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Some new *N*-substituted pyrrolidin-2-ones, cyclic analogues of baclofen and of 3-(5-methoxybenzo[*b*]furan-2-yl)- γ -aminobutyric acid, have been prepared and characterized, starting from 4-(4-chlorophenyl)-pyrrolidin-2-one and 4-(5-methoxybenzo[*b*]furan-2-yl)pyrrolidin-2-one.

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Several neurological and neuropsychiatric disorders, such as epilepsy, Huntington's, and Parkinson's diseases, have been reported to be associated with a decrease in the γ -aminobutyric acid levels in the central nervous system [1-2]. These observations suggest that increasing levels of γ -aminobutyric acid in the central nervous system may be useful in the treatment of such neuropsychiatric disorders. Unfortunately, the administration of γ -aminobutyric acid is not efficient because, under normal conditions, it very poorly crosses the blood-brain barrier, presumably as a result of its low lipophilicity [3]; the brain penetration index for γ -aminobutyric acid was found to be 1% regardless of the mode of administration and dose [4]. Among the different strategies used to increase the brain uptake of γ -aminobutyric acid [5], the prodrug approach using γ -lactam derivatives is one of the most promising: thus 1-acyl-2-pyrrolidinone derivatives gave γ -aminobutyric acid-like depressant effects on the central nervous system, and anticonvulsant and sedatives actions [2] are observed with aniracetam **1** and pramiracetam **2**. In the same way, an anti-amnesic activity was observed with 1-arylmethyl-5-alcoxy-pyrrolidin-2-ones [6].

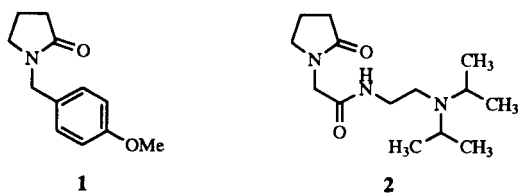


Figure 1

Baclofen **3** is a selective γ -aminobutyric acid type B receptor agonist, structurally related to γ -aminobutyric acid, which is used clinically in the treatment of spasticity [7]. It acts as a skeletal muscle relaxant, by inhibiting the excitatory neurotransmitter release into motor neurones of the spinal cord [8].

The cyclic analogues **4**, **5**, **6** of baclofen showed muscle relaxant activity [9]; as for the 5-methoxybenzo[*b*]furan-2-yl analog **7** of baclofen, it is a selective γ -aminobutyric acid type B receptor antagonist [10-14], mainly used as a biochemistry marker.

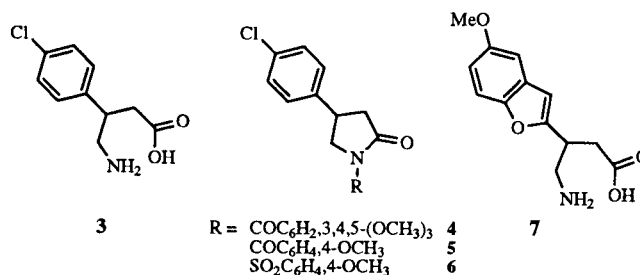


Figure 2

On the other hand, cognitive deficits and memory loss are frequently associated with aging (benign senescent forgetfulness), senile dementia, and primary degenerative dementia (Alzheimer's disease) [15]. Due to demographic changes and the strong increase in mean life expectancy in developed countries, the incidence of cognitive disorders in the population is likely to grow [16]. The development of therapeutic approaches in the treatment of cognitive disorders is thus a real and urgent problem nowadays. Among the possible therapeutic interventions, pyrrolidin-2-one derivatives [17] such as piracetam **8** and related nootropics are currently used for their facilitatory effects for learning and memory in animals models [18].

