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Full Paper

Synthesis and Antidepressant Evaluation of Three *para*-Benzoquinone Mono-oximes and Their Oxy Derivatives

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Abstract: A series of three *para*-benzoquinone mono-oximes and four oxy-derivatives were prepared and tested for their antidepressant properties. The (4*E*) oxime of 2-isopropyl-5-methyl-*para*-benzoquinone (**4**) and the corresponding 2-diethylamino-ethyl derivative (**10**) present antidepressant activities and were slightly more potent than the reference standard.

Keywords: Oximes, *para*-benzoquinones, antidepressant activity.

1. Introduction

Depression is a syndrome or collection of symptoms which occur together with sufficient frequency to constitute a recognizable clinical condition. The most common symptoms are apathy, fatigue, depressed mood, depressive thought content and diminished concentration. Theoretical approaches to depression tend to be either strongly biological or strongly psychological in nature. It is now clear that a variety of different factors are implicated in the etiology of depression. There is no doubt that new antidepressants are needed. Existing drugs have undesirable side-effects which reduce compliance with therapy and significant numbers of depressives do not make a satisfactory response [1].

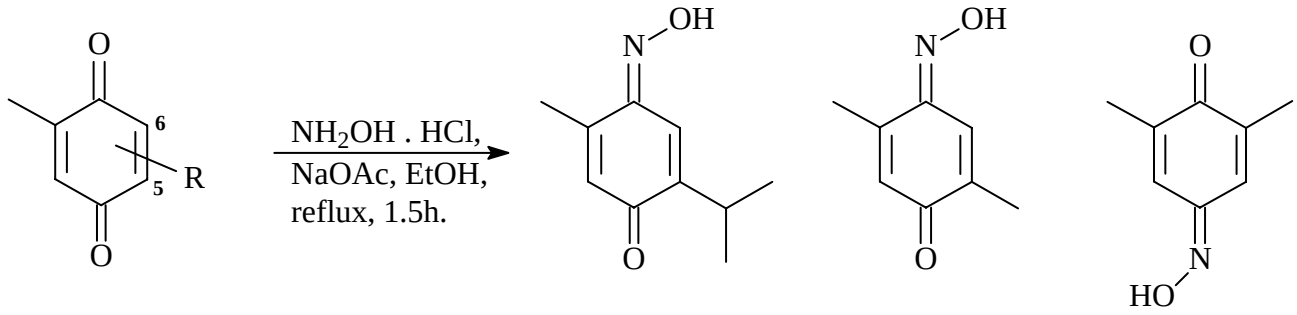
In recent years much work has been published on oxime derivatives with different pharmacological properties: for example: anti-tumor [2], anti-microbial, anticonvulsant [3,4], anti-arrhythmic, analgesic and anesthetic properties [5,6]. Many oximes also have been studied to investigate their antidepressant activity [7-9]. Since some oxime derivatives have therapeutic potential as antidepressant drugs, the main aim of the present work was to synthesize several structurally-related

oximes and to submit them to a preliminary screening to determine the relationship between the structures and their antidepressant activity.

2. Results and Discussion

The mono-oximes **4-6** were synthesized in 80, 90 and 82 % yields, respectively, (Scheme 1) by oximation of the corresponding *para*-benzoquinones **1-3** under standard conditions [10,11].

