2-Amino-2-oxazolines, VII: Influence of Structural Parameters on the Antidepressant Activity of 5-(1-Aryl-4-piperazino)methyl-2-amino-2-oxazolines

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A series of 5-(1-aryl-4-piperazino)methyl-2-amino-2-oxazolines has been prepared and screened for antidepressant activity. Their lipophilic behaviour has been discussed in relation to the nature and the position of substituents on the aromatic ring. The influence of steric effects on the pharmacological activity has been investigated using experimental methods (X-ray diffraction, NMR) and theoretical calculations (semi-empirical quantum mechanics). The *ortho*-substitution on the phenyl ring or the C-α substitution on the piperazine ring by a methyl group results in the same effects *i.e.* an increase of the angle between the two rings up to 64° (X-ray and calculation) and a loss of the antidepressant activity. Using NMR, only the influence of the *ortho*-substitution has been observed.

2-Amino-2-oxazoline, 7. Mitt.: Einfluß von Strukturparametern auf die antidepressive Wirkung von 5-(1-Aryl-4-piperazino)methyl-2-amino-2-oxazolinen

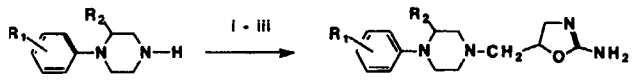
Eine Serie der Titelverbindungen wurde hergestellt und auf antidepressive Wirkung untersucht. Die Lipophilie-Eigenschaften werden in Bezug auf Art und Stellung der Substituenten am aromat. Ring diskutiert. Der Einfluß sterischer Effekte auf die pharmakologische Aktivität wurde experimentell (Röntgenstrukturanalyse, NMR) und durch Berechnungen (Semiempirische Quantenmechanik) untersucht; *o*-Substitution der Phenylgruppe oder eine Methylsubstitution an C-α des Piperazinrings führen zu demselben Effekt: der Winkel zwischen den Ringen wird auf 64° vergrößert, und die antidepressive Wirkung geht verloren. Durch NMR-Untersuchungen läßt sich nur der Einfluß der *o*-Substitution beobachten.

A new antidepressant drug (COR 3224) which is the most active compound of a series of 5-(1-aryl-4-piperazino)methyl-2-amino-2-oxazolines synthesized in our group has been recently described[1]. From the pharmacological data obtained in this series, we have got an insight into the main molecular properties related to the activity[2]. In particular we have shown that the nature and the position of the substituents on the aromatic ring are crucial for the antidepressant activity.

In order to extend our study we prepared and tested as antidepressants new 5-(1-aryl-4-piperazino)methyl-2-amino-2-oxazolines. Using some compounds bearing a methyl substituent on the aromatic and/or on C-2 of the piperazine ring, we have tried to gain more information about the influence of the substitution effects in relation to a steric free-rotational hindrance between the phenyl and the piperazine rings.

Results

New 5-(1-aryl-4-piperazino)methyl-2-amino-2-oxazolines (Table 1) have been obtained in a two steps reaction: treatment of an 1-aryl-4-piperazine with epichlorhydrin followed by a dehydrohalogenation with NaOH led to the 1-(1-aryl-4-piperazino)-2,3-epoxypropane. The epoxide has been converted without further purification to the corresponding 5-(1-aryl-4-piperazino)methyl-2-amino-2-oxazoline by condensation with monosodium cyanamid salt.



i : epichlorhydrin, EtOH ; ii : NaOH ; iii : NaNHCN, MeOH

Except **2** and **4**, all products have been screened for their pharmacological activity. LD_{50}s evaluated after single oral administration were higher than 300 mg/kg. Compounds **1** and **3** presented a slight antidepressant activity evidenced in mice by the inhibition of reserpine induced hypothermia test. The antidepressant activity of **1** has been studied using the apomorphine hypothermia interaction in mice according to *Puech*[3]. Compound **1** exhibited a slight activity with an ED_{30} = 18 mg/kg compared with ED_{30} = 4 and 6.2 mg/kg for imipramine and viloxazine, respectively. Fig. 1 shows that in methoxy substituted compounds the order of activity is 4-OCH_3 > 3-OCH_3 > 2-OCH_3 (for 3-OCH_3 and 2-OCH_3 derivatives a statistically significant activity was only noticed with the upper dose, *i.e.* 64 mg/kg). This result con-

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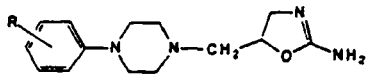
firmed the influence of the phenyl substitution position already noticed for chlorine and methylated compounds. By reference to the 3-CH_3 substituted compound the introduction of a second CH_3 on the *ortho*-position in 2,3-dimethylated compound **6** appeared to be detrimental.



