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BRIEF ARTICLE

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Synthesis and Biological Evaluation of 3,7-Diazabicyclo[4.3.0]nonan-8-ones as Potential Nootropic and Analgesic Drugs

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Supporting Information

ABSTRACT: A series of *cis* and *trans* 3,7-diazabicyclo[4.3.0]nonan-8-ones has been synthesized and tested for their ability to revert scopolamine-induced amnesia in the mouse passive-avoidance test. The racemates of the most potent compounds **4** and **7** were separated and tested, but no enantioselectivity was found for the nootropic activity. Compounds **4** and **7** and their enantiomers displayed interesting antihyperalgesic activity in two models of neuropathic pain (streptozotocin-induced and oxalilplatin-induced neuropathy) in comparison with pregabalin.

INTRODUCTION

Cognition enhancers, or nootropics, are compounds that stimulate cognitive performance, acting through several different mechanisms, such as the modulation of signal transduction cascade or neurogenesis.[1] These substances can be useful in several kinds of cognitive dysfunctions, such as age-related memory deficits, neurodegenerative disorders, other neuropsychiatric conditions such as schizophrenia, and attention-deficit hyperactivity disorders.[2−6] Among nootropics, piracetam and piracetam-like compounds (Chart 1) have been studied for almost 4 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.[7,8] Although these substances are in general well tolerated, their use as nootropics is controversial because of the lack of a common mechanism of action at the molecular level. As a matter of fact, some members of the series have been shown to modulate neurotransmitter receptors (i.e., aniracetam, nefiracetam) or to bind to synaptic vesicle 2A protein (i.e., levetiracetam, brivaracetam). For others, such as the lead compound piracetam, the biological target has not been identified yet. Interestingly, for some members of this class, like those reported in Chart 1, the efficacy in some models of neuropathic pain has been shown,[9] although the mechanism of action is still unknown.

It has previously been reported that **1** (DM232, Chart 1) and **2** (DM235, Chart 1) show potent cognition-enhancing properties. Compound **1** shares some structural similarity with piracetam (the 2-oxopyrrolidine ring); however, **1** and its analogues **2** and **3a** (MN19, Chart 1), where the 2-oxopyrrolidine ring is no longer present, are 3−4 orders of magnitude more potent than piracetam.[10] These compounds are well tolerated in rodents, but their potential development has been hindered because their mechanism of action has not been clarified. In fact, **1** and **2** did not show affinity toward the most important central receptors or transporters. These compounds are able to increase acetylcholine release from rat brain and nitric oxide production in rat adipocytes, the latter effect being antagonized by nicotinic antagonists such as mecamylamine and methyllycaconitine.[11] There is evidence that AMPA receptors are involved in the cognition-enhancing effect of these compounds.[12] However, a direct interaction of **1** and **2** with nicotinic or AMPA receptors in vitro has not been proven yet.

In order to find new potent compounds, some 3,7-diazabicyclo-[4.3.0]nonan-8-ones **4**−**9** were designed. These substances represent rigid analogues of 4-acetylaminopiperidines, such as **3a** where the acetamido group has been constrained into a 2-oxopyrrolidine ring. The substituents on the nitrogen atom in position 3 were chosen among those giving, in the previous series, the most interesting results. The ring closure introduces two stereogenic centers into the molecule. Both the *cis* and *trans* isomers were studied, and in order to study enantioselectivity, the enantiomers of the most active compounds (**4** and **7**) were prepared. Compounds **4**−**9** were tested for their cognition-enhancing activity in the mouse passive avoidance test; moreover, since piracetam-like nootropics show interesting analgesic properties, their antihyperalgesic activity in two models of neuropathic pain was determined. Interestingly, two structural analogues of **1** were already reported to possess antihyperalgesic activity on the chronic constriction injury model of neuropathic pain.[13]

CHEMISTRY

Compounds **4**−**9** were prepared according to Scheme 1. Commercially available *N*-benzylpiperidone was transformed into ester **10** by treatment with LDA and ethyl bromoacetate.

