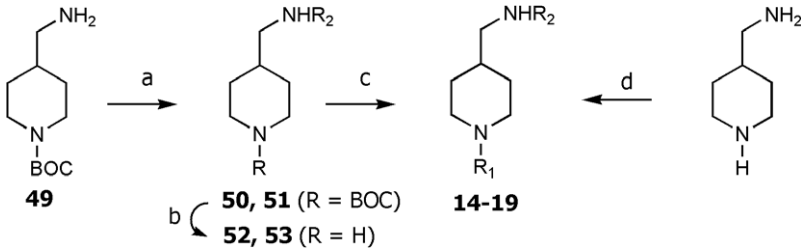
In a continuing effort to find new potent analogues of unifiram and sunifiram, and to collect information to clarify the mechanism of action of these substances, we made further structural modifications on the lead molecules DM235 and MN19: (a) one of the amide linkages of the diacyl-piperazine moiety was introduced into the 6-membered ring, synthesizing 1-alkyl and 1-acyl-2-oxopiperazine derivatives (general structure D, compounds **1**–**6** and **7**–**13**, respectively); (b) the exocyclic amide group of 4-aminopiperidines has been spaced from the ring by inserting a methylene unit (general structure E, compounds **14**–**19**); (c) the symmetric 4-aminopiperidine group has been changed into a 3-aminopiperidine moiety (general structure F, compounds **20**–**32**), and (d) the three-carbon chain spacer has been restored by synthesizing 3-aminomethylpiperidines (general structure G, compounds **33**–**38**). The last two modifications bring into the molecule an asymmetric centre; thus, we decided to first evaluate the activity of the racemates, eventually leaving the synthesis of the enantiomers to a subsequent step. In the new series (D–G) of compounds, the R_1 and R_2 groups were chosen among those giving, in the previous A–C series, the most interesting compounds. All the designed compounds maintain a diamidic structure, a feature which is important for high nootropic activity.[11]

2. Chemistry

Compounds **1**–**13** were prepared following the procedure reported in Scheme 1. Reaction of N^4-BOC-piperazin-2-one[14] with alkyl bromides in DMF under basic conditions (NaH)[15] gave compounds **39**–**41**,[16] which were deprotected with trifluoroacetic acid to **42**–**44**[17–19] and treated with the suitable acid derivative to yield compounds **1**–**6**. Reac-



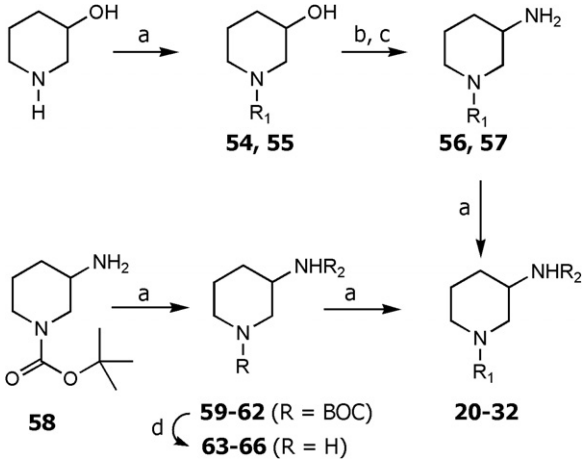
Scheme 1. Reagents and conditions: (a) NaH, R_1Br, DMF; (b) CF_3COOH 0 °C; (c) $(R_2)_2O$ or R_2Cl, TEA; (d) LHMDS, R_1Cl, THF, −78 °C. For R_1 and R_2 see Tables 3 and 5.



Scheme 2. Reagents and conditions: (a) R_2Cl, Et_3N, $CHCl_3$; (b) 2N HCl, AcOEt; (c) R_1Cl, Et_3N, $CHCl_3$; (d) 4-F–$C_6H_4SO_2Cl$, CH_3CN. For R_1 and R_2 see Table 3.

tion of the unprotected 2-oxo-piperazine with the suitable acid derivative gave compounds **45**–**48**, which were treated with lithium bis(trimethyl)silyl amide and the suitable acyl or benzoyl chloride at low temperature[20] to give compounds **7**–**13**.

The 4-aminomethyl derivatives **14**–**19** were prepared according to the procedure reported in Scheme 2. *tert*-Butyl 4-(aminomethyl)piperidine-1-carboxylate **49**[21] was treated with propionyl chloride or 4-fluorobenzenesulfonyl chloride to give compounds **50** and **51**,[22] which were deprotected to **52**–**53** under acidic conditions and treated with the suitable acyl or sulfonyl chloride to give compounds **14**–**18**. Compound **19** was obtained by reaction of the unprotected 4-aminomethylpiperidine with 4-fluorobenzenesulfonyl chloride.



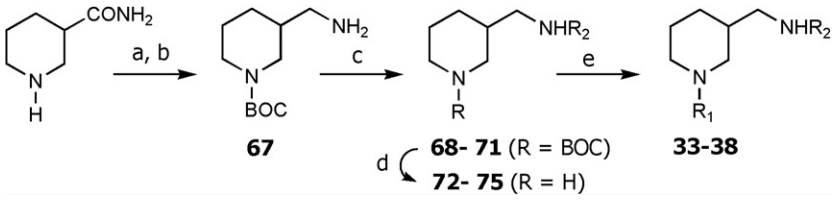
Scheme 3. Reagents and conditions: (a) acyl halide, or sulfonyl halide, or anhydride, Et_3N, CH_2Cl_2 or $CHCl_3$; (b) CrO_3/H_2SO_4, CH_3COCH_3; (c) $AcONH_4$, $NaBH_3CN$, MeOH; (d) HCI 2N, AcOEt. For R_1 and R_2 see Experimental and Table 3.

3-Aminopiperidine derivatives were obtained by two different approaches (Scheme 3): commercially available 3-hydroxypiperidine was transformed under standard conditions into compounds **54**–**55**, which were oxidized by means of the Jones reagent and transformed into the corresponding 3-aminopiperidines **56**–**57** by reaction with ammonium acetate and sodium cyanoborohydride; these compounds were then treated with the suitable acid chloride yielding **20**–**25**. This pathway was not suitable for compounds having an acyl moiety on the piperidine nitrogen atom, and therefore an alternative method was used: *tert*-butyl 3-aminopiperidine-1-carboxylate **58**, prepared according to De Costa,[23] was treated with the suitable benzoyl, acyl or sulfonyl chloride to yield **59**–**62**, which were deprotected to **63**–**66** and transformed into **26**–**32** under standard conditions.

The 3-aminomethyl derivatives **33**–**38** were prepared as reported in Scheme 4: *tert*-butyl 3-(aminomethyl)piperidine-1-carboxylate **67**[24] was synthesized from commercially available nipecotamide and treated with the suitable benzoyl, acyl or sulfonyl chloride to yield compounds **68**–**71**, which were deprotected to **72**–**75** and transformed in the usual way into compounds **33**–**38**.

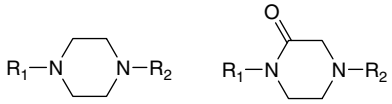
3. Pharmacology

The studied compounds were tested as cognition enhancers in the mouse passive avoidance test of Jarvik and Kopp,[25] slightly modified by us.[26] Results are expressed as MED (minimal effective dose) and are reported in Tables 1 and 2, in comparison with the corresponding piperazine (B1–B5, Table 1) and 4-aminopiperidine (C1–C4, Table 2) analogues, which have been previously characterized.[10,13]



Scheme 4. Reagents and conditions: (a) Boc_2O, DMAP, CH_3CN; (b) $LiAlH_4$ THF; (c) R_2Cl, Et_3N, $CHCl_3$; (d) HCI 2N, AcOEt; (e) R_1Cl, Et_3N, $CHCl_3$. For R_1 and R_2 see Tables 3 and 4.

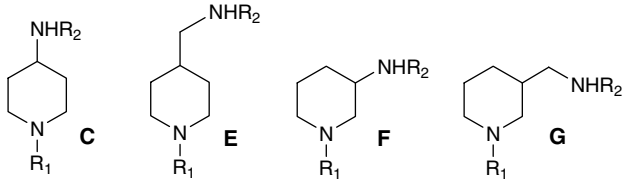
Table 1. Minimal effective doses (MED) of piperazinones in the passive avoidance test, in comparison with the corresponding piperazine derivatives[a]



Treatment	Structure	R_1	R_2	MED (mg/kg)	Training session (s)	Retention session (s)	Δ
Saline							88.2
Scopolamine (S)							28.0
S + **1**	D	$CH_2C_6H_5$	COC_2H_5	10	13.6 ± 4.5	77.3 ± 9.9*	63.7
S + **7**	D	COC_6H_5	$COCH_3$	10	18.3 ± 3.6	78.1 ± 9.5^	59.8
S + **9**	D	COC_2H_5	$SO_2C_6H_4F$	0.3	18.2 ± 3.6	89.1 ± 11.4*	70.9
S + **10**	D	$COCH_3$	$SO_2C_6H_4F$	0.3	16.2 ± 2.5	81.5 ± 7.5^	65.3
S + **11**	D	COC_2H_5	COC_6H_5	10	13.8 ± 2.6	76.2 ± 8.1^	62.4
S + **12**	D	$COCH_3$	COC_6H_5	10	16.6 ± 3.1	88.5 ± 9.3	71.9
S + DM235	B	COC_2H_5	COC_6H_5	0.001	20.5 ± 3.4	91.5 ± 8.0*	71.0
S + B1	B	$COCH_3$	COC_6H_5	10	11.3 ± 5.3	119.0 ± 11.2*	107.7
S + B2	B	COC_2H_5	$SO_2C_6H_4F$	0.01	15.9 ± 3.2	90.6 ± 8.2*	74.7
S + B3	B	$COCH_3$	$SO_2C_6H_4F$	0.01	19.8 ± 4.1	89.0 ± 18.3^	69.2
S + B4	B	C_3H_7	$SO_2C_6H_4F$	1.0	15.3 ± 3.9	96.7 ± 9.9*	81.4
S + B5	B	$CH_2C_6H_5$	COC_2H_5	10	12.8 ± 4.1	93.9 ± 8.7*	81.1

[a] The compounds were injected sc 30 min before the training session. Results are expressed as MED (minimal effective dose); each value represents the mean of 14–22 mice. Scopolamine (1.5 mg/kg ip) was injected immediately after punishment. $^{\wedge}P < 0.05$, $^{*}P < 0.01$ in comparison with scopolamine treated mice. Δ is the difference between latency times registered in the training session and the retention session. Compounds B1–B5 and DM235 have been previously reported,[10] and their activity is reported here, together with that of the new analogues, for comparative purposes.

