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Short communication

Synthesis of some novel oxime ether derivatives and their activity in the 'behavioral despair test'

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Abstract – In this study, a new series of 2-aminoethyloxime ether derivatives of some aralkylketones was synthesized. Their structures have been elucidated by UV, IR, ^{1}H-NMR, ^{13}C-NMR, mass spectra and elementary analysis. These compounds were then screened for their inhibition of immobility as an indicator of possible antidepressant activities by using the 'behavioral despair test'. Results showed that all the new compounds decreased the immobility time, however, the inhibition observed with **AO3**, **AO4** and **HO1** was significantly higher compared to fluvoxamine ($p < 0.01$). © Elsevier, Paris

fluvoxamine / aminoethyloxime ether derivatives, structural analysis / behavioral despair test

1. Introduction

Depression is a major mental disorder. Drugs used in the treatment of depression are limited in their clinical use due to their side effects which are particularly important in the case of elderly people and patients with cardiovascular disorders. These sedative, hypotensive, anticholinergic and cardiac side effects are usually caused by the interaction of the antidepressant drugs with neurotransmitter receptor systems other than serotonine. Therefore, new therapeutic agents targeted at serotonine receptors is a challenge since evidence on an impaired central serotoninergic system is growing [1–4].

A new group of antidepressant drugs with little or no effect on noradrenaline and/or dopamine uptake has taken its place in therapy. These drugs are selective serotonine uptake inhibitors. Therefore, there is a need for drugs with specific inhibitory effect on neuronal serotonine uptake inhibition in addition to the available tricyclic antidepressants which primarily act on noradrenaline reuptake.

Fluvoxamine maleate (*figure 1*) is a second-generation antidepressant drug which selectively inhibits neuronal serotonine reuptake. In the absence of other major pharmacological effects it appears that its antidepressant activity stems from the facilitation of serotoninergic neurotransmission as a result of reuptake inhibition. Fluvoxamine has fewer anticholinergic side effects (dry mouth, abnormal accomodation) than classical tricyclic antidepressants and seems to be devoid of cardiotoxic and proconvulsive effects [5].

Considering these pharmacological advantages, preparations of 2-aminoethyloxime ethers of aralkylketones similar to fluvoxamine were planned and synthesized (*figure 2*). Acetophenone and the CNS effective compounds haloperidol and primaperone were used as starting materials. The new compounds were screened for their possible antidepressant activities by using the 'behavioral despair test' [6, 7]. Those found to be active underwent detailed study.

2. Chemistry

As indicated in *figures 2* and *3* three types of ketones **1** were used for the preparation of oxime ether derivatives. Acetophenone oxime **2** was prepared according to the literature [8]. Acetophenone derivatives **AO1–9** were obtained from their oxime **2** by using methods A and B. The condensation of ketones **1** with hydroxylamine ethyl ether derivatives **4** [9] (**HO1–6** and **PO1–6**) was the most convenient way of obtaining oxime ethers of the butyrophenone series.

*Correspondence and reprints

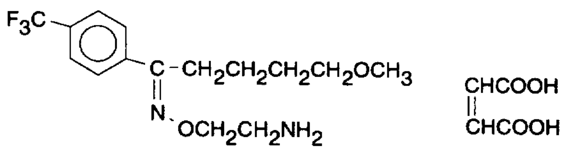


Figure 1. Fluvoxamine maleate.

Interestingly the butyrophenone ketones always gave an '*E* and *Z*' isomer mixture of oxime ethers. The ratio for compound **HO1** was 1:1. This mixture was separated by flash chromatography. The structures of the isomers were elucidated by using NMR techniques [10–12]. Some of the physical properties of compounds **AO1–9**, **HO1–6**, **PO1–6** are given in *tables I* and *II*.