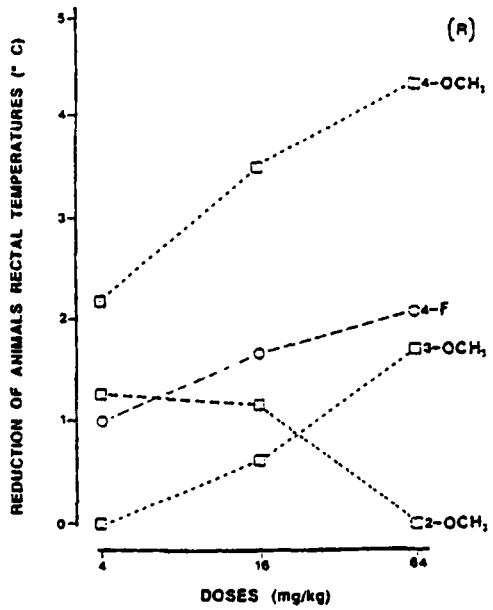


Fig. 1: Reduction of the reserpine induced hypothermia *vs* doses

Another result concerned the introduction of a methyl group on the piperazine moiety. In the inhibition of reserpine induced hypothermia test the compounds **8** and **9** were not effective up to 64 mg/kg. By comparison with pharmacological results *versus* the corresponding non substituted compounds[2], the introduction of a methyl group on the piperazine moiety gave unfavorable effects.

We first attempted to discuss these results in terms of lipophilicity. We recently developed a chromatographic determination of the lipophilicity of 5-(1-aryl-4-piperazino)methyl-2-amino-2-oxazolines leading to the measurement of the chromatographic capacity factor log k'_W [4]. An excellent correlation was established between the partition coefficient (log $P_{o/w}$) and log k'_W. For the three OCH_3 substituted compounds the log k'_W values were quite similar (1.79 ± 0.08); similar results were obtained for the three monomethylated compounds (2.43 ± 0.13). In compounds **8** and **9** the introduction of a methyl group on the piperazine ring did not greatly affect the log k'_W values in relation to the non-substituted products. These fragmental data indicated that the decrease of pharmacological activity *in vivo* was not simply related to the lipophilic behaviour of the studied 2-amino-2-oxazolines.

The unfavorable effects of substitution (*ortho*-position of the phenyl ring and C-2 position of the piperazine ring) seemed to be related to a steric free-rotational hindrance between the two rings.

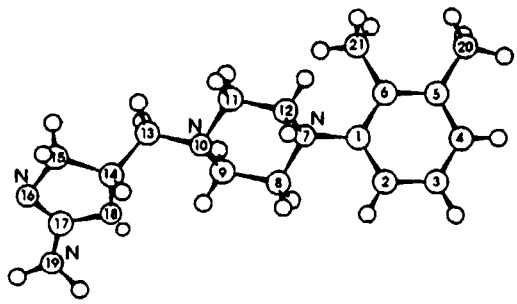


Fig. 2: Solid state conformation of **6**.

The solid state conformation of compound **6** is depicted in Fig. 2. Of interest for the purpose of this work one must notice the sp^3 character of N(7). According to [5] its hybridization state is related to the special "nitrogen-torsion" angle τ_N defined as R1-N-R3-R2 where Rs are substituents at N. For compound **6** τ_N (C1-N7-C8-C12) = 132° is comparable with the value of 138° found for the non-substituted compound COR 3224[6] and characteristic for a sp^3 nitrogen.