Table 2. Minimal effective doses (MED) of tested compounds in the mouse passive avoidance test[a]



Treatment	Structure	R_1	R_2	MED (mg/kg)	Training session (s)	Retention session (s)	Δ
Saline					14.8 ± 2.9	99.5 ± 5.3	84.7
Scopolamine (S)					15.5 ± 3.2	42.5 ± 5.7	27.0
S + **15**	E	COC_6H_5	COC_2H_5	1.0	15.9 ± 3.4	89.4 ± 10.1*	73.5
S + **18**	E	COC_2H_5	$SO_2C_6H_4F$	1.0	18.2 ± 3.5	83.1 ± 10.4*	64.9
S + **19**	E	$SO_2C_6H_4F$	$SO_2C_6H_4F$	1.0	14.3 ± 2.7	73.8 ± 8.1^	59.5
S + **20**	F	$SO_2C_6H_4F$	COC_2H_5	1.0	16.4 ± 3.5	75.1 ± 10.3^	58.7
S + **21**	F	$SO_2C_6H_4F$	$COCH_3$	1.0	14.2 ± 2.7	78.5 ± 7.9^	64.3
S + **22**	F	$SO_2C_6H_4F$	SO_2CHMe_2	1.0	15.3 ± 3.4	81.3 ± 9.0*	66.0
S + **25**	F	SO_2CHMe_2	$SO_2C_6H_4F$	10	15.5 ± 3.8	83.7 ± 9.2*	68.2
S + **26**	F	$COCH_3$	$SO_2C_6H_4F$	1.0	16.2 ± 3.5	76.5 ± 8.6^	60.3
S + **27**	F	COC_2H_5	$SO_2C_6H_4F$	10	16.3 ± 4.5	77.1 ± 9.2^	60.8
S + **28**	F	COC_6H_5	SO_2CHMe_2	1.0	15.1 ± 3.6	91.6 ± 9.8*	76.5
S + **29**	F	$COCH_3$	COC_2H_5	1.0	15.3 ± 4.4	95.3 ± 8.8*	80.0
S + **32**	F	COC_2H_5	COC_6H_5	1.0	14.3 ± 2.8	87.5 ± 9.5*	73.2
S + **35**	G	$SO_2C_6H_4F$	$COCH_3$	10	14.1 ± 3.6	66.5 ± 7.2^	52.4
S + **37**	G	$SO_2C_6H_4F$	COC_2H_5	10	12.2 ± 3.3	63.8 ± 7.5^	51.6
S + MN19	C	$SO_2C_6H_4F$	$COCH_3$	0.01	14.5 ± 3.8	90.6 ± 12.5^	76.1
S + C1	C	$SO_2C_6H_4F$	COC_2H_5	0.1	17.6 ± 3.9	103.4 ± 9.5*	85.8
S + C2	C	COC_6H_5	COC_2H_5	0.1	18.0 ± 4.7	121.0 ± 11.3*	103.0
S + C3	C	$COCH_3$	$SO_2C_6H_4F$	0.1	23.5 ± 5.3	126.8 ± 13.8*	92.6
S + C4	C	COC_2H_5	$SO_2C_6H_4F$	10	15.6 ± 4.7	108.2 ± 8.4*	103.0

[a] All drugs were administered sc 30 min before training session. Each value represents the mean of 11–19 mice. Scopolamine (1.5 mg/kg ip) was injected immediately after punishment. $^{\wedge}P < 0.05$; $^{*}P < 0.01$ in comparison with scopolamine-treated mice. Compounds C1–C4 and MN19 have been previously reported,[13] and their activity is reported here, together with that of the new analogues, for comparative purposes.

4. Results and discussion

All the synthesized compounds were tested in the mouse passive-avoidance test to evaluate their nootropic activity. The compounds showing anti-amnesic activity below the 10 mg/kg minimal effective dose are reported in Tables 1 and 2; the remaining compounds (**2**–**6**, **8**, **13**, **14**, **16**, **17**, **23**, **24**, **30**, **31**, **32**, **34**, **36** and **38**) did not show activity up to the same dose. It must be kept in mind that biological tests performed in vivo do not allow sound structure–activity relationships to be derived, since the activity can be the result of both pharmacokinetic and pharmacodynamic factors, which may be differently affected by structural modifications. However, the in vivo test on cognition-enhancing activity is, for the moment, the only way to characterize this class of substances, at least as long as the biological target(s) has (have) not been identified.

In the piperazinone series (Table 1), activity is maintained in compounds having the acyl, but not the alkyl, substituent, on the N^1 nitrogen atom. In fact, among compounds **1**–**6**, only **1** shows a modest activity in the passive avoidance test, with a potency similar to that displayed by its deoxy analogue B5. Some activity is restored in the 1-acyl derivatives, since compounds **9** and **10** show MED below 1 mg/kg; however also in this series there is a consistent loss of potency (1–4 orders of magnitude) with respect to piperazines DM235 and B1–B4. The introduction of a carbonyl moiety into the piperazine ring is therefore detrimental for activity. This may be due to unfavourable steric and/or electronic interactions of the endocyclic carbonyl group within the active site of the biological target, or to an unfavourable conformational effect on the N^1-substituent. These findings suggest that, in order to maintain high nootropic potency, the acyl moieties of both amide linkages should be exocyclic.

Insertion of a methylene unit between the ring and the exocyclic amide moiety in the 4-substituted piperidines has mixed effects on the potency (Table 2). In fact, in some instances the spacing of the amidic group from the piperidine ring gave compounds which are less potent or inactive with respect to the parent compounds (compounds **14**, **15** and **17** compared to MN19, C2 and C3, respectively); on the contrary, **18** is 10-fold more potent than C4.

Shifting of the amino group from position 4 to position 3 on the piperidine ring gave interesting results. Compounds **20**–**22**, **26**, **28**, **29** and **32** were able to reverse scopolamine-induced amnesia with minimal effective doses of 1 mg/kg; on the contrary, the insertion of an additional methylene unit in position 3 is detrimental for activity, since compounds **33**–**38** are less active, or inactive, with respect to the parent 3-amino and 4-aminopiperidines. Although the potency of 3-aminopiperidine derivatives is lower compared to their 4-aminopiperidine analogues, the results reported in Table 2 show that the 1,4 substitution on the 6-membered ring is not essential for activity, and that the exocyclic amide moiety can be shifted to position 3 to obtain interesting compounds, which could be possibly optimized.

The intrinsic difficulty in this research is the lack of knowledge regarding the mechanism of action of this class of substances, which precludes the use of a suitable in vitro test for their optimization and development. Nevertheless, from the newly synthesized compounds some useful information has been obtained to understand the structural requirements for high nootropic activity in this class of compounds. In addition, the 3-aminopiperidine moiety seems a promising scaffold to obtain new potent cognition-enhancers.

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). Yields are given after purification, unless differently stated. 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. A mixture of the starting material (1 mmol), triethylamine (1.5 equiv) and the anhydride, acyl or sulfonyl chloride (1.05 equiv) in ethanol-free $CHCl_3$ (4 mL) was stirred at room temperature for 2–24 h, then treated with a saturated solution of $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was collected, dried (Na_2SO_4) and the solvent was removed giving a residue which was purified by flash chromatography or by trituration from petroleum ether. The compounds prepared according to this method are reported in Table 3, together with other experimental details; in some instances (compounds **5**, **6**, **19**, **20**, **22**, **25**, **45**, **46**, **54** and **55**) the solvent and the reaction temperature have been changed. The synthesis of **19** was performed without triethylamine. The NMR-spectra of the compounds, synthesized according to this method, are reported in Table 6.

5.1.2. Synthesis of *tert*-butyl 4-alkyl-3-oxopiperazine-1-carboxylate derivatives (39–41). A solution of N^4-BOC-2-oxopiperazine[14] (1 mmol) in anhydrous DMF (12 mL) was treated with NaH (60% oil dispersion, 1.1 equiv) and the suitable alkyl bromide (1.1 equiv), and stirred at room temperature for 24–48 h. The mixture was treated with H_2O and extracted with ethyl acetate; drying (Na_2SO_4) and removal of the solvent gave a residue which was used as such in the following step (**39**, **41**) or purified by flash chromatography (**40**) using abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/petroleum ether 180:9.9:360:360:900 as eluent.

tert-Butyl 4-ethyl-3-oxopiperazine-1-carboxylate (**39**) (60% yield). ^{1}H NMR ($CDCl_3$) δ: 1.14 (t, 3H, J = 4.0 Hz);

