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Synthesis and Antimicrobial Activities of Some N-Alkoxy α, β-Unsaturated Oxime Ethers

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ABSTRACT

The synthesis, spectral characterization and microbial activity evaluation of a series of some N-alkoxy (and acyloxy) α, β-unsaturated oxime ethers were carried out. The products obtained were characterized and tested for bioactivity against Stapphylococcus aurreus, Escherichia coli, Candidas albicans and Sacharomyces cereviciae. Alkyl halides and a group of compounds comprising of acyl chlorides derived from fatty acids of palm oil (palmitic acid, oleic acid) were coupled with cinnamaldoxime and crotonaldoxime to form the ethers or esters.

Key words: oxime ethers, Synthesis, characterization, microbial activity.

INTRODUCTION

References to the potential of oxime ethers and their derivatives as anti-microbial drugs abound in literature [1-5]. Oxime ethers have also found many uses in recent years as non-steroidal anti inflammatory drugs, mold inhibitory active compounds in poultry science, anti-protozoan, insect growth regulator, and herbicides and as various materials with steroidal effects. Most of the work done so far on this class of compounds is on oxime ethers but very little on the α, β-unsaturated analogues.

Despite the growing list of antimicrobial agents, their clinical value has been limited by their relatively high risk of toxicity, the emergence of drug resistance, and insufficiencies in their antimicrobial activity. Since the environmental and economic requirements imposed on modern-day antibiotics are continually increasing, with regard to the spectrum of action, toxicity, selectivity, application rate, formation of residues, and favourable preparability, a constant task is to develop new antibiotics which in some areas at least have advantages over their known counterparts. This situation has led to an ongoing search for potent broad spectrum antimicrobial agents with low side effects, which can be administered both orally and parenterally.

In this series, fatty acid derivatives (a natural product) obtained from palm oil have been incorporated and the effect of the additional α, β-unsaturation is expected to enhance their antimicrobial activity and physiological tolerance in humans and other animals.

It has been revealed that coupling of two or more biodynamic molecules result in enhanced biological activity [6]. Numerous previous workers have shown that the oxime ether group is one such group that are biologically active in many instances [7-10]. The hydrophobic nature of the long alkyl groups of fatty acids is a useful property in some pharmacological media [11].

The *in vitro* antibacterial activity of the oxime-ether derivatives were evaluated by disk diffusion method against culture of *Staphylococcus aureus and Escherichia coli, Candida albicans and Sacharomyces cereviciea*.

MATERIALS AND METHODS

The Infrared spectra were recorded on Perkin-Elmer Model 1310 spectrophotometer and Buck Scientific S 500 Infra-red spectrophotometer. The ^{1}H and ^{13}C nmr spectra of 1**a, 1b, 1c, 1d** and 2a-f were run at 250 MHz while ^{1}H, ^{13}C, ^{13}C-DEPT, ^{1}H-^{1}H coupling correlation, and ^{1}H- ^{13}C ^{1}J correlations were run at 400 MHz for products 1**a** and 1**b,** the O-alkyl cinnamaldoxime ethers, using deuterated chloroform and carbon tetrachloride as solvent and tetramethylsilane (Tms) as internal standard. The chemical shifts are given in **δ** (ppm) scale. Elemental analysis was determined on a Yanaco CHN Corder Elemental analyzer. Cinnamaldehyde, crotonaldehyde, tetrahydrofuran (THF), and hydroxyl amine hydrochloride were purchased from Zayo-Sigma, representatives of Sigma-Aldrich in Nigeria. Column chromatography was performed using silica gel 60 (230–400 mesh, Merck). Solid reagent compounds were used with their melting points uncorrected. However, liquids were redistilled to remove stabilizers and other impurities. All liquid oxime ethers were purified by redistillation under reduced pressure.

Antimicrobial activities of the synthesised compounds were determined with the previously reported standard methods [12-13, 10, 14] at the Department of Microbiology, Faculty of Natural Sciences, Kogi State University, Anyigba.

General method for preparation of oximes:
A mixture of redistilled aldehyde, 9.43g(0.0714 mol); hydroxyl amine hydrochloride, 4.97g(0.0715mol); triethylamine, 7.24g, 11.0cm^3(0.0715mol) in methanol is heated at reflux for 1 hour. Methanol is removed by distillation and the cooled residue washed once with water and recrystallized with dilute ethanol.

