Salvador Vega* and Juan A. Díaz [1]

Instituto de Química Médica, CSIC, Juan de la Cierva, 3, 28006 Madrid, Spain

Received March 28, 1997
Revised May 15, 1997

As part of an investigation directed to the search of new neurotropic agents we have prepared a number of hydroxy and hydroximino derivatives of the novel thieno and pyrazolo[2,1]benzothiazepine ring systems. Assignments of the *Z* and *E* hydroximino isomers were performed by study of their ^1H and ^{13}C nmr spectra and NOE experiments.

J. Heterocyclic Chem., **34**, 1191 (1997).

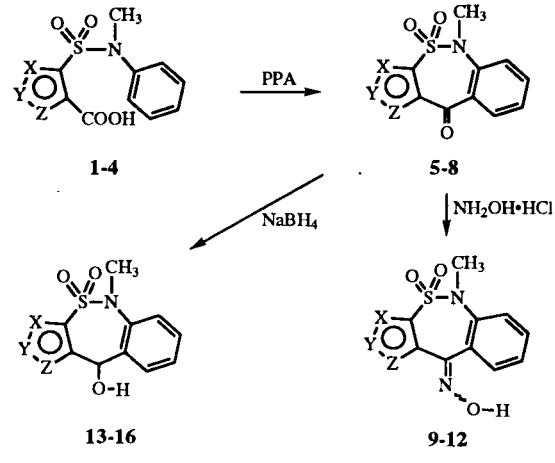
Almost four decades ago, the introduction of imipramine into clinical practice constituted a new weapon in the arsenal of molecules able to combat depression. Since 1950s, this and other compounds of the imipramine type, known as tricyclic antidepressants (desipramine, amitriptyline, nortriptyline, *etc.*), have become the most frequently prescribed neuroactive drugs [2]. During the last ten years, however, reliance upon these drugs declined because of the introduction of the so called second-generation antidepressants which is comprised by new tricyclic compounds like maprotiline, amoxapine or lofrepamine, and other estructurally and pharmacologically atypical drugs such as nomifensin, trazodone, viloxazine, mianserin, paroxetine, bupropion, and fluoxetine [3]. Although these newer compounds are more selective and less toxic in overdosage than classical antidepressants, none of them, however, proved to be more effective or faster in the onset of action than older antidepressants [4].

Research in these traditional fields continues, but future trends focus upon new mechanisms of action. Tianeptine, an effective antidepressant with a neurochemical profile different from that of tricyclic or atypical drugs, exerts its action through one of these novel mechanisms. In contrast to classical tricyclic antidepressants, which inhibit 5-HT uptake, this compound stimulates serotonin uptake in the rat brain and rat as well as human platelets [5-7].

We have recently described the synthesis of the first representatives of the new heterocyclic ring systems thieno-[3,4-*c*][2,1]benzothiazepine 4,4-dioxide, thieno[3,2-*c*]-[2,1]benzothiazepine 4,4-dioxide, and pyrazolo[3,4-*c*][2,1]-benzothiazepine 10,10-dioxide [8-10]. This paper deals with the preparation of several hydroximino and hydroxy derivatives of these new ring systems, which were designed as thiophene and pyrazole bioisosteres of tianeptine and were also assessed for their antidepressant activity.

The preparation of the title compounds was carried in two steps from the corresponding trioxo-thieno and trioxo-pyrazolo[2,1]benzothiazepines **5-8**, which had been previously synthesized by intramolecular cyclodehydration of sulfonamidocarboxylic acids **1-4** with polyphosphoric acid (Scheme) [8,9]. Thus, reaction of these carbonyl derivatives with hydroxylamine hydrochloride in pyridine yielded the corresponding oximes **9-12** as mixtures of the *Z* and *E*

Scheme



1-4 **5-8** **13-16** **9-12**

1, 5, 9, 13: X = CH; Y = S; Z = CH
2, 6, 10, 14: X = CH; Y = CH; Z = S
3, 7, 11, 15: X = N; Y = NCH_3; Z = CH
4, 8, 12, 16: X=N; Y=NH; Z=CH

isomers which were easily distinguished by ^1H nmr spectroscopy [11]. In the pyrazole oxime mixtures **11** and **12**, both isomers could be separated by fractional crystallization or column chromatography, which permitted their independent structural study and the identification of their physicochemical and analytical characteristics.