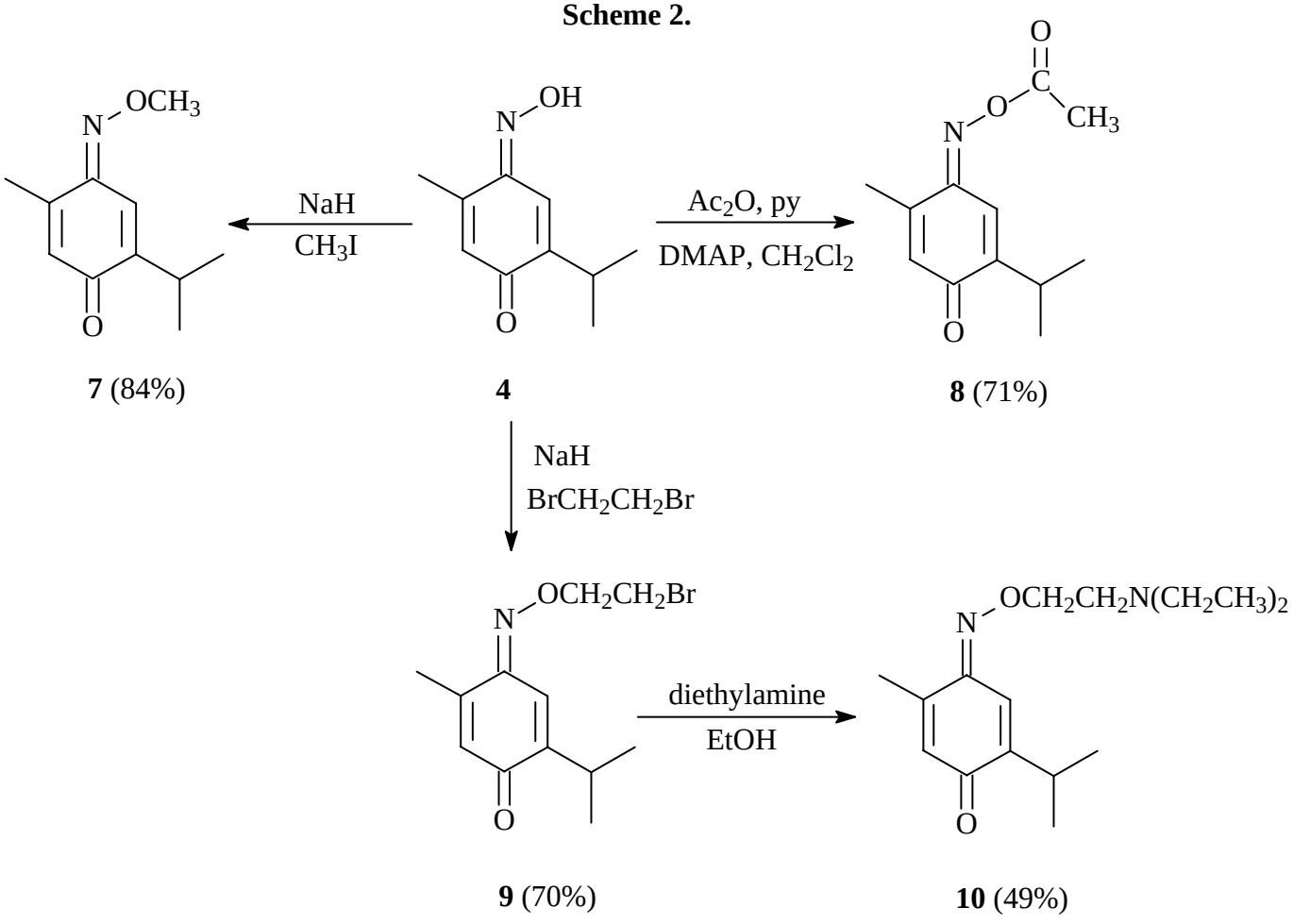
Scheme 1.



1 R = 5- *i*-Pr
2 R = 5- Me
3 R = 6- Me

4 (80%) **5** (90%) **6** (82%)

Scheme 2.



7 (84%) **4** **8** (71%)

9 (70%) **10** (49%)

The mono-oxime derivatives **7-9** (Scheme 2) were obtained by standard alkylation and acylation reactions of compound **4**. The ether **7** was synthesized in 84% yield with methyl iodide whereas reaction of **4** with acetic anhydride resulted in **8** in 71% yield. Treatment of **4** with dibromoethane gave the bromide **9** in 70% yield, which was further converted with diethylamine into the amine **10** in 49% yield.

Antidepressant activity

None of the compounds tested caused mortality up to a dose of 100 mg/kg i.p. in mice. The antidepressant evaluation of the compounds is presented in Table 1.

Table 1. Antidepressant activity of compounds **4**-**10**.

Compound	Dose (mg/kg i.p.)	Duration of immobility (sec ± S.E.M.)
Control	---	205.5 ± 4.4
Imipramine	15	178.3 ± 7.8*
4	10	174.8 ± 8.9*
5	10	188.8 ± 12.7
6	10	183.8 ± 14.6
7	10	207.1 ± 6.0
8	10	212.5 ± 4.3
9	10	189.5 ± 5.8
10	10	175.1 ± 7.8*

*$p < 0.05$

The forced swimming test showed a relationship between structure and antidepressant activity. Compounds **4** and **10** were shown to be nearly equipotent and slightly more potent than imipramine, the drug used as reference standard.