Table 1: Physical data of 5-(1-aryl-4-piperazino)methyl-2-amino-2-oxazolines

N°	R_1	R_2	F °C solvt	logk'_w	Yield	N°	R_1	R_2	F °C solvt	logk'_w	Yield
1	4-F	H	167 c	1.61	25	6	2,3-diCH$_3$	H	178 c	2.9	23
2	2-F	H	114 c	1,54	28	7	3-CF$_3$	H	159 b	2.89	22
3	2-OCH$_3$	H	136 c	1.72	18	8	4-CH$_3$	CH$_3$	147 a	2.35	32
4	4-NO$_2$	H	191 b		11	9	3-OCH$_3$	CH$_3$	122 d	1.64	14
5	2-OEt	H	121 a	2.08	25	10	2-CH$_3$	H	126 a	2.51	43

Recrystallization solvents a: heptane, b: trichloroethylene
c: tetrachloroethylene, d: diisopropyl ether

In the 2-amino-2-oxazolines series if R belongs to a pyrimidine ring, τ_N = 164° responds for a nitrogen with a strong sp^2 character. In the same way we compared the C_{Ar}-N bond lengths measured in the crystalline state: 1.346(3) Å for the pyrimidino compound (N sp^2), 1.414(4) Å for the non-substituted compound, and 1.430(3) Å for the dimethyl derivative **6** (N sp^3).

No difference could be noted between the ortho substituted **6** and the non-substituted compounds either in the nitrogen hybridization state or in the C_{Ar}-N bond lengths.

From X-ray data and semi-empirical calculations we compared the angle θ between the phenyl ring and the mean-plane of the piperazine ring in 1-phenylpiperazine, 1-(2-methylphenyl)piperazine, and 1-phenyl-2-methylpiperazine. As expected, the introduction of a methyl substituent induces a free rotational hindrance for the phenyl ring: θ = 47° (X-ray) and 64° (calculated) when the methyl is on the phenyl ring, whereas θ_{calc} = 53° when the methyl is on the piperazine ring *vs* θ = 21° (X-ray) and 31° (calculated) in the non-substituted derivative. This calculation shows that the steric hindrance is more important in the *ortho*-substituted phenyl compound than in the C-2 piperazine one.

In order to examine the behaviour of 5-(1-aryl-4-piperazino)methyl-2-amino-2-oxazolines in solution, some of them were submitted to a 500 MHz NMR study. Compounds **6**, **8**, **9**, and **10** were chosen as templates. The 5-[1-(3-methoxy)phenyl-4-piperazino]methyl-2-amino-2-oxazoline (**11**)[2] may account for the non-perturbed derivatives (no substituent on *ortho*- or α-position). In the particular case of **6**, the four β-protons of the piperazine ring appeared as a broad and ill-defined singlet. In order to confirm our attribution, a 2D NMR experiment was performed using a COSY sequence (Fig. 3). Final results are summarized in Table 2. For **11**, the α-piperazine protons are deshielded by about 0.5 ppm from the β-protons suggesting some conjugation between the N(7) lone pair and the aromatic π electrons. For **6** and **10**, the deshielding effect is only 0.2 ppm accounting now for the loss of conjugation: the α and β piperazine protons are in an almost identical environment. For **8** and **9** the α-methylene group reverts more or less to its original position (deshielding = 0.4 ppm). The α-methine protons appear deshielded (0.5 to 0.7 ppm *vs* the α-CH_2) due to the methyl substitution. The recorded spectra of the reference compounds 5-piperidinomethyl- (**12**) and 5-[(2-methyl)piperidino]methyl-2-amino-2-oxazolines (**13**)[7] give a 0.5 ppm deshielding effect of the methine group *vs* the methylene one. NMR experiments show no effect in the C-2 substituted compounds spectra but evidence a noticeable perturbation in the *ortho*-substituted ones.