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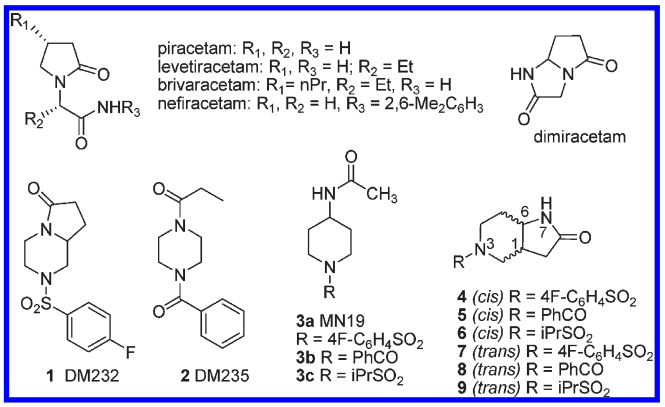
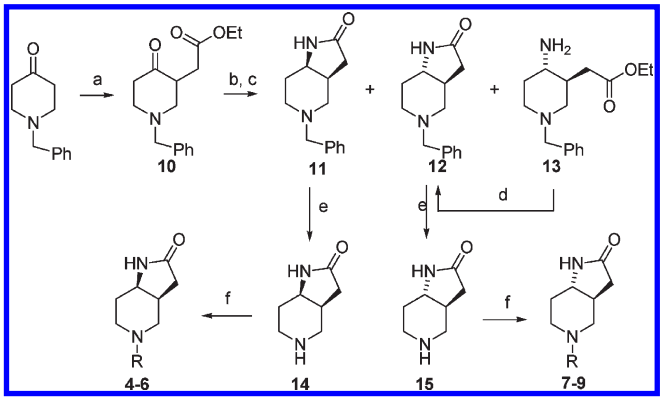
Chart 1



Scheme 1[a]



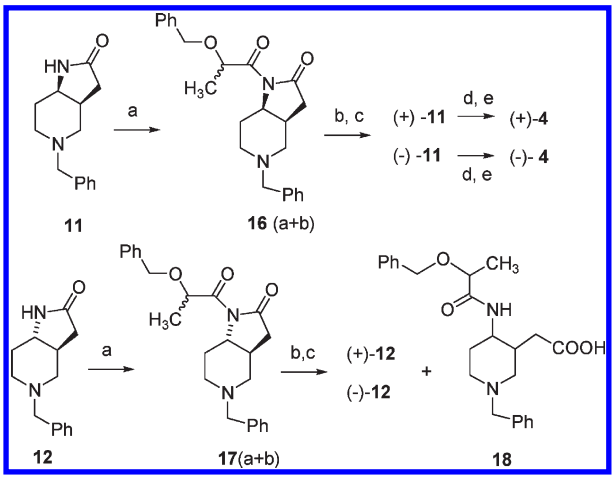
[a] (a) LDA, $BrCH_2COOEt$, THF, −78 °C; (b) $AcONH_4$, $NaBH_3CN$, MeOH; (c) chromatographic separation; (d) 100 °C; (e) H_2/Pd/C, abs EtOH; (f) RCl, Et_3N, CH_3CN.

Reductive amination with ammonium acetate gave a 2:1 mixture of *cis* and *trans* 3-benzyl-3,7-diazabicyclo[4.3.0]nonan-8-ones **11** and **12**, which were separated by column chromatography. A small amount of *trans* ethyl 2-(4-amino-1-benzylpiperidin-3-yl)acetate **13** was recovered and transformed into **12** by heating at 100 °C. Catalytic hydrogenation, followed by treatment of **14** and **15** with 4-fluorobenzenesulfonyl chloride, benzoyl chloride, or isopropylsulfonyl chloride gave, respectively, *cis* derivatives **4**−**6** and their *trans* analogues **7**−**9**.

