Acta Pharmaceutica Turcica
XXXX (3) 131-135 (1998)

STUDIES ON THE SYNTHESIS AND ANTIDEPRESSANT ACTIVITY OF SOME NEW OXIME-ETHER DERIVATIVES

BAZI YENİ OKSİM-ETER TÜREVLERİNİN SENTEZİ VE ANTİDEPRESAN AKTİVİTELERİ ÜZERİNDE ÇALIŞMALAR

RAHMİYE ERTAN[1], OYA BOZDAĞ[1], BETÜL KESİCİ [2], ERHAN PALASKA[2], MEVLÜT ERTAN[2]*

Faculty of Pharmacy, Department of Pharmaceutical Chemistry, [1]Ankara University, [2]Hacettepe University, Ankara- Turkey

In this study, seven new 2-methyl-3-carbmethoxy-4-(3-nitrophenyl)-1,4,5,6,7,8-hexahydroquinoline-5-one-O-(2-(N-substituted amino)ethyl)oxime derivatives have been synthesized by reacting hexahydroquinoline structure which contains ketone group with corresponding 2-amino-2-oxyethyl-N-substituted amines. Their chemical structures have been proved by IR, ^{1}H-NMR, Mass spectra and elementary analysis. Their antidepressant activities were investigated by "Porsolt Behavioral Despair Test". All the compounds were active when compared with controls. However, 2-methyl-3-carbmethoxy-4-(3-nitrophenyl) -1,4,5,6,7,8-hexahydroquinoline-5-one-O-(2-(N,N-diethylamino)ethyl)oxime showed higher inhibition of immobility.

Bu çalışmada yedi yeni 2 - metil - 3 -karbmetoksi -4-(3-nitrofenil)-5-okso-1,4,5,6,7,8-heksahidrokinolin -5-on-O-(2-(N-sübstitüe amino)etil)oksim türevi, keton grubu taşıyan heksahidrokinolin bileşiği ile uygun 2-amino-2-oksietil-N-sübstitüe aminlerle reaksiyona sokularak elde edilmiştir. Sentez edilen bileşiklerin kimyasal yapıları IR, ^{1}H-NMR, Mass spektrumları ve elemanter analizleri ile kanıtlanmıştır. Bileşiklerin antidepresan aktiviteleri "Porsolt Davranışsal Unutsuzluk Testi" (Porsolt Behavioral Despair Test) ile incelenmiş, kontrol grubu ile kıyaslandığında tüm bileşikler antidepresan aktivite göstermişlerdir. 2-Metil-3-karbmetoksi - 4 - (3 - nitrofenil)-1,4,5,6,7,8-heksahidrokinolin-5-on-O-(2-(N,N-dietilamino)etil)oksim ile en yüksek aktivite gözlenmiştir.

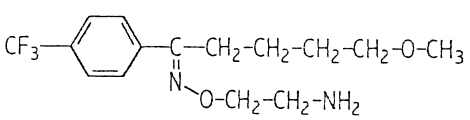
Keywords: *Hexahydroquinolin oximes; Antidepressant activity*

Anahtar kelimeler: *Heksahidrokinolin oksimler; Antidepresan aktivite*

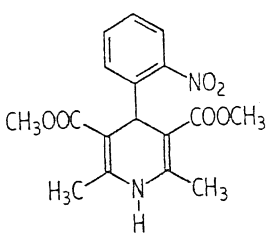
Introduction

Numerous studies have been published on β_2-selective adrenergic blocking (1-4) and antidepressant activities (5-7) of N-substituted amino-2-hydroxypropyl oxime ethers (fluvoxamine (**I**)). On the other hand, calcium channel antagonists nifedipine (**II**), nitrendipine and nimodipine exhibit antidepressant activity(8).

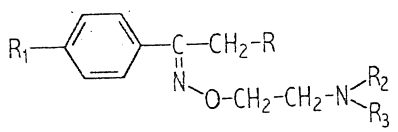
In our previous studies, we synthesized some oxime-ether derivatives of acetophenone, haloperidol, primaperon(**III**) and reported their antidepressant activity (9).