Conclusion

In this series of 2-amino-2-oxazolines, the lowering of the antidepressant activity is not simply related to their lipophilic behaviour. Compounds with an *ortho* methyl substituent on the phenyl ring or with a methyl substituent at C-2 of the piperazine ring have been studied using experimental

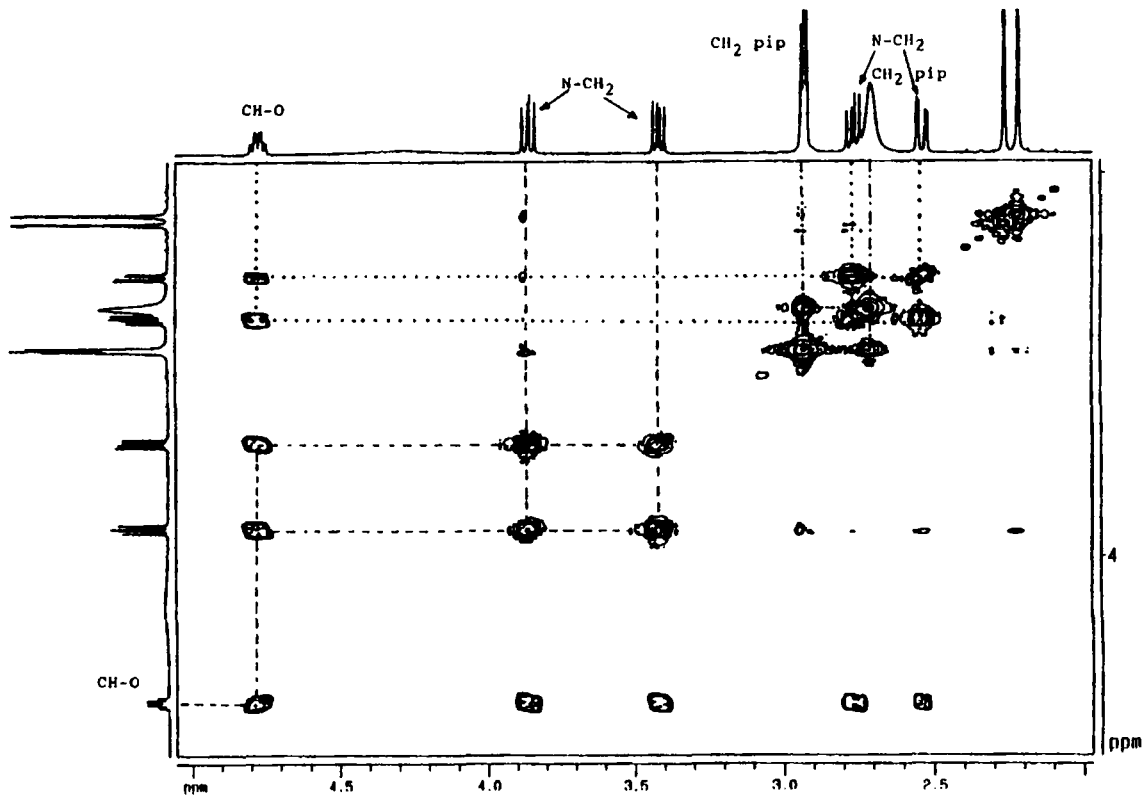
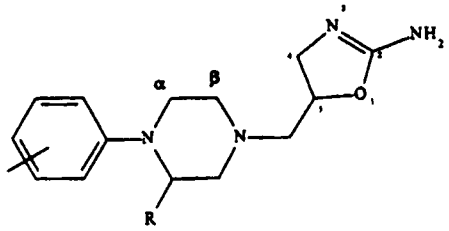
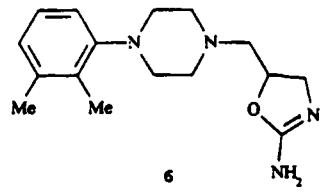


Fig. 3: 2D COSY map of **6** showing the intercorrelation of the protons

Table 2: Chemical shifts of piperazine protons at 500 MHz



R on piperazine	Σ	Number	α-protons	β-protons
none	2,3-Me	6	2.9	2.7
R = Me	4-Me	8	3.6 (1H) 3.1 (2H)	2.6 - 2.7
R = Me	3-MeO	9	3.8 (1H) 3.2 (1H) 3.1 (1H)	2.6 - 2.7
none	2-Me	10	2.95	2.7
none	3-MeO	11	3.2	2.7



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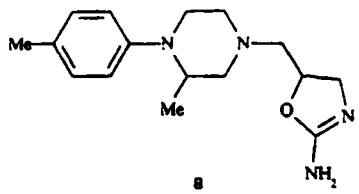