3. Experimental protocols

3.1. Chemistry

Fluvoxamine, Haloperidol and Primaperone were supplied from Eczacıbaşı Pharmaceutical (Istanbul, Turkey), Ali Raif Pharmaceutical (Istanbul, Turkey) and Servier Pharmaceutical (Istanbul, Turkey), respectively. Melting points were determined with a Buchi SMP 20 capillary melting point apparatus and are uncorrected. UV spectra were determined with a Shimatzu UV 160A spectrophotometer. IR spectra were recorded on a IRFT Bruker IFS 88 spectrophotometer. ^{1}H-NMR spectra were recorded with a Bruker AC 500, 360, 300, 200, 80 MHz instrument using TMS as an internal standard and $CDCl_3$, DMSO-d_6 as solvents. ^{13}C-NMR spectra were recorded on a Bruker AC 200 MHz spectrometer. All chemical shifts are reported as δ (ppm) values. Mass spectra were recorded on a VG analytical 70–250 S spectrometer using EI and NH_4 CI methods. Elementary analyses were made on a Carlo Erba 1108 instrument at the Institut de Recherche Servier, Suresnes (France). Flash chromatography was carried out on a Merck Silica gel 60 (230–400 mesh ASTM). All the chemical reagents were purchased from E. Merck (Darmstadt, Germany) and Aldrich (Milwaukee, WI, USA).

3.1.1. Synthesis of the compounds

Method A: Acetophenone oxime **2** (0.01 mol) was treated with haloalkylamine•HCl (0.01 mol) in NaOEt (Na°/abs. EtOH (0.01 mol/20 mL)) and stirred at room temperature for two days [8].

Method B: **2** (0.01 mol) was added to the solution of 0.01 mol Na° in 20 mL of abs. EtOH. 0.02 mol of dibromoethane and 20 mL of DMF were added, and the mixture was heated at 65 °C for 40 h under stirring. The 0.01 mol of **3** so obtained was heated at 60 °C for 24 h with 0.03 mol of the pertinent sec. amine in 25 mL of EtOH. After evaporation in vacuo, 25 mL of 2 N HCl was added and extracted with ether (3 x 25 mL). The HCl layer was made basic with 2 N NaOH and extracted with ether (3 x 50 mL). The combined ether extracts were dried on Na_2SO_4 and concentrated. The oily product was dissolved in abs. EtOH. Dry HCl gas was passed through the solution and anhydrous ether was added. The precipitated product was filtered, dried and crystallized from EtOAc.

Method C: **1** (0.01 mol) was treated with **4** (0.01 mol) in pyridine/abs. EtOH (2/10 mL) and refluxed for 32 h. After evaporation in vacuo, the residue was dissolved in water and washed with petroleum ether, alkalized with 50% NaOH solution and extracted with $CHCl_3$ (3 x 25 mL). The chloroform extract was washed with 5% $NaHCO_3$ solution and water, then dried on Na_2SO_4 and concentrated. The oily product was purified over silica gel by column chromatography.

3.1.2. Computational analysis

Molecular mechanic calculations were performed using the Chem-X software package (Chemical Design Ltd., Oxfordshire, UK) on an Pentium-100 computer. The selected compounds were built within Chem-X and bond angles and lengths were optimized with the Gasteiger method. Conformational analyses were performed by employing the CONFORMERS option within Chem-X. The C6–C8 and N12–O13 bonds of **AO3** and **HO1**, respectively, were defined as the rotatable bonds and the default parameters were used. The CONFORMERS function was used to locate the various energy minima available to each molecule by randomly perturbing torsions, minimizing and eliminating duplicates. Hydrogen atoms were included during the optimization process but omitted for display. Torsion angles were defined by clockwise rotations around the appropriate bonds, and molecular geometries were obtained after the lowest molecular energy minimization was done for each compound. In conformational calculations the molecules were considered with their primer amine chain in the neutral form.

3.2. Pharmacology

20–25 g albino mice (local breed) were used which were housed in groups of 6 under laboratory conditions with free access to food and water for at least 24 h prior to testing.

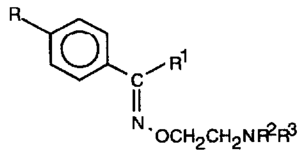
The synthesized compounds were dissolved in DMSO and administered to mice intraperitoneally at 10 mg/kg in 0.1 mL doses 1 h prior to testing. One hour after the injection, animals were dropped into 30 cm diameter cylinders filled with water and the immobility times were determined between 3 and 6 min (n = 6).