Table 3. Experimental details for the products of acylation or sulfonylation

N	Structure[a]	R_1	R_2	Starting compound	Reagent	Time (h)	Yield (%)	Purification method (eluent)[i]	Mp (°C)	Anal
1	D	CH_2Ph	COC_2H_5	**44**	C_2H_5COCl	2	67	A (II)	[j]	$C_{14}H_{18}N_2O_2$
2	D	CH_2Ph	$COCH_3$	**44**	CH_3COCl	2	82	A (II)	[j]	[l]
3	D	nC_3H_7	COPh	**43**	PhCOCl	24	40	A (II)	[j]	$C_{14}H_{18}N_2O_2$
4	D	nC_3H_7	$SO_2C_6H_4F$	**43**	F–$C_6H_4SO_2Cl$	24	50	A (II)	133–134	$C_{13}H_{17}FN_2O_3S$
5	D	C_2H_5	$SO_2C_6H_4F$	**42**	F–$C_6H_4SO_2Cl$	24[f]	54	A (II)	108–109	$C_{12}H_{15}FN_2O_3S$
6	D	C_2H_5	SO_2CHMe_2	**42**	Me_2CHSO_2Cl	24[f]	35	A (II)	56	$C_9H_{18}N_2O_3S$
14	E	$SO_2C_6H_4F$	COC_2H_5	**52**	F–$C_6H_4SO_2Cl$	6	94	B	126–127	$C_{15}H_{21}FN_2O_3S$
15	E	COPh	COC_2H_5	**52**	PhCOCl	24	99	A (V)	[k]	$C_{16}H_{22}N_2O_2$
16	E	SO_2CHMe_2	$SO_2C_6H_4F$	**53**	Me_2CHSO_2Cl	48	57	A (V)	130–131	$C_{15}H_{23}FN_2O_4S_2$
17	E	$COCH_3$	$SO_2C_6H_4F$	**53**	CH_3COCl	2	86	B	104–106	$C_{14}H_{19}FN_2O_3S$
18	E	COC_2H_5	$SO_2C_6H_4F$	**53**	C_2H_5COCl	4	98	B	132–133	$C_{15}H_{21}FN_2O_3S$
19	E	$SO_2C_6H_4F$	$SO_2C_6H_4F$	[c]	F–$C_6H_4SO_2Cl$	0.5[g]	45	B	195–196	$C_{18}H_{20}F_2N_2O_4S_2$
20	F	$SO_2C_6H_4F$	COC_2H_5	**56**	$(C_2H_5CO)_2O$	12 h[g]	69	A (I)	184–185	$C_{14}H_{19}FN_2O_3S$
21	F	$SO_2C_6H_4F$	$COCH_3$	**56**	$(CH_3CO)_2O$	2	86	B	170–171	$C_{13}H_{17}FN_2O_3S$
22	F	$SO_2C_6H_4F$	SO_2CHMe_2	**56**	Me_2CHSO_2Cl	48[f,g]	12	A (VII)	175–176	$C_{14}H_{21}FN_2O_4S_2$
23	F	SO_2CHMe_2	COC_2H_5	**57**	$(C_2H_5CO)_2O$	2	99	B	76–77	$C_{11}H_{22}N_2O_3S$
24	F	SO_2CHMe_2	$COCH_3$	**57**	$(CH_3CO)_2O$	2	74	B	65–66	$C_{10}H_{20}N_2O_3S$
25	F	SO_2CHMe_2	$SO_2C_6H_4F$	**57**	F–$C_6H_4SO_2Cl$	3[f]	57	A (I)	120–123	$C_{14}H_{21}FN_2O_4S_2$
26	F	$COCH_3$	$SO_2C_6H_4F$	**63**	CH_3COCl	4	99	B	110–112	$C_{13}H_{17}FN_2O_3S$
27	F	COC_2H_5	$SO_2C_6H_4F$	**63**	C_2H_5COCl	4	99	B	100–101	$C_{14}H_{19}FN_2O_3S$
28	F	COPh	SO_2CHMe_2	**64**	PhCOCl	2	84	A (III)	107–109	$C_{15}H_{22}N_2O_3S$
29	F	$COCH_3$	COC_2H_5	**65**	CH_3COCl	12	79	B	80–83	$C_{10}H_{18}N_2O_2$
30	F	COPh	COC_2H_5	**65**	PhCOCl	2	40	A (III)	79	$C_{15}H_{20}N_2O_2$
31	F	$COCH_3$	COPh	**66**	CH_3COCl	4	99	B	77	$C_{14}H_{18}N_2O_2$
32	F	COC_2H_5	COPh	**66**	C_2H_5COCl	2	60	A (III)	80–83	$C_{15}H_{20}N_2O_2$
33	G	$COCH_3$	COPh	**74**	CH_3COCl	12	64	A (I)	[k]	$C_{15}H_{20}N_2O_2$
34	G	COC_2H_5	COPh	**74**	C_2H_5COCl	12	99	I	[k]	$C_{16}H_{22}N_2O_2$
35	G	$SO_2C_6H_4F$	$COCH_3$	**72**	F–$C_6H_4SO_2Cl$	12	38	I	148–149	$C_{14}H_{19}FN_2O_3S$
36	G	COPh	$COCH_3$	**72**	PhCOCl	12	40	A (V)	147–148	$C_{15}H_{20}N_2O_2$
37	G	$SO_2C_6H_4F$	COC_2H_5	**73**	F–$C_6H_4SO_2Cl$	12	35	A (I)	[k]	$C_{15}H_{21}FN_2O_3S$
38	G	$COCH_3$	$SO_2C_6H_4F$	**75**	CH_3COCl	12	43	A (V)	141–142	$C_{14}H_{19}FN_2O_3S$
45	D	H	CH_3CO	[d]	$(CH_3CO)_2O$	2[g,h]	91	A (III)	98–99	[m]
46	D	H	C_2H_5CO	[d]	$(C_2H_5CO)_2O$	0.5[g,h]	90	A (III)	[k]	[m]
47	D	H	COPh	[d]	PhCOCl	24	81	A (IV)	[k]	[m]
48	D	H	$SO_2C_6H_4F$	[d]	F–$C_6H_4SO_2Cl$	24	68	A (IV)	154–156	$C_{10}H_{11}FN_2O_3S$
50	E	BOC	COC_2H_5	**49**	C_2H_5COCl	48	46	A (V)	[k]	$C_{14}H_{26}N_2O_3$
51	E	BOC	$SO_2C_6H_4F$	**49**	F–$C_6H_4SO_2Cl$	48	99	A (V)	122–123	[n]
54	[b]	$SO_2C_6H_4F$	—	[e]	F–$C_6H_4SO_2Cl$	4[g,h]	99	None	83–84	$C_{11}H_{14}FNO_3S$
55	[b]	SO_2CHMe_2	—	[e]	Me_2CHSO_2Cl	3[g,h]	30	A (VI)	[k]	$C_8H_{17}NO_3S$
59	F	BOC	$SO_2C_6H_4F$	**58**	F–$C_6H_4SO_2Cl$	2	94	A (I)	[k]	$C_{16}H_{23}FN_2O_4S$
60	F	BOC	SO_2CHMe_2	**58**	Me_2CHSO_2Cl	48	39	A (I)	—	$C_{13}H_{26}N_2O_4S$
61	F	BOC	COC_2H_5	**58**	C_2H_5COCl	2	78	A (I)	95–96	$C_{13}H_{24}N_2O_3$
62	F	BOC	COPh	**58**	PhCOCl	2	97	A (I)	[j]	[o]
68	G	BOC	$COCH_3$	**67**	CH_3COCl	17	60	A (V)	120–122	$C_{13}H_{24}N_2O_3$
69	G	BOC	COC_2H_5	**67**	C_2H_5COCl	17	65	A (V)	115–118	$C_{14}H_{26}N_2O_3$
70	G	BOC	COPh	**67**	PhCOCl	17	43	A (VIII)	120	$C_{18}H_{26}N_2O_3$
71	G	BOC	$SO_2C_6H_4F$	**67**	F–$C_6H_4SO_2Cl$	17	24	A (VIII)	130–132	$C_{17}H_{25}FN_2O_4S$

[a] For the meaning of D–G see Chart 1.
[b] *N*-Sulfonyl-3-hydroxypiperidine.
[c] 4-Aminomethylpiperidine.
[d] 2-Oxopiperazine.
[e] 3-Hydroxypiperidine.
[f] CH_3CN was used as solvent.
[g] The reactions were run at the following temperatures: 60 °C (compound **20**), 80 °C (compound **22**), 0 °C (compounds **45**, **46**, **54** and **55**).
[h] CH_2Cl_2 was used as solvent.
[i] Purification methods: (A) flash chromatography (eluents: I—abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/petroleum ether 180:9.9:360:360:900; II—abs EtOH/NH_4OH/CH_2Cl_2/petroleum ether 65:8:340:60; III—$CHCl_3$/MeOH/NH_4OH 90:10:1; IV—$CHCl_3$/MeOH/NH_4OH 80:20:1; V—$CHCl_3$/MeOH/NH_4OH 95:5:0.5; VI—abs EtOH/NH_4OH/CH_2Cl_2/Et_2O/petroleum ether 45:2.5:180:180:450; VII—$CHCl_3$/MeOH/NH_4OH 99:1:0.1; VIII—$CHCl_3$/MeOH 98:2); (B) trituration from petroleum ether.
[j] Oil.
[k] Waxy solid.
[l] See Ref. 27.
[m] See Ref. 28.
[n] See Ref. 22.
[o] See Ref. 29.

Table 4. Experimental details for the synthesis of compounds obtained by removal of BOC using HCl/AcOEt

N	Structure[d]	R_2	Starting compound	Reaction time (h)	Yield (%)	Anal
52	E	COC_2H_5	**50**	3	74	$C_9H_{18}N_2O$
53[a]	E	$SO_2C_6H_4F$	**51**	48	79	$C_{12}H_{17}FN_2O_2S$
63[b]	F	$SO_2C_6H_4F$	**59**	48	86	$C_{11}H_{15}FN_2O_2S$
64	F	SO_2CHMe_2	**60**	48	49	$C_8H_{18}N_2O_2S$
65	F	COC_2H_5	**61**	48	30	$C_8H_{16}N_2O$
66	F	COC_6H_5	**62**	48	22	[e]
72	G	$COCH_3$	**68**	12	99	[f]
73	G	COC_2H_5	**69**	12	69	$C_9H_{18}N_2O$
74	G	COC_6H_5	**70**	19	80	$C_{13}H_{18}N_2O$
75[c]	G	$SO_2C_6H_4F$	**71**	24	52	$C_{12}H_{17}FN_2O_2S$

[a] Mp 160–161 °C.
[b] Mp 143–144 °C.
[c] Purified by flash chromatography. Eluent: abs EtOH/NH_4OH/CH_2Cl_2/petroleum ether 65:8:340:60.
[d] For the meaning of E–G see Chart 1.
[e] See Ref. 29.
[f] See Ref. 30.