(I)



(II)

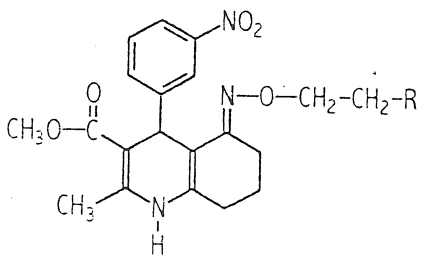


(III)

In this study, seven new 2-methyl-3-carbmethoxy-4-(3-nitrophenyl)-1,4,5,6,7,8-hexahydroquinoline-5-one-O-(2-(N-substituted amino)ethyl)oxime derivatives (Compounds **6a-g**) have been synthesized by reacting the hexahydroquinoline derivative which contains ketone group with corresponding 2-amino-2-oxyethyl-N-substituted amines. Their

*Correspondence

chemical structures have been proved by IR, ^{1}H-NMR, Mass spectra and elementary analysis. Their antidepressant activities were investigated by "Porsolt Behavioral Despair Test".



Compounds *6a-g*

Materials and Methods

Chemistry

Melting points: Thomas Hoover Capillary Melting Point Apparatus (uncorrected), TLC: Silica gel GF_{254}, IR Spectra: Perkin Elmer 1720 X FT-IR (KBr pellets), ^{1}H-NMR Spectra: Bruker ARX 400 MHz ($CDCl_3$, TMS), Mass Spectra: Finnigan Mat 311A (70 eV).

*2-Methyl-3-carbmethoxy-4-(3-nitrophenyl)-1,4,5,6,7, 8-hexahydroquinoline-5-one(**4**):*

1.511g 3-nitrobenzaldehyde (0.01 mol) ***(1)***, 1.121g 1,3-cyclohexanedione (0.01 mol) ***(2)*** and 1.151 g methylaminocrotonate (0.01 mol) ***(3)*** were dissolved in 25 ml of ethanol and heated under reflux for 12 h. The solution was evaporated in vacuo, the residue was crystallized from ethanol/water.

*2-Amino-2-oxyethyl-N-substituted amines (**5a-g**):*

1.051 g hydroxyurethane (0.01 mol) (10) and N-substituted aminoethylchloride hydrochloride (0.01 mol) were dissolved in ethanolic potassium hydroxide (0.02 mol) and refluxed for 5 h. The solution was filtered, evaporated and extracted with water/chloroform. The organic layer was concentrated and the residue was heated with 30% hydrochloric acid, evaporated in vacuo and crystallized from ethanol/ether.

*2-Methyl-3-carbmethoxy-4-(3-nitrophenyl)-1,4,5,6,7, 8-hexahydroquinoline-5-one-O-(2-(N-substitutedamino) ethyl)oximes (**6a-g**):*

0.342 g 2-methyl-3-carbmethoxy-4-(3-nitrophenyl) -1,4,5,6,7,8-hexahydroquinoline-5-one (0.01 mol) and appropriate 2-amino-2-oxyethyl-N-substituted amine derivatives (0.01 mol) were heated in pyridine/absolute ethanol for 32 h. The mixture was evaporated to dryness in vacuo and residue was dissolved in water and treated with sodium hydroxide. The aqueous solution was extracted with chloroform and the organic fraction was dried with anhydrous sodium sulfate and evaporated to dryness and the residue was purified with column chromatography (Silica gel 60, 230-400 mesh).

Pharmacology

Local breed, male albino (20-25 g) mice were used in Porsolt forced swimming test (Behavioral Despair Test) with free access to food and water.

*Test Procedure (*11,12*):*

The compounds were dissolved in dimethylsulfoxide. All compounds were injected i.p. at 20 mg/kg dose level in a constant volume 5 ml/kg 1 h before testing. The mice were dropped into the cylinder (25 cm height, 15 cm diameter containing 15 cm of water at 21-23°C) and left there for 6 min. After 3 min. initially vigorously struggling animals were immobile. Immobility times during the following 3 min. period were measured.

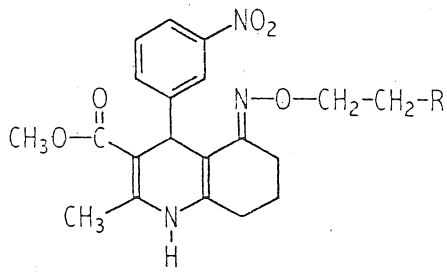
Results and Discussion

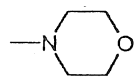
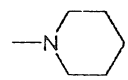
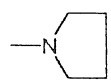
Seven new 2-methyl-3-carbmethoxy-4-(3-nitrophenyl)-1,4,5,6,7,8-hexahydroquinoline -5-one-O-(2-(N-substituted amino) ethyl) oxime derivatives (**6a-g**) have been synthesized by reacting hexahydroquinoline derivative which contains ketone group with corresponding 2-amino-2-oxyethyl-N-substituted amines (Scheme 1).

