Bioorganic & Medicinal Chemistry Letters 25 (2015) 1700–1704

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

# Substituted piperazines as nootropic agents: 2- or 3-phenyl derivatives structurally related to the cognition-enhancer DM235

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ARTICLE INFO

*Article history:*
Received 10 December 2014
Revised 27 February 2015
Accepted 2 March 2015
Available online 12 March 2015

*Keywords:*
Sunifiram
Cognition-enhancers
Piracetam-like compounds
Mouse passive-avoidance test
Piperazines

ABSTRACT

A series of 2-phenyl- or 3-phenyl piperazines, structurally related to DM235 and DM232, two potent nootropic agents, have been prepared and tested in the mouse passive-avoidance test, to assess their ability to revert scopolamine-induced amnesia. Although the newly synthesized molecules were less potent than the parent compounds, some useful information has been obtained from structure–activity relationships. A small but significant enantioselectivity has been found for the most potent compound **5a**.



Cognitive processes are a set of physiological activities, including attention, learning, memory, reasoning, which are impaired in several psychiatric disorders, such as Alzheimer's disease (AD), or in age-related conditions such as Mild Cognitive Impairment.[1] Several cellular mechanisms have been found to modulate cognition, offering different strategies to overcome cognitive dysfunction. Recently, Froestl et al. have reviewed cognitive enhancers according to their molecular targets,[2–4] including in their survey also compounds whose mechanism of action has not been fully elucidated, such as piracetam, **1** and **2**.[2]

We have previously described the cognition-enhancing activity of **1** and **2** (respectively, DM232, Unifiram, and DM235, Sunifiram, Chart 1) which potently reversed scopolamine-induced amnesia in different behavioral tests in rodents.[5] Due to the presence of a 2-oxopyrrolidine ring, DM232 can be formally related to piracetam; however, the cognition-enhancing potency of DM232 and some of its analogues is 3- 4 orders of magnitude higher than that of the lead. In addition, the pyrrolidinone ring of **1** can be opened, to give **2**, without loss of activity,[6] while this structural feature is pivotal for the activity of piracetam analogues.[7] Anyway, DM232 and DM235, as well as piracetam, do not show affinity for the most common neurotransmitter receptors and ion channels, thus making the discovery of the molecular target difficult. Evidence has been found that the cognition-enhancing activity of **1** and **2** involves modulation of cholinergic and glutamatergic transmission.[8–10]

In an attempt to find new substances which could help to derive structure–activity relationships in this class of compounds, and possibly to elucidate their mechanism of action, we designed new analogs, structurally related to DM235 (**2**), carrying a substituent on the piperazine ring (Chart 1, general formula I). In a previous work we prepared and tested 2- and 3-methylpiperazines **3a**–**d**,[6] whose difference in activity (Table 1) could be related to the position of the methyl group: when it was close to the aliphatic amide moiety, the compound was inactive or less active than when it was close to the aromatic amide or sulfonamide. This result was explained with a steric effect of the methyl ring precluding the correct orientation of the aliphatic amide moiety. Although compounds **3a**–**d** were less potent than the leads **1** and **2**, and also than **4** (DM194,[6] Chart 1), the 4-fluorobenzenesulfonamide analog of **2**, we reasoned that other substituents, with different electronic features with respect to a methyl group, could establish with the

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http://dx.doi.org/10.1016/j.bmcl.2015.03.009
0960-894X/