Table 5. Experimental details for the synthesis of compounds **7**–**13**

N	R_1	R_2	Reaction time (h)	Extraction	Purification[a]	Yield (%)	Mp (°C)	Anal
7	COC_6H_5	$COCH_3$	3	AcOEt	A	43	135–136	$C_{13}H_{14}N_2O_3$
8	COC_6H_5	COC_2H_5	0.5	Et_2O	A	30	[b]	$C_{14}H_{16}N_2O_3$
9	COC_2H_5	$SO_2C_6H_4F$	24	AcOEt	B	20	130–131	$C_{13}H_{15}FN_2O_4S$
10	$COCH_3$	$SO_2C_6H_4F$	3.5	AcOEt	B	11	115–116	$C_{12}H_{13}FN_2O_4S$
11	COC_2H_5	COC_6H_5	0.5	Et_2O	A	67	106–107	$C_{14}H_{16}N_2O_3$
12	$COCH_3$	COC_6H_5	0.5	Et_2O	A	22	[b]	$C_{13}H_{14}N_2O_3$
13	$SO_2C_6H_4F$	$COCH_3$	24	Et_2O	A	15	[b]	$C_{12}H_{13}FN_2O_4S$

[a] (A) Trituration with petroleum ether; (B) flash chromatography ($CHCl_3$/MeOH/NH_4OH 90:10:1 as eluent).
[b] Waxy solid.

1.46 (s, 9H); 3.32 (t, 2H, J = 5.6 Hz); 3.44 (q, 2H, J = 4.0 Hz); 3.62 (t, 2H, J = 5.6 Hz); 4.03 (s, 2H) ppm. Anal $C_{11}H_{20}N_2O_3$ (C, H, N).

tert-Butyl 4-propyl-3-oxopiperazine-1-carboxylate (**40**) (46% yield). ^{1}H NMR ($CDCl_3$) δ: 0.90 (t, 3H, J = 7.2 Hz); 1.45 (s, 9H); 1.52–1.63 (m, 2H); 3.31–3.38 (m, 4H); 3.62 (t, 2H, J = 5.2 Hz); 4.06 (s, 2H) ppm ^{13}C NMR ($CDCl_3$) δ: 11.20, 20.23, 28.30, 46.24, 47.72, 48.62, 80.75, 153.84, 165.63 ppm. Anal $C_{12}H_{22}N_2O_3$ (C, H, N).

tert-Butyl 4-benzyl-3-oxopiperazine-1-carboxylate[16] (**41**) ^{1}H NMR ($CDCl_3$) δ: 1.47 (s, 9H); 3.26 (t, 2H, J = 5.2 Hz); 3.59 (t, 2H, J = 5.2 Hz); 4.17 (s, 2H); 4.63 (s, 2H); 7.26–7.34 (m, 5H) ppm.

5.1.3. General procedures for the removal of BOC. (A) The N^4-BOC-N^1-alkyl-2-oxopiperazine derivatives **39**–**41** (1 mmol) were treated with TFA (2 mL) at 0 °C, the solution was allowed to warm to room temperature and stirred for 3 h. The solvent was removed under vacuum and the residue was treated with a saturated solution of $NaHCO_3$ and extracted with ethyl acetate. Drying (Na_2SO_4) and removal of the solvent gave a residue which was used as such in the following step. According to this method the following 1-alkyl-2-oxopiperazines were obtained.

4-Ethyl-3-oxopiperazine (**42**)[17] ^{1}H NMR (DMSO-d6) δ: 1.01 (t, 3H, J = 7.2 Hz); 2.85 (t, 2H, J = 5.6 Hz); 3.17–3.32 (m, 6H) ppm.

4-Propyl-3-oxopiperazine (**43**)[18] ^{1}H NMR ($CDCl_3$) δ: 0.94 (t, 3H, J = 7.2 Hz); 1.58–1.64 (m, 2H); 2.21 (br s, 1H); 3.12 (t, 2H, J = 5.0 Hz); 3.33–3.39 (m, 4H); 3.56 (s, 2H) ppm.

4-Benzyl-3-oxopiperazine (**44**)[19] ^{1}H NMR ($CDCl_3$) δ: 2.13 (br s, 1H); 3.05 (t, 2H, J = 5.2 Hz); 3.24 (t, 2H, J = 5.2 Hz); 3.62 (s, 2H); 4.62 (s, 2H); 7.27–7.38 (m, 5H) ppm.

(B) The suitable starting material (1 mmol) was dissolved in the minimum amount of ethyl acetate and 2 N HCl (1 mL) was added. The mixture was stirred at room temperature for the suitable time, then the solvent was evaporated under vacuum, the residue was treated with a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. Drying (Na_2SO_4) and removal of the solvent gave a residue, mainly as an oil, which was used as such in the following step. The compounds prepared according to this method are reported in Table 4, together with other experimental details. NMR-spectra are reported in Table 7.

5.1.4. Synthesis of compounds 7–13. A solution of the suitable N^4-substituted-2-piperazinone (1 mmol) in anhydrous THF (5 mL), kept at −78 °C, was treated with LiHMDS (1 equiv) and, after 5 min stirring, with the suitable acyl or sulfonyl chloride (1.2 equiv). The mixture was allowed to warm to room temperature, then it was treated with a saturated solution of NaCl. After removal of the solvent under vacuum, the residue was