Of the three mono-oximes studied only **4** was active, indicating the relevance of the isopropyl group for the antidepressant activity in this series. The oxime ethers **7** and **9**, as well as the acetyl mono-oxime **8**, present no statistical difference from the control group in reducing the immobility time of mice. The amine derivative **10** significantly shortened this immobility period, which is perhaps not surprising considering that its structure is similar to the second-generation antidepressant drug fluvoxamine [8].

The behavioural despair test is a classic model very well known for screening of new antidepressant drugs. The onset of immobility is delayed by pretreatment with a wide variety of antidepressants. Effective agents include tricyclics, MAOIs, most atypical antidepressants, deprivation of rapid eye movement sleep and electroconvulsive shock [1]. Indeed, there is a significant correlation between the potency of antidepressants in the behavioural despair test and their clinical potency, which has not been demonstrated with any other animal model of depression [12].

The preliminary screening results reported in this paper show that compounds **4** and **10** are psychoactive, evidencing a pharmacological profile of an antidepressant drug. Our results also

suggested that by appropriate structural modification of *para*-benzoquinone mono-oximes, it may be possible to develop novel therapeutic agents against depression.

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3. Experimental Section

Chemistry

GLC analyses were conducted on a Shimadzu GC-17A instrument equipped with a flame-ionization detector, using a DB-1 (30 m x 0.25 mm) glass column. Column chromatography was performed on silica gel 60 (70-230 mesh ASTM Merck). Radial thin-layer chromatography was carried out on a Chromatotron model 8924 (silica gel 60PF274 Merck). Melting points were determined on a Microquímica MQWAPF-301 apparatus and are uncorrected. Infrared spectra were recorded with a Bomen Hartman & Braun MB-Series spectrometer. ^{1}H- and ^{13}C- NMR spectra were recorded at 200 or 50 MHz, respectively, either on a Bruker ARX-200 or a Bruker DRX-400 spectrometer in $CDCl_3$ with TMS as internal standard. The mass spectra were recorded on a Micromass mass spectrometer Quattro LC, coupled with a chemical ionization source (reagent MeOH) under atmospheric pressure (APCI). Microanalyses were performed on a Fisons EA 1108 CHNS-O analyzer, at the Chemistry Department, Universidade Federal de São Carlos. Solvents were purified prior to use: dichloromethane and hexane were refluxed over P_2O_5, distilled and stored over molecular sieves; pyridine was stirred and refluxed over KOH, distilled and stored over KOH; acetic anhydride was stirred over P_2O_5 and K_2CO_3, distilled and stored over molecular sieves.

General procedure for the syntheses of the oximes **4, 5** *and* **6:**

A solution of the hydroxylamine hydrochloride (0.221 g, 3.18 mmol) and sodium acetate (0.169 g, 2.08 mmol) were added to *para*-benzoquinone (1.22 mmol) in EtOH (11.70 ml), and the resulting mixture was stirred and refluxed for 1.5 hours. After the solvent was evaporated under reduced pressure, the solid residue was diluted in water (50 mL) and extracted with a mixture of ethyl acetate and ethyl ether (1:1, 3 × 20 mL). The organic layer was washed with aqueous $NaHCO_3$ (3 × 20 mL) and NaCl (3 × 20 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The solid residue was washed with hexane (4 × 20 mL) to eliminate soluble impurities.

(4E)-2-isopropyl-5-methylbenzo-1,4-quinone 4-oxime (**4**)

Yield: 80%; Mp 142.6-143.2 ^{o}C; lit. 140 ^{o}C [13], IR ($\nu_{max.}$, KBr, cm^{-1}): 3180, 2964, 1639, 1605, 1439, 1241, 1056; ^{1}H-NMR δ: 1.13 (6H, d, *J*=6.8 Hz), 2.20 (3H, d, *J*=1.3 Hz), 3.07 (1H, d hept, *J*=1.1 and 6.8 Hz), 6.27 (1H, q, *J*=1.3 Hz), 7.56 (1H, d, *J*=1.1 Hz); ^{13}C-NMR δ: 16.8, 21.5, 26.3, 118.2, 128.4,

146.0, 147.9, 150.1, 186.8; MS m/z (%): 180 $[M+1]^+$ (100), 163 (4), 109 (28); Anal. Calcd. for $C_{10}H_{13}NO_2$: 7.82 (N), 67.02 (C), 7.31 (H); Found: 7.56 (N), 67.11 (C), 7.55 (H).