The configuration of these isomers was based on the observation of their ^1H and ^{13}C nmr spectra as well as the spectroscopic data of other oximes found in the bibliography [12]. Thus, for example, the isomer **11a**, which is in major proportion in the mixture **11**, and the starting ketone **5** exhibited pyrazole proton chemical shifts at 8.80 and 8.20 ppm respectively (Figure 1). This deshielding effect could be explained by the interaction of the lone pairs of the oxime oxigen atom with the adjacent pyrazole proton and, consequently, the structure of (Z) 4,9-dihydro-2,9-dimethyl-10,10-dioxo-4-hydroximino-2*H*-pyrazolo[3,4-c]-[2,1]benzothiazepine was assigned to **11a**. Conversely, the pyrazole proton signal of the minor isomer **11b** appeared at 8.17 ppm, very close to that of the same proton in ketone **5**, indicating that the hydroximino group must be in position *E* with respect to the pyrazole ring [13].

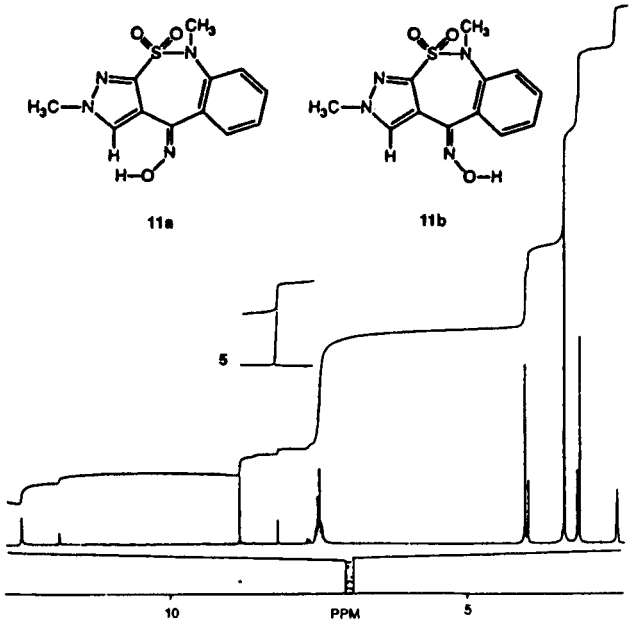
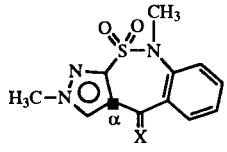


Figure 1.

Correct *Z* and *E* assignments of these two isomers were also realized by comparison of the ^{13}C nmr spectra of ketone **5** and the mixture **11** (Table 1). Ketone **5** showed the signal of the pyrazole carbon atom in position α to the carbonyl carbon atom at 120.6 ppm, while isomers **11a** and **11b** exhibited the signal of the carbon atom in position α to the carbon bearing the hydroximino group at 110.1 and 116.7 ppm respectively. The upfield shift observed in the α carbons of both isomers is undoubtedly due to the smaller electronegativity of the nitrogen atom relative to the oxigen atom. As outlined in Table 1, the most abundant isomer **11a** show a $\Delta\delta$ = -10.5 ppm and the minor isomer **11b** a $\Delta\delta$ = -3.9 ppm. Since it had been previously described [12] that this upfield shift of the oxime α carbons is generally greater -*i. e.* $\Delta\delta$ is more negative- in the isomers which present a *Z* configuration of the hydroxyl group respect to the α carbon, it could be concluded that the compound obtained in major proportion in the reaction of ketone **5** with hydroxylamine hydrochloride was the *Z* hydroximino pyrazolobenzothiazepine **11a**.