Typical procedure for preparation of oximes
Preparation of Cinnamaldoxime
Amixture of cinnamaldehyde, 9.43g (0.0714); hydroxyl amine hydrochloride, 4.97g (0.0715 mol); triethyl amine, 7.24g, 11.0 mL(0.0715mol) in methanol was heated at reflux for 1 hr. Methanol was removed by distillation and the cooled residue washed once with water and recrystallized with dilute ethanol. Yield: 5.0g

General methods for the preparation of oxime ethers*:*
Direct Alkoxyamination of carbonyl compound
0.011mol (0.9g) of alkoxyamine hydrochloride and 1.5 mL of triethylamine is dissolved in 8 mL of methanol. After stirring the mixture for 5 minutes it is added over 20 minutes to a stirred solution of 0.011 mol of redistilled aldehyde in 5mls of methanol maintained at room

temperature. The resulting mixture is stirred for another 30 minutes and then heated at reflux for 30 more minutes, allowed to cool to room temperature and then quenched with 10 mL of cold water. The product is extracted with 2 x 5 mL of chloroform. The combined extracts is washed once with 5mL of cold water and dried over anhydrous sodium sulphate. The chloroform is evaporated off and the imine vacuum distilled.

Alkylation of oxime with silver oxide as catalyst and base
Silver oxide (0.017mol) is added in small portions to a cooled solution of aldoxime (0.016mol) in alkyl bromide, 50 mL. The mixture is heated at reflux for 24 hours. The resulting solution is filtered hot and the residue washed 3 times with 10 mL of chloroform each time. The filtrate is concentrated by distillation. The residue is vacuum-distilled to give the oxime ether.

Alkylation or acylation of Oximes with Potassium carbonate as base:
The oxime (3.6 mmol), K_2CO_3 (0.55 g, 4 mmol) and an appropriate alkyl halide or acid chloride (3.6 mmol) are mixed in absolute acetone or DMF [10, 7]. The mixture is refluxed at 90^{o}C for 12 hours to complete the reaction. After cooling to room temperature, the mixture is poured into water. If a solid separates it would be filtered off, washed with copious water and recrystallized from ethanol [10], otherwise, the product is extracted from the mixture trice with about 5mL of chloroform, washed once with water and the chloroform evaporated off under vacuum and the oxime ether is purified by vacuum distillation.

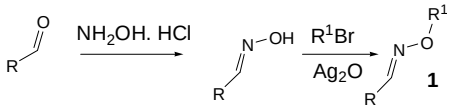
Preparation of Silver Oxide:
Add dilute sodium hydroxide solution (0.2 mol/dm^3) gradually to 10% aqueous silver nitrate solution until the silver nitrate solution is alkaline. Filter and wash the residue thoroughly with distilled water.

Typical procedures: 3-Phenylpropenal o-ethyl oxime (**1a**)
Silver oxide (3.94 g, 0.017mol) was added in small portions to a cooled solution of cinnamaldoxime (5.00g, 0.016 mol) in ethyl bromide (50 mL). The mixture was heated at reflux for 12 h. The resulting mixture was filtered while still hot and the residue washed thrice with chloroform (10 mL), the filtrate was concentrated by distillation and the residue distilled under vacuum. Oil, b.p. 100-102 ºC (10 mmHg) 5.55 cm^3 (78%), d 0.994g/mL, IR(cm^{-1} , neat): 2820-2920, 1613, 1030; ^{1}H-nmr ($CDCl_3$): δ 1.25 (t, *J* = 12.5Hz, 3H, Me), 4.05-4.20(q, *J* = 12.5Hz, 2H, CH_2O), 6.7-6.8 (m, 2H, CH=CH), 7.1-7.4 (m, 5H, ArH), 7.8 (d, *J* = 12.5Hz, 1H, N=CH). ^{13}C-nmr ($CDCl_3$):δ 150.5,138.0, 136.0,129.0, 127.5,127.0,122.0, 70.0, 16.0. Anal. Calc. (%) for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99; O, 9.13. Found: C, 75.60; H, 7.20, N, 7.54; O, 9.20.

RESULTS AND DISCUSSION

The oxime ethers in this series were synthesised via three methods: The first method is by direct alkoxymation of the corresponding oxime. O-methyl cinnamaldoxime ether, 1a, was obtained in excellent yield (78%) by this method. This method is convenient because methyl chloride and methyl bromide and even iodomethane are fairly volatile compounds and would have required that the reaction be carried out under pressure higher than atmospheric pressure if any of the other methods available were used.