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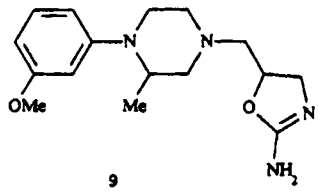

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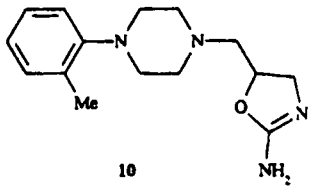

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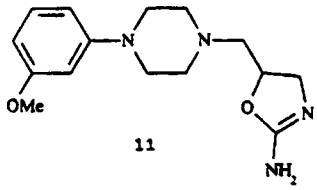

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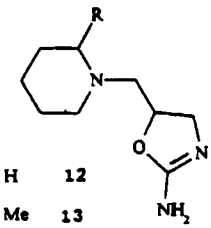

R = H 12

R = Me 13

methods (X-ray, NMR) and theoretical methods (semi-empirical calculations). The findings of X-ray and conformational analyses enlighten the influence of the substitution (*ortho* and C-2 positions), the *ortho* substitution giving a θ angle higher than the C-2 substitution. Using NMR, only the influence of the *ortho*-substitution has been observed. The electronic density around the (CH_n) in α of N(7) is enhanced by the *ortho* methyl substituent suggesting a loss of conjugation between the N(7) lone pair and the π electrons. These results obtained on methyl substituted compounds, may be applied to other *ortho* substituted compounds and may account for the decrease of the pharmacological activity.

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Experimental Part

As an example of the general procedure for the preparation of 5-(1-aryl-4-piperazino)methyl-2-amino-2-oxazolines we describe the synthesis of compound **8**. - IR spectra: Beckman Acculab spectrometer. - Melting points: Kofler hot-stage, uncorrected.

*5-[1-(4-Methylphenyl)-4-(2-methyl)piperazino]methyl-2-amino-2-oxazoline (**8**)*

18.5 g (0.2 mole) of epichlorhydrin was added dropwise at 40°C to a stirred mixture of 38 g (0.2 mole) of 1-(4-methylphenyl)-2-methylpiperazine in 200 ml of ethanol. The reaction mixture was stirred during 6 h of 40°C. After addition of 8 g (0.2 mole) of NaOH in ethanol the mixture was stirred during 15 h at room temp. and then filtered. After evaporation of the ethanol, the residue was dissolved in ether and filtered. The ether phase was concentrated and the crude 1-[1-(4-methylphenyl)-4-(2-methylpiperazino)]-2,3-epoxypropane, obtained as an oil, was washed 3x with hot heptane. 36.9 g (0.15 mole) of this epoxyde were added dropwise at 20°C to a stirred solution of monosodium cyanamid salt (9.6 g, 0.15 mole) in 200 ml of methanol. Stirring was prolonged during 36 h. Then the mixture was concentrated under reduced pressure and the residue was extracted 3x with ether. After filtration and elimination of the solvent, the oily crude 2-amino-2-oxazoline was crystallized from heptane (yield 32%). Mp. 147°C. - IR (KBr): 3400, 1685 cm^{-1}.

Pharmacological evaluation

The reserpine hypothermia interaction was studied according to a classical procedure [2,8]. Imipramine (ED_{30} = 1.2 mg/kg) and viloxazine (6.1 mg/kg) were included as standards.

X-ray crystallography and geometry optimisation

Crystals of compound **6** were obtained by slow evaporation of a solution in ethyl acetate/chloroform.

$C_{16}H_{24}N_4O$, M = 288.4, monoclinic, space group $P2_1/c$
a = 19.837(3) Å, b = 7.853(2) Å, c = 10.543(2) Å, β = 100.6(1)°
V = 1614(1) $Å^3$, Z = 4, D_c = 1.18 g · cm^{-3}

A crystal of dimensions 0.30x0.15x0.05 mm was selected from the recrystallized material. Intensity data were collected on a fully automated Enraf-Nonius CAD-4 diffractometer using graphite monochromated CuKα radiation ($\bar{\lambda}$ = 1.54178 Å). 2747 symmetry-independent reflections up to θ = 65° were measured of which 1672 significant diffraction maxima [$I \geq 3\sigma(I)$] were used in the refinements. Data were corrected for *Lorentz* and polarization effects but not for absorption (μ = 6.2 cm^{-1}).