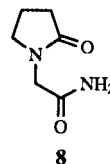


Figure 3

In other respects, prolylendopeptidase is a serine protease that specifically cleaves peptidyl proline bonds [19], hydrolyzing many biologically active peptides, including thyrotropin-releasing hormone, substance P, angiotensin II, oxytocin, and bradykinin [20-21]. This enzyme also degrades arginine vasopressin and this may facilitate learning and memory [22]. Yoshimoto reported that prolylendopeptidase inhibitors such as 1-[1-(benzyloxycarbonyl)-L-prolyl]prolinal (Z-Pro-prolinal) **9** reversed scopolamine induced amnesia in the passive avoidance learning test in rats [23-24] and that the anti-amnesic effects of these compounds were approximately parallel to their inhibition potential towards prolylendopeptidase *in vitro* [23-25]. Some nootropic γ -lactams such as aniracetam **1** and pramiracetam **2** are also inhibitors of prolylendopeptidase [24].

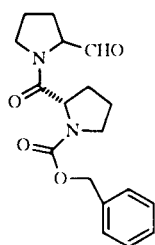
**9**

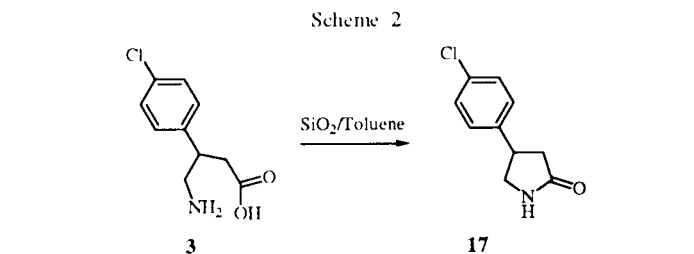
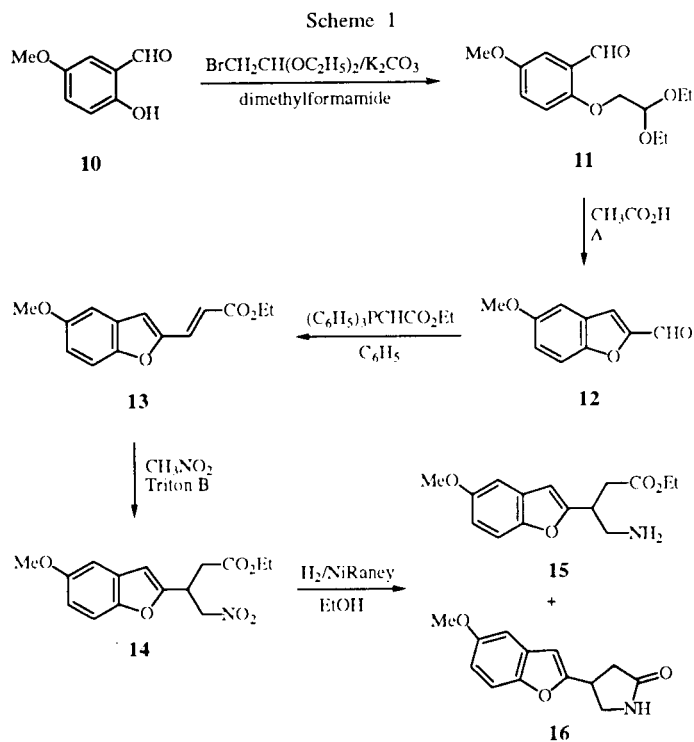
Figure 4

In this paper, we deal with the synthesis of new pyrrolidin-2-ones, cyclic analogues of **3** and **7** in order to increase their lipophilicity and brain penetration.