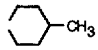
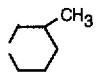
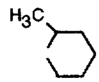
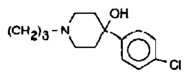
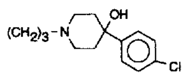
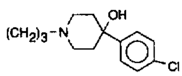
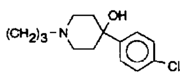
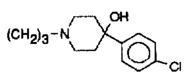
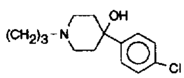
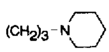
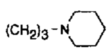
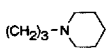
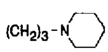
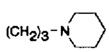
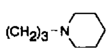
DMSO was used as control and results were compared to results obtained with fluvoxamine which was selected as the reference compound. The Dunnet test was employed for statistical analysis. The results are given in *table III*.

4. Results

An interesting point was found between acetophenone-derived oxime ethers (**AO1–9**) and butyrophenone compounds (**HO1–6, PO1–6**): the latter showed a mixture of stereo-isomers while the former exist only as one isomer as a result of the reaction process. In acetophenone derivatives, the ^{1}H-NMR spectra indicated that the O–CH_2 protons were located between 4.3 and 4.5 ppm which is consistent [8] with the values found in the literature (*table IV*).

Although limited conformational calculations have been performed for acetophenone and butyrophenone



Code	R	R^1	R^2	$R^2+R^{3\,a}$	R^3
I: Acetophenone derivatives					
AO1	H	CH_3	CH_3		H
AO2 [8]	H	CH_3	CH_3		CH_3
AO3	H	CH_3	C_2H_5		H
AO4	H	CH_3	C_2H_5		C_2H_5
AO5	H	CH_3	n-C_3H_7		H
AO6	H	CH_3	$CH(CH_3)_2$		H
AO7	H	CH_3			
AO8	H	CH_3			
AO9	H	CH_3			
II: Haloperidol derivatives					
HO1	F		H		H
HO2	F		CH_3		CH_3
HO3	F		C_2H_5		C_2H_5
HO4	F				
HO5	F				
HO6	F				
III: Primaperone derivatives					
PO1	F		H		H
PO2	F		CH_3		CH_3
PO3	F		C_2H_5		C_2H_5
PO4	F				
PO5	F				
PO6	F				

[a]R^2+R^3: heterocyclic nitrogen compounds.

Figure 2. Synthesized compounds.

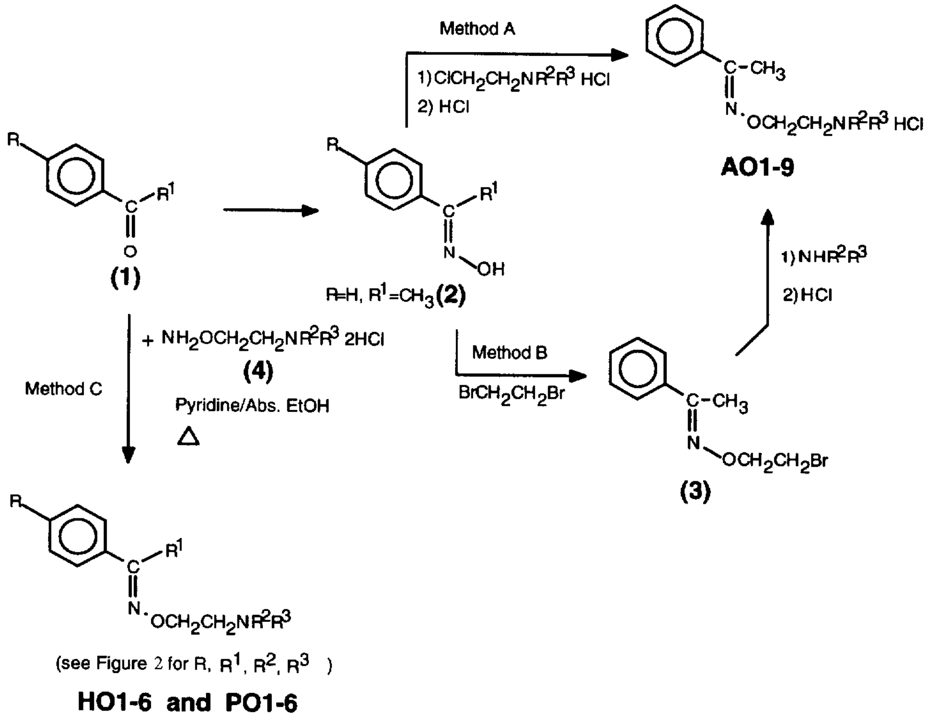


Figure 3. Synthesis of oxime ether derivatives.