The structure was solved by the direct methods using MULTAN 80 [9] and refined by block-diagonal least-squares with anisotropic thermal parameters. H-atoms, introduced in theoretical positions or in positions derived from difference *Fourier* maps, were refined with isotropic thermal parameters. The final R factor was 0.045 (286 variables).

Fragments of 1-phenylpiperazine, 1-(2-methylphenyl)piperazine and 1-phenyl-2-methylpiperazine were rebuilt from crystal structures [6] using CHEM-X [9]. The geometries were fully optimized using semi-empirical calculations. The MOPAC-program[10] and the Austin Model 1 (AM1) method[11] available in CHEM-X were used for this purpose.

This study is closely related to a conformational analysis performed with CNDO/2 method on some 1-arylpiperazines[12].

NMR study

Bruker AMX-500 spectrometer, $CDCl_3$, TMS as internal standard. The spectra were processed using the last version of Bruker UXNMR software. ^{13}C spectra were recorded using JMOD technique. The COSY map was recorded using the standard Bruker pulse program with 256 experiments of 2 K and 8 scans each. Chemical shifts of studied compounds (δ ppm).

*5-[1-(2,3-Dimethylphenyl)-4-piperazino]methyl-2-amino-2-oxazoline (**6**)*

^{1}H-NMR: 2.22 and 2.26 (2s, 3+3 H, 2 Ar-Me); 2.54 (dd; 1H, J = 3.6; 13.5 Hz, 4-H_a, oxazoline); 2.70 (m; 4H, 2 CH_2, β piperazine); 2.76 (ddd; 1H, J = 0.5; 8.3; 13.6 Hz, 4-H_b, oxazoline); 2.93 (t, 4H, J = 4.7 Hz, 2 CH_2, α piperazine); 3.42 (ddd; 1H, J = 0.5; 7.4; 12.2 Hz, N-CH_{2a}); 3.86 (ddd; 1H, J = 0.5; 9.0; 12.2 Hz, N-CH_{2b}); 4.78 (ddddd; 1H, J = 0.5; 3.6; 7.4; 8.3; 8.9 Hz, CH-O); 6.90 and 6.91 (2d; 1H each, J = 7.8 Hz, Ar 4-H and Ar 6-H); 7.07 (t; 1H, J = 7.8 Hz, Ar 5-H). - **^{13}C-NMR**: 13.78 and 20.45: 2 Ar-Me; 51.87 and 54.11: 2x2 CH_2-N piperazine; 56.52 and 62.78: 2 CH_2-N; 77.89: CH-O; 116.56: ArC-6; 124.88 and 125.71: ArC-4 and ArC-5; 131.11: ArC-2; 137.77: ArC-3; 151.39: ArC-1; 160.87: N=C-O.

*5-[1-(3-Methoxyphenyl)-4-(2-methyl)piperazino]methyl-2-amino-2-oxazoline (**9**)*

^{1}H-NMR: 1.08 (d; 3H, J = 6.5 Hz, C-CH_3); 2.48 (ddd; 1H, J = 3.6; 11.0; 14.0 Hz, CH, β piperazine); 2.55 (dd; 1H, J = 4.3; 13.5 Hz, 4-H_a oxazoline); 2.59 (dd; 1H, J = 3.4; 11.0 Hz, CH, β piperazine); 2.66 (dd; 1H, J = 7.2; 13.4 Hz, 4-H_b oxazoline); 2.69 (m; 1H, CH, β piperazine); 2.82 (m; 1H, CH, β piperazine); 3.12 (ddd; 1H, J = 3.2; 9.7; 13.0 Hz) and 3.20 (dt; 1H, J = 11.9; 3.8 Hz, Ar-N-CH_2 piperazine); 3.49 (dd; 1H, J = 7.4; 12.2 Hz, N-CH_{2a}); 3.78 (s; 3H, OCH_3); 3.81 (dt; 1H, J = 6.6; 3.3 Hz, CH-CH_3); 3.86 (dd; 1H, J = 8.9; 12.1 Hz, N-CH_{2b}); 4.74 (dddd; 1H, J = 4.3; 7.2; 7.4; 8.9 Hz, CH-O); 6.42 (ddd; 1H, J = 8.2; 2.4; 0.6 Hz; Ar 4-H); 6.46 (t; 1H, J = 2.4 Hz, Ar 2-H); 6.53 (ddd; 1H, J = 8.2; 2.4; 0.6 Hz, Ar 6-H); 7.16 (t; 1H, J = 8.2 Hz, Ar 5-H).

^{13}C-NMR: (2 diastereoisomers in 85/15 ratio) 13.51: CH_3-C; 44.99: CH_2-N; 51.17: CH-N piperazine; 54.25: CH_2-N; 55.08: OCH_3; 56.55, 59.28 and 62.23: 3 CH_2-N; 78.49: CH-O; 103.73; ArC-2; 104.48: ArC-4; 110.02: ArC-6; 129.66: ArC-5; 151.59: ArC-1; 160.60 and 160.75: ArC-3 and N=C-O.

minor isomer: 13.41: CH_3-C; 44.77: CH_2-N; 51.17: CH-N piperazine; 53.88: CH_2-N; 55.08: OCH_3; 56.50, 59.75 and 62.23: 3 CH_2-N; 78.29: CH-O; 103.62: ArC-2; 104.39: ArC-4; 109.91: ArC-6; 129.66: ArC-5; 151.59: ArC-1; 160.60 and 160.75: ArC-3 and N=C-O.

*5-[1-(4-Methylphenyl)-4-(2-methyl)piperazino]methyl-2-amino-2-oxazoline (**8**)*

^{1}H-NMR: 1.01 (d; 3H, J = 6.4 Hz, C-CH_3); 2.28 (s; 3H, Ar-CH_3); 2.53 (dd; 1H, J = 4.2; 13.3 Hz; 4-H_a oxazoline); 2.54 (m; 1H, CH-N); 2.59 (ddd; 1H, J = 3.9; 7.4; 11.1 Hz, CH-N); 2.67 (dd; 1H, J = 7.6; 13.4 Hz, 4-H_b oxazoline); 2.71 (m; 2H, CH_2, β piperazine); 3.10 (m; 1H, Ar-N-CH_2 piperazine); 3.46 (dd; 1H, J = 7.4; 12.2 Hz, N-CH_{2a}); 3.63 (m; 1H, CH-CH_3); 3.85 (dd; 1H, J = 9.0; 12.2 Hz, N-CH_{2b}); 4.74 (ddd; 1H, J = 4.2; 7.5; 11.7 Hz, CH-O); 6.87 (d; 2H, J = 8.4 Hz, 2 ArH); 7.07 (d; 2H, J = 8.4 Hz, 2 ArH). - **^{13}C-NMR**: (only traces of a second diastereoisomer) 14.21: CH_3-C; 20.41: Ar-Me; 47.43: CH_2-N; 51.90: CH-N piperazine; 54.35, 56.49, 59.78 and 62.33: 4 CH_2-N; 78.25: CH-O; 119.00: ArC-2 and ArC-6; 129.50: ArC-5 and ArC-3; 129.99: ArC-4; 148.14: ArC-1; 160.83: N=C-O.

*5-[1-(2-Methylphenyl)-4-piperazino]methyl-2-amino-2-oxazoline (**10**)*

^{1}H-NMR: 2.30 (s; 3H, Ar-Me); 2.54 (dd; J = 3.4; 13.5 Hz, 4-H_a oxazoline); 2.70 (br. s; 4H, 2 CH_2, β piperazine); 2.77 (dd; J = 8.3; 13.5 Hz, 4-H_b oxazoline); 2.95 (m; 4H, 2 CH_2; α piperazine); 3.43 (dd; 1H, J = 7.5; 12.2 Hz, N-CH_{2a}); 3.87 (dd; 1H, J = 9.1; 12.2 Hz, N-CH_{2b}); 4.79 (dddd; 1H, J = 9.1; 8.3; 7.5; 3.4 Hz, CH-O); 6.98 (t; 1H, J = 7.4 Hz, Ar-H); 7.02 (d; 1H, J = 7.8 Hz, Ar-H); 7.16 (t; 1H, J = 7.4 Hz, Ar-H); 7.17 (d; 1H, J =

7.8 Hz, Ar-H). - **^{13}C-NMR**: 17.83: Ar-Me; 51.42 and 54.12: 2x2 CH_2-N piperazine; 56.62 and 62.88: 2 CH_2-N; 77.88: CH-O; 118.92: ArC-6; 123.10: ArC-4; 126.52: ArC-2; 130.98: ArC-5; 132.47: ArC-3; 151.30: ArC-1; 160.91: N=C-O.

5-[1-(3-Methoxyphenyl)-4-piperazino]methyl-2-amino-2-oxazoline (**11**)

^{1}H-NMR: 2.52 (dd; 1H, J = 3.6; 13.6 Hz, 4-H_a oxazoline); 2.69 (m; 4H, 2 CH_2, β piperazine); 2.74 (dd; 1H, J = 8.2; 13.6 Hz, 4-H_b oxazoline); 3.22 (m; 4H, 2 CH_2 piperazine); 3.42 (dd; 1H, J = 7.4; 12.2 Hz, N-CH_{2a}); 3.79 (s; 3H, OCH_3); 3.86 (dd; 1H, J = 9.0; 12.2 Hz; N-CH_{2b}); 4.77 (dddd; 1H, J = 3.5; 7.5; 8.2; 9.0 Hz, CH-O); 6.42 (ddd; 1H, J = 8.2; 2.4; 0.6 Hz, Ar 4-H); 6.46 (t; 1H, J = 2.4 Hz, Ar 2-H); 6.53 (ddd; 1H, J = 8.2; 2.4; 0.6 Hz, Ar 6-H); 7.16 (t; 1H, J = 8.2 Hz, Ar 5-H). - **^{13}C-NMR**: 48.49 and 53.59: 2x2 CH_2-N piperazine; 55.11: OCH_3; 56.65 and 62.64: 2 CH_2-N; 78.10: CH-O; 102.53: ArC-2; 104.44: ArC-4; 108.82: ArC-6; 129.70: ArC-5; 152.60: ArC-1; 160.57 and 160.61: ArC-3 and N=C-O.

5-(Piperidino)methyl-2-amino-2-oxazoline (**12**)

^{1}H-NMR: 1.43 (m; 2H, CH_2, γ piperidine); 1.60 (m; 4H, 2 CH_2, β piperidine); 2.39 (dd; 1H, J = 3.6; 13.5 Hz, 4-H_a oxazoline); 2.45 (m; 4H, 2 CH_2, α piperidine); 2.65 (dd; 1H, J = 8.3; 13.5 Hz, 4-H_b oxazoline); 3.36 (dd; 1H, J = 7.4; 12.2 Hz, N-CH_{2a}); 3.83 (dd; 1H, J = 8.9; 12.2 Hz, N-CH_{2b}); 4.79 (dddd; 1H, J = 8.9; 8.3; 7.4; 3.6, Hz, CH-O).

5-[(2-Methyl)piperidino]methyl-2-amino-2-oxazoline (**13**)

^{1}H-NMR: 1.06 (d; 3H, J = 6.2 Hz, C-CH_3); 1.33 (m; 2H, CH_2, γ piperidine); 1.61 (m; 4H, 2 CH_2, β piperidine); 2.22-2.32 (m; 2H, CH_2, α piperidine); 2.32 (dd; 1H, J = 3.5; 14.1 Hz, 4-H_a oxazoline); 2.92 (m; 1H, CH-CH_3, α piperidine); 2.98 (dd; 1H, J = 8.4; 14.1 Hz, 4-H_b oxazoline); 3.35 (dd; 1H, J = 7.2; 12.1 Hz, N-CH_{2a}); 3.81 (dd; 1H, J = 8.9; 12.1 Hz, N-CH_{2b}); 4.72 (dddd; 1H, J = 8.9; 8.4; 7.2; 3.5 Hz, CH-O).

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