Table 1



Compound	X	δα (ppm)	$\Delta\delta = \delta\alpha_{(X = NOH)} - \delta\alpha_{(X = O)}$
5	O	120.6	-
11a	N-OH	110.1	-10.5
11b	N-OH	116.7	-3.9

Nevertheless, the above assignments were confirmed by experiments of homonuclear NOE difference spectroscopy (Figure 2). As expected, upon irradiation of the hydroxyl proton of the major isomer an enhancement in the pyrazole proton signal was observed, which indicated the close proximity of both hydrogen atoms in space. Likewise, irradiation at the pyrazole proton resonance led to a strong enhancement not only of the hydroxyl proton signal but also of the pyrazole methyl singlet, permitting therefore to assign in an unequivocal way the *Z* configuration for the isomer **11a**.

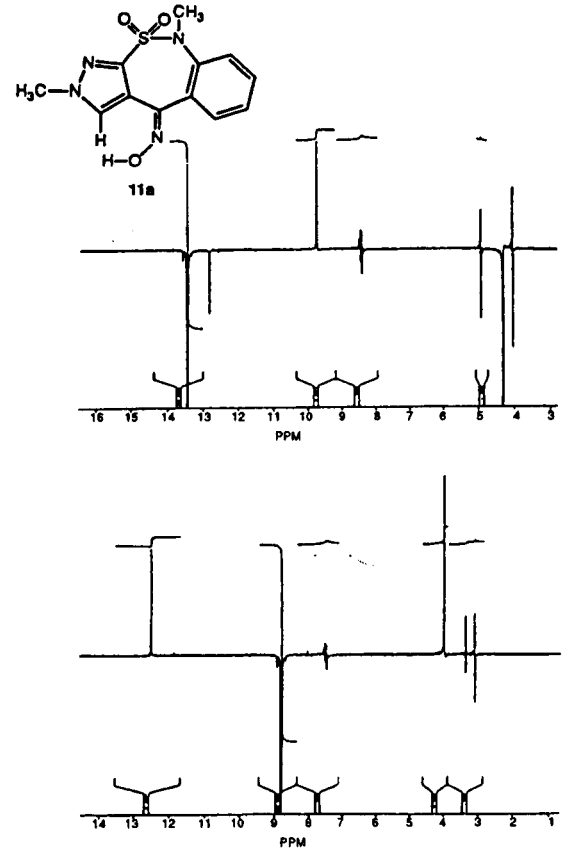


Figure 2.

This reasoning also permitted the elucidation, in an analogous manner, the configuration of the *Z* and *E* isomers and their relative proportions in the other oxime mixtures. With the exception of mixture **9** in which both isomers were in a 1:1 proportion, in the remaining mixtures the *Z* isomers predominated. These results agree with the Karabatsos rule [14], according to which the more abundant isomer is the less sterically hindered. In our case they should be the isomers with the hydroxyl group in the "cis" position relative to the heterocycle.

Oxime mixtures **9** and **10** only could be separated by high-pressure liquid chromatography, using reverse-phase

analytical columns. Figure 3 illustrates the satisfactory resolution reached for the isomers of both mixtures using a mixture of acetonitrile/water (30:70, v/v) as the mobile phase. The proportion of *Z* and *E* isomers in the mixtures were consistent with those calculated from ^{1}H nmr spectroscopy.

On the other hand, reduction of **5-7** with sodium borohydride in methanol [15] afforded the respective hydroxyl derivatives **13-15** in good yields. Ketone **8**, however, did not give under these reaction conditions the expected alcohol **16**; all attempts to prepare this compound with this and other common reduction reagents resulted in recovery of starting material. The use of bis (2-methoxyethoxy)-aluminium sodium salt as the reducing agent in this reaction [16] was also unsuccessful. This apparent inertia of **8** can be attributed to the formation of a complex between its pyrazole NH group and the reducing agent since it is known that hydrides usually react with active hydrogens rather than with other functional groups.

