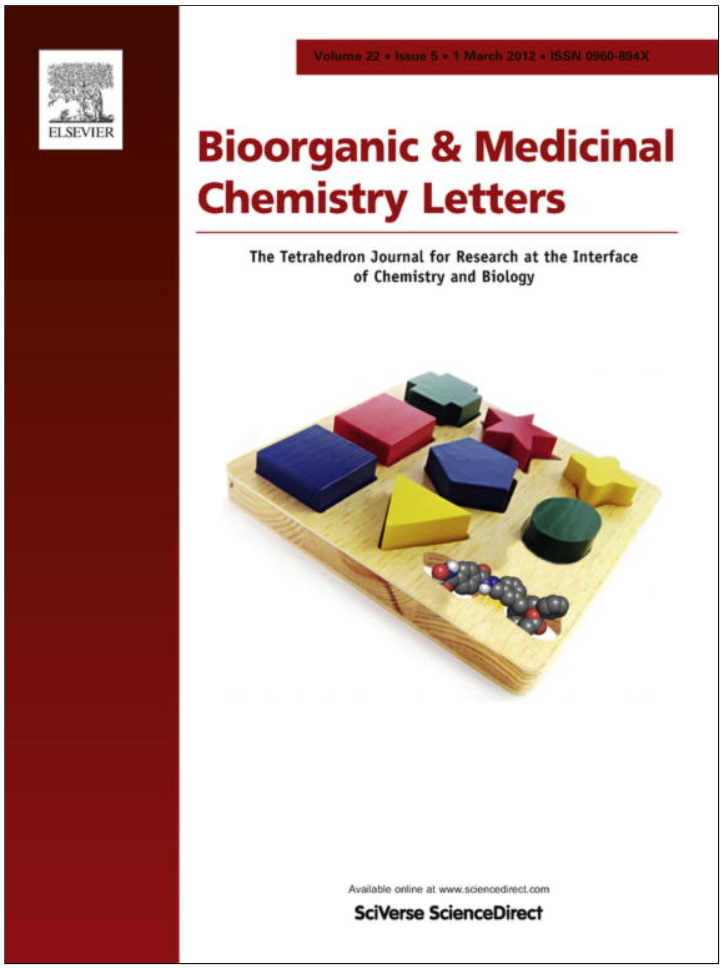

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Influence of ring size on the cognition-enhancing activity of DM235 and MN19, two potent nootropic drugs

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ABSTRACT

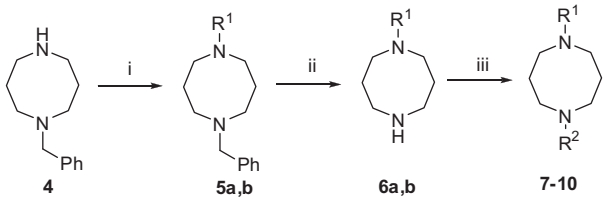
A series of analogs of DM235 and MN19, characterized by rings with different size, have been prepared and evaluated for their nootropic activity in the mouse passive-avoidance test. It was found that the optimal ring size for the analogs of DM235, showing endocyclic both amidic groups, is 6 or 7 atoms. For the compounds structurally related to MN19, carrying an exocyclic amide group, the piperidine ring is the moiety which gives the most interesting compounds.

Nootropic drugs are compounds able to improve learning and memory, by acting through many different mechanisms which may involve neurotransmitter receptors or enzymes.[1–4] These compounds are potentially useful in pathologies where cognitive functions are attenuated, such as Alzheimer's disease, ADHD, schizophrenia, or to counteract the cognitive decline connected to age. Among nootropics, piracetam and piracetam-like compounds have been reported to improve cognitive performance in several different conditions. This class of compounds lacks a common mechanism of action, although for some members the modulation of the cholinergic and glutamatergic systems has been disclosed.[5,6]

Somehow related to piracetam is DM232 (Unifiram, **1**, Chart 1). This compound shares with piracetam the 2-oxopirrolidine ring, but differs from the lead for its nootropic potency, being some orders of magnitude more potent in several behavioral tests.[7] Structural modification of **1** led to DM235[8] (sunifiram, **2**, Chart 1) and MN19[9] (sapunifiram, **3**) which showed a nootropic potency similar to **1**. These compounds have been reported to stimulate cholinergic and glutamatergic systems,[9,10] but the precise biological target has not been clarified yet.