Table I. Yields and physicochemical properties of series I.

Compound	Method	Yield (%)	M.p. (°C)	Formula[a]	IR (cm^{-1}) (C=N)
AO1	B	35.3	148–152	$C_{11}H_{16}N_2O$	1614
AO2	A	20.7	121–123	$C_{12}H_{18}N_2O$	1610
AO3	B	70.0	146	$C_{12}H_{18}N_2O$	1610
AO4	A	23.0	116–118	$C_{14}H_{22}N_2O$	1615
AO5	B	54.0	134–135	$C_{13}H_{20}N_2O$	1612
AO6	B	47.2	153	$C_{13}H_{20}N_2O$	1610
AO7	B	52.5	127–128	$C_{16}H_{24}N_2O$	1612
AO8	B	61.2	185–186	$C_{16}H_{24}N_2O$	1612
AO9	B	52.5	132	$C_{16}H_{24}N_2O$	1610

[a]All of the compounds are HCl salts.

Table II. Yields and physicochemical properties of series II and III.

Compound[a]	Yield (%)	Formula[b]	IR (cm^{-1}) (C=N)
HO1	39.7	$C_{23}H_{29}ClFN_3O_2$	1603
HO2	61.2	$C_{25}H_{33}ClFN_3O_2$	1603
HO3	76.9	$C_{27}H_{37}ClFN_3O_2$	1603
HO4	52.2	$C_{27}H_{35}ClFN_3O_3$	1609
HO5	43.3	$C_{28}H_{37}ClFN_3O_2$	1603
HO6	67.7	$C_{27}H_{35}ClFN_3O_2$	1603
PO1	56.1	$C_{17}H_{26}FN_3O$	1605
PO2	72.9	$C_{19}H_{30}FN_3O$	1603
PO3	55.2	$C_{21}H_{34}FN_3O$	1610
PO4	50.9	$C_{21}H_{32}FN_3O_2$	1603
PO5	64.0	$C_{22}H_{34}FN_3O$	1603
PO6	69.0	$C_{21}H_{32}FN_3O$	1603

[a]All of the compounds are viscous–liquid, and were synthesized by method C; [b]elementary analyses of all the compounds revealed values for C, H and N within ±0.4% of the theoretical results.

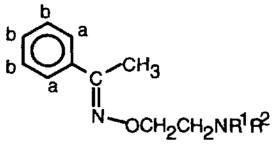
Table III. The results of antidepressant activity of the synthesized compounds.

	(3'–6') Immobility time (sec ± S.E.M.)	Immobility inhibition (%)
Control	40.300 ± 7.10	0.00
Fluvoxamine	14.957 ± 3.95	62.89
AO1	16.530 ± 2.80	58.98
AO2	10.040 ± 1.50	75.09
AO3	1.328 ± 0.50	96.71
AO4	5.605 ± 1.50	86.09
AO5	11.468 ± 2.40	71.54
AO6	18.715 ± 3.10	46.44
AO7	14.928 ± 2.40	62.96
AO8	15.183 ± 1.60	62.33
AO9	11.461 ± 1.30	71.56
HO1	5.465 ± 0.50	86.44
HO2	18.130 ± 3.10	55.01
HO3	18.770 ± 2.80	53.42
HO4	18.520 ± 2.90	54.04
HO5	19.570 ± 3.60	51.44
HO6	13.490 ± 2.30	66.53
PO1	15.690 ± 4.40	61.07
PO2	15.560 ± 2.60	61.39
PO3	25.550 ± 5.10	36.60
PO4	17.910 ± 2.80	55.57
PO5	19.710 ± 2.50	51.09
PO6	23.807 ± 3.10	40.93

derivatives, it was thought that it could have been useful to determine the possibility of syn- and anti-isomers obtained from synthesis. The molecular conformation of **AO3** is determined by two principal torsion angles τ_1 (C6–C8–N12–O13) and τ_2 (C8–N12–O13–C14) which define the positions of the side chain in syn- and anti-isomers (*table V*). For **HO1** isomers, the torsion angles in the connecting amine chain are defined dependent for the conformational analysis due to the fact of merely explaining the syn- and anti-isomer formation (*table VI*).