Table 6. Spectroscopic data for compounds reported in Table 3

N	[^{1}H] NMR ($CDCl_3$) δ:	[^{13}C] NMR ($CDCl_3$) δ:
1[a]	1.16 (t, 3H, *J* = 7.6 Hz); 2.34–2.38 (m, 2H); 3.26–3.28 (m, 2H); 3.63 (t, *J* = 5.2 Hz, 33.3%) and 3.78 (t, *J* = 5.2 Hz, 66.6%) (2H); 4.21 (s, 66.6%) and 4.34 (s, 33.3%) (2H); 4.63 (s, 2H); 7.25–7.37 (m, 5H) ppm	26.53, 29.69, 38.72, 42.46, 45.21, 45.63, 46.32, 48.93, 49.81, 50.10, 127.62, 127.77, 127.90, 128.24, 128.39, 135.91, 164.68, 172.23 ppm
2[a]	2.10 (s, 33.3%) and 2.12 (s, 66.6%) (3H); 3.25–3.32 (m, 2H); 3.63 (t, *J* = 4.0 Hz, 33.3%) and 3.76 (t, *J* = 4.0 Hz, 66.6%) (2H); 4.21 (s, 66.6%) and 4.32 (s, 33.3%) (2H); 4.63 (s, 66.6%) and 4.64 (s, 33.3%) (2H); 7.25–7.33 (m, 5H) ppm	21.10, 21.34, 38.58, 43.38, 45.16, 45.56, 46.16, 49.68, 49.83, 50.11, 127.78, 127.89, 127.93, 128.24, 128.85, 135.86, 136.03, 164.57, 165.57, 168.62, 168.95 ppm
3	0.93 (t, 3H, *J* = 7.6 Hz); 1.61 (q, 2H, *J* = 7.6 Hz); 3.37–3.48 (m, 4H); 3.89–4.02 (m, 2H), 4.08–4.25 (m, 2H), 7.44 (s, 5H) ppm	11.22, 20.23, 29.68, 48.55, 48.61, 127.29, 128.53, 130.49, 170.13, 183.40 ppm
4	0.89 (t, 3H, *J* = 6.8 Hz); 1.54 (q, 2H, *J* = 6.8 Hz); 3.31–3.42 (m, 6H); 3.71 (s, 2H); 7.25–7.28 (m, 2H); 7.82–7.85 (m, 2H) ppm	11.14, 20.09, 43.08, 46.14, 48.52, 48.75, 116.73 (d, *J* = 22 Hz), 130.58 (d, *J* = 9 Hz); 163.34, 165.59 (d, *J* = 255 Hz) ppm
5	1.10 (t, 3H, *J* = 7.2 Hz); 3.32–3.35 (m, 2H); 3.39–3.44 (m, 4H); 3.70 (s, 2H); 7.18–7.33 (m, 2H); 7.81–7.83 (m, 2H) ppm	11.98, 41.66, 43.05, 45.46, 48.78, 116.72 (d, *J* = 23 Hz), 130.57 (d, *J* = 10 Hz), 131.16, 163.07, 165.58 (d, *J* = 255 Hz) ppm
6	1.18 (t, 3H, *J* = 7.2 Hz); 1.38 (d, 6H, *J* = 6.8 Hz); 3.24 (sept, 1H, *J* = 6.8 Hz); 3.43 (t, 2H, *J* = 5.2 Hz); 3.48 (q, 2H, *J* = 7.2 Hz); 3.62 (t, 2H, *J* = 5.2 Hz); 4.00 (s, 2H) ppm	12.07, 16.60, 41.83, 43.38, 46.67, 48.92, 53.76, 163.78 ppm
14	1.15 (t, 3H, *J* = 7.6 Hz); 1.27–1.46 (m, 2H); 1.49–1.58 (m, 1H); 1.75 (d, 2H, *J* = 13.2 Hz); 2.17–2.30 (m, 4H); 3.14 (t, 2H, *J* = 6.4 Hz); 3.80 (d, 2H, *J* = 13.2 Hz); 5.59 (br s, 1H); 7.20–7.28 (m, 2H); 7.76–7.80 (m, 2H) ppm	9.90, 29.10, 29.62, 35.37, 44.32, 46.00, 116.29 (d, *J* = 23 Hz), 130.24 (d, *J* = 9 Hz), 132.35, 165.17 (d, *J* = 254 Hz), 174.08 ppm
15	1.18 (t, 3H, *J* = 7.6 Hz); 1.15–1.32 (m, 1H); 1.74–1.87 (m, 4H); 2.23 (q, 2H, *J* = 7.6 Hz); 2.71–3.32 (br m, 4H); 3.71–3.78 (m, 1H); 4.69–4.82 (m, 1H); 5.59–5.68 (m, 1H); 7.41 (s, 5H) ppm	10.01, 25.50, 28.60, 28.80, 36.54, 44.69, 119.83, 126.79, 128.47, 175.01, 178.23 ppm
16	1.12–1.29 (m, 2H); 1.33 (d, 6H, *J* = 6.8 Hz); 1.61–1.71 (m, 1H); 1.77 (d, 2H, *J* = 12.8 Hz); 2.81–2.87 (m, 4H); 3.17 (quint, 1H, *J* = 6.8 Hz); 3.84 (m, 2H, *J* = 12.8 Hz); 4.64–4.68 (m, 1H); 7.21–7.28 (m, 2H); 7.88–7.91 (m, 2H) ppm	16.75, 30.01, 36.15, 46.11, 48.33, 53.34, 116.43 (d, *J* = 22 Hz), 129.73 (d, *J* = 9 Hz), 136.05, 165.10 (d, *J* = 253 Hz) ppm
17	1.01–1.19 (m, 2H); 1.62–1.84 (m, 3H); 2.09 (s, 3H); 2.49–2.55 (m, 1H); 2.85–2.89 (m, 2H); 3.00–3.05 (m, 1H); 3.82–3.85 (m, 1H); 4.56–4.68 (m, 2H); 7.20–7.28 (m, 2H); 7.88–7.91 (m, 2H) ppm	21.30, 23.50, 36.46, 37.21, 48.28, 116.36 (d, *J* = 23 Hz), 129.69 (d, *J* = 10 Hz), 138.20, 169.30 (d, *J* = 254 Hz), 175.17 ppm
18	1.01–1.18 (m, 2H); 1.12 (t, 3H, *J* = 7.4 Hz); 1.65–1.85 (m, 3H); 2.33 (q, 2H, *J* = 7.4 Hz); 2.46–2.58 (m, 1H); 2.81–2.84 (m, 2H); 2.93–2.99 (m, 1H); 3.75–3.86 (m, 1H); 4.58–4.61 (m, 1H); 7.17–7.26 (m, 2H); 7.77–7.90 (m, 2H) ppm	9.58, 26.56, 29.89, 36.57, 41.45, 45.21, 116.34 (d, *J* = 22 Hz), 129.69 (d, *J* = 9 Hz), 136.21, 165.01 (d, *J* = 253 Hz), 172.26 ppm
19	1.24–1.34 (m, 2H); 1.44–1.50 (m, 1H); 1.75 (d, 2H, *J* = 12.0 Hz); 2.22–2.28 (m, 2H); 2.83 (t, 2H, *J* = 6.8 Hz); 3.82 (m, 2H, *J* = 12.0 Hz); 4.41–4.44 (m, 1H); 7.19–7.26 (m, 4H); 7.76–7.81 (m, 2H); 7.84–7.89 (m, 2H) ppm	28.43, 34.67, 45.57, 47.34, 116.63 (d, *J* = 23 Hz), 116.51 (d, *J* = 24 Hz), 129.43 (d, *J* = 9 Hz), 130.53 (d, *J* = 10 Hz), 141.20, 141.70, 165.04 (d, *J* = 254 Hz), 165.15 (d, *J* = 255 Hz) ppm
20	1.19 (t, 3H, *J* = 7.6 Hz); 1.49–1.56 (m, 1H); 1.65–1.82 (m, 3H); 2.27 (q, 2H, *J* = 7.6 Hz); 2.63–2.68 (m, 1H); 2.85 (dd, 1H, *J* = 11.8 Hz, *J* = 2.4 Hz); 3.26 (dd, 1H, *J* = 11.8 Hz, *J* = 4.0 Hz); 3.40–3.46 (m, 1H); 4.13–4.18 (br m, 1H); 6.01 (br s, 1H); 7.22–7.28 (m, 2H); 7.77–7.80 (m, 2H) ppm	9.87, 21.42, 28.20, 29.59, 43.99, 46.54, 50.51, 116.45 (d, *J* = 23 Hz), 130.27 (d, *J* = 9 Hz), 132.20, 166.57 (d, *J* = 254 Hz), 173.76 ppm
21	1.48–1.69 (m, 1H); 1.72–1.83 (m, 3H); 2.03 (s, 3H); 2.60–2.65 (m, 1H); 2.82 (dd, 1H, *J* = 11.6 Hz, *J* = 2.8 Hz); 3.27 (dd, 1H, *J* = 11.6 Hz, *J* = 4.4 Hz); 3.44–3.46 (m, 1H); 4.15–4.17 (m, 1H); 5.93–5.95 (m, 1H); 7.22–7.28 (m, 2H); 7.77–7.80 (m, 2H) ppm	21.41, 23.37, 28.25, 44.01, 46.55, 50.56, 116.49 (d, *J* = 22 Hz), 130.29 (d, *J* = 10 Hz), 132.08, 165.29 (d, *J* = 254 Hz), 169.65 ppm
22	1.27–1.38 (m, 1H); 1.33–1.38 (m, 6H); 1.55–1.63 (m, 1H); 1.69–1.78 (m, 2H); 1.84–1.98 (m, 1H); 2.87–2.92 (m, 1H); 2.96–3.07 (m, 1H); 3.09–3.22 (m, 2H); 3.62–3.74 (m, 1H); 4.57–4.59 (m, 1H); 7.22–7.36 (m, 2H); 7.78–7.81 (m, 2H) ppm	16.78, 21.61, 30.79, 46.27, 48.87, 51.81, 54.46, 116.54 (d, *J* = 22 Hz), 130.32 (d, *J* = 9 Hz), 133.02, 165.29 (d, *J* = 254 Hz) ppm
23	1.17 (t, 3 H, *J* = 7.6 Hz); 1.34–1.36 (m, 6H); 1.60–1.88 (m, 4H); 2.24 (q, 2H, *J* = 7.6 Hz); 3.09–3.23 (m, 2H); 3.34–3.44 (m, 2H); 3.59–3.63 (m, 1H); 4.00–4.06 (br m, 1H); 6.08 (br s, 1H) ppm	9.80, 16.67, 22.35, 28.51, 29.82, 44.13, 46.93, 50.56, 53.43, 173.50.
24	1.34–1.40 (m, 6H); 1.58–1.90 (m, 4H); 2.02 (s, 3H); 3.08–3.17 (m, 1H); 3.19–3.24 (m, 1H); 3.35 (dd, 1H, *J* = 13.2 Hz, *J* = 2.8 Hz); 3.45 (dd, 1H, *J* = 13.2 Hz, *J* = 3.6 Hz); 3.63–3.66 (m, 1H); 4.00–4.10 (m, 1H); 6.07 (br s, 1H) ppm	16.97, 22.57, 23.12, 28.65, 44.55, 46.78, 50.45, 53.35, 169.87 ppm
25	1.30 (d, 6H, *J* = 6.8 Hz); 1.50–1.67 (m, 2H); 1.72–1.75 (m, 2H); 3.00–3.04 (m, 1H); 3.14 (sept, 1H, *J* = 6.8 Hz); 3.27–3.44 (m, 4H); 5.31 (br s, 1H); 7.19–7.24 (m, 2H); 7.92–7.96 (m, 2H) ppm	16.67, 22.94, 30.47, 46.49, 48.81, 51.20, 53.49, 116.44 (d, *J* = 22 Hz), 128.84 (d, *J* = 9 Hz), 133.10, 166.38 (d, *J* = 254 Hz) ppm
26	1.38–1.83 (m, 4H); 2.11 (s, 3H); 3.21–3.50 (m, 4H); 3.68–3.70 (m, 1H); 4.84 (br s, 1H); 7.21–7.26 (m, 2H); 7.79–7.96 (m, 2H) ppm	21.40, 22.11, 22.91, 30.37, 30.96, 41.59, 46.54, 46.61, 49.33, 49.71, 52.39, 116.44 (d, *J* = 22 Hz), 129.63 (d, *J* = 9 Hz), 137.81, 165.08 (d, *J* = 253 Hz), 169.83 ppm

Table 6 (*continued*)