In the second method, silver (I) oxide is used as a base and oxidising agent to give excellent yields of oxime ethers without the usual accompanying formation of nitrones and also without the use of a separate solvent since the alkyl or acyl halide also served as the solvent (Scheme 1).

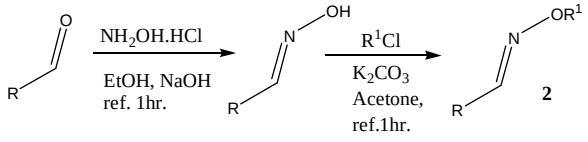


	R	R^1
1a.	PhCH=CH	CH_3CH_2-
1b.	PhCH=CH	CH_3-
1c.	CH_3CH=CH	CH_3CH_2-
1d.	CH_3CH=CH	CH_3-

Scheme 1

We believe that the reaction involves silver I ion complex formation between silver and the oxime nitrogen. Like in the silver mirror test reaction, conversion occurs without attacking any double bonds. In this case, the C=N double bond is not attacked, thereby preventing the alkylation of nitrogen that results in nitrone formation. The reaction, like in the silver mirror test, leaves a deposit of pure silver in the form of tiny pellets of silver metal and silver halide in the product mixture. This method was used to prepare compounds 1b, 1c and 1d.

The third method of oxime ether or ester formation involved the use of potassium carbonate as base and acetone as solvent (Scheme 2).



	R	R^1
2a.	PhCH=CH	$CH_3(CH_2)_7CH=CH(CH)_7CO$
2b.	PhCH=CH	$CH_3(CH_2)_{14}CO$
2c.	CH_3CH=CH	$CH_3(CH_2)_7CH=CH(CH)_7CO$
2d.	CH_3CH=CH	$CH_3(CH_2)_{14}CO$
2e.	PhCH=CH	PhCH
2f.	PhCH=CH	PhCO

Scheme **2**

Compounds 2a, 2b, 2c, 2d, 2e and 2f were prepared using this method because the alkyl or acyl halides involved have relatively high boiling points and cannot be easily distilled off without decomposing the products. Acetone was used because it had the low boiling point suitable for the recovery of the products. The products 2a-f were passed through a column of silica gel with ethyl acetate/hexane (1:2) mixture to eliminate traces of nitrone.

It is easy to monitor and confirm the transformations as the reaction proceeds from the aldehydes through the oximes to the corresponding oxime ethers. The absence of the C=O band of the carbonyl compounds (Cinnamaldehyde and crotonaldehyde) and the existence of a broad =N-OH band centred around 3166 cm^{-1} in the IR spectrum of the oximes is the evidence the aldehydes were transformed into the oximes. The –OH proton appears as a broad singlet at around 13.0 ppm in the ^{1}H-NMR spectrum. This peak disappears upon alkylation or acylation of the oxime.

3-Phenylpropenal o-ethyl oxime (**1a**)
Oil, b.p. 100-102 ºC (10 mmHg) 5.55 cm^3 (78%), d 0.994g/mL, IR(cm^{-1}, neat): 2820-2920, 1613 (C=N), 1030 (N-O); ^{1}H-nmr ($CDCl_3$): δ 1.25 (t, *J* = 12.5Hz, 3H, Me), 4.05-4.20(q, *J* = 12.5Hz, 2H, CH_2O), 6.7-6.8 (m, 2H, CH=CH), 7.1-7.4 (m, 5H, ArH), 7.8 (d, *J* = 12.5Hz, 1H, N=CH). ^{13}C-nmr ($CDCl_3$):δ 150.5,138.0, 136.0,129.0, 127.5,127.0,122.0, 70.0, 16.0. Anal. Calc. (%) for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99; O, 9.13. Found: C, 75.60; H, 7.20, N, 7.54; O, 9.20.
N-Methoxy-4-phenyl-1-azabutadiene or *3-Phenylpropenal O-methyl oxime ether* (1b)

(**1b**). Oil, b.p. 103 ºC (10 mmHg), Yield: 1.75g (70%), *d* 0.994g/mL, IR (cm^{-1} , neat): 2820-2920, 1613, 1030; ^{1}H-nmr ($CDCl_3$): δ 4.1 (s, 3H, MeO), 6.8-6.9 (m, 2H, CH=CH), 7.3-7.5(m, 5H, Ar-H), 7.9 (d, *J* = 10.0Hz, 1H, N=CH),. ^{13}C-nmr ($CDCl_3$): δ 150.5,140.0,138.5,129.0, 128.0, 127.0, 122.0, 63.0. Anal Calc. (%) for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69; O, 9.93. Found: C, 74.20; H, 6.99; N, 8.88; O, 9.61.