The *cis* and *trans* stereochemistry was assessed by means of NMR. The NOESY spectrum of **4** showed a correlation between the peaks relative to H-1 and H-6, which are absent in the NOESY spectrum of **7**, allowing the assignment of a *cis* configuration to **4** and the *trans* configuration to **7**. In addition, the NOESY spectrum of **7** showed interactions between H-6 and protons in positions 2 and 4, which are closer in space in the *trans* isomer with respect to the *cis* one. These correlations were absent in the NOESY spectrum of **4**. Other evidence is reported in the Supporting Information.

The enantiomers of **4** were obtained according to Scheme 2. Amide **11** was treated with *n*-BuLi and (*R*)-2-benzyloxypropionyl chloride to obtain **16** as a 1:1 mixture of diastereoisomers, which were separated by chromatography, obtaining the single diastereoisomers **16a** and **16b**. The chromatographic separation was not efficient, since **16a** and **16b** were obtained in 40% and

Scheme 2[a]



[a] (a) *n*-BuLi, (*R*)-BnOCH(CH_3)COCl, THF, −78 °C; (b) chromatographic separation; (c) LiOH, 30% H_2O_2,THF/H_2O; (d) H_2/Pd/C, abs EtOH; (e) 4-F-C_6H_4-SO_2Cl, Et_3N, CH_3CN.

25% yields after two separations. Compounds **16a** and **16b** were treated separately with lithium hydroperoxide according to Evans,[14] to obtain (+)-**11** and (−)-**11**. Catalityc hydrogenation followed by treatment with 4-fluorobenzenesulfonyl chloride gave (+)-**4** and (−)-**4**. Their enantiomeric excess was the same as the commercially available (*R*)-2-benzoyloxypropionic acid (97%),[15] as shown by the NMR spectrum of **16a** and **16b**.

The same sequence of reactions was attempted on **12**. On this isomer chromatographic separation was more efficient, but the hydrolysis of diastereoisomers **17a** and **17b** proved to be difficult, since only small amounts of (+)-**12** and (−)-**12** were obtained, the main product (**18**) deriving from hydrolysis of the endocyclic amide linkage. Therefore, (+)-**7** and (−)-**7** were obtained by chiral HPLC separation of *rac*-**7** on Chiracel OD-H using 2-propanol−hexane as mobile phase, with ee higher than 99% (see Supporting Information). The low availability of the enantiomers of **4** and **7** did not allow the determination of their absolute configuration.

PHARMACOLOGY

The compounds were tested for their ability to revert scopolamine-induced amnesia in the mouse passive-avoidance test of Jarvik and Kopp,[16] slightly modified by us (see Supporting Information). The compounds were dissolved in saline and tested ip up to a dose of 10 mg/kg. The results are expressed as the minimal effective dose (MED, mg/kg) and are reported in Table 1, in comparison with piracetam, **3a**, and previously described 4-aminopiperidines **3b** and **3c**.[17] Compounds were considered inactive if they did not show activity up to a dose of 10 mg/kg, which is 4 orders of magnitude higher than the MED of the leads **1** and **2**.

The antihyperalgesic activity of **4** and **7** (racemate and enantiomers) was determined by means of the hot-plate test in the diabetic neuropathy induced by streptozotocin on mice and by means of the paw-pressure test in oxaliplatin induced hyperalgesia on rats.

RESULTS AND DISCUSSION

All the synthesized compounds were able to revert scopolamine-induced amnesia, with the exception of **6**. The 4-fluorobenzenesulfonyl substituent brought the highest activity into the molecules, since *rac*-**4** and *rac*-**7** show the lowest MED; on the contrary, the isopropylsulfonyl group was the least effective, since **6** is inactive