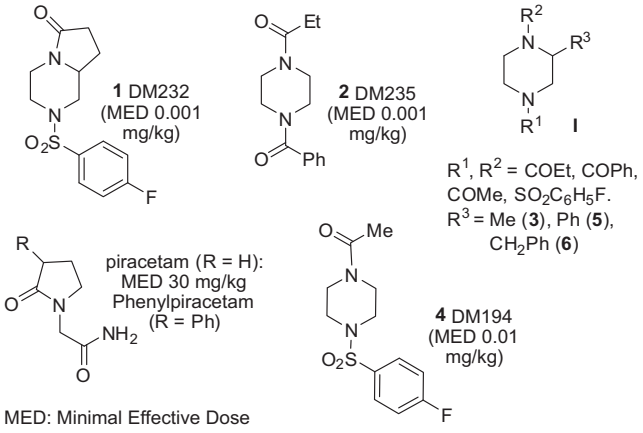
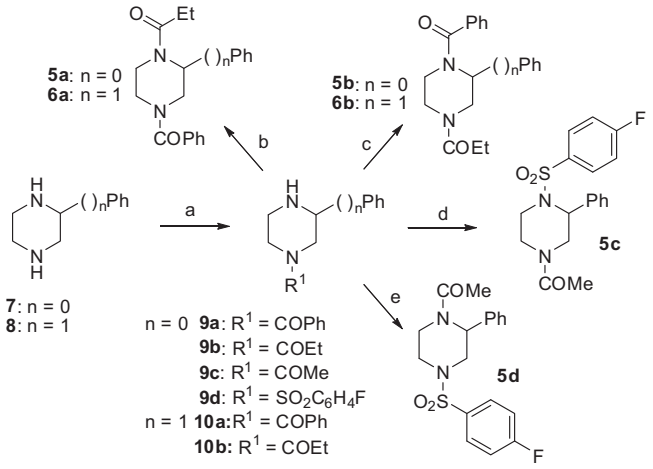



**Chart 1.**




**Scheme 1.** Reagents: (a) $R^1Cl$, $Et_3N$; (b) EtCOCl, $Et_3N$; (c) PhCOCl, $Et_3N$; (d) 4F-$C_6H_4SO_2Cl$, $Et_3N$; (e) MeCOCl, $Et_3N$.

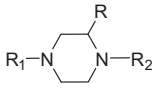
biological target more productive interactions, possibly restoring some potency. Therefore, the piperazine ring of leads **2** and **4** has been decorated with substituents with different size and electronic properties ($R^3$, Chart 1, general formula I). In this work, we report the synthesis and biological evaluation of the phenyl and phenylmethyl derivatives **5** and **6**, and of the enantiomers of the most potent derivative **5a**. Interestingly, the introduction of a phenyl ring on piracetam gave phenylpiracetam (Chart 1), endowed with interesting nootropic properties (reviewed in Ref. 11).

2-Phenylpiperazine **7** and 2-phenylmethylpiperazine **8** were prepared, respectively, according to Webster[12] and Zindell[13] and treated sequentially with the suitable acyl or sulfonyl chloride (Scheme 1) to give monoamides **9a–d** and **10a**,**b**, and diamides **5a–d** and **6a**,**b**.

To obtain the enantiomers of **5a**, the synthetic pathway (Scheme 2, described for the *R* enantiomer) started from the commercially available chiral phenylglycine: therefore, (*R*)-**11** was prepared from (*R*)-phenylglycine according to Refs. 14,15, and treated with diethyl oxalate to give (*R*)-**12.** Reduction with $LiAlH_4$ gave (*R*)-**7**; subsequent reaction with benzoyl chloride gave (*R*)-**9a**, and treatment with propionyl chloride yielded (*R*)-**5a**. In the same way (*S*)-**5a** was obtained starting from (*S*)-**11**. Enantioselective HPLC analysis on (*R*)-**9a** and (*S*)-**9a** showed a ee of 89% and 88%, respectively (Fig. 1).