Indeed, the molecular mechanics energy levels of the **AO3** derivative obtained from the Chem-X molecular modeling program indicated a difference between the anti-(*E*) and syn-(*Z*) isomer of the derivatives. Acccording to these data the anti-isomer prefers the lower energy state which indicated that it could be obtained preferentially to the syn-isomer as is seen in synthesis procedure.

Table IV. ^{1}H-NMR spectral data of the acetophenone oxime ethers.

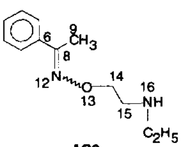


AO1–9

Compound	CH_3	OCH_2	NCH_2	R^1, R^2	*a*	*b*	NH
AO1[a]	2.31 (s, 3H)	4.4 (t, 2H)	3.25 (t, 2H)	2.6 (s, 3H, CH_3)	7.7 (m, 2H)	7.4 (m, 3H)	9.2 (s, 2H)
AO2[a]	2.25 (s, 3H)	4.5 (t, 2H)	3.4 (m, 2H)	2.8 (s, 6H, CH_3)	7.7 (m, 2H)	7.4 (m, 3H)	11.1 (s, 1H)
AO3[a]	2.3 (s, 3H)	4.56 (t, 2H)	3.25 (t, 2H)	1.25 (t, 3H, CH_3), 3.1 (m, 2H, CH_2)	7.7 (m, 2H)	7.45 (m, 3H)	9.2 (s, 2H)
AO4[a]	2.24 (s, 3H)	4.56 (t, 2H)	3.38 (m, 2H)	1.25 (t, 6H, CH_3), 3.17 (m, 4H, CH_2)	7.7 (m, 2H)	7.4 (m, 3H)	9.2 (s, 1H)
AO5[a]	2.25 (s, 3H)	4.45 (t, 2H)	3.3 (t, 2H)	0.9 (t, 3H, CH_3), 1.7 (m, 2H,CH_2), 2.9 (t, 2H, NCH_2)	7.7 (m, 2H)	7.45 (m, 3H)	9.2 (s, 2H)
AO6[a]	2.3 (s, 3H)	4.45 (t, 2H)	3.3 (t, 2H)	1.3 (d, 6H, CH_3), 3.32 (m, 1H, CH)	7.7 (m, 2H)	7.45 (m, 3H)	9.5 (s, 2H)
AO7[b]	2.25 (s, 3H)	4.47 (t, 2H)	2.8 (t, 2H)	1.06 (d, 3H, CH_3), 1.6 (m, 1H, CH), 1.8–2.0 (m, 4H, CH_2), 3.4–3.7 (m, 4H, NCH_2)	7.65 (m, 2H)	7.4 (m, 3H)	9.75 (s, 1H)
AO8[a]	2.21 (s, 3H)	4.47 (t, 2H)	3.4 (t, m, 4H (& NCH_2))	0.9 (d, 3H,CH_3), 1.4–2.0 (m, 5H, CH, CH_2), 2.6 (t, 1H, NCH_2), 2.9 (t, 1H, NCH_2)	7.69 (m, 2H)	7.45 (m, 3H)	9.75 (s, 1H)
AO9[a]	2.22 (s, 3H)	4.5 (t, 2H)	3.4 (m, 2H)	1.3 (d, 3H, CH_3), 1.6–2.0 (m, 6H, CH_2), 2.8–3.0 (m, 2H, NCH_2), 3.5–3.6 (m, 1H, CH)	7.7 (m, 2H)	7.45 (m, 3H)	9.75 (s, 1H)

[a]DMSO-d_6; [b]$CDCl_3$.

Table V. Molecular mechanic energies and torsional geometry of **AO3** derivatives.



AO3

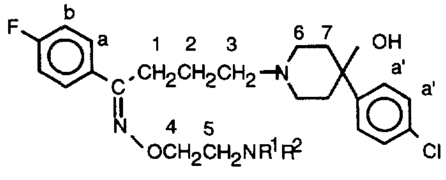
Compounds	AO3 (syn)	AO3 (anti)
Molecular mechanic energy values (kcal/mol)	12.2425	8.1831
C6–C8–N12–O13	–17.46	176.14
C9–C8–N12–O13	162.90	–3.90
C8–N12–O13–C14	–175.46	176.51
N12–O13–C14–C15	–79.64	–85.56
O13–C14–C15–N16	–175.48	–174.40

On the other hand, the butyrophenone derivatives were obtained in different *E*/*Z* ratios. The highest ratio (1:1) was found for compound **HO1** in which the isomers were separated by flash chromatography (**HO1a**, **HO1b**). The syn- and anti-isomers were determined by ^{1}H-NMR spectroscopy (*tables VI* and *VII*) and ^{13}C-NMR (*table VIII*).