Structural manipulation on leads **1**–**3** allowed to derive some structure–activity relationships, showing that a diamidic structure is important for activity.[11] In addition, it was previously reported that the enlargement of the piperazine ring of DM235 into an azepane moiety produced compounds with potency similar to **2**, while the contraction to imidazolidine decreased activity.[12] As a continuation of this research, we wanted to check the effect of further ring expansion on the diazacyclic moiety, synthesizing the corresponding diazocanes (Chart 1, general formula A). Moreover, in order to check the optimal ring size also in analogs showing an exocyclic amide group, the piperidine ring of MN19 was substituted with nitrogen-containing saturated heterocycles with 4–8 atoms (general formulas B–E). The acyl and sulfonyl groups which decorate the structures were chosen among those giving, in the previous series, the most interesting compounds.

The general procedure for the synthesis of compounds **7**–**10** is reported in Scheme 1. 1-Benzyl-1,5-diazocane **4** was prepared according to Ref. 13 and treated with the suitable acyl chloride to give amides **5a,b**. The protecting group was removed by catalytic hydrogenation to give secondary amines **6a,b** which were



4 5a,b 6a,b 7-10

Scheme 1. Reagents and conditions: (i) R^1Cl, Et_3N, $CHCl_3$; (ii) H_2/Pd/C; (iii) R^2Cl, Et_3N, $CHCl_3$. (a) $R^1 = COCH_3$; (b) $R^1 = COC_2H_5$.

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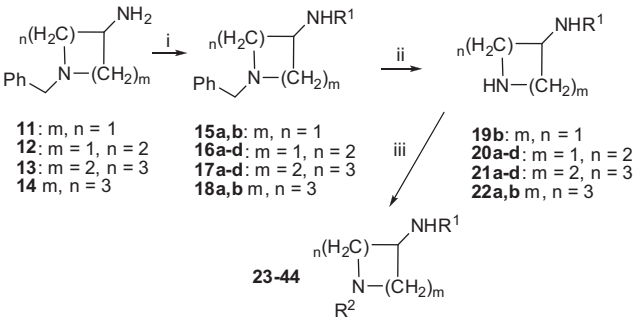
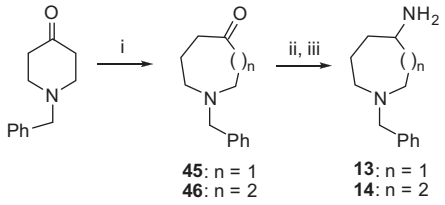


Scheme 2. Reagents and conditions: (i) R^1Cl, Et_3N, $CHCl_3$; (ii) H_2/Pd/C; (iii) R^2Cl, Et_3N, $CHCl_3$. Compound **12** and its enantiomers were commercially-available. (a) $R^1 = COCH_3$; (b) $R^1 = COC_2H_5$; (c) $R^1 = COPh$; (d) $R^1 = SO_2C_6H_4$-pF.



Scheme 3. Reagents and conditions: (i) *N*-methyl-*N*-nitrosourea (Ref. 17). (ii) $NH_2OH.HCl$, base: (iii) $LiAlH_4$, THF.