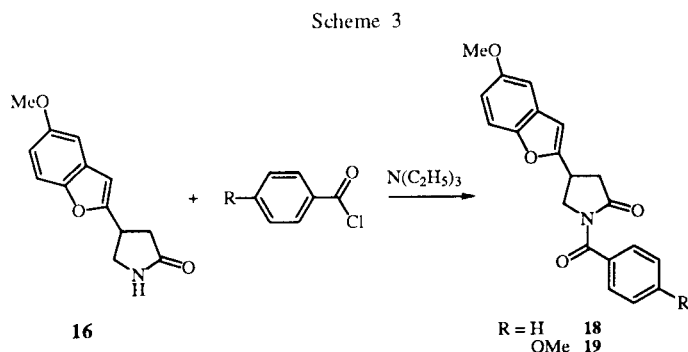
The first starting compounds of these syntheses **4**-(5-methoxybenzo[*b*]furan-2-yl)pyrrolidin-2-one **16** was prepared in five steps from commercially available salicylaldehyde **10** according to the literature methods (Scheme 1) [14]. Salicylaldehyde **10** was reacted with bromoacetaldehyde diethylacetal in dimethylformamide to give compound **11**. This product was cyclized to 5-methoxybenzo[*b*]furan-2-ylcarboxaldehyde **12** by heating in acetic acid. The treatment of aldehyde **12** with (carbethoxymethylene)triphenylphosphorane in benzene at reflux gave adduct **13**, which was treated by nitromethane at 85° to afford the nitro ester **14**. The catalytic reduction of compound **14** at atmospheric pressure led to a mixture of aminoester **15** and lactam **16** whose heating at 100° gave pure lactam **16**.

4-(4-chlorophenyl)pyrrolidin-2-one **17** was prepared from baclofen **3** by cyclisation in boiling toluene in the presence of silica gel (Scheme 2) [9]; alternately this product can be obtained by heating **3** at melting point for a few minutes [26].

The direct acylation [2,10] of 4-arylpyrrolidin-2-one **16**, with acyl chlorides, at room temperature, in the presence

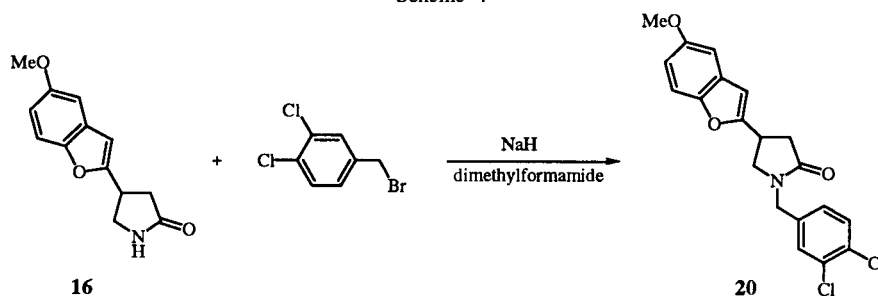


of triethylamine, gave 1-acylpyrrolidin-2-one derivatives **18** and **19** in average yield (Scheme 3). The crude products obtained could easily be purified by recrystallization.



Treatment of the sodium salt of 4-arylpyrrolidin-2-one **16**, with 3,4-dichlorobenzyl bromide in dimethylformamide [27], provided a 60% yield in 1-(3,4-dichlorobenzyl)-4-(5-

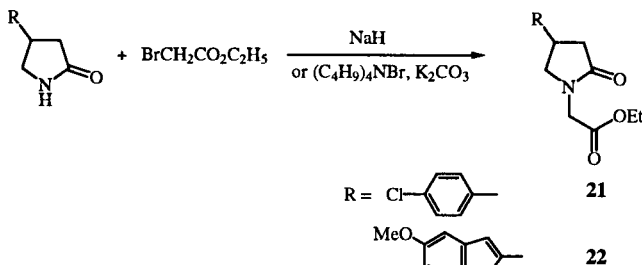
Scheme 4



methoxybenzo[*b*]furan-2-yl)pyrrolidin-2-one **20** (Scheme 4). This oil was purified by semipreparative high performance liquid chromatography.

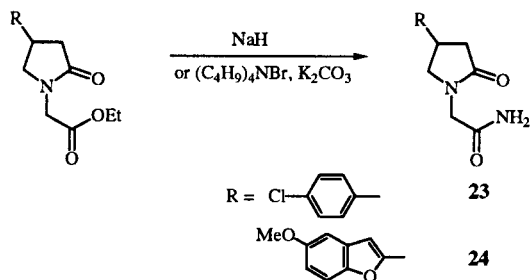
The 1-alkyl-4-arylprrrolidin-2-one **21** and **22** were obtained by reaction of ethyl bromoacetate with the sodium salt of 4-arylprrrolidin-2-one **16** and **17** [28-29] (70 and 80% yield) or by alkylation of the pyrrolidinone **16** and **17** in phase transfert conditions, using potassium carbonate as the base [29-32] (66 and 86%) (Scheme 5). The expected products were obtained after purification by preparative high performance liquid chromatography.