N	[^{1}H] NMR ($CDCl_3$) δ:	[^{13}C] NMR ($CDCl_3$) δ:
27	1.15 (t, 3H, J = 6.8 Hz); 1.28–1.82 (m, 4H); 2.39–2.40 (m, 2H); 3.20–3.50 (m, 4H); 3.70–3.78 (m, 1H); 4.92–5.01 (m, 1H); 7.21–7.25 (m, 2H); 7.90–7.94 (m, 2H) ppm	9.43, 22.53, 22.95, 26.42, 30.70, 31.11, 41.65, 45.79, 46.74, 49.50, 49.91, 51.49, 116.46 (d, J = 22 Hz), 129.71 (d, J = 9 Hz), 138.93, 165.10 (d, J = 254 Hz), 170.63 ppm
28	1.27–2.19 (m, 11 H); 2.91–3.65 (br m, 4H); 3.65–4.24 (br m, 2H); 7.43 (s, 5H) ppm	16.56, 23.26, 27.59, 32.29, 54.23, 127.09, 128.52, 129.96, 135.41, 171.60 ppm
29	1.11–1.19 (m, 3H); 1.54–1.68 (m, 1H); 1.69–1.78 (m, 1H); 1.83–1.84 (m, 1H); 1.92–1.94 (m, 1H); 2.10 (s, 3H, 66.6%); 2.13 (s, 3H, 33.3%); 2.16–2.25 (m, 2H); 3.11–3.22 (m, 1H); 3.32–3.68 (m, 2H); 3.73–3.77 (m, 1H); 3.91–3.98 (m, 1H); 5.62 (br s, 1H, 66.6%); 5.74 (br s, 1H, 33.3%) ppm	9.84, 21.46, 22.57, 23.05, 29.46, 29.57, 29.80, 41.78, 45.59, 45.88, 46.20, 46.99, 50.91, 169.63, 173.71 ppm
30	1.16–1.42 (m, 3H); 1.65–2.38 (m, 8H); 3.46–3.53 (m, 1H); 3.74 (d, 1H, J = 12.8 Hz); 4.05–4.15 (m, 1H); 5.32–6.09 (br s, 1H); 7.44 (s, 5H) ppm	9.80, 21.56, 22.30, 22.32, 29.69, 43.80, 48.50, 127.18, 128.54, 130.02, 135.43, 182.79, 187.82 ppm
31	1.68–2.08 (m, 4H); 2.12 (s, 3H, 60%); 2.19 (s, 3H, 40%); 3.34–4.18 (m, 5H); 6.15 (br s, 1H, 60%); 6.63 (br s, 1H, 40%); 7.29–7.56 (m, 3H); 7.76–7.77 (m, 2H) ppm	21.43, 22.76, 23.20, 29.28, 29.84, 41.83, 46.56, 46.64, 47.23, 50.85, 126.13, 126.97, 128.54, 128.62, 131.48, 131.74, 134.13, 134.30, 167.15, 167.50, 169.70, 170.62 ppm
32	1.09–1.21 (m, 3H); 1.61–1.90 (m, 3H); 2.05–2.20 (m, 1H); 2.31–2.48 (m, 2H); 3.25–3.69 (m, 3H); 3.83–4.17 (m, 2H); 6.18 (br s, 1H, 63%); 6.67 (br s, 1H, 37%); 7.45–7.54 (m, 3H); 7.75–7.77 (m, 2H) ppm	9.58, 22.95, 26.65, 30.06, 41.96, 46.64, 50.06, 126.90, 128.66, 131.77, 134.22, 167.12, 171.23 ppm
33	1.49–1.61 (m, 2H); 1.67–1.76 (m, 1H); 1.82–2.02 (m, 2H); 2.12 (s, 3H); 2.94–3.08 (m, 1H); 3.38–3.47 (m, 2H); 3.51–3.63 (m, 2H); 3.65–3.81 (m, 1H); 7.27 (br s, 1H); 7.40–7.48 (m, 3H); 7.85–7.87 (m, 2H) ppm	21.18, 23.63, 27.67, 34.78, 40.67, 44.96, 47.74, 127.04, 128.51, 131.35, 134.45, 168.20 ppm
34	1.10–1.18 (m, 3H); 1.41–1.59 (m, 2H); 1.64–1.78 (m, 1H); 1.79–1.99 (m, 2H); 2.24–2.43 (m, 2H) 2.92–3.09 (m, 1H); 3.34–3.56 (m, 2H); 3.60–3.78 (m, 3H); 7.21–7.26 (br s, 1H); 7.42–7.48 (m, 3H); 7.81–7.85 (m, 2H) ppm	9.76, 23.80, 24.39, 26.51, 34.93, 40.73, 45.09, 46.84, 127.06, 128.57, 131.54, 134.50, 168.72, 173.98 ppm
35	1.04–1.07 (m, 1H); 1.59–1.64 (m, 1H); 1.68–1.79 (m, 2H); 1.81–1.96 (m, 1H); 2.00 (s, 3H); 2.28–2.33 (m, 1H); 2.48–2.53 (m, 1H); 3.11–3.23 (m, 2H); 3.42–3.51 (m, 2H); 6.04 (br s, 1H); 7.20–7.24 (m, 2H); 7.75–7.79 (m, 2H) ppm	23.20, 23.69, 27.45, 35.86, 42.05, 46.72, 49.63, 116.38 (d, J = 23 Hz), 130.21 (d, J = 9 Hz), 132.30, 165.19 (d, J = 254 Hz), 170.66 ppm
36	1.38–1.54 (m, 1H); 1.55–1.71 (m, 1H); 1.72–1.97 (m, 3H); 2.05 (br s, 3H); 2.12–2.25 (m, 1H); 2.92–3.01 (m, 1H); 3.23–3.38 (m, 1H); 3.43–3.59 (m, 1H); 3.53–3.82 (m, 1H); 3.93–4.06 (m, 1H); 5.61 (br s, 1H, 25%); 6.44 (br s, 1H, 75%); 7.40–7.43 (m, 5H) ppm	9.10, 26.70, 28.51, 32.02, 33.98, 37.81, 49.16, 126.91, 128.55, 129.78, 135.20, 143.42 ppm
37	1.07–1.12 (m, 1H); 1.15–1.23 (m, 3H); 1.60–1.79 (m, 3H); 1.80–1.90 (m, 1H); 2.22–2.32 (m, 2H); 2.34–2.36 (m, 1H); 2.52–2.57 (m, 1H); 3.14–3.18 (m, 1H); 3.22–3.26 (m, 1H); 3.41–3.48 (m, 2H); 5.83 (br s, 1H); 7.20–7.29 (m, 2H); 7.75–7.78 (m, 2H) ppm	9.96, 23.63, 27.41, 29.70, 35.87, 41.76, 46.72, 49.54, 116.37 (d, J = 23 Hz), 130.19 (d, J = 9 Hz), 132.40, 165.18 (d, J = 253 Hz), 174.07 ppm
38	1.31–1.42 (m, 1H); 1.45–1.54 (m, 1H); 1.60–1.70 (m, 1H); 1.71–1.89 (m, 2H); 2.08 (s, 3H); 2.70–2.81 (m, 1H); 2.82–2.98 (m, 1H); 2.99–3.10 (m, 1H); 3.21–3.32 (m, 1H); 3.48–3.56 (m, 1H); 3.86–3.94 (m, 1H); 5.78 (br s, 1H); 7.17–7.21 (m, 2H); 7.87–7.92 (m, 2H) ppm	9.20, 21.20, 24.03, 27.77, 35.28, 44.69, 47.45, 116.24 (d, J = 20 Hz), 129.73 (d, J = 9 Hz), 136.78, 167.30 (d, J = 254 Hz), 178.40 ppm
45[a]	2.13 (s, 60%) and 2.16 (s, 40%) (3H); 3.38–3.41 (m, 60%) and 3.41–3.46 (m, 40%) (2H); 3.68 (t, 40%, J = 5.2 Hz) and 3.82 (t, 60%, J = 5.2 Hz) (2H); 4.13 (s, 60%) and 4.24 (s, 40%) (2H); 6.88 (br s, 60%) and 7.16 (br s, 40%) (1H) ppm	
46[a]	1.14 (t, 3H, J = 7.2 Hz); 2.32–2.38 (m, 2H); 3.36–3.39 (m, 56%) and 3.39–3.43 (m, 44%) (2H); 3.64 (t, 44%, J = 5.2 Hz) and 3.79 (t, 56%, J = 5.2 Hz) (2H); 4.09 (s, 56%) and 4.21 (s, 44%) (2H); 7.55 (br s, 56%) and 7.83 (br s, 44%) (1H) ppm	
47	3.35–3.53 (br m, 1H); 3.53–4.10 (br m, 2H); 4.20–4.50 (m, 2H); 7.44–7.47 (m, 5H) ppm	
48	3.34–3.36 (m, 2H); 3.49–3.50 (m, 2H); 3.75 (s, 2H); 5.88 (br s, 1H); 7.26–7.29 (m, 2H); 7.85–7.86 (m, 2H) ppm	
50	1.08–1.16 (m, 2H); 1.17 (t, 3H, J = 7.6 Hz); 1.46 (s, 9H); 1.66–1.68 (m, 3H); 2.23 (q, 2H, J = 7.6 Hz); 2.69 (t, 2H, J = 12.4 Hz); 3.12–3.21 (m, 2H); 4.10–4.13 (m, 2H); 5.62 (br s, 1H) ppm	9.96, 28.45, 29.77, 36.41, 43.66, 44.84, 79.41, 154.82, 173.99 ppm
51	1.08–1.16 (m, 2H); 1.45 (s, 9H); 1.61–1.72 (m, 3H); 2.59–2.68 (m, 2H); 2.82–2.85 (m, 2H); 4.10–4.17 (m, 2H); 4.91 (br s, 1H); 7.19–7.23 (m, 2H); 7.87–7.89 (m, 2H) ppm	28.43, 29.53, 36.46, 48.56, 79.53, 116.38 (d, J = 22 Hz), 129.71 (d, J = 9 Hz), 136.88, 154.96, 165.07 (d, J = 254 Hz) ppm

(*continued on next page*)

Table 6 (*continued*)