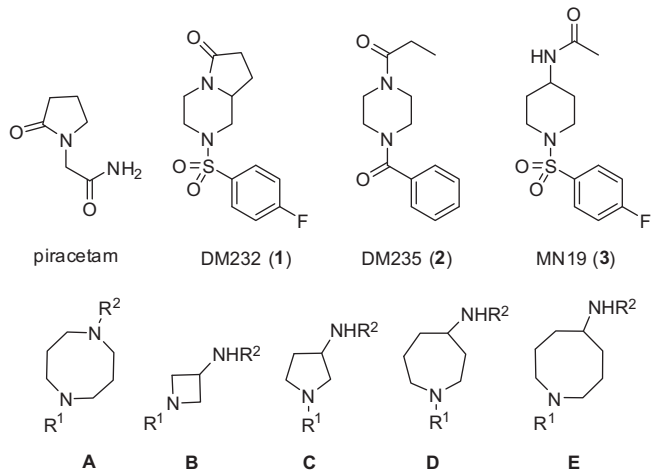


Chart 1. Reference molecules and general formulas of the new compounds reported in this Letter.

transformed into the desired compounds by treatment with the suitable acyl or sulfonyl chloride.

The same pathway was used to prepare compounds **23**–**44** starting from amines **11**–**14** (Scheme 2). Amine **11**[14] was prepared from 1-benzylazetidin-3-ol mesylate[15] by reaction with aqueous ammonia. Amine **12** and its enantiomers were commercially available. Amine **13**[16] and **14** were prepared from *N*-benzylazepan-4-one **45**[17] and 1-benzylazocan-5-one **46**,[18] respectively, by reaction with hydroxylamine and reduction of the resulting oximes with lithium aluminium hydride (Scheme 3).

Compound **46** was obtained in low yield as byproduct in the preparation of **45** starting from benzylpiperidone and *N*-methyl-*N*-nitrosourea according to Ref. 18 (Scheme 3): differently from what reported by Blizzard[16] for the CBZ-protected 4-azepanone, the ring expansion of **45** gave only the symmetric ketone **46**, while the isomeric *N*-benzyl-4-azocanone was not detected in the complex reaction mixture. Attempts to improve the yield by changing the reaction conditions were not successful; therefore **46** was prepared in higher yields as reported in Ref. 18.

Regarding the azetidin-3-amine series, only the propionamide derivatives **23** and **24** were synthesized, since compound **15a** proved to be unstable. Therefore, due also to the low potency of **23** and **24**, the synthesis of their *N*-acetyl analogs was abandoned.

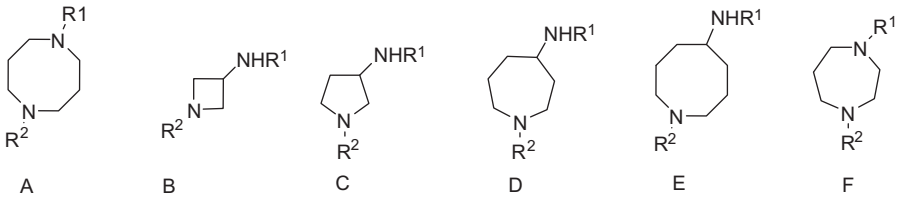
The mouse passive-avoidance test of Jarvik and Kopp,[19] slightly modified by us (see Supplementary data and Ref. 12) was used to measure the nootropic activity of the synthesized compounds. The substances were dissolved in saline and tested i.p. up to the dose of 10 mg/kg; the results are expressed as the Minimal Effective Dose (MED, mg/kg) and are reported in Table 1, in comparison with previously-synthesized analogs with different ring size. Compounds were considered inactive if they did not show activity up to the dose of 10 mg/kg, which is three and four orders of magnitude higher than the MED of the lead compounds MN19 and DM235, respectively.

Unexpectedly, diazocanes **7**–**10** were completely devoid of activity when tested up to the highest dose. This is surprising since their diazepane analogs (compounds F1 and F2, Table 1) were active at doses below 1.0 mg/kg.[12] Apparently, further expansion of the seven-membered ring abolished activity. Previous work has shown[12] that the contraction of the piperazine moiety into the imidazolidine ring, or the shift of the two amidic functions from piperazines to hexahydropyrimidines gave compounds showing MED between 1 and 10 mg/kg. Therefore, from these studies we can conclude that in the diazacyclic derivatives, the optimal ring size is six or seven atoms, with at least two carbon units between the two amidic functions; one unit decrease or increase in the number of atoms within the ring reduced or abolished, respectively, the nootropic activity.