5. Discussion of the chemical results

As shown in *table VI*, the higher δ ppm values of 4.4 ppm for O–CH_2 in **HO1b** indicates an *E* isomer in contrast with **HO1a** which shows a resonance at a higher field with a 0.2 ppm difference in δ value merging from the anisotropic diamagnetic influence of the phenyl ring. This is also confirmed by literature findings [8, 10].

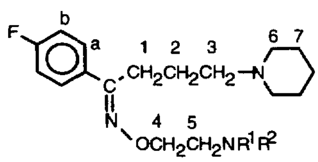
Table VI. ^{1}H-NMR spectral data of the haloperidol oxime ethers (in $CDCl_3$).



HO1–6

Compound	
HO1a (syn)	1.7–2.1 (m,6H,2+7), 1.8 (s,2H,NH_2), 2.4–2.6 (m,6H,3+6), 2.7–2.9 (m,2H,1), 3.0 (t,2H,5), **4.2 (t,2H,4)**, 7.02 (2H,b), 7.3–7.4 (4H,a'), 7.62 (2H,a)
HO1b (anti)	1.7–2.1 (m,6H,2+7), 2.0 (s,2H,NH_2), 2.4–2.6 (m,6H,3+6), 2.7–2.9 (m,2H,1), 3.55 (t,2H,5), **4.4 (t,2H,4)**, 7.02 (2H,b), 7.3–7.4 (4H,a'), 7.62 (2H,a)
HO2	1.65 (s,1H,OH), 1.7–2.1 (m,6H,2+7), 2.3 (s,6H,CH_3), 2.4–2.6 (m,6H,3+6), 2.66 (t,2H,5), 2.76 (m,2H,1), 4.28 (t,2H,4), 7.05 (2H,b), 7.4 (4H,a'), 7.62 (2H,a)
HO3	1.1 (t,6H,NCH_3), 1.7–2.1 (m,7H,2+7+OH), 2.4–2.5 (m,6H,3+6), 2.6 (q,4H,NCH_2), 2.7–2.8 (m,4H,1+5), 4.25 (t,2H,4), 7.1 (2H,b), 7.3–7.4 (4H,a'), 7.65 (2H,a)
HO4	1.7 (m,1H,OH,with propyl side chain), 1.8 (m,2H,2), 2.1 (m,2H,1), 2.4 (m,4H,7), 2.55 (m,6H,3+6), 2.75 (m,6H,5+NCH_2(morpholin)), 3.7 (t,4H,OCH_2(morpholin)), 4.32 (t,2H,4), 7.1 (2H,b), 7.3–7.4 (4H,a'), 7.65 (2H,a)
HO5	1.6 (s,1H,OH), 1.7–2.1 (m,12H,2+7+CH_2(piperidin)), 2.4–2.6 (m,10H,3+6+NCH_2(piperidin)), 2.7–2.8 (m,4H,1+5), 4.3 (t,2H,4), 7.03 (2H,b), 7.4 (4H,a'), 7.65 (2H,a)
HO6	1.6 (s,1H,OH), 1.7–2.1 (m,10H,2+7+CH_2(pyrrolidin)), 2.4–2.7 (m,12H,3+6+5+NCH_2(pyrrolidin)), 2.8 (m,2H,1), 4.3 (t,2H,4), 7.0 (2H,b), 7.4 (4H,a'), 7.62 (2H,a)

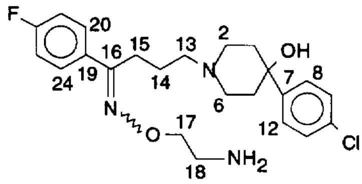
Table VII. ^{1}H-NMR spectral data of the primaperone oxime ethers (in $CDCl_3$).