Scheme 5



Amides **23** and **24**, analogues of piracetam, were prepared by ammoniolysis of the corresponding ethyl esters **21** and **22** with methanolic ammonia [28]. The crude products were purified by recrystallization (Scheme 6).

Scheme 6



The structures of these new pyrrolidinones were established by elemental analysis and spectral data. Biological properties will be reported elsewhere.

EXPERIMENTAL

Melting points were determined by using a Büchi SMP 20 and are uncorrected; analytical thin layer chromatography (tlc) was performed on precoated Kieselgel 60F₂₅₄ plates (Merck); the IR spectra were recorded on a Beckman Acculab IV spectrometer and the nmr spectra on a Bruker WP80 at 80 MHz or a Bruker AC300 at 300 MHz, using tetramethylsilane as an internal reference. Elemental analysis were performed by the "Service Central de Microanalyses" of CNRS in Vernaison, France. Preparative high performance liquid chromatographies were realised on a system Modul Prep (JOBIN-YVON) with a refractometric RI IOTA detector and a UV Spectromonitor D (LDC) detector.

1-Benzoyl-4-(5-methoxybenzo[*b*]furan-2-yl)pyrrolidin-2-one (**18**).

Benzoyl chloride (0.13g, 0.9 mmole) was slowly added to a solution of 4-(5-methoxybenzo[*b*]furan-2-yl)pyrrolidin-2-one **16** (0.21 g, 0.9 mmole) and triethylamine (0.12 ml, 0.9 mmole) in dry tetrahydrofuran (15 ml). The mixture was stirred for 48 hours at room temperature, the precipitate of triethylamine hydrochloride was filtered and the solvent was evaporated under vacuum. The oily residue obtained was washed with ether and filtered, yield 63%, mp 165-167° (acetone); tlc (ethyl acetate) *R_f* 0.65; ir (potassium bromide): (ν cm⁻¹) 1685, 1760, 3100; ¹H nmr (80 MHz) (deuteriochloroform): δ ppm 3.00 (d, *J* = 7.7 Hz, 2H), 3.85 (s, 3H), 3.80-4.40 (m, 3H), 6.55 (s, 1H), 6.9 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.00 (d, *J* = 2.0 Hz, 1H), 7.35-7.75 (m, 6H)

Anal. Calcd. for C₂₀H₁₇NO₄: C, 71.62; H, 5.12; N, 4.18; O, 19.08. Found C, 71.38; H, 5.31; N, 4.26; O, 19.13.

1-(4-Methoxybenzoyl)-4-(5-methoxybenzo[*b*]furan-2-yl)pyrrolidin-2-one (**19**).

4-Methoxybenzoyl chloride (0.17 g, 1.2 mmoles) was slowly added to a solution of 4-(5-methoxybenzo[*b*]furan-2-yl)pyrrolidin-2-one **16** (0.21 g, 0.9 mmole) and triethylamine (0.17 ml, 1.2 mmoles) in dry tetrahydrofuran (15 ml). The solution was stirred for 48 hours at room temperature, the precipitate of triethylamine hydrochloride was filtered and the solvent evaporated under vacuum. The residue obtained was basified with a sodium hydroxyde solution (1N), then extracted with ethyl acetate and washed with water. After drying, the solvent was evaporated. The residue was washed with ether and filtered, yield 46%, mp 176-177° (acetone); tlc (ethyl acetate) *R_f* 0.63; ir (potassium bromide): (ν cm⁻¹) 1655, 1735, 2945; ¹H nmr (80 MHz) (deuteriochloroform): δ ppm 2.85-3.05 (m, 2H), 3.85 (s, 3H), 3.85 (s, 3H), 3.7-4.35 (m, 3H), 6.55 (s, 1H), 6.80-7.80 (m, 7H).