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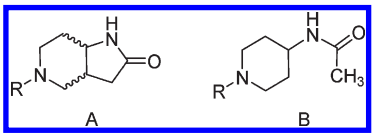
Table 1. Minimal Effective Dose (MED) of the Compounds against Scopolamine-Induced Amnesia in the Mouse Passive Avoidance Test, in Comparison with 4-Aminopiperidines[a]



treatment	structure	R	MED (mg/kg)	Δ(s)
saline				82.9
S				25.4^
4 + S	*cis*-A	$SO_2C_6H_4F$	0.1	66.5**
(−)-**4** + S	*cis*-A	$SO_2C_6H_4F$	0.1	53.1**
(+)-**4** + S	*cis*-A	$SO_2C_6H_4F$	0.1	48.1*
5 + S	*cis*-A	COPh	3.0	53.2**
6 + S	*cis*-A	$SO_2C_3H_7$	na[c]	
7 + S	*trans*-A	$SO_2C_6H_4F$	1.0	75.8**
(+)-**7** + S	*trans*-A	$SO_2C_6H_4F$	1.0	79.2**
(−)-**7** + S	*trans*-A	$SO_2C_6H_4F$	1.0	70.9**
8 + S	*trans*-A	COPh	3.0	55.4**
9 + S	*trans*-A	$SO_2C_3H_7$	10.0	65.9**
3a + S[b]	B	$SO_2C_6H_4F$	0.01	76.1**
3b + S[b]	B	COPh	10	100.7**
3c + S[b]	B	$SO_2C_3H_7$	1.0	75.4**
piracetam + S			30	82.4**

[a] All compounds were dissolved in saline and injected ip 20 min before training session. Each value represents the mean of 8−18 mice. Scopolamine (S) was injected immediately after punishment. The scores of training and retention sessions are reported in Supporting Information. * $P < 0.05$. ** $P < 0.01$ in comparison with scopolamine-treated mice. ^ $P < 0.01$ in comparison with saline-treated mice. [b] From ref 17. [c] This compound did not revert scopolamine-induced amnesia at doses up to 10 mg/kg ip.

and **9** shows a MED of 10 mg/kg. The same trend of activity was found in the 4-aminopiperidine series (**3**), where the 4-fluorobenzenesulfonyl derivatives were among the most potent compounds and the isopropylsulfonyl ones the least active.[17] The *cis*−*trans* configuration is important for the activity of diastereoisomers **4** and **7**, since the *cis* isomer **4** is more potent than its *trans* analogue **7**. The same trend is not observed for the other diastereomeric couples. As a matter of fact, **5** and **8** are equipotent and **9** shows a MED of 10 mg/kg while its *cis* isomer **6** is devoid of activity up to this dose. Different from what happened for the enantiomers of **1**, where the *R* isomer was 3−10 times more potent than the *S* form,[18] no enantioselectivity is observed in the nootropic activity of **4** and **7**.

Overall, these results show that the reduction of conformational flexibility did not increase the nootropic potency of 4-acetylaminopiperidines, as the sulfonyl derivatives are at least 10-fold less active than **3a** and **3c**, while only the benzoyl derivatives **5** and **8** show a modest increase of activity (MED 3 mg/kg) when compared to **3b** (MED 10 mg/kg).[17] Nevertheless, this class of compounds is still 1−2 orders of magnitude more active than piracetam, whose minimal effective dose in the same test is 30 mg/kg.

Since, as stated in the introduction, several 2-oxopyrrolidine derivatives show activity in animal models of neuropathic pain, *rac*-**4**, *rac*-**7**, their enantiomers, and **3a** were tested in a mouse model of diabetic neuropathy (Table 2). Pregabalin, administered at 30 mg/kg po was taken as reference. Both *rac*-**4** (10 mg/kg ip) and *rac*-**7** (3 mg/kg ip) completely reverted streptozotocin-induced thermal hyperalgesia in the mouse hot plate test. *rac*-**4** was inactive at a dose of 3 mg/kg ip. Again, no enantioselectivity is observed for **4**, since both optical isomers were active in this test. On the contrary, there is enantioselectivity for **7**: while (+)-**7** has an efficacy comparable to the racemate, its levorotatory isomer is devoid of activity at a dose of 3 and 10 mg/kg. In this model, the activity of **3a** is short-lasting, since it reverted thermal hyperalgesia at 15 min from administration, but after this time it was devoid of activity.