PO1–6

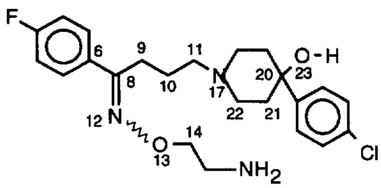
Compound	
PO1	1.3–1.9 (m,8H,2+7), 2.3 (m,6H,3+6), 2.7–2.8 (m,4H,1+5), 4.3 (t,2H,4), 7.0–7.6 (m,4H,a+b)
PO2	1.3–1.9 (m,8H,2+7), 2.3 (m,6H,3+6), 2.3 (s,6H,CH_3), 2.7 (t,2H,5), 2.8 (m,2H,1), 4.3 (t,2H,4), 7.0–7.6 (m,4H,a+b)
PO3	1.1 (t,6H,CH_3), 1.3–1.9 (m,8H,2+7), 2.3 (m,6H,3+6), 2.6 (q,4H,NCH_2), 2.7–2.8 (m,4H,1+5), 4.25 (t,2H,4), 7.0–7.6 (m,4H,a+b)
PO4	1.3–1.9 (m,8H,2+7), 2.3 (m,6H,3+6), 2.6 (m,6H,5+NCH_2(morpholin)), 2.8 (t,2H,1), 3.7 (t,4H,OCH_2(morpholin)), 4.3 (t,2H,4), 7.0–7.6 (m,4H,a+b)
PO5	1.3–1.9 (m,14H,2+7+CH_2(piperidin)), 2.3 (m,6H,3+6), 2.5 (m,4H,NCH_2(piperidin)), 2.7–2.8 (m,4H,1+5), 4.3 (t,2H,4), 7.0–7.6 (m,4H,a+b)
PO6	1.3–1.9 (m,12H,2+7+CH_2(pyrrolidin)), 2.3 (m,6H,3+6), 2.6 (m,4H,NCH_2(pyrrolidin)), 2.7–2.8 (m,4H,1+5), 4.3 (t,2H,4), 7.0–7.6 (m,4H,a+b)

Table VIII. The ^{13}C-NMR values of **HO1a** and **HO1b** derivatives.



Carbon	Anti(**HO1b**)	Syn(**HO1a**)	Carbon	Anti(**HO1b**)	Syn(**HO1a**)
2, 6	24.01	23.98	**15**	**24.69**	**27.1**
3, 5	49.42	49.36	17	71.03	71.06
4	76.46	76.40	18	58.26	58.21
7	147.12	146.97	**19**	**115.24**	**112.34**
8, 12	126.20	126.12	20, 24	132.80	132.78
9, 11	128.44	128.41	21, 23	115.67	115.62
10	132.80	132.78	22	165.90	165.80
13	41.74	41.72	C=N	157.66	157.61
14	38.56	38.52			

Table IX. Molecular mechanic energies and torsional geometry of **HO1** derivatives.



Compounds	**HO1a** (syn)	**HO1b** (anti)
Molecular mechanic energy values (kcal/mol)	12.5785	12.3896
C6–C8–N12–O13	–14.9	176.8
C8–N12–O13–C14	165.1	–3.5
C9–C8–N12–O13	–174.1	–175.7
N12–C8–C9–C10	–93.4	–90.4
C6–C8–C9–C10	86.6	89.5
C9–C10–C11–N17	170.9	173.4
C22–C21–C20–O23	–68.1	–69.4

As can be seen from the values given in *table VIII*, the shielding effect of the oxime oxygen onto the C15 atom seems to be determining for the anti- and syn-isomers [11, 12]. C15 of compound **HO1** for the anti-isomer type (**HO1b**) shows the signal at 24.69 δ ppm, in contrast with the syn-isomer, resonating 2.4 ppm lower than the anti-isomer. Indeed, the syn-isomer (**HO1a**) verifies the difference in C19 at 112.34 δ ppm with a 2.9 ppm difference with respect to the anti-isomer and hence at higher field strength.

Table IX indicates molecular mechanic energy values obtained using the Chem-X Molecular Modeling Program as explained in the previous section. The syn- and anti-isomers show a small difference in their optimized molecular mechanic energy calculation.

The ratio of the syn- and anti-isomers show that these isomers should be obtained in equal quantities in the synthesis procedure. The data obtained from Chem-X also confirm this finding due to the preferential molecular mechanic energies of each isomer.

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