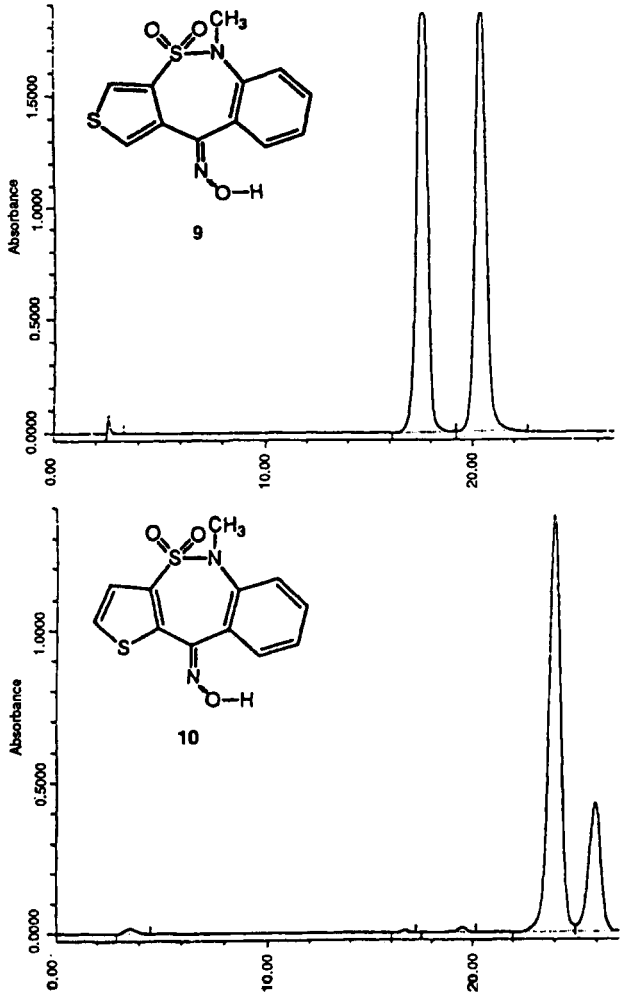


Figure 3.

EXPERIMENTAL

Melting points were determined on a Gallenkamp capillary apparatus and are uncorrected. The ir spectra were recorded using a Shimadzu IR-435 instrument. The ^{1}H nmr spectra were measured with a Bruker AM-200 and a Varian XL-300 spectrometer. Chemical shift values are reported relative to tetramethylsilane in appropriate solvents. The purity of compounds was verified by thin-layer chromatography (tlc) which was run on silica gel GF_{254} (E. Merck) with cyclohexane-ethyl acetate mixtures (2:1 and 1:1 v/v respectively) as eluents. Medium-pressure chromatography was performed using 230-400 mesh silica gel purchased from E. Merck, Inc. Microanalysis were performed at the Centro Nacional de Química Orgánica on a Perkin-Elmer 2400 CHN analyzer.

Z and *E* Hydroximinohetero[2,1]benzothiazepines **9-12**.

General Method.

A solution of the corresponding trioxothieno or trioxopyrazolo [2,1]benzothiazepine **5-8** (0.04 mole) and hydroxylamine hydrochloride (11.12 g, 0.16 mole) in dry pyridine was heated at reflux temperature for 24 hours. After cooling, the reaction mixture was poured onto ice water (500 ml) and the precipitated crystalline solid was collected, washed with water and dried to give the respective oximes **9-12** as mixtures of the *Z* and *E* isomers. The relative percentages of these isomers were calculated from the ^{1}H nmr spectra of the mixtures.

5,10-Dihydro-4,4-dioxo-10-hydroximino-5-methylthieno[3,4-*c*]-[2,1]benzothiazepine **9**.