The influence of ring size on activity was checked also for the exocyclic amide derivatives, structurally related to MN19. To this aim, the piperidine ring of **3** was contracted to azetidine (**23**, **24**) and pyrrolidine (**25**–**32**) or enlarged to azepane (**33**–**40**) and azocane (**41**–**44**). One atom contraction to pyrrolidines, or enlargement to azepanes gave a general decrease of potency; a further variation to azetidine or azocanes is even more detrimental, although the azocane sulfonyl derivatives maintain some activity. In the whole set of compounds, only pyrrolidine **28** shows a MED comparable to MN19 (0.1 mg/kg); this compound shows some enantioselectivity in its ability to revert scopolamine-induced amnesia, the *S* isomer being 10 times more active than the *R* form. A similar enantioselectivity ratio was found for the enantiomers of DM232,[20] while for some bicyclic analogs of MN19 no enantioselectivity was observed in the passive-avoidance test.[21]

As it happened also for other analogs, a particular combination of substituent does not produce the same effect in all the series synthesized so far. For instance, the combination between 4-*F*-benzenesulfonyl and acetyl groups gave the most interesting compound (**3**, MN19) in the 4-aminopiperidine series, but the same pattern gave in the 4-aminoazepane series an inactive compound (**34**); homologation of the acetyl residue to propionyl decreased activity in the 4-aminopiperidine series,[9] while activity increased in the aminopyrrolidine series and did not change in the 3-aminopiperidine derivatives.[22] These differences can be explained by the fact that the biological activity measured in vivo is affected by both pharmacokinetic and pharmacodynamic factors, on which structural modifications may produce different effects. Unfortunately, the lack of knowledge about the biological target makes it impossible to perform in vitro studies, where pharmacodynamic factors should be largely predominant. Following the same reasoning, it may be possible that the different activity of the enantiomers

Table 1
Minimal Effective Dose (MED) of the compounds against scopolamine-induced amnesia in the mouse passive avoidance test, in comparison with reference substances[a]