The formula, melting points, % yields of the compounds are listed in Table 1. All spectral data are in accordance with assumed structures. The IR spectra of the compounds showed N-H stretching bands at 3430, 3300, 3220 cm^{-1} and C=O stretching bands at 1665 cm^{-1}. In ^{1}H-NMR spectra, H^7, H^6, H^8 and H^4 protons of hexahydroquinoline ring were seen at 1.80-2.15, 2.40-2.45, 2.60-2.65 and 5.20-5.25 ppm respectively. In Mass spectra, all the compounds have molecular ion peaks (M^+). The base peak of the compounds belong to the fragmentation given below.

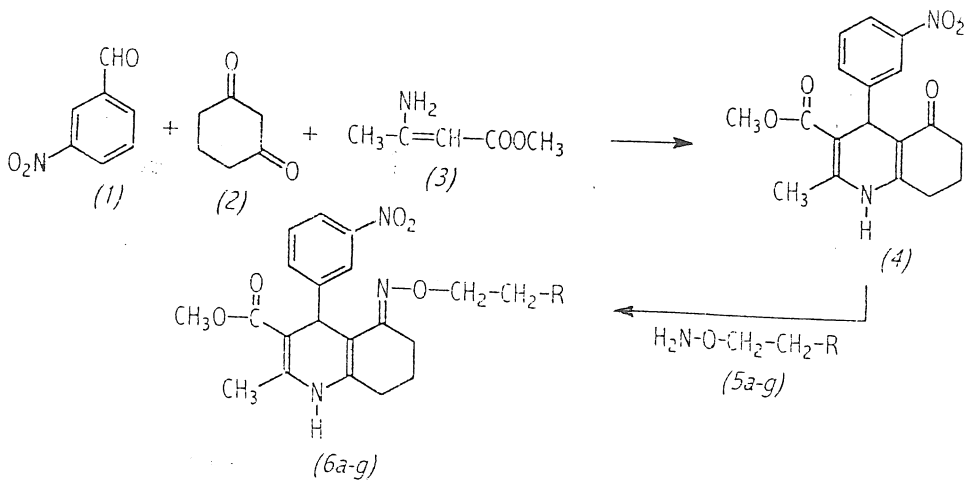
The 2 - methyl - 3 - carbmethoxy - 4 - (3-nitrophenyl)-1; 4, 5, 6, 7, 8 - hexahydroquinoline - 5 - one - O - (2 - (N - substituted amino) ethyl) oximes were screened for their antidepressant activities using Porsolt forced swimming (behavioral despair) test. There are a number of tests used to evaluate antidepressant activities of drugs. Among these, Porsolt forced swimming (behavioral despair) test is the widely accepted and used screened method for new molecules, since it is effective in predicting the activity of a wide variety of antidepressants. Table 3 shows that all our compounds were active when compared with

Table 1. Formula, melting points and % yields of the compounds



Compound no	R	m.p. °C	% Yields	Formula
6a	$-NH_2$	130-2	51.3	$C_{20}H_{24}N_4O_5$
6b	$-N(CH_3)_2$	143	69.3	$C_{22}H_{28}N_4O_5$
6c	$-N(C_2H_5)_2$	177-8	34.7	$C_{24}H_{32}N_4O_5$
6d	$-N(C_3H_7)_2$ (i)	85-7	63.6	$C_{26}H_{36}N_4O_5$
6e		176	53.9	$C_{24}H_{30}N_4O_6$
6f		152	58.5	$C_{25}H_{32}N_4O_5$
6g		186-7	75.5	$C_{24}H_{30}N_4O_5$

Elementary analyses for C, H, N are within ±0.4% of theoretical values



Scheme 1. Sythesis of the compounds

Table 2. IR, ^{1}H-NMR and Rf values of the Compounds

Compound no	IR	^{1}H-NMR [a]	R_f values
6a	3436, 3300, 3220, 1665, 1531, 1380, 1248, 1233, 1088, 850, 783, 768	1.81(2H,m,hexahydroquinoline H^7), 2.41(2H,m,hexahydroquinoline H^6), 2.55(3H,s, CH_3-), 2.62 (2H,m, hexahydroquinoline H^8), 2.82(2H,t,-CH_2-N), 3.61(3H,s,$COOCH_3$), 4.32(2H,t,N-O-CH_2-), 5.23(1H,s, hexahydroquinoline H^4), 7.32-8.18(4H,m,phenyl prot.), 9.51(1H,s, -NH)	0.84 [c] 0.17 [d]
6b [b]		2.33(6H,s,-$N(CH_3)_2$),	0.93 [c] 0.23 [d]
6c		1.25(6H,t,-$N(CH_2\underline{C}H_3)_2$), 3.17(4H,m,-$N(\underline{C}H_2CH_3)_2$),	0.92 [c] 0.33 [d]
6d		1.32(12H,d,-$N(CH(\underline{C}H_3)_4)_2$), 3.32(2H,m,-$N(\underline{C}H(CH_3)_4)_2$)	0.91 [c] 0.85 [d]
6e		2.75(4H,t,morf.H^3,H^5), 3.70(4H,t,morf. H^2,H^6)	0.96 [c] 0.60 [d]
6f		1.30-1.90(6H,m,piper.H^3-H^5), 2.30 (4H,m,piper.H^2,H^6)	0.95 [c] 0.84 [d]
6g		1.70-2.10 (4H,t,pyrrol H^3,H^4), 2.30 (4H,t,pyrrol H^2,H^5)	0.90 [c] 0.22 [d]