N	[^{1}H] NMR ($CDCl_3$) δ:	[^{13}C] NMR ($CDCl_3$) δ:
54	1.38–1.47 (m, 1H); 1.60–1.68 (m, 1H); 1.75–1.82 (m, 1H); 1.84–1.91 (m 1H); 2.05 (br s, 1H); 2.68–2.74 (m, 1H); 2.78–2.83 (m, 1H); 3.13–3.19 (m, 1H); 3.36 (dd, 1H, J = 11.2 Hz, J = 3.2 Hz); 3.86–3.92 (m, 1H); 7.21–7.28 (m, 2H); 7.78–7.81 (m, 2H) ppm	21.79, 31.64, 46.20, 52.49, 65.67, 116.40 (d, J = 22 Hz), 130.28 (d, J = 9 Hz), 134.31, 165.22 (d, J = 254 Hz) ppm
55	1.35 (d, 6 H, J = 6.8 Hz); 1.52–1.62 (m, 2H); 1.83–1.92 (m, 2H); 2.03 (br s, 1H); 3.07–3.15 (m, 1H); 3.17–3.25 (m, 2H); 3.37–3.42 (m, 1H); 3.59 (dd, 1H, J = 12.8 Hz, J = 3.6 Hz); 3.82 (m, 1H) ppm	16.74, 22.43, 31.88, 46.52, 52.61, 53.42, 65.75 ppm
59	1.38–1.49 (m, 1H); 1.42 (s, 9H); 1.61–1.69 (m, 1H); 1.70–1.76 (m, 1H); 2.96–3.71 (m, 6H); 5.42–5.45 (m, 1H); 7.17–7.21 (m, 2H); 7.90–7.93 (m, 2H) ppm	
60	1.39 (d, 6H, J = 6.8 Hz); 1.47 (s, 9H); 1.51–1.78 (m, 4H); 1.93–2.01 (m, 1H); 3.17–3.29 (m, 2H); 3.46–3.52 (m, 1H); 3.70–3.75 (m, 2H); 4.34 (br s, 1H) ppm	16.77, 22.76, 28.36, 32.10, 44.62, 49.66, 54.33, 80.13, 193.22 ppm
61	1.13 (t, 3H, J = 7.6 Hz); 1.46 (s, 9H); 1.47–1.80 (m, 4H); 2.20 (q, 2H, J = 7.6 Hz); 3.27–3.56 (m, 4H); 3.91–4.09 (m, 1H); 5.65 (br s, 1H) ppm	9.86, 22.48, 28.36, 29.74, 45.13, 79.84, 173.24, 175.82 ppm
62	1.46 (s, 9H); 1.51–1.87 (m, 3H); 3.30–3.79 (m, 5H); 4.09–4.21 (m, 1H); 6.40 (br s, 1H); 7.42–7.49 (m, 3H); 7.75–7.77 (m, 2H) ppm	19.24, 22.24, 28.38, 29.54, 48.62, 80.10, 126.90, 128.55, 131.50, 134.54, 162.41, 166.99 ppm
68	1.17–1.32 (m, 1H); 1.36–1.47 (m, 1H); 1.45 (s, 9H); 1.59–1.82 (m, 3H); 1.98 (s, 3H); 2.68–3.75 (m, 6H); 6.15 (br s, 1H) ppm	23.20, 23.90, 27.82, 28.27, 28.40, 28.96, 35.61, 41.78, 79.49, 154.98, 170.29 ppm
69	1.17 (t, 3H, J = 7.6 Hz); 1.30–1.45 (m, 1H); 1.46–1.50 (m, 1H); 1.46 (s, 9H); 1.62–1.99 (m, 3H); 2.24 (q, 2H, J = 7.6 Hz); 2.86–3.70 (m, 6H); 5.59 (br s, 1H) ppm	9.57, 23.95, 28.06, 28.27, 28.36, 28.88, 35.72, 40.01, 79.62, 154.89, 174.08 ppm
70	1.43–1.52 (m, 2H); 1.47 (s, 9H); 1.65–1.73 (m, 1H); 1.82–1.97 (m, 2H); 3.16–3.87 (br m, 6H); 6.81–7.02 (br s, 1H), 7.42–7.52 (m, 3H); 7.81–7.82 (m, 2H) ppm	23.63, 27.82, 28.21, 28.42, 35.21, 38.20, 79.52, 126.98, 127.70, 128.64, 134.62, 154.20, 167.65 ppm
71	1.22–1.34 (m, 1H); 1.35–1.50 (m, 1H); 1.44 (s, 9H); 1.57–1.78 (m, 4H); 2.78–2.82 (m, 1H); 2.92–3.14 (m, 2H); 3.17 (br s, 1H); 3.35–3.62 (m, 2H); 7.18–7.22 (m, 2H); 7.88–7.91 (m, 2H) ppm	23.46, 27.88, 28.38, 35.59, 45.21, 46.64, 49.26, 79.75, 116.29 (d, J = 22 Hz), 129.70 (d, J = 10 Hz), 136.30, 155.29, 164.98 (d, J = 253 Hz) ppm

[a] Mixture of conformers.

treated with a saturated solution of $NaHCO_3$ and extracted with Et_2O or ethyl acetate. Drying (Na_2SO_4) and removal of the solvent gave a residue which was purified in a suitable way (Table 5). The NMR-spectra of compounds **7**–**13** are reported in Table 8.

5.1.5. Synthesis of compounds 56 and 57. The suitable 3-hydroxy-*N*-sulfonylpiperazine (compound **54** or **55**, 1 equiv) was dissolved in acetone (5 mL) and the Jones reagent (1.1 equiv) was added at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2–4 h, then the reaction was quenched with 2-propanol. After filtration, the mixture was treated with saturated $NaHCO_3$ and extracted with Et_2O; the organic phase was washed with a saturated solution of NaCl, dried (Na_2SO_4) and the solvent was removed under vacuum, giving a residue which was purified no further. The following compounds were prepared.

5.1.5.1. 1-(4-Fluorophenylsulfonyl)piperidin-3-one. From compound **54**, mp 100–101 °C; 78% yield. ^{1}H NMR ($CDCl_3$) δ: 2.02–2.09 (m, 2H); 2.42 (t, 2H, J = 6.8 Hz); 3.34 (t, 2H, J = 6 Hz); 3.64 (s, 2H); 7.25–7.29 (m, 2H); 7.81–7.85 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$) δ: 22.78, 37.96, 44.54, 55.56, 116.69 (d, J = 23 Hz), 130.39 (d, J = 9 Hz), 131.83, 165.43 (d, J = 254 Hz) ppm. IR ν (cm^{-1}): 1729 (CO).

5.1.5.2. 1-(Isopropylsulfonyl)piperidin-3-one. From compound **55**, oil; 55% yield. ^{1}H NMR ($CDCl_3$) δ: 1.34 (d, 6H, J = 6.8 Hz); 2.03–2.10 (m, 2H); 2.52 (t, 2H, J = 6.4); 3.21 (sept, 1H, J = 6.8 Hz); 3.55 (t, 2H, J = 6 Hz); 3.86 (s, 2H) ppm. ^{13}C NMR ($CDCl_3$) δ: 16.66, 23.95, 38.18, 44.76, 53.67, 55.87 ppm.

A solution of the suitable carbonyl compound (1 equiv) in MeOH (6 mL for each mmol of reagent) was treated with ammonium acetate (10 equiv) and $NaBH_3CN$ (0.9 equiv). The mixture was stirred at room temperature for 48 h under N_2 atmosphere, then the solvent was evaporated under vacuum and the residue was treated with 2 N HCl and extracted with AcOEt. The aqueous layer was made alkaline with 10% NaOH and extracted with AcOEt, the organic phase was dried (Na_2SO_4) and the solvent was removed under vacuum, giving an oily residue. According to this procedure, the following compounds were prepared.

5.1.5.3. 1-(4-Fluorophenylsulfonyl)piperidin-3-amine 56. 35% yield. ^{1}H NMR ($CDCl_3$) δ: 1.13–1.17 (m, 1H); 1.63–1.68 (m, 1H); 1.78–1.84 (m, 2H); 2.08 (br s, 2H); 2.28–2.33 (m, 1H); 2.48–2.54 (m, 1H); 7.20–7.25 (m, 2H); 7.76–7.80 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$) δ: 22.92, 32.37, 46.17, 47.24, 53.67, 116.33 (d, J = 23 Hz), 130.25 (d, J = 9 Hz), 132.35, 166.44 (d, J = 254 Hz) ppm. IR ν (cm^{-1}): 3367 (NH). Anal $C_{11}H_{15}FN_2O_2S$ (C, H, N).

5.1.5.4. 1-(Isopropylsulfonyl)piperidin-3-amine 57. 38% yield after purification by flash chromatography