Treatment	Structure	R^1	R^2	Dose (mg/kg)	Training session (s)	Retention session (s)	Δ
Saline					16.5 ± 2.9	108.2 ± 7.1	91.7
S					18.1 ± 3.0	43.8 ± 4.1	25.7
7 + S	A	$COCH_3$	COPh	n.a. [b]	–	–	–
8 + S	A	$COCH_3$	$SO_2C_6H_4F$	n.a. [b]	–	–	–
9 + S	A	COC_2H_5	COPh	n.a. [b]	–	–	–
10 + S	A	COC_2H_5	$SO_2C_6H_4F$	n.a. [b]	–	–	–
23 + S	B	COC_2H_5	$SO_2C_6H_4F$	10	18.5 ± 3.1	62.6 ± 8.5^	44.1
24 + S	B	COC_2H_5	COPh	n.a. [b]	–	–	–
25 + S	C	$COCH_3$	COPh	10	15.8 ± 3.2	86.1 ± 8.3*	70.3
26 + S	C	$COCH_3$	$SO_2C_6H_4F$	1.0	17.9 ± 2.6	68.9 ± 6.1*	51.0
27 + S	C	COC_2H_5	COPh	1.0	16.4 ± 2.5	61.8 ± 7.0^	45.4
28 + S	C	COC_2H_5	$SO_2C_6H_4F$	0.1	17.1 ± 3.4	65.9 ± 5.3^	48.8
(S)-**28** + S	C	COC_2H_5	$SO_2C_6H_4F$	1.0	16.7 ± 2.6	73.3 ± 7.5*	56.6
(R)-**28** + S	C	COC_2H_5	$SO_2C_6H_4F$	10	15.7 ± 2.8	85.1 ± 9.1*	69.4
29 + S	C	COPh	$COCH_3$	1.0	13.5 ± 2.8	61.6 ± 7.7^	48.1
30 + S	C	COPh	COC_2H_5	n.a. [b]	–	–	–
31 + S	C	$SO_2C_6H_4F$	$COCH_3$	n.a. [b]	–	–	–
32 + S	C	$SO_2C_6H_4F$	COC_2H_5	n.a. [b]	–	–	–
33 + S	D	$COCH_3$	COPh	n.a. [b]	–	–	–
34 + S	D	$COCH_3$	$SO_2C_6H_4F$	n.a. [b]	–	–	–
35 + S	D	COC_2H_5	COPh	1.0	15.6 ± 2.7	78.3 ± 8.1*	62.7
36 + S	D	COC_2H_5	$SO_2C_6H_4F$	10	16.7 ± 3.2	63.5 ± 8.1^	46.8
37 + S	D	COPh	$COCH_3$	1.0	16.8 ± 3.2	87.2 ± 9.1*	70.4
38 + S	D	COPh	COC_2H_5	1.0	15.8 ± 2.9	85.2 ± 9.1*	69.4
39 + S	D	$SO_2C_6H_4F$	$COCH_3$	1.0	19.1 ± 3.0	64.9 ± 7.6*	45.8
40 + S	D	$SO_2C_6H_4F$	COC_2H_5	10	14.8 ± 3.9	96.2 ± 9.8*	81.4
41 + S	E	$COCH_3$	COPh	n.a. [b]	–	–	–
42 + S	E	$COCH_3$	$SO_2C_6H_4F$	1.0	19.1 ± 3.2	63.9 ± 7.9^	44.8
43 + S	E	COC_2H_5	COPh	n.a. [b]	–	–	–
44 + S	E	COC_2H_5	$SO_2C_6H_4F$	10	14.9 ± 2.7	87.1 ± 8.2*	72.2
Piracetam + S[c]	–	–	–	30	15.2 ± 3.5	97.6. ± 9.1*	82.4
2 + S[d]	–	–	–	0.001	20.5 ± 3.4	91.5 ± 8.0*	71.0
3 + S[e]	–	–	–	0.01	14.5 ± 3.8	90.6 ± 12.5*	76.1
F1 + S[f]	F	$COCH_3$	COPh	0.01	17.3 ± 3.6	77.2 ± 8.4*	59.9
F2 + S[f]	F	COC_2H_5	COPh	0.1	16.2 ± 2.6	88.1 ± 7.3*	71.9

* P <0.01 in comparison with scopolamine-treated mice.
[a] All compounds were dissolved in saline and injected i.p. 20 min before training session. Each value represents the mean of 8–18 mice. Scopolamine (S) was injected immediately after punishment.
^ P <0.05.
[b] This compound did not revert scopolamine-induced amnesia at doses up to 10 mg/kg i.p.
[c] From Ref. 21.
[d] From Ref. 8.
[e] From Ref. 9.
[f] Compounds **F1** and **F2** have been previously characterized,[12] and their activity is reported here, together with that of the new analogs, for comparative purposes.

of **28** is mainly due to pharmacodynamic or to pharmacokinetic reasons, or it is a combination of both properties. Obviously other explanations cannot be ruled out, such as a different binding mode for the various series, or the interaction with a different biological target.

In conclusion, a series of derivatives of DM235 and MN19 were synthesized which show cognition-enhancing activity, with potency similar to piracetam. The new compounds allowed to derive further structure–activity relationships; in particular it was found that for the diazacyclic series the optimal ring size is six atoms with at least two carbon atoms between the two amidic functions, and also the seven-member diazepane ring is well tolerated. For the derivatives carrying one exocyclic amide group, the 4-aminopiperidine moiety is the one giving the best results. Work is continuing to elucidate the biological target of this class of cognition-enhancers.

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Supplementary data

Supplementary data (synthetic procedures and biological tests) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2012.01.045.

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