This compound was obtained in 94% yield from ketone **5** as a white solid which was a mixture of both isomers, *Z* (**9a** 49%) and *E* (**9b** 51%); ^{1}H nmr (dimethyl-d_6 sulfoxide): **9a**,. δ 12.01 (s, 1H, OH, exchangeable with deuterium oxide), 8.50 (d, J = 3.3 Hz, 1H, thiophene), 8.39 (d, J = 3.3 Hz, 1H, thiophene), 7.60-7.42 (m, 4H, benzene), 3.18 (s, 3H, CH_3); **9b**, δ 12.36 (s, 1H, OH, exchangeable with deuterium oxide), 8.41 (d, J = 3.4 Hz, 1H, thiophene), 7.97 (d, J = 3.4 Hz, 1H, thiophene), 7.60-7.42 (m, 4H, benzene), 3.14 (s, 3H, CH_3).

5,10-Dihydro-4,4-dioxo-10-hydroximino-5-methylthieno[3,2-*c*]-[2,1]benzothiazepine **10**.

This compound was obtained in 79% yield from ketone **6** as a yellow solid which was a mixture of both isomers, *Z* (**10a** 69%) and *E* (**10b** 31%); ^{1}H nmr (dimethyl-d_6 sulfoxide): **10a**, δ 13.46 (s, 1H, OH, exchangeable with deuterium oxide), 8.02 (d, J = 5.5 Hz, 1H, thiophene), 7.65-7.48 (m, 4H, benzene), 7.45 (d, J = 5.5 Hz, 1H, thiophene), 3.17 (s, 3H, CH_3); **10b**, δ 12.58 (s, 1H, OH, exchangeable with deuterium oxide), 7.73 (d, J = 5.5 Hz, 1H, thiophene), 7.65-7.48 (m, 4H, benzene), 7.39 (d, J = 5.5 Hz, 1H, thiophene), 3.18 (s, 3H, CH_3).

4,9-Dihydro-2,9-dimethyl-10,10-dioxo-4-hydroximino-2H-pyrazolo[3,4-*c*][2,1]benzothiazepine **11**

This compound was obtained in 96% yield from ketone **7** as a white solid which was a mixture of the two isomers, *Z* (**11a** 73%) and *E* (**11b** 27%).

Both isomers were isolated by heating **11** (3 g) in a mixture of acetonitrile (45 ml) and 2-propanol (5 ml) at reflux temperature. After cooling, pure **11a** (1.3 g) crystallized as a white solid of mp 282-284° dec; ir (potassium bromide): 3150, 1345, 1155 cm^{-1}; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 12.50 (s, 1H, OH, exchangeable

with deuterium oxide), 8.80 (s, 1H, pyrazole), 7.57-7.40 (m, 4H, benzene), 3.99 (s, 3H, CH_3) 3.10 (s, 3H, CH_3).

Anal. Calcd. for $C_{12}H_{12}N_4O_3S$: C, 49.30; H, 4.14; N, 19.17; S, 10.97. Found: C, 49.38; H, 4.21; N, 19.20; S, 11.24.

The mother liquors were concentrated *in vacuo* and the residue was purified by column chromatography using a mixture of chloroform-ethanol (9:1 v/v) as the eluent and 230-240 mesh silica gel, to give **11b** as a white solid of mp 274-276° dec; ir (potassium bromide): 3450 (OH), 1330 and 1150 (SO_2) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): 11.88 δ (s, 1H, OH, exchangeable with deuterium oxide), 8.17 (s, 1H, pyrazole), 7.67 (m, 1H, benzene), 7.57-7.37 (m, 3H, benzene), 3.95 (s, 3H, CH_3) 3.15 (s, 3H, CH_3).

Anal. Calcd. for $C_{12}H_{12}N_4O_3S$: C, 49.30; H, 4.14; N, 19.17; S, 10.97. Found: C, 48.95; H, 4.18; N, 19.32; S, 11.05.