Table 7. Spectroscopic data for the compounds reported in Table 4

N	[^{1}H] NMR ($CDCl_3$) δ:	[^{13}C] NMR ($CDCl_3$) δ:
52	1.05–1.21 (m, 2H); 1.16 (t, 3H, J = 7.6 Hz); 1.57–1.69 (m, 3H); 2.08 (br s, 1H); 2.21 (q, 2H, J = 7.6 Hz); 2.55–2.61 (m, 2H); 3.07–3.15 (m, 4H); 5.66 (br s, 1H) ppm	9.97, 29.76, 30.94, 36.49, 45.33, 46.19, 174.29 ppm
53	1.05–1.19 (m, 2H); 1.53–1.66 (m, 1H); 1.67–1.70 (m, 2H); 1.93 (br s, 1H); 2.56–2.62 (m, 2H); 2.74 (d, 2H, J = 6.8 Hz); 3.10–3.13 (m, 2H); 7.20–7.24 (m, 2H); 7.88–7.92 (m, 2H) ppm	30.55, 36.44, 45.96, 48.98, 116.32 (d, J = 22 Hz), 129.71 (d, J = 10 Hz), 136.82, 165.01 (d, J = 254 Hz) ppm
63	1.45–1.51 (m, 2H); 1.65–1.67 (m, 2H); 2.52 (dd, 1H, J = 11.6 Hz, J = 6.4 Hz); 2.72–2.73 (m, 2H); 2.86 (dd, 1H, J = 11.6 Hz, J = 2.8 Hz); 3.33–3.39 (m, 1H); 7.17–7.28 (m, 2H); 7.91–7.93 (m, 2H) ppm	23.10, 31.12, 46.15, 49.72, 51.96, 116.28 (d, J = 23 Hz), 129.64 (d, J = 9 Hz), 137.42, 164.94 (d, J = 253 Hz) ppm
64	1.39 (d, 6H, J = 6.8 Hz); 1.50–1.67 (m, 2H); 1.71–1.92 (m, 2H); 2.70–2.83 (m, 4H); 3.07 (dd, 1H, J = 11.6 Hz, J = 2.8 Hz); 3.14 (sept, 1H, J = 6.8 Hz); 3.44–3.50 (m, 1H); 4.75 (br s, 1H) ppm	16.75, 32.11, 46.25, 50.27, 52.80, 52.99, 54.10 ppm
65	1.16 (t, 3H, J = 7.6 Hz); 1.49–1.60 (m, 2H); 1.63–1.77 (m, 2H); 1.96 (br s, 1H); 2.21 (q, 2H, J = 7.6 Hz); 2.58–2.63 (m, 1H); 2.77–2.79 (m, 2H); 3.00 (dd, 1H, J = 11.8 Hz, J = 3.2 Hz,); 3.93–3.96 (m, 1H); 6.03 (br s, 1H) ppm	9.96, 23.63, 29.87, 30.12, 45.33, 46.53, 51.48, 172.89 ppm
66	1.52–1.61 (m, 1H); 1.74–1.82 (m, 4H); 2.76–2.86 (m, 3H); 3.10 (dd, 1H, J = 11.8 Hz, J = 2.8 Hz); 4.19–4.20 (m, 1H); 6.76 (br s, 1H); 7.43–7.51 (m, 3H); 7.81–7.83 (m, 2H) ppm	23.43, 30.03, 45.79, 46.68, 51.53, 126.95, 128.51, 131.30, 135.10, 169.68 ppm
72	1.15–1.29 (m, 1H); 1.57–1.73 (m, 1H); 1.75–1.96 (m, 3H); 2.01–2.06 (m, 1H); 2.03 (s, 3H); 2.46–2.51 (m, 1H); 2.70 (td, 1H, J = 12.0 Hz, J = 2.8 Hz); 2.77–3.24 (m, 3H); 3.93 (br s, 1H); 6.14 (br s, 1H) ppm	23.12, 24.39, 28.26, 36.05, 42.91, 45.74, 49.28, 170.72 ppm
73	1.08–1.20 (m, 1H); 1.17 (t, 3H, J = 7.6 Hz); 1.42–1.52 (m, 1H); 1.67–1.72 (m, 2H); 1.78–1.81 (m, 1H); 2.21 (q, 2H, J = 7.6 Hz); 2.36 (t, 1H, J = 10.8 Hz); 2.59 (t, 1H, J = 10.8 Hz); 2.80 (br s, 1H); 2.99–3.20 (m, 4H); 5.89 (br s, 1H) ppm	9.99, 24.09, 28.11, 29.63, 35.92, 42.67, 45.68, 49.14, 174.39 ppm
74	1.22–1.36 (m, 1H); 1.59–1.62 (m, 1H); 1.75–1.79 (m, 1H); 1.84–1.88 (m, 1H); 1.94–1.98 (m, 1H); 2.53–2.59 (m, 1H); 2.68–2.73 (m, 1H); 2.90–3.08 (m, 1H); 3.19–3.22 (m, 1H); 3.33–3.41 (m, 2H); 3.66–3.69 (br m, 2H); 6.83 (br s, 1H); 7.36–7.52 (m, 3H); 7.77–7.89 (m, 2H) ppm	23.76, 27.93, 35.58, 43.12, 45.47, 48.92, 127.00, 128.46, 131.28, 134.32, 167.94 ppm
75	1.23–1.28 (m, 1H); 1.35–1.40 (m, 1H); 1.48–1.55 (m, 1H); 1.64–1.71 (m, 1H); 1.72–1.88 (m, 2H); 2.09 (br s, 1H); 2.69–2.96 (m, 2H); 3.07–3.15 (m, 1H); 3.20–3.33 (m, 1H); 3.42–3.54 (m, 1H); 3.75–3.77 (m, 1H); 5.64 (br s, 1H); 7.18–7.22 (m, 2H); 7.88–7.91 (m, 2H) ppm	35.40, 36.77, 23.95, 24.21, 27.84, 28.40, 44.96, 45.13, 46.00, 47.37, 49.96, 116.22 (d, J = 23 Hz), 129.72 (d, J = 9 Hz), 136.35, 169.51 (d, J = 254 Hz) ppm

Table 8. Spectroscopic data for compounds **7**–**13**

N	[^{1}H] NMR ($CDCl_3$) δ:	[^{13}C] NMR ($CDCl_3$) δ:
7[a]	2.15 (s, 48%) and 2.19 (s, 52%) (3H); 3.82 (t, 52%, J = 5.6 Hz) and 4.03 (t, 48%, J = 5.6 Hz) (2 H); 3.90–3.95 (m, 2H); 4.26 (s, 48%) and 4.39 (s, 52%) (2H); 7.40–7.59 (m, 5H) ppm	21.35, 21.53, 39.74, 43.02, 43.13, 43.65, 46.96, 50.49, 128.28, 128.70, 132.34, 132.43, 134.86, 166.91, 169.11, 169.26, 172.54, 172.60 ppm
8[a]	1.19–1.24 (m, 3H); 2.36–2.47 (m, 2H); 3.84 (t, 49%, J = 5.4 Hz) and 4.04 (t, 51%, J = 5.4 Hz) (2 H); 3.95–3.96 (m, 2H); 4.28 (s, 49%) and 4.42 (s, 51%) (2H); 7.42–7.55 (m, 5H) ppm	8.99, 26.55, 39.80, 42.74, 43.11, 43.17, 47.10, 49.70, 128.24, 128.36, 128.57, 134.88, 167.09, 168.08, 172.55 ppm
9	1.31 (t, 3H, J = 7.2 Hz); 2.89 (q, 2H, J = 7.2 Hz); 3.37 (t, 2H, J = 5.4 Hz); 3.86–3.88 (m, 4H); 7.26–7.30 (m, 2H); 7.83–7.87 (m, 2H) ppm	8.78, 33.06, 42.51, 43.20, 50.14, 116.88 (d, J = 23 Hz), 130.46 (d, J = 9 Hz), 131.22, 165.69 (d, J = 255 Hz), 166.21, 176.39 ppm
10	2.52 (s, 3H); 3.37 (t, 2H, J = 5.6 Hz); 3.85–3.89 (m, 4H); 7.27–7.31 (m, 2H); 7.84–7.86 (m, 2H) ppm	27.52, 42.50, 43.14, 50.12, 116.91 (d, J = 22 Hz), 130.60 (d, J = 9 Hz), 137.12, 165.71 (d, J = 255 Hz), 166.30, 172.41 ppm
11	1.12–1.16 (m, 3H); 2.90–3.05 (m, 2H); 3.55–3.96 (m, 4H); 4.22–4.58 (m, 2H); 7.43 (br s, 5H) ppm	8.78, 31.31, 33.02, 35.75, 42.51, 127.25, 128.76, 130.68, 134.26, 167.52, 170.13, 176.31 ppm
12	2.60 (s, 3H); 3.65–4.05 (m, 4H); 4.31–4.62 (m, 2H); 7.45–7.50 (m, 5H) ppm	27.50, 39.20, 42.12, 44.61, 127.39, 128.77, 130.71, 134.20, 167.66, 170.13, 172.37 ppm
13[a]	2.09 (s, 50%) and 2.19 (s, 50%) (3H); 3.76–3.82 (m, 50%) and 3.87–3.93 (m, 50%) (2H); 3.96–4.02 (m, 50%) and 4.03–4.08 (m, 50%) (2H); 4.17 (s, 50%) and 4.18 (s, 50%) (2H); 7.13–7.31 (m, 2H); 8.08–8.12 (m, 2H) ppm	

[a] Mixture of conformers.

(abs EtOH/NH_4OH/CH_2Cl_2/petroleum ether 65:8:340:60 as eluent). ^1H NMR ($CDCl_3$) δ: 1.20–1.29 (m, 1H); 1.34 (d, 6H, $J = 6.8$ Hz); 1.57–1.66 (m, 3H); 1.75–1.79 (m, 1H); 1.92–1.97 (m, 1H); 2.66–2.71 (m, 1H); 2.90–2.97 (m, 2H), 3.18 (sept, 1H, $J = 6.8$ Hz); 3.58–3.61 (m, 1H); 3.67–3.72 (m, 1H) ppm. IR ν (cm^{-1}): 3367 (NH). Anal $C_8H_{18}N_2O_2S$ (C, H, N).

5.1.6. Synthesis of *tert*-butyl 3-(aminomethyl)piperidine-1-carboxylate 67. A solution of commercially available nipecotamide (4 g, 31.2 mmol), Boc_2O (8.8 g, 40 mmol, 1.3 equiv) and DMAP (380 mg, 0.1 equiv) in anhydrous CH_3CN (60 mL) was stirred at room temperature under N_2 atmosphere for 24 h, then the solvent was removed under vacuum. The residue was treated with CH_2Cl_2, washed with saturated $NaHCO_3$; the aqueous phase was extracted again with CH_2Cl_2 and the combined organic phases were washed consecutively with a saturated solution of NH_4Cl, H_2O and a saturated solution of NaCl. After drying (Na_2SO_4) and removal of the solvent under vacuum, a residue was obtained which was purified by flash chromatography ($CHCl_3$/MeOH/NH_4OH 95:5:0.5 as eluent) giving *tert*-butyl 3-carbamoylpiperidine-1-carboxylate in 63% yield. ^1H NMR ($CDCl_3$) δ: 1.42–1.56 (m, 2H); 1.49 (s, 9H); 1.59–1.63 (m, 1H); 1.90–1.98 (m, 2H); 2.33–2.46 (m, 1H); 2.92–3.50 (bm, 2H); 3.52–3.95 (bm, 1H); 5.60 (br s, 1H); 6.52 (br s, 1H) ppm. This compound (0.5 g, 2.19 mmol) was dissolved in anhydrous THF and treated at 0 °C with $LiAlH_4$ (0.08 g, 2.19 mmol). The mixture was allowed to warm to room temperature, stirred for 24 h and then quenched with ice. The solvent was removed under vacuum, the residue was treated with a saturated solution of $NaHCO_3$ and extracted with AcOEt; the organic layer was collected and dried (Na_2SO_4). After removal of the solvent under vacuum, a residue was obtained which was purified by means of flash chromatography ($CHCl_3$/MeOH 98:2 as eluent) giving the desired compound in 21% yield. ^1H NMR ($CDCl_3$) δ: 0.85–0.90 (m, 1H); 1.08–1.26 (m, 3H); 1.43 (s, 9H); 1.38–1.52 (m, 1H); 1.59–1.68 (m, 1H); 1.78–1.81 (m, 1H); 2.49–2.61 (m, 2H); 2.84–2.90 (m, 1H); 3.63–3.68 (m, 1H); 3.75–3.78 (m, 1H); 3.85 (br s, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ: 28.43, 28.48, 33.20, 40.93, 41.08, 44.95, 79.39, 154.95 ppm.

5.2. Pharmacology

The mouse passive-avoidance test was performed according to a previously published protocol.[26]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2007.10.050.

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