The compounds were tested in the passive-avoidance test of Jarvik and Kopp,[16] using a slightly modified procedure applied in our previous work.[17] The substances were dissolved in DMSO/saline (1:10) solution and tested s.c. in a 1:10 dilution sequence; the results are expressed as the Minimal Effective Dose (MED, mg/kg). Compounds were considered inactive if they did not show activity

**Table 1**
Minimal Effective Dose (MED) of the compounds against scopolamine-induced amnesia in the mouse passive avoidance test, in comparison with reference substances **2–4**




| Treatment | R | $R_1$ | $R_2$ | *c*Log*P*[b] | MED (mg/kg) | Training session | Retention session | Δ |
|---|---|---|---|---|---|---|---|---|
| Saline | — | — | — | — | — | 15.5 ± 2.6 | 104.8 ± 7.5 | 89.3 |
| S | — | — | — | — | — | 14.1 ± 2.1 | 47.2 ± 8.3 | 33.1 |
| **9a** + S | Ph | COPh | H | 2.71 | >10 | — | — | — |
| **9b** + S | Ph | COEt | H | 1.72 | >10 | — | — | — |
| **9c** + S | Ph | COMe | H | 1.26 | >10 | — | — | — |
| **9d** + S | Ph | $SO_2C_6H_4F$ | H | 2.18 | >10 | — | — | — |
| **5a** + S | Ph | COPh | COEt | 3.47 | 0.1 | 17.7 ± 2.5 | 60.2 ± 9.6^ | 42.5 |
| (*S*)-**5a** + S | Ph | COPh | COEt | 3.47 | 1.0 | 13.2 ± 3.0 | 75.3 ± 9.1* | 62.1 |
| (*R*)-**5a** + S | Ph | COPh | COEt | 3.47 | 0.1 | 14.5 ± 2.1 | 61.2 ± 8.7^ | 46.7 |
| **5b** + S | Ph | COEt | COPh | 3.47 | 1.0 | 15.2 ± 2.4 | 72.9 ± 9.5* | 57.7 |
| **5c** + S | Ph | COMe | $SO_2C_6H_4F$ | 2.49 | 10 | 13.9 ± 2.2 | 79.5 ± 11.6* | 65.6 |
| **5d** + S | Ph | $SO_2C_6H_4F$ | COMe | 2.49 | >10 | — | — | — |
| **6a** + S | $CH_2Ph$ | COPh | COEt | 3.72 | 1.0 | 18.4 ± 2.3 | 76.3 ± 8.8^ | 57.9 |
| **6b** + S | $CH_2Ph$ | COEt | COPh | 3.72 | 1.0 | 18.2 ± 3.0 | 89.3 ± 9.5* | 71.1 |
| **2** + S[a] | H | COEt | COPh | 1.95 | 0.001 | 20.5 ± 3.4 | 91.5 ± 8.0* | 71.0 |
| **3a** + S[a] | $CH_3$ | COPh | COEt | 2.28 | >10 | — | — | — |
| **3b** + S[a] | $CH_3$ | COEt | COPh | 2.28 | 0.1 | 21.0 ± 5.3 | 81.2 ± 9.6^ | 60.2 |
| **3c** + S[a] | $CH_3$ | COMe | $SO_2C_6H_4F$ | 1.29 | 0.1 | 16.6 ± 4.1 | 99.2 ± 8.5* | 82.6 |
| **3d** + S[a] | $CH_3$ | $SO_2C_6H_4F$ | COMe | 1.29 | 1.0 | 12.5 ± 3.9 | 96.4 ± 10.1* | 83.9 |
| **4** + S[a] | H | $SO_2C_6H_4F$ | COMe | 0.97 | 0.01 | 19.8 ± 4.1 | 89.0 ± 18.3* | 69.2 |
| Piracetam + S[a] | — | — | — | −1.18 | 30 | 15.2 ± 3.5 | 97.6. ± 9.1* | 82.4 |

All compounds were dissolved in saline containing 10% DMSO and injected s.c. 20 min before the training session. Each value represent the mean of 8–16 mice. Scopolamine (S, 1.5 mg/kg ip) was injected immediately after punishment. ^$P$<0.05, *$P$<0.01 in comparison with scopolamine-treated mice.

[a] From Ref. 6.

[b] Calculated on the web by means of Osiris Property Explorer (http://www.organic-chemistry.org/prog/peo/).