But-2-enal O-methyl oxime (**1c**).

Oil, b.p. 103 ºC (10 mmHg), d 0.894g/mL, Yield: 2.8mL 77.8%; IR (cm^{-1} , neat): 2820-2920, 1613 (C=N), 1030; ^{1}H-NMR ($CDCl_3$): δ 1.4 (dd, J_1 = 7Hz, J_2 = 1Hz, 3H, Me); 4.0 (s, 3H, MeO-) 5.4-5.9 (m, 2H, CH=CH); 7.9 (d, *J* = 7Hz, 1H, N=CH); ^{13}C-NMR ($CDCl_3$) δ 163.0, 137.0, 124.0, 55.0, 17.0; Anal. Calc (%) for C_5H_9NO: C, 60.58; H, 9.15; N, 14.13, O, 16.14. Found: C, 60.42; H, 9.11; N, 14.08; O, 16.50.

But-2-enal O-ethyl oxime (1d).

Oil, b.p. 107-110 ºC (12 mmHg); Yield: 1.30 mL (78%), d 0.901g/mL; IR (cm^{-1}): 2820-2920, 1613, 1030; ^{1}H-NMR ($CDCl_3$): δ 1.4 (m, 6H, Me); 4.1, (q, *J* = 8Hz, 2H, CH_2O); 5.5-5.8 (m, 2H, CH=CH); 7.9 (d, *J* = 7Hz, 1H, N=CH); ^{13}C-NMR ($CDCl_3$) δ164.0, 137.0, 124.0, 64.0, 17.0, 12.0. Anal. Calc. (%) for $C_6H_{11}NO$: C, 63.68; H, 9.80; N, 12.38; O, 14.14. Found: C, 63.40; H, 9.30; N, 12.20; O, 14.10.

2a. O-Palmitoyl cinnamaldoxime ether

Yield: 78%. m.p. 110-112^{o}C. IR (cm^{-1}):3010-3020(Ar & olefinic C-H str.), 2820-2920(methyl & methylene str. C-H), 1740(C=O str.), 1613, 1660(conjugated olefinic protons), 1465, 1380(methyl and methylene C-H bend), 1030(-C-O-N, str.). ^{1}H-nmr ($CDCl_3$): δ 0.90(t, 3H, CH_3),1.40 (sextet, 2H, CH_2), 1.35(quintet, 22H, CH_2), 1.65(quintet, 2H, CH_2), 2.02(t, 2H, O-CH_2), 6.7-6.8 (m, 2H, CH=CH), 7.1-7.4 (m, 5H, ArH), 7.8 (d, J = 12.5Hz, 1H, N=CH); ^{13}C-NMR ($CDCl_3$) δ172.0, 33.3, 32.5, 30.3, 30.3, 30.3, 30.3, 30.3, 30.3, 30.3, 30.0, 30.0,29.7, 25.4, 23.1,14.0.

O-Oleoyl cinnamaldoxime ether (2b)

Yield: 12g, 85%; m.p., 118-121^{o}C. IR (cm^{-1}):3010-3020(Ar & olefinic C-H str.), 2820-2920(methyl & methylene str. C-H), 1740(C=O str.), 1613, 1660(conjugated olefinic protons), 1465, 1380(methyl and methylene C-H bend), 1030(-C-O-N, str.). ^{1}H-nmr ($CDCl_3$): δ 0.9(t, 3H, CH_3),1.35(quintet, 14H, CH_2), 1.40(m, 6H, CH_2), 1.65(quintet,3H, CH_2), 2.2(2q, 4H, allylic H),2.35(t, 2H, CH_2), 5.3(q, 1H, CH), 5.7(q, 1H, CH), 6.7-6.8 (m, 2H, CH=CH), 7.1-7.4 (m, 5H, ArH), 7.8 (d, J = 12.5Hz, 1H, N=CH). ^{13}C-NMR ($CDCl_3$): δ 177.0, 163.7,131.7, 140.1, 134.9, 130.2, 128.4, 127.7,126.2,120.6, 33.6, 33.4, 32.5, 31.2, 30.8, 30.6, 30.5, 30.4, 30.3, 30.1, 30.0, 29.7, 25.1, 23.1, 14.

Crotonaldoximyl palmitate or O-palmitoyl crotonaldoxime ether (2c)

Yield: 8.10g (74%); m.p. 101^{o}C. IR, cm^{-1}: 2820-2920, 1613, 1030 ^{1}H-nmr (CCl_4): δ0.9 (t, 3H, Me); 1.30(quintet, 24H, CH_2), 1.65(quintet, 2H, CH_2), 1.90(Dd, J=7Hz and J=1Hz,3H, CH_3), 2.4(t, 2H, OC-CH_2); 5.0(m, 1H, =CH-), 5.8 (m, 1H, CH=); 7.9 (d, 1H, N=CH). ^{13}C-nmr ($CDCl_3$) δ174.0, 163.7, 137.0, 124.2, 34.16, 32.12, 29.90, 29.88, 29.82, 29.78, 29.70, 29.68, 29.66, 29.56, 29.47, 29.37, 25.13, 22.84, 17.50, 14.13.

Crotonaldoximyl oleate (2d)

Yield: 9.8g (82%), m.p. 112^{o}C. IR, cm^{-1}: 2820-2920, 1613, 1030 ^{1}H-nmr (CCl_4): δ0.9 (t, 3H, CH_3); 1.35(quintet or m, 20H, CH_2), 1.60(quintet, 2H, CH_2), 1.90(Dd, J=7Hz and J=1Hz,3H, CH_3), 2.05(m, 4H, allylic H) 2.35(t, 2H, OC-CH_2); 5.0(m, 1H, =CH-), 5.3(m, 2H, CH=CH), 5.8

(m, 1H, CH=); 7.9 (d, 1H, N=CH). ^{13}C-nmr ($CDCl_3$) δ:173.2, 163.7, 137.0, 130.5, 130.2, 34.10, 32.64, 32.0, 31.94, 29.69, 29.61, 29.53,29.35, 29.22, 29.16, 29.09, 28.99, 24.88, 22.71, 17.5, 14.13.

Benzyl cinnamaldoxime ether (2e)
Yield: 6.8g, 84%. m.p. 101-102^{o}C. IR, cm^{-1}: 2820-2920, 1613, 1030 ^{1}H-nmr (CCl_4): δ4.80(s, 2H, CH_2), 6.7-6.8(m, 2H, CH=CH), 7.14-7.50(m, 10H, Ar-H), 7.80 (*J* = 12.5Hz, d, 1H, N=CH). ^{13}C-nmr ($CDCl_3$) δ:163.7, 140.9, 140.1, 134.9, 128.7, 128.4, 127.7, 127.4, 127.3, 126.2, 120.6, 76.8.

Benzoyl cinnamaldoxime ether (2f)
6.6g, 77%; mp 115-116^{o}C. IR, cm^{-1}: 2820-2920, 1613, 1030 ^{1}H-nmr (CCl_4): δ 6.7-6.8(m, 2H, CH=CH), 7.14-7.50(m, 10H, Ar-H), 7.80 (*J* = 12.5Hz, d, 1H, N=CH). ^{13}C-nmr ($CDCl_3$) δ:172.0, 163.7, 140.1, 134.9, 133.7, 130.6, 130.1, 128.45, 128.4, 127.7, 126.2, 126.0.

Antimicrobial Activities
The title compounds 1a-d and 2a-f were screened for their biological activities *in vitro* against four selected microogarnisms including *S. aureus, S. cervicea, E. coli and C. albicans* at concentrations of 500 and 2000 µg/mL solutions according to procedures described previously.

Compounds 1a, 1b, 1a, and 1b were found to have some inhibitory antifungal effect against *C. albicans* and *S. cerevicea* with 1a having the activity at 500µg/mL and 2000µg/mL. 1b also has some inhibitory activity against *S. aureus* and *E. coli*, while 2b also has some inhibitory activity against *S. aureus.* The inhibitory activities were higher at the higher concentration of 2000µg/mL. 2d only showed antimicrobial activity at the higher concentration of 2000µg/mL against S.cerevicea and C. albicans.

Table1. Antimicrobial effect of 500µg/mL of α, β-Unsaturated oxime ethers

Compound	S. aureus	S. cerevicea	E. coli	C. albicans
1a	-	15	-	12
1b	11	17	13	10
1c	-	-	-	-
1d	-	-	-	-
2a	-	11	-	10
2b	-	-	-	-
2c	-	-	-	-
2d	-	-	-	-
2e	-	-	-	-
2f	-	-	-	-

Compound concentrations = 500 µg/mL; the symbol (-) means that the compounds had no activity against the microorganisms. The figures are growth inhibition zones measured in millimetres including disc diameter (8 mm). Larger inhibitory zones indicate higher strength of bioactivity.

Table2. Antimicrobial effect of 2000µg/mL of α, β-Unsaturated oxime ethers

Compound	S. aureus	S. cerevicea	E. coli	C. albicans
1a	-	18	-	14
1b	11	21	14	13
1c	-	-	-	-
1d	-	-	-	-
2a	-	16	14	13
2b	10	11	-	12
2c	-	-	-	-
2d	-	10	-	13
2e	-	-	-	-
2f	-	-	-	-

Compound concentrations = 2000 µg/mL; the symbol (-) means that the compounds had no activity against the microorganisms. The figures are growth inhibition zones measured in millimetres including disc diameter (8 mm). Larger inhibitory zones indicate higher strength of bioactivity.

CONCLUSION

The synthesis of O-alkylated or acylated α, β-unsaturated oxime ethers derived from cinnamaldehyde and crotonaldehyde has been achieved. The structures and configurations of these compounds were confirmed with the aid of IR, ^{1}H-NMR and ^{13}C-NMR. The compounds were tested for bioactivity and disappointingly, only 1a and 1b as well as 2a and 2b seem to have any significant inhibitory anti fungal activity against of *Candidas albicans* and *S. cerevicea.*

An area in which further investigation will be interesting is to find out what the Minimum Inhibitory Concentration (MIC) for each of the compounds for these microorganisms against which they are active.

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REFERENCES

[1] J.V. Dijk and J.E. Davies **(1976)**. U.S. Philips Corporation, U.S. Pat. 3.841.937.
[2] O. Bozdag-Dundar *Acta Pharmaceutica Turcica* 45:131-135 **(2003)**
[3] A. Balsamo, B. Macchia, A. Martinelli, E. Orlandini, A. Rossello, F. Macchia, G. Brocalli and P. Domiano. **(1990)**. *Eur. J. Med.Chem*. 25: 227-235.
[4] R. Sun ; M.Y. Lü; L. Chen; Q. S. Li; H. B. Song, H; F. C. Bi; R. Q. Huang; Q. M. Wang(**2008**) *J. Agric. Food Chem.* **2008**, *56*, 11376.
[5] S. A. Khan, Thesis submitted for the degree of Doctor of Philosophy in Chemistry in the Department of Chemistry, Jamia Milla Islamia, NewDelhi- 110025. December, **2006**
[6] R. R. Kamble, S. S. Belgur, R. Aladikatti and I. A. Khazi, *Chem. Pharm. Bull.* 57(1) 16- 21, **2009**

[7] J. X. Fang, T. T. Wang, Z. F. Qin, X. Zhang, X. Qin, Y. Q. Li, J. B. Liu, H. B. Yu, and H. Dai. *ARKIVOC* **2009** (vii) 126-142.
[8] R. G. Franzén. *J Comb Chem*. **2000** May-Jun; 2(3):195-214
[9] J. Kast, N. Meyer, U. Mislitz, A. Harreus, H. Rang, M. Gerber, H. Walter, K. O. Westphalen, (1995)US Patent 5407896. Apr. 18, **1995**.
[10] A. Çukurovali, C. Kirilmis, M. Koca, M. Ahmedzade, and C. Kazaz. *Molecules* **2005**, *10*, 1399–1408
[11] J. H. Chern, C. C. Lee, C. S. Chang, Y. C. Lee, C. L.Tai, Y. T. Lin, K. S. Shia, C. Y. Lee, and S. R. Shih. *Bioorg. Med. Chem. Lett.* **2004** Oct. 18; 14(20):5051-5056.
[12] M. Tuncbilek, O. Bozdag, G. A. Kilcigil, N. Altanlar, E. Buyukbingol. *Arzneim. Forsch. Drug Res*. 49 **(1999)**853–857.
[13] H. Goker, S. Ozden, A. M. Ozturk, N. Altanlar. (2000) *Il Farmaco* 55 (2000) 715–718
[14] E. I. Elnima, M. U. Zubair, And A. A. Al-badr. *Antimicrobial Agents and Chemotherapy*, Jan. **1981**, p.29-32 Vol. 19, No. 1