These results show that in the metabolic model of neuropathy **4** (racemate and enantiomers), *rac*-**7** and (+)-**7** showed an efficacy comparable to that of pregabalin, the most clinically used compound. Moreover, they were able to revert hyperalgesia after a single administration. Several substances, such as aldose reductase inhibitors, antioxidants, and PKC or PARP inhibitors, can prevent thermal hyperalgesia in streptozotocin-diabetic rodents only after repeated administration (see ref 19 and references cited therein). When compared to other analogues of piracetam, the potency of **4** (racemate and enantiomers), *rac*-**7**, and (+)-**7** was similar to that of nefiracetam and levetiracetam (10 and 20 mg/kg, respectively).[20,21] In the same model, these molecules were able to control pain completely. Moreover, the efficacy of the new compounds is comparable with that of lacosamide, kinin B1 receptor antagonists, gabapentin, and oxacarbazepine[22,23] and higher than that of amitriptyline.[24]

Compounds **3a**, *rac*-**4** and its enantiomers, and *rac*-**7** were further evaluated in the rat oxaliplatin-induced hyperalgesia by means of the paw-pressure test, in comparison with pregabalin (30 mg/kg po, Figure 1). The compounds were administered ip at 10 mg/kg. While **3a** was inactive in this test, both *rac*-**4** and *rac*-**7** were able to revert mechanical hyperalgesia induced by oxaliplatin with higher efficacy with respect to pregabalin. As far as the enantiomers of **4** are concerned, some enantioselectivity is observed in this test, since the reversal of hyperalgesia obtained by (−)-**4** is more effective and longer lasting than that of (+)-**4**.

Chronic neuropathic pain is frequently observed in patients receiving antitumoral chemotherapy.[25] Also, the use of oxaliplatin, the third-generation platinum-based chemotherapy in clinical practice, is significantly limited by the development of a painful peripheral neuropathy. Treatment with the above-mentioned antineoplastic drug (and vincristine and paclitaxel) frequently causes in the oncologic patient the development of neuropathy,[26] which is often responsible for the therapy interruption. It is important to note that there is currently no completely effective treatment to prevent or reverse this painful condition. Inhibitors of second messengers implicated in other painful peripheral neuropathy models (protein kinase A, protein kinase C, nitric oxide, calcium, and caspase) had no effect in this model after peripheral administration.[27] Antioxidants such as α-lipoic acid and vitamin C (50−100 mg/kg iv) were able to reduce by 50% the oxaliplatin-induced mechanical hyperalgesia; acetyl-L-carnitine (at the same doses) showed higher efficacy (75%). Venlafaxine (7.5 mg/kg) and mexiletine (100 mg/kg) were effective in this model.[27,28] No evidence exists about the activity of piracetam-like compounds in this kind of hyperalgesia. Here we report the first evidence that nootropic compounds are effective against this kind of neuropathy. As a matter of fact, *rac*-**4**, (−)-**4**, and *rac*-**7** were able to decrease pain sensation with efficacy comparable (80%) with that of acetyl-L-carnitine,[27] at doses 5−10 times lower. On the other hand, the reference compound pregabalin did not show an analogous efficacy, relieving pain by only 50%.

Table 2. Effect of 4 and 7, Their Enantiomers, and 3a on the Hyperalgesia Induced by Streptozotocin in Mouse Hot-Plate Test in Comparison with Pregabalin[a]