4,9-Dihydro-10,10-dioxo-4-hydroximino-9-methyl-1H-pyrazolo[3,4-*c*][2,1]benzothiazepine **12**.

This compound was obtained in 76% yield from ketone **8** as a white solid which was a mixture of the two isomers, *Z* (**12a** 86%) and *E* (**12b** 14%).

Both isomers were isolated by heating **12** (2 g) in a mixture of ethyl acetate (50 ml) and cyclohexane (5 ml) at reflux temperature. After cooling, pure **12a** (1.1 g) crystallized as a white solid of mp 243-246° dec; ir (potassium bromide): 3150 (OH), 1350 and 1150 (SO_2) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 12.45 (s, 1H, OH, exchangeable with deuterium oxide), 8.78 (s, 1H, pyrazole), 7.57-7.46 (m, 4H, benzene), 3.10 (s, 3H, CH_3).

Anal. Calcd. for $C_{11}H_{10}N_4O_3S$: C, 47.47; H, 3.62; N, 20.13; S, 11.52. Found: C, 47.70; H, 3.76; N, 19.88; S, 11.21.

Treatment of mother liquors as above, and after column chromatography of the residue, **12b** was isolated as a white solid of mp 239-242° dec; ir (potassium bromide): 3250 (OH), 1350 and 1150 (SO_2) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 11.84 (s, 1H, OH, exchangeable with deuterium oxide), 8.20 (s, 1H, pyrazole), 7.67 (m, 1H, benzene), 7.55-7.45 (m, 3H, benzene), 3.15 (s, 3H, CH_3).

Anal. Calcd. for $C_{11}H_{10}N_4O_3S$: C, 47.47; H, 3.62; N, 20.13; S, 11.52. Found C, 47.65; H, 3.45; N, 20.21; S, 11.48.

Hydroxy-hetero[2,1]benzothiazepines **13-15**.

General Method.

To a stirred suspension of the thieno or pyrazolo [2,1]benzothiazepine **5-7** (0.05 mole) in methanol (100 ml), cooled to 0°, was added portionwise sodium borohydride (3.78 g, 0.1 mole). The mixture was stirred at room or reflux temperature for 1 hour. The solvent was evaporated *in vacuo* and the residue washed with cold water and dried to give the desired alcohols **13-15** which were recrystallized from the appropriate solvent.

5,10-Dihydro-4,4-dioxo-10-hydroxy-5-methylthieno[3,4-*c*]-[2,1]benzothiazepine **13**.

This compound was obtained in 97% yield from **5** (room temperature) as a white solid of mp 145-147° (toluene); ir (potassium bromide): 3500 (OH), 1300 and 1130 (SO_2) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 8.25 (d, J = 3.7 Hz, 1H, thiophene), 7.55-7.30 (m, 5H, 4H benzene and 1H thiophene), 6.45 (s, 1H, OH, exchangeable with deuterium oxide), 6.05 (s, 1H, CH), 3.35 (s, 3H, CH_3).

Anal. Calcd. for $C_{12}H_{11}NO_3S_2$: C, 51.22; H, 3.94; N, 4.98; S, 22.79. Found: C, 51.15; H, 3.87; N, 5.27; S, 22.96.

5,10-Dihydro-4,4-dioxo-10-hydroxy-5-methylthieno[3,2-*c*]-[2,1]benzothiazepine **14**.

This compound was obtained in 95% yield from **6** (reflux temperature) as a white solid of mp 150-153° dec; (toluene); ir (potassium bromide): 3450 (OH), 1310 and 1140 (SO_2) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 7.80-7.35 (m, 5H, 4H benzene and 1H thiophene), 7.25 (d, J = 5.5 Hz, 1H, thiophene), 6.55 (s, J = 5.8 Hz, 1H, CH), 6.10 (d, J = 5.8 Hz, 1H, OH, exchangeable with deuterium oxide), 3.45 (s, 3H, CH_3).