(1*E*)-*2,5-dimethylbenzo-1,4-quinone oxime* (**5**)

Yield: 90%; Mp 126.5-127.4 ^oC; IR ($\nu_{max.}$, KBr, cm^{-1}): 3232, 2889, 1642, 1611, 1353, 1187, 1025; ^1H-NMR δ: 2.03 (3H, d, *J*=1.4 Hz), 2.19 (3H, d, *J*=1.3 Hz), 6.31 (1H, q, *J*=1.3 Hz), 7.63 (1H, q, *J*=1.4 Hz); ^{13}C-NMR δ: 15.8, 16.8, 121.5, 128.2, 138.9, 146.9, 150.2, 187.9; MS (m/z (%): 152 $[M+1]^+$ (100), 124 (5), 109 (7); Anal. Calcd. for $C_8H_9NO_2$: 9.27 (N), 63.56 (C), 6.00 (H). Found: 9.13 (N), 63.13 (C), 5.88 (H).

(4E)-2,6-dimethylbenzo-1,4-quinone oxime (**6**)

Yield: 82%; Mp 138.4-139.0 ^oC; IR ($\nu_{max.}$, KBr, cm^{-1}): 3216, 2853, 1632, 1604, 1423, 1199, 1058; ^1H-NMR δ: 2.01 (3H, d, *J*=1.1 Hz), 2.04 (3H, d, *J*=1.2 Hz), 7.02 (1H, q, *J*=1.1 Hz), 7.58 (1H, q, *J*=1.2 Hz); ^{13}C-NMR δ: 15.7, 16.3, 120.5, 133.8, 136.4, 139.0, 149.2, 187.8; MS m/z (%): 152 $[M+1]^+$ (100), 138 (5), 122 (14); Anal. Calcd. for $C_8H_9NO_2$: 9.27 (N), 63.56 (C), 6.00 (H). Found: 9.28 (N), 63.23 (C), 5.98 (H).

(4E)-2-isopropyl-5-methylbenzo-1,4-quinone 4-(O-methyloxime) (**7**)

A solution of **4** (0.100 g; 0.56 mmol) in dichloromethane (2.5 mL) and THF (0.1 mL), was added to sodium hydride (60%, 0.020 g, 0.83 mmol, previously washed several times with dry hexane) and the resulting mixture was stirred for 1 hour at room temperature. Methyl iodide (0.16 mL, 2.57 mmol) was added and the reaction was allowed to stand at room temperature for 18 hours. The mixture was diluted with water (20 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with aqueous NH_4Cl (3 × 20 mL), dried over anhydrous Na_2SO_4 and the solvents were evaporated under reduced pressure. The oily residue was purified by radial thin-layer chromatography (9:1 hexane-ethyl acetate as eluent) to provide a pure sample of **7**: (0.091 g, 0.470 mmol, 84% yield). IR ($\nu_{max.}$, KBr, cm^{-1}): 2972, 1637, 1613, 1518, 1372, 1240; ^1H-NMR δ: 1.12 (6H, d, *J*=6.8 Hz), 2.16 (3H, d, *J*=0.8 Hz), 3.06 (1H, d hept, *J*=6.8, 0.8 Hz), 3.46 (3H, s), 6.26 (1H, d, *J*=0.8 Hz), 7.38 (1H, d, *J*=0.8 Hz); ^{13}C-NMR δ: 16.8, 22.1, 26.6, 63.7, 118.4, 129.1, 145.6, 149.0, 149.6, 186.7; MS m/z (%): 194 $[M+1]^+$ (100), 179 (26), 164 (30), 152 (5); Anal. Calcd. for $C_{11}H_{15}NO_2$: 7.25 (N), 68.37 (C), 7.82 (H). Found: 6.98 (N), 67.99 (C), 7.72 (H).

(4E)-2-isopropyl-5-methylbenzo-1,4-quinone 4-(O-acetyloxime) (**8**)