		licking latency in mice (s)				
			after treatment			
pretreatment	treatment (mg/kg ip)	before treatment	15 min	30 min	45 min	60 min
saline	saline	18.2 ± 0.8	18.1 ± 1.1	18.0 ± 1.5	17.8 ± 1.5	18.4 ± 1.6
STZ	saline	10.3 ± 0.7	9.4 ± 1.3	10.1 ± 0.8	9.3 ± 1.2	10.4 ± 1.2
saline	(±)-**4** (10)	14.9 ± 1.1	16.3 ± 1.5	16.9 ± 1.1	15.8 ± 1.7	16.3 ± 1.5
STZ	(±)-**4** (10)	9.2 ± 0.7	16.2 ± 1.2*	15.8 ± 1.0*	17.4 ± 1.4*	17.1 ± 1.6*
saline	(−)-**4** (10)	17.2 ± 0.9	17.0 ± 1.3	16.4 ± 1.5	16.5 ± 1.2	17.0 ± 1.6
STZ	(−)-**4** (10)	10.1 ± 0.7	15.3 ± 1.2*	16.5 ± 0.9*	16.1 ± 1.3*	14.8 ± 0.8^
saline	(+)-**4** (10)	15.8 ± 1.0	16.7 ± 1.2	16.8 ± 1.6	15.4 ± 1.3	17.1 ± 1.5
STZ	(+)-**4** (10)	9.4 ± 0.7	15.7 ± 1.3*	16.2 ± 1.2*	15.3 ± 1.1*	14.2 ± 1.6^
saline	(±)-**7** (3)	15.9 ± 1.1	15.9 ± 1.3	16.6 ± 1.8	17.2 ± 1.6	17.0 ± 1.3
STZ	(±)-**7** (3)	10.7 ± 0.9	14.9 ± 1.2*	14.1 ± 1.1*	12.7 ± 1.4^	11.5 ± 1.6
saline	(+)-**7** (3)	16.1 ± 0.9	16.9 ± 1.5	15.8 ± 1.0	17.0 ± 1.3	17.4 ± 1.1
STZ	(+)-**7** (3)	11.0 ± 1.1	14.3 ± 1.3*	13.7 ± 1.3*	12.4 ± 1.0	10.5 ± 0.9
saline	(−)-**7** (3)	16.5 ± 0.9	17.3 ± 0.9	16.4 ± 1.5	16.6 ± 1.1	16.3 ± 1.5
STZ	(−)-**7** (3)	9.2 ± 0.8	10.4 ± 1.0	9.7 ± 0.9	8.8 ± 1.0	10.0 ± 1.3
saline	**3a**	15.8 ± 0.7	16.5 ± 0.9	15.7 ± 1.2	16.3 ± 1.4	15.6 ± 1.5
STZ	**3a**	9.9 ± 0.9	15.6 ± 1.2*	12.4 ± 1.5	10.4 ± 1.1	11.2 ± 0.8
saline	pregabalin[b]	14.3 ± 0.9	16.7 ± 1.3	17.1 ± 1.0	16.1 ± 1.2	17.0 ± 0.9
STZ	pregabalin[b]	9.8 ± 0.8	15.3 ± 1.1*	16.7 ± 1.3*	15.7 ± 0.9*	15.7 ± 0.9*

[a] Streptozotocin (STZ), 200 mg/kg ip, was dissolved in citrate buffer and injected 30 days before experiment. Each value represents the mean of at least 10 mice. * $P < 0.01$. ^ $P < 0.05$ in comparison with STZ-treated mice. [b] Pregabalin was administered at 30 mg/kg po.