Anal. Calcd. for $C_{12}H_{11}NO_3S_2$: C, 51.22; H, 3.94; N, 4.98; S, 22.79. Found C, 50.97; H, 4.26; N, 4.85; S, 23.07.

4,9-Dihydro-2,9-dimethyl-10,10-dioxo-4-hydroxy-2H-pyrazolo[3,4-*c*][2,1]benzothiazepine **15**.

This compound was obtained in 77% yield from **7** (reflux temperature) as a white solid of mp 160-162° (ethanol); ir (potassium bromide): 3500 (OH), 1310 and 1160 (SO_2) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 7.80 (s, 1H, pyrazole), 7.65-7.30 (m, 4H, benzene), 6.30 (d, J = 4.5 Hz, 1H, OH, exchangeable with deuterium oxide), 5.90 (d, J = 4.5 Hz, 1H, CH), 3.80 (s, 3H, CH_3) 3.30 (s, 3H, CH_3).

Anal. Calcd. for $C_{12}H_{13}N_3O_3S$: C, 51.61; H, 4.66; N, 15.05; S, 11.47. Found C, 51.88; H, 4.78; N, 15.30; S, 11.73.

Acknowledgements.

The financial support of this work by the Comisión Interministerial de Ciencia y Tecnología (CICYT), Madrid, Spain (research grant SAF 96-0111), and ADIR et Cie., Paris, France, is gratefully adknowledged. We are also indebted to our Department of Analysis for all analytical data and to Mr. Francisco Caballero for technical help in preparing this manuscript.

REFERENCES AND NOTES

[1] Present address: Synthélabo, S. A. Avda. de la Industria 31, 28100 Alcobendas, Madrid, Spain.

[2] L. H. Leonard, Mechanisms of Drug Action, Vol **1**, ed, G. N. Woodruff, 1986, 203.

[3] R. M. Pinder and J. H. Wieringa, *Med. Res. Rev.*, **13**, 259 (1993).

[4] D. Leysen and R. M. Pinder, *Annu. Rep. Med. Chem.*, **29**, 1 (1995).

[5] E. Mocaër, M. C. Rettori and A. Kamoun, *Clin. Neuropharmacol.*, **11**, 32 (1988).

[6] G. Kato and A. F. Weitsch, *Clin. Neuropharmacol.*, **11**, 43 (1988).

[7] C. Labrid, J. Moleyre, J. C. Poignant, C. Malen, E. Mocaër and A. Kamoun, *Clin. Neuropharmacol.*, **11**, 21 (1988).

[8] J. A. Díaz and S. Vega, *J. Heterocyclic Chem.*, **31**, 93 (1994).

[9] S. Vega and J. A. Díaz, *J. Heterocyclic. Chem.*, **30**, 1509 (1993).

[10] E. Arranz, J. A. Díaz, E. Morante, C. Pérez and S. Vega, *J. Heterocyclic Chem.*, **33**, 151 (1996).

[11] J. M. Bastian, A. Ebnöther and E. Jucker, *Helv Chim. Acta*, **54**, 283 (1971).

[12] B. Jamart-Gregoire, P. Caubère, M. Blanc, J. P. Gnassounou and C. Advenier, *J. Med. Chem.*, **32**, 315 (1989) .

[13] M. Anastasia, P. Ciuffreda, A. Fiecchi and A. Scala, *J. Chem. Soc., Perkins Trans*, **1**, 2126 (1986).

[14] G. J. Karabatsos, G. D. Graham and F. M. Vane, *J. Am. Chem. Soc.*, **84**, 753 (1962).

[15] E. Arribas, and S. Vega, *J. Heterocyclic Chem.*, **21**, 161 (1984).

[16] M. Kapka, V. Chvalovski, K. Kochloeff and M. Kraus, *Collect. Czech. Chem. Commun.*, **34**, 118 (1969).