Pyridine (0.34 mL) was added to a mixture of **4** (0.100 g, 0.56 mmol), DMAP (catalytic amount) and acetic anhydride (0.13 mL, 1.36 mmol). The resulting mixture was stirred for 20 hours at room temperature. The mixture was diluted with ethyl ether (20 mL) and washed successively with 10% aqueous $CuSO_4$ (3 × 20 mL), 5% aqueous $NaHCO_3$ (2 × 20 mL) and distilled water (20 mL), dried

over Na_2SO_4 and the solvent was evaporated under reduced pressure. The solid residue was purified by radial thin-layer chromatography (9:1 hexane-ethyl acetate as eluent) to provide a pure sample of **8**: (0.088 g, 0.40 mmol, 71% yield). Mp 68.4 – 70.4 °C; IR ($\nu_{max.}$, KBr, cm^{-1}): 2965, 1785, 1650, 1630, 1601, 1522, 1249, 1150; ^{1}H-NMR δ: 1.13 (6H, d, *J*=6.9 Hz), 2.26 (3H, d, *J*=1.4 Hz), 2,37 (3H, s), 3.09 (1H, d hept, J^1=1.1 Hz and J^2=6.9 Hz), 6.39 (1H, d, *J*=1.4 Hz), 7.39 (1H, d, *J*=1.1 Hz); ^{13}C-NMR δ: 17.3, 19.8, 21.7, 34.1, 118.4, 131.1, 145.5, 151.9, 154.1, 168.9, 186.7; MS m/z (%): 222 $[M+1]^+$ (45), 180 (100), 164 (24), 152 (18), 138 (30), 110 (90); Anal. Calcd. for $C_{12}H_{15}NO_3$: 6.33 (N), 65.14 (C), 6.79 (H). Found: 6.00 (N), 64.89 (C), 6.56 (H).

(4E)-2-isopropyl-5-methylbenzo-1,4-quinone 4-[O-(2-bromoethyl)-oxime] (**9**)

A solution of **4** (0.118 g, 0.66 mmol) in dichloromethane (2.5 mL) and THF (0.1 mL) was added to sodium hydride (60%, 0.020 g, 0.83 mmol, previously washed several times with dry hexane) and the resulting mixture was stirred for 1 hour at room temperature. Dibromoethane (0.11 mL, 1.32 mmol) was added and the reaction was allowed to stand at room temperature for 6 hours. The mixture was diluted with water (20 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, washed with aqueous NH_4Cl (3 × 20 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The oily residue was purified by radial thin-layer chromatography (9:1 hexane-ethyl acetate as eluent) to provide a pure sample of **9**: (0.132 g, 0.46 mmol, 70% yield). IR ($\nu_{max.}$, KBr, cm^{-1}): 2963, 1630, 1623, 1424, 1239, 1077, 1010; ^{1}H-NMR δ: 1.11 (6H, d, *J*=6.7 Hz), 2.14 (3H, s), 3.05 (1H, m), 3.62 (2H, t, *J*=6.3 Hz), 4.59 (2H, t, *J*=6.3 Hz), 7.39 and 6.28 (2H,s); ^{13}C-NMR δ: 16.8, 21.6, 26.7, 28.9, 75.0, 118.5, 129.5, 133.3, 145.4, 149.6, 186.7; MS m/z (%): 287 $[M+1]^+$ (100), 268 (10), 235 (15), 179 (45), 163 (18); Anal. Calcd. for $C_{12}H_{16}NO_2Br$: 4.89 (N), 50.37 (C), 5.64 (H). Found: 4.76 (N), 50.24 (C), 5.54 (H).

(4E)-2-isopropyl-5-methylbenzo-1,4-quinone-(O-[2-(diethylamino)-ethyl]-oxime) (**10**)

A solution of (**9**) (0.40 g; 1.39 mmol) in EtOH (15 ml) was added to diethylamine (0.43 ml, 0.307 g; 4.2 mmol) and the resulting mixture was stirred for 6 hours at room temperature. The solvent and excess diethylamine were evaporated under reduced pressure. The oily residue was purified by radial thin-layer chromatography (9:1 hexane-ethyl acetate as eluent) to provide a pure sample of **10**: (0.192 g, 0.69 mmol, 49% yield). IR ($\nu_{max.}$, KBr, cm^{-1}): 2966, 1640, 1626, 1466, 1306, 1240, 1044; ^{1}H-NMR δ: 1.10 (6H, t, *J*=7.2 Hz), 1.15 (6H, d, *J*= 6.9 Hz), 2.15 (3H, d, *J*=1.3 Hz), 2.7 (4H, q, *J*=7.2 Hz), 2.95 (2H, t, *J*=5.9 Hz), 3.08 (1H, d hept, J^1=1.1, J^2=6.9 Hz), 4.5 (2H, t, *J*= 5.9 Hz), 6.28 (1H, q, *J*= 1.3 Hz), 7.39 (1H, d, *J*= 1.1 Hz); ^{13}C-NMR δ: 11.2, 16.8, 21.7, 26.7, 47.5, 50.8, 74.2, 118.6, 129.2, 145.5, 149.3, 149.9, 186.7; MS m/z (%): 279 $[M+1]^+$ (100), 164 (13), 116 (11); Anal. Calcd. for $C_{16}H_{24}N_2O_2$: 10.06 (N), 69.03 (C), 9.41 (H). Found: 9.80 (N), 68.65 (C), 9.12 (H).