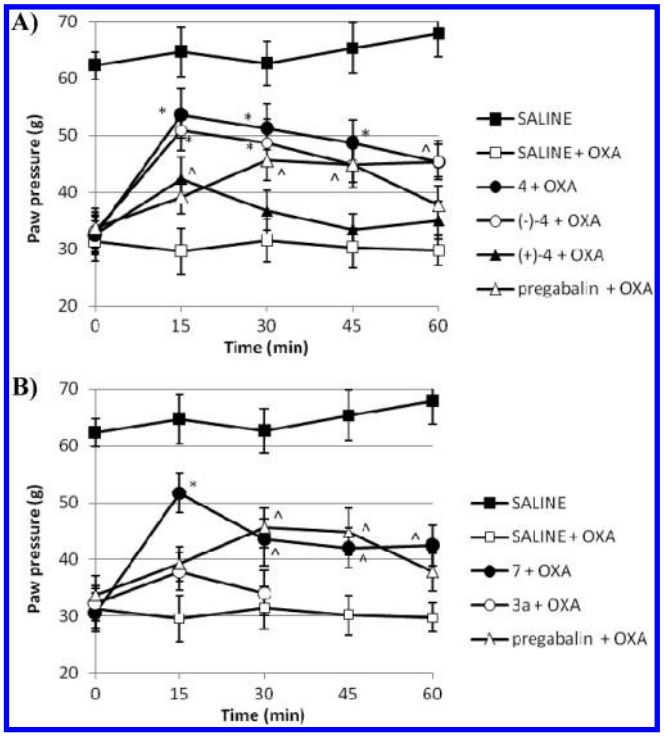


Figure 1. Effect of compounds (10 mg/kg, single administration, ip) on oxaliplatin-induced hyperalgesia in the rat paw-pressure test in comparison with pregabalin (30 mg/kg po). Oxaliplatin (OXA, 2.4 mg/kg) was administered for 5 consecutive days every week (15 ip injections, cumulative dose 36 mg/kg). There were 4 rats per group. (A) *rac*-**4**, (+)-**4**, and (−)-**4**; (B) *rac*-**7** and **3a**; (∗) $P < 0.01$, (∧) $P < 0.05$.

In conclusion, the introduction of conformational constraints into **3a** has not increased the nootropic potency in the mouse passive-avoidance test but still gave compounds 1−2 order of magnitude more potent than piracetam. The most active compounds are *rac*-**4** and its enantiomers, which show a minimal effective dose only 10 times higher than **3a**. While geometrical isomerism was important for activity, the *cis* 4-fluorobenzenesulfonyl derivative **4** being more active than its *trans* isomer **7**, there is no enantioselectivity in the nootropic activity of compounds. On the contrary, enantioselectivity was observed when the compounds were tested on two models of neuropathy: (+)-**7** (3 mg/kg) is able to revert streptozotocin-induced thermal hyperalgesia in the mouse hot plate test, while its levorotatory isomer is devoid of activity at the same dose and at 10 mg/kg. As far as **4** is concerned, in the oxaliplatin-induced hyperalgesia the reversal obtained by (−)-**4** is more effective and longer lasting than that produced by (+)-**4**, while in streptozotocin-induced diabetic neuropathy the two enantiomers have the same efficacy. This difference may be due to a different pharmacokinetic of the compounds in mouse and rat or to the interaction with a different biological target. As a matter of fact, as reported above, several compounds have been shown to be active on one model but not on the other, indicating that different, yet unknown, mechanisms can be involved. Nevertheless it is confirmed that these compounds are promising agents for the treatment of neuropathic pain, including that induced by chemotherapy.

EXPERIMENTAL SECTION

Chemistry. All melting points were taken on a Büchi apparatus and are uncorrected. NMR spectra were recorded on a Bruker 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

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chromatography (Kieselgel 40, 0.063- 0.200 mm; Merck) or flash chromatography (Kieselgel 40, 0.040−0.063 mm; Merck). Optical rotation was measured at a concentration of 1 g/100 mL (c = 1), unless otherwise stated, with a Perkin-Elmer polarimeter (accuracy 0.002°). 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. The synthesis of **4** is described below as representative. The syntheses of all other compounds are reported in the Supporting Information.

***cis* 3-(4-Fluorophenylsulfonyl)-3,7-diazabicyclo[4.3.0]nonan-8-one (4).** To a solution of **14** (50 mg) in acetonitrile (15 mL), Et_3N (1.5 equiv) and 4-fluorobenzenesulfonyl chloride (1 equiv) were added. After being stirred for 2 h at room temperature, the mixture was diluted with H_2O (20 mL), made alkaline with Na_2CO_3 (10% solution), and extracted with dichloromethane. After drying and removal of the solvent under vacuum, the residue was purified by flash chromatography ($CHCl_3$/MeOH 9:1 as eluent), obtaining the title compound in 73% yields, mp 190 °C. Anal. ($C_{13}H_{15}FN_2O_3S$) C, H, N.

■ ASSOCIATED CONTENT

Supporting Information. Synthetic procedures and pharmacological methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

LDA, lithium diisopropylamide; MED, minimal effective dose; PKC, protein kinase C; PARP, poly ADP-ribose polymerase; ee, enantiomeric excess

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