Anal. Calcd. for C₂₁H₁₉NO₅: C, 69.02; H, 5.25; N, 3.83; O, 21.90. Found: C, 68.81; H, 5.26; N, 3.77; O, 21.62.

1-(3,4-Dichlorobenzyl)-4-(5-methoxybenzo[*b*]furan-2-yl)pyrrolidin-2-one (**20**).

A sodium hydride dispersion (50% in mineral oil, 0.05 g, 0.99 mmole) was added to a solution of 4-(5-methoxybenzo[*b*]furan-2-yl)pyrrolidin-2-one **16** (0.21 g, 0.9 mmole) in dimethylformamide (10 ml) under an argon atmosphere at room temperature. The mixture was stirred for 45 minutes, then a solution of 3,4-dichlorobenzyl bromide (0.27 ml, 0.99 mmole) in dimethylformamide was added and the stirring was continued for 3 hours. Water was carefully added and the solution was extracted with ether. After drying and evaporation under vacuum, the residue was purified by semi-preparative high performance liquid chromatography (silicagel 10 μ m, ethyl acetate-hexane 80/20 (v/v), $\lambda = 345$ nm), yield 60%; tlc (ethyl acetate-hexane 80/20 (v/v)) R_f , 0.33; ir (potassium bromide): (ν cm^{-1}) 1690, 2935; ^1H nmr (80 MHz) (deuteriochloroform): δ ppm. 2.80 (d, $J = 6.3$ Hz, 2H), 3.35-3.75 (m, 3H), 3.80 (s, 3H), 4.45 (s, 2H), 6.40 (s, 1H), 6.80 (dd, $J = 2.7, 8.9$ Hz, 1H), 6.95 (d, $J = 2.5$ Hz, 1H), 6.75-7.45 (m, 4H).

Anal. Calcd. for $\text{C}_{20}\text{H}_{17}\text{Cl}_2\text{NO}_3$: C, 61.55; H, 4.40; Cl, 18.16; N, 3.59; O, 12.30. Found: C, 60.99; H, 4.47; Cl, 18.67; N, 3.47; O, 12.41.

1-Ethoxycarbonylmethyl-4-(4-chlorophenyl)pyrrolidin-2-one (**21**) with Sodium Hydride.

A solution of 4-(4-chlorophenyl)pyrrolidin-2-one **17** (0.51 g, 2.6 mmoles) in tetrahydrofuran (10 ml) was slowly added to a sodium hydride suspension (50% in mineral oil, 0.19 g, 3.9 mmoles) in tetrahydrofuran. The mixture was refluxed and ethyl bromoacetate (0.43 ml, 3.9 mmoles) was added. The refluxing was continued for 16 hours. After cooling, water was added and the solution was extracted with ether and dried with sodium sulfate. The solvent was evaporated and the residue obtained was purified by preparative high performance liquid chromatography (silica gel 5-40 μ m, dichloromethane-methanol 99/1 (v/v), $\lambda = 310$ nm), yield 70%.

With Potassium Carbonate.

A mixture of 4-(4-chlorophenyl)pyrrolidin-2-one **17** (0.51 g, 2.6 mmoles), tetrabutylammonium bromide (0.42 g, 1.3 mmoles) and potassium carbonate (1.80 g, 13.0 mmoles) in acetonitrile (4 ml) was stirred for 3 hours at room temperature. Ethyl bromoacetate (0.37 ml, 3.3 mmoles) was slowly added and the mixture was stirred at 60° for 12 hours, then for 2 days at room temperature. The mixture was filtered and the solvent evaporated under vacuum. The oil residue was purified by preparative high performance liquid chromatography (silica gel 5-40 μ m, dichloromethane-methanol 99/1 (v/v), $\lambda = 310$ nm), yield 66%; tlc (chloroform-methanol 60/40 (v/v)) R_f , 0.85; ir (potassium bromide): (ν cm^{-1}) 1700, 1755, 2990; ^1H nmr (80 MHz) (deuteriochloroform): δ ppm 1.25 (t, $J = 7.1$ Hz, 3H), 2.35-2.85 (m, 2H), 3.40-3.90 (m, 3H), 4.15 (s, 2H), 4.05-4.40 (q, $J = 7.1$ Hz, 2H), 7.10-7.40 (m, 4H).

Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{ClNO}_3$: C, 59.68; H, 5.73; Cl, 12.58; N, 4.97; O, 17.04. Found: C, 59.49; H, 5.89; Cl, 12.19; N, 4.61; O, 17.50.

1-Ethoxycarbonylmethyl-4-(5-methoxybenzo[*b*]furan-2-yl)pyrrolidin-2-one (**22**).

With Sodium Hydride.

A solution of 4-(5-methoxybenzo[*b*]furan-2-yl)pyrrolidin-2-one **16** (0.23 g, 1.0 mmole) in tetrahydrofuran (5 ml) was slowly added to sodium hydride suspension (50% in mineral oil,

0.07 g, 1.5 mmoles) in tetrahydrofuran. The mixture was refluxed and ethyl bromoacetate (0.17 ml, 1.5 mmoles) was added. The refluxing was continued for 16 hours. After cooling, water was added and the solution was extracted with ether and dried with sodium sulfate. The solvent was evaporated and the residue obtained was purified by preparative high performance liquid chromatography (silica gel 5-40 μ m, dichloromethane-methanol 99/1 (v/v), $\lambda = 310$ nm), yield 80%.

With Potassium Carbonate.

A mixture of 4-(5-methoxybenzo[*b*]furan-2-yl)pyrrolidin-2-one **16** (0.51 g, 2.2 mmoles) tetrabutylammonium bromide (0.35 g, 1.1 mmoles) and potassium carbonate (1.52 g, 11.0 mmoles) in acetonitrile (4 ml) was stirred for 1 hour at room temperature then ethyl bromoacetate (0.31 ml, 2.8 mmoles) was slowly added. The mixture was stirred at 60° for 3 hours then for 2 days at room temperature. The mixture was filtered and the solvent evaporated under vacuum. The oil residue was purified by preparative high performance liquid chromatography (silica gel 5-40 μ m, dichloromethane-methanol 99/1 (v/v), $\lambda = 310$ nm), yield 86%; tlc (dichloromethane-methanol 95/5 (v/v)) R_f , 0.62; ir (potassium bromide): (ν cm^{-1}) 1695, 1765, 2940; ^1H nmr (80 MHz) (deuteriochloroform): δ ppm. 1.30 (t, $J = 7.2$ Hz, 3H), 2.65-2.95 (m, 2H), 3.85 (s, 3H), 3.60-3.95 (m, 3H), 4.25 (s, 2H), 4.10-4.35 (q, $J = 7.2$ Hz, 2H), 6.50 (s, 1H), 6.85 (dd, $J = 2.9, 8.6$ Hz, 1H), 6.95 (d, $J = 2.9$ Hz, 1H), 7.30 (d, $J = 8.6$ Hz, 1H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{19}\text{NO}_5$: C, 64.33; H, 6.05; N, 4.41; O, 25.21. Found: C, 63.93; H, 6.09; N, 4.24; O, 25.55.

1-[2-Oxo-4-(4-chlorophenyl)]pyrrolidinacetamide (**23**).

A solution of 1-ethoxycarbonylmethyl-4-(4-chlorophenyl)pyrrolidin-2-one **21** (0.45 g, 1.6 mmoles) in methanol (20 ml) was cooled at -35° and a 20% aqueous ammonia solution (1 ml) was added to the stirred mixture. The stirring was continued for 30 minutes at 0° and for 15 hours at room temperature, then the solvent was evaporated. The residue was washed in ether. The solid was filtered and recrystallized from ethyl acetate, yield 65%, mp 133-136°; tlc (chloroform-methanol 60/40 (v/v)) R_f , 0.80; ir (potassium bromide): (ν cm^{-1}) 1675, 1720, 3180, 3395; ^1H nmr (80 MHz) (deuteriochloroform): δ ppm 2.30-2.70 (m, 2H), 3.40-3.95 (m, 3H), 4.00 (s, 2H), 5.75 and 6.15 (2 bs, 2H), 7.05-7.45 (m, 4H).

Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{ClN}_2\text{O}_2$: C, 57.03; H, 5.20; Cl, 14.03; N, 11.08; O, 12.66. Found: C, 57.26; H, 5.46; Cl, 13.64; N, 11.10; O, 12.54.

1-[2-Oxo-4-(5-methoxybenzo[*b*]furan-2-yl)]pyrrolidinacetamide (**24**).

A solution of 1-ethoxycarbonylmethyl-4-(5-methoxybenzo[*b*]furan-2-yl)pyrrolidin-2-one **22** (0.68 g, 2.1 mmoles) in methanol (20 ml) was cooled at -35°. The mixture was stirred and saturated with ammonia, and the stirring was continued for 15 hours at room temperature. The solvent was evaporated and the residue was washed in ether. The solid was filtered and recrystallized from ethyl acetate, yield 63%, mp 174-176°; tlc (dichloromethane-methanol 95/5 (v/v)) R_f , 0.21; ir (potassium bromide): (ν cm^{-1}) 1675, 1710, 3155, 3320; ^1H nmr (300 MHz) (deuteriochloroform): δ ppm 2.75-2.95 (m, 2H), 3.70-4.10 (m, 5H), 3.85 (s, 3H), 5.45 and 6.15 (2 bs, 2H), 6.50 (s, 1H), 6.90 (dd, $J = 2.6, 8.9$ Hz, 1H), 7.00 (d, $J = 2.5$ Hz, 1H), 7.30 (d, $J = 8.9$ Hz, 1H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_4$: C, 62.48; H, 5.60; N, 9.71; O, 22.20. Found: C, 62.46; H, 5.61; N, 9.70; O, 22.42.