Acute toxicity

The toxicity study was performed with different doses of compounds to groups of mice (n = 10) administered intraperitoneally (i.p.), and mortality was recorded for 48 h [14].

Pharmacology

The forced swimming (behavioural despair) test was employed on 6-8 week old male Swiss albino mice (weighing 28-36 g). The animals were maintained at constant room temperature (23 ± 1°C) and on a 12/12 hour light-dark cycle (light from 07:00 to 19:00 hours) with free access to food and water. They were acclimatized for a minimum of 7 days.

The synthesized compounds (10 mg/kg) and imipramine (15 mg/kg) were dissolved in 5% Tween 80 and saline (0.9%), respectively. They were injected i.p. into mice (n = 6) in dose/volume of 1 mL/100 g, one hour prior to testing. Saline was used as control. One hour after injection the mice were placed one at a time into a plexi-glass cylinder (22 cm height, 10 cm diameter) containing 8 cm height of water at 24 °C and the immobility time of each mouse was measured between 2 and 6 min [15].

Statistical analysis

Analysis of variance and Student's "t" test were made and the results were considered significant when $p < 0.05$.

References

1. Willner, P. Behavioural models in psychopharmacology: theoretical, industrial, and clinical perspectives; Cambridge University Press: Cambridge, U.K., **1991**; pp. 94-105.
2. Soga, S.; Sharma, S.V.; Shiotsu, Y.; Shimizu, M.; Tahara, H.; Yamaguchi, K.; Ikuina, Y.; Murakata, C., Tamaoki, T., Kurebayashi, J., Schulte, T.W., Neckers, L.M., Akinaga, S. *Cancer Chemoth. Pharm.* **2001**, *48*, 435-445.
3. Karakurt, A.; Dalkara, S.; Ozalp, M.; Ozbey, S.; Kendi, E.; Stables, J.P. *Eur. J. Med. Chem.* **2001**, *36*, 421-433.
4. Brightman, T.; Ye, J. H.; Ortiz-Jimenez, E.; Flynn, E.J.; Wu, W.H.; McArdle, J.J. *Brain Res.* **1995**, *678*, 110-116.
5. Aboul-Enein, M.N.; El-Azzouny, A.; Abdallah, N.A.; Maklad, Y.A.; Saleh, O.A.; Ebeid, M. Y. *Il Farmaco* **1998**, *53*, 197-208.
6. Schenone, S.; Bruno, O.; Ranise, A.; Bondavalli, F; Filippelli, W.; Falcone, G.; Rinaldi, B. *Il Farmaco*, **2000**, *55*, 495-498.
7. Davrinche, C.; Nguyentrixuong, E.; Elhamad, Y.; Reynaud, P.; Rinjard, P.;Tran, G. *Eur. J. Med. Chem.* **1992**, *27*, 765-778.
8. Bozdag, O.; Gumusel, B.; Demirdamar, R.; Buyukbingol, E.; Rolland, Y.; Ertan, R. *Eur. J. Med. Chem.* **1998**, *33*, 133-141.
9. Ertan, R.; Bozdag, O.; Kesici, B.; Palaska, E.; Ertan, M. *Acta Pharm. Turc*. **1998**, *40*, 131-135.
10. Suginome, H.; Ohki, T., Nagaoka, A.; Senboku, H. *J. Chem. Soc. Perkin Trans.1*, 1**992**, 1849-1854.
11. Sharghi, H.; Sarvari, M. H. *Synlett.* **2001**, *1*, 99-101.
12. Willner, P. *Psychopharmacology* **1984**, *83*, 1-16.
13. Goldschmidt, H.; Schmidt, H. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2060-2065.

14. Litchfield J.J.; Wilcoxon F.J. *J. Pharmacol. Exp. Ther.* **1949**, *96*, 99-113.
15. Porsolt, R.D.; Le Pichon, M.; Jalfre, M. *Nature* **1977**, *266*, 730–732.

Sample availability: Available from the authors.