[a] For the compounds 6b-6g only the protons at the amine portion are quoted, [b] since hexahydroquinoline group are more or less constant, [c]Silicagel GF_{254}, $CHCl_3$:MeOH: NH_3 (10:2:0.1), [d] EtOAc:n-Hexane:NH_3 (10:1:0.3)

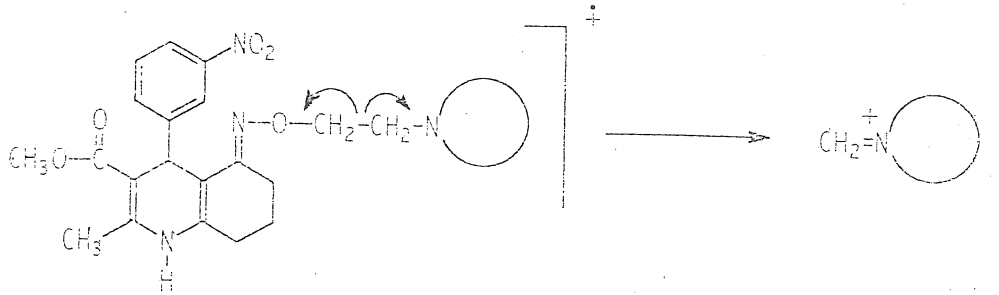


Table 3. Antidepressant Activities of the Compounds

Compound no	Duration of immobility(s) Mean (S.E.)[a]	%Change from control
6a	274(45.67)	-18.2
6b	256 (42.67)	-23.6
6c	109 (18.17)	-67.5
6d	308 (51.33)	-8.10
6e	282 (47.00)	-15.7
6f	258 (43.00)	-22.8
6g	202 (33.67)	-39.9
Fluvoxamin	54 (9.00)	-83.9
Control	335	-

[a]95% confidence limits (Dunnet's test); n=6

controls. However with the compound 6c the observed inhibition of immobility was higher.

References

1. Leclerc, G., Mann, A., Wermuth, C.G., Bleth, N., Schwartz, J.: J. Med. Chem. 20, 1657 (1977)
2. Imbs, J.L., Miesch, F., Schwartz, J., Velly, J., Leclerc, G., Mann, A., Vermuth, C.G.: Brit. J. Pharmacol. 60, 357 (1977)
3. Tandon, V.K., Chandra, A., Dua, P.R., Srimal, R.C.: Arch. Pharm. 326, 221 (1993)
4. Kleeman, A.: Arzneim Forsch./Drug Res. 31, 1178 (1981)
5. Philips, N.V.: Gloeilampenfabriken Neth. Appl. 67 17, 001 (Cl. C 07c) 17 Jun. 1969, Appl. 14 Dec. 1967. Ref; CA: 71, 123962p (1969)
6. Philips, N.V.: Gloeilampenfabriken Neth. Appl. 75 03, 310 (Cl. C07C131/00), 22 Sep .1976, Appl. 75/3, 310, 20 Mar. 1975. Ref; CA: 86, 72203s (1977)
7. Benfield, P., Word, A.: Drugs 32, 313 (1986)
8. Mogilnicka, E., Czyrak, A., Maj, J.: Eur. J. Pharm. 138, 413 (1987)
9. Bozdağ, O.: Studies on the Synthesis and Biological Activity of Some New Oxime-Ether Derivatives, Dissertation, Univ. of Ankara (1993)
10. Hantzsch, A.: Ber. 27, 1254 (1884)
11. Porsolt, R.D., Bertin, A., Jalfre, M.: Arch. Int. Pharmacodyn. 229, 327 (1977)
12. Bilgin, A.A., Palaska, E., Sunal, R.:Arzneim. Forsch/Drug Res. 43, 1041 (1993)

Accepted: 13.01.1998