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REFERENCES AND NOTES

- [a] This work was performed in the Laboratoire de Pharmacie Chimique et Chimie Thérapeutique.
- [1] C. Saturnino, A. Capasso, P. Saturnino, G. De Martino, L. Sorrentino, J. C. Lancelot and M. Robba, *J. Pharm. Belg.*, **52**, 57 (1997).
- [2] H. Sasaki, Y. Mori, J. Nakamura and J. Shibasaki, *J. Med. Chem.*, **34**, 628 (1991).
- [3] J. W. Mandema, A. Hoogerkamp and R. A. A. Mathôt, *Eur. J. Drug Metab. Pharmacokinet.*, **18**, 41 (1993).
- [4] V. E. Shashoua, J. N. Jacob, Ridge, A. Campbell and R. J. Baldessarini, *J. Med. Chem.*, **27**, 659 (1984).
- [5] Y. Madrid, L. Feigenbaum Langer, H. Brem. and R. Langer, *Adv. Pharmacol.*, **22**, 291 (1991).
- [6] E. Toja, C. Corini, C. Zirotti, F. Barzaghi and G. Galliani, *Eur. J. Med. Chem.*, **26**, 415 (1991).
- [7] C. Dollery, *Therapeutic Drugs*, Churchill Livingstone Editors, London, 1991 p83.
- [8] Y. B. Yu, M. R. Duchon and J. T. Biscoe, *Eur. J. Pharmacol.*, **141**, 371 (1987).
- [9] G. Pifferi, R. Nizzola and A. Gristoni, *Il Farmaco*, **49**, 453 (1994).
- [10] P. Berthelot, C. Vaccher, A. Musadad, N. Flouquet, M. Debaert and M. Luyckx, *J. Med. Chem.*, **30**, 743 (1987).
- [11] P. Berthelot, C. Vaccher, N. Flouquet, M. Luyckx, C. Brunet, T. Boulanger, J. P. Fripiat, D. P. Vercauteren, M. Debaert, G. Evrard and F. Durant, *Eur. J. Med. Chem.*, **26**, 395 (1991).
- [12] D. L. Hammond and L. M. May, *Eur. J. Pharmacol.*, **229**, 227 (1992).
- [13] D. T. Beattie, D. K. Curtis, M. Debaert, C. Vaccher and P. Berthelot, *Neuroscience Letters*, **100**, 292 (1991).
- [14] M. Ansar, S. Al Akoum Ebrik, R. Mouhoub, P. Berthelot, C. Vaccher, M. P. Vaccher, N. Flouquet, D. H. Caignard, P. Renard, B. Pirard, M. C. Rettori, G. Evrard, F. Durant and M. Debaert, *Eur. J. Med. Chem.*, **31**, 449 (1996).
- [15] F. M. Herskenson and W. H. Moos, *J. Med. Chem.*, **29**, 1125 (1986).
- [16] J. P. Kan, *Eur. J. Med. Chem.*, **27**, 565 (1992).
- [17] E. R. Ganzu, J. M. Hoover, S. I. Gracom and M. V. Ninterman, *Drug Dev. Res.*, **18**, 177 (1989).
- [18] C. Altomare, S. Cellamare, A. Carotti, G. Casini, M. Ferappi, E. Gavuzzo, F. Mazza, P.A. Carrupt, P. Gaillard and B. Testa, *J. Med. Chem.*, **38**, 170 (1995).
- [19] S. Wilk, *Life Sci.*, **33**, 2149 (1983).
- [20] T. C. Friedmann, M. Orłowski and S. Wilk, *J. Neurochem.*, **42**, 237 (1984).
- [21] T. Yoshimoto, T. Nishimura, T. Kita and D. Tsuru, *J. Biochem. (Tokyo)*, **94**, 1179 (1983).
- [22] G. L. Kovacs, B. Bohus, D. H. G. Versteeg, R. De Kloet and D. De Wied, *Brain Res.*, **175**, 303 (1979).
- [23] T. Yoshimoto, *Nippon Nogei Kagaku Kaishi*, **58**, 1147 (1984); *Chem. Abstr.*, **102**, 58123h (1985).
- [24] T. Yoshimoto, K. Kado, F. Matsubara, N. Koriyama, H. Kaneto and D. Tsuru, *J. Pharmacobio. Dyn.*, **10**, 730 (1987).
- [25] Y. Tanaka, S. Niwa, H. Niskioka, T. Yamanaka, M. Torizuka, K. Yoshinaga, N. Kobayashi, Y. Ikeda and H. Arai, *J. Med. Chem.*, **37**, 2071 (1994).
- [26] L. Borka, *Acta Pharm. Suec.*, **16**, 345 (1979).
- [27] P. W. Baures, D. S. Egleston, K. F. Erchard, L. B. Cieslinski, J. J. Torphy and S. B. Christensen, *J. Med. Chem.*, **36**, 3274 (1993).
- [28] D. E. Butler, I. C. Nordin, Y. J. L'Italien, L. Zweisler, P. H. Poshel and J. G. Mariott, *J. Med. Chem.*, **27**, 684 (1984).
- [29] M. Pinza, C. Farina, A. Cerri, V. Pfeiffer, M. T. Riccaboni, S. Banfi, R. Biagetti, O. Pozzi, M. Magnani and L. Dinigotti, *J. Med. Chem.*, **36**, 4214 (1993).
- [30] L. Angelucci, P. Calvisi, R. Catini, V. Cosentino, R. Cozzolino, P. De Witte, O. Ghirardi, F. Giannessi, A. Giuliani, D. Guaraldi, D. Misi, M. T. Ramacci, C. Scolastico and M. O. Tinti, *J. Med. Chem.*, **36**, 1511 (1993).
- [31] G. Pifferi and M. Pinza, *Il Farmaco*, **32**, 602 (1977).
- [32] R. Pellegata, M. Pinza, G. Pifferi, A. Gaiti, R. Mozzi, B. Tirillini and G. Porcellati, *Il Farmaco*, **